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Proazaphosphatranes: a highly effective class of triaminophosphine ligands in palladium-catalyzed cross-coupling reactions

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Proazaphosphatranes: A highly effective class of triaminophosphine ligands in palladium-catalyzed cross-coupling reactions

by

Sameer Urgaonkar

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
John G. Verkade, Major Professor
Richard C. Larock
Nicola L. Pohl
Robert J. Angelici
Klaus Schmidt-Rohr

Iowa State University

Ames, Iowa

2004

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Sameer Urgaonkar

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

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For the Major Program

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LIST OF ABBREVIATIONS

Ac	acetyl
aq	aqueous
atm	atmospheric pressure
BINAP	2,2'-bis(diphenylphsophino)-1,1'-binaphthyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
br	broad
Br	bromide
br s	broad singlet
i-Bu	*iso*-butyl
n-Bu	butyl
°C	degrees celsius
cat.	catalytic
Cl	chloride
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
D*t*BPF	1,1'-bis(di-*tert*-butylphosphino)ferrocene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DPEphos	bis(2-diphenylphosphinophenyl)ether
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane

eq	equation
equiv	equivalent
Et	ethyl
h	hour(s)
HMPT	hexamethylphosphorus triamide
HRMS	high resolution mass spectrometry
Hz	Hertz
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
min	minute(s)
mL	milliliters
mmol	millimole(s)
m.p.	melting point
n	normal
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
neo-Pent	*neo*-pentyl
Ph	phenyl
PPF-OMe	1-[2-(diphenylphosphino)ferrocenyl]ethyl methyl ether
i-Pr	*iso*-propyl
Q-phos	di-*tert*-butylphosphinopentaphenylferrocene
rt(RT)	room temperature
s	singlet
t	triplet
TBAA	tetrabutylammonium acetate
TBAB	tetrabutylammonium bromide

TBAF	tetrabutylammonium fluoride
TBAOH	tetrabutylammonium hydroxide
tert	tertiary
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
o-tol	*ortho*-tolyl
TON	turnover number
Xantphos	9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene

ACKNOWLEDGMENTS

I would like to, first and foremost, sincerely express my gratitude to my Ph.D. supervisor, Professor John Verkade, for his continuous academic and financial support, encouragement, and guidance throughout my Ph.D. career. I am very grateful to him for the trust and confidence he had in me even in times when research results came slowly and for giving me the freedom to pursue the research of my interest. I realize that not every Professor does that! I also want to thank him for teaching me how to write scientific papers and patents, for polishing my presentations and of course, this thesis, and for allowing me to visit my home country thrice in 5 years. I must say that I have been quite lucky in this regard.

Next, I would like to acknowledge my committee members, Professors Richard Larock, Nicola Pohl, Robert Angelici, and Klaus Schmidt-Rohr, for their time, suggestions, and letters of support.

I would now like to especially thank my parents (Dr. A. D. Urgaonkar and Dr. S. Urgaonkar) and brothers (Sandeep and Pankaj) for their never-ending love and support.

I would also like to thank past and present Verkade group members. My special thanks to Dr. M. Nagarajan, a former post-doc in Verkade's group, with whom I collaborated in several projects and to Dr. Nirmal Kumar Jana (Jana Babu) who was always ready to help and share his glassware. I am also sincerely thankful to Brandon M. Fetterly, who will also receive his Ph.D. degree very soon, for not only discussing chemistry with me, but also for teaching me to drive. Because of his help, I was able to drive confidently and safely to places such as South Dakota, Chicago, Minneapolis, St. Louis and Philadelphia. I wish him the very best in finding a suitable faculty position. I also wish to thank Dr. Weiping Su for his collaboration in the Stille project and for inviting me to collaborate on my first *J. Am. Chem. Soc.* paper. I warmly thank other group members: Dr. Chinta Reddy Venkat Reddy, Dr. Nandakumar Valsan, Dr. J. V. Kingston, Dr. Young-Jo Kim, Dr. Jnaneshwara Ganesh Kindel, Prof. A. Wrobleswki, Dr. Ju-Hua Xu and Dr. Jingsong You for their valuable advice and friendly help. I wish all the best to our new group members Steve, Reed, and Kuldeep.

My research was also influenced in various ways by members of other groups, for which I am very grateful. I would especially like to warmly thank Kwang-Seuk Ko (Professor Pohl's group) for allowing me to work on his computer for editing scanned spectra.

I also sincerely thank Dr. Verkade's secretaries: Karen Lind, Spring Smith and Sheri Diercks for their invaluable help.

Finally, I thank my friends here in Ames: Firoz, Anuj, Sachet, Mrinmoy, Sachin, Vijay, Tanay and Saurabh for making my stay really comfortable and enjoyable. I wish them all the best in their future endeavors.

ABSTRACT

In recent years proazaphosphatranes of type $P(RNCH_2CH_2)_3N$ have proven their synthetic utility as catalysts and as stoichiometric bases in a variety of organic transformations. Herein are described their application as a supporting ligand for palladium in palladium-catalyzed cross-coupling reactions, such as Buchwald-Hartwig amination, Stille, and Suzuki reactions. Screening of various proazaphosphatranes (R = Me, Et, *i*-Pr, *i*-Bu, *neo*-Pent) revealed that the electron-rich, bulky, and commercially available $P(i\text{-}BuNCH_2CH_2)_3N$ is the most effective ligand of this series in the aforementioned reactions. Aryl halides (bromides and iodides), including notoriously unreactive aryl chlorides, have been shown to participate in these processes.

It has also been discovered that for certain combinations of substrates in palladium-catalyzed Stille reactions, the proazaphosphatranes $P(PhCH_2NCH_2CH_2)_3N$ and $P(PhCH_2NCH_2CH_2)_2N(i\text{-}BuNCH_2CH_2)$ provided even more active palladium catalysts than $P(i\text{-}BuNCH_2CH_2)_3N$.

Additionally, the synthesis of the new bicyclic triaminophosphine ligand $P(i\text{-}BuNCH_2)_3CMe$ and its efficacy in Buchwald-Hartwig amination reactions is demonstrated. This ligand provides a remarkably general, efficient, and mild palladium catalyst for aryl iodide amination. This ligand also allows a weak base, such as Cs_2CO_3, to function in these reactions.

Finally, the first general protocol for the ligand-, copper-, and amine-free Sonogashira reaction has been developed. The success of this method hinges on the use of tetrabutylammonium acetate as the base.

CHAPTER 1. GENERAL INTRODUCTION

Thesis Organization

This thesis contains twelve chapters (including the present chapter). Except chapters 1 and 12, all the other chapters are based on papers that have either been published or accepted for publication in scientific journals. The ^{1}H, ^{13}C, and ^{31}P NMR spectra (where appropriate) for the reaction products have been compiled in appendices, which appear at the end of the thesis. Also, since several chapters have the same reaction products, effort have been made to avoid duplication of the spectra and thus have been provided only once.

The first chapter titled "**GENERAL INTRODUCTION**" introduces various palladium-catalyzed cross-coupling reactions, giving importance to Suzuki, Stille, Sonogashira, and Buchwald-Hartwig amination reactions, which are the main focus of my research. This section also gives a literature review on the aforementioned reactions. Lastly, this section describes our motivation for entering into this field of research.

The second chapter titled "**P(*i*-BuNCH$_2$CH$_2$)$_3$N: AN EFFECTIVE LIGAND IN THE PALLADIUM-CATALYZED AMINATION OF ARYL BROMIDES AND IODIDES**" describes our efforts in finding a suitable proazaphosphatrane to function as an ancillary ligand for palladium in the Buchwald-Hartwig amination reaction of aryl bromides and iodides. Screening of various proazaphosphatranes and the scope and limitations of the catalyst system constitute the basis of this chapter.

The third chapter titled "**P[N(*i*-Bu)CH$_2$CH$_2$)$_3$N: A VERSATILE LIGAND FOR THE Pd-CATALYZED AMINATION OF ARYL CHLORIDES**" extends the scope of the Pd/P(N*i*-BuCH$_2$CH$_2$)$_3$N catalyst system to the amination of aryl chlorides, which are cheaper and more widely available than either aryl bromides or iodides. However, they are less reactive. In this chapter, it is shown that by a slight modification of reaction conditions developed for the Buchwald-Hartwig amination reaction of aryl bromides and iodides, electronically diverse aryl chlorides can be couplied with an array of amines.

The fourth chapter titled "**SCOPE AND LIMITATIONS OF Pd$_2$(dba)$_3$/P(*i*BuNCH$_2$CH$_2$)$_3$N-CATALYZED BUCHWALD-HARTWIG AMINATION REACTIONS OF ARYL CHLORIDES**" presents in detail our work on Buchwald-Hartwig

amination of aryl chlorides. This chapter also provides some insight into the reasons for the catalytic activity/inactivity of various proazaphosphatranes in amination reactions.

The fifth chapter titled "**PALLADIUM/PROAZAPHOSPHATRANE-CATALYZED AMINATION OF ARYL HALIDES POSSESSING A PHENOL, ALCOHOL, ACETANILIDE, AMIDE OR AN ENOLIZABLE KETONE FUNCTIONAL GROUP: EFFICACY OF $LiN(SiMe_3)_2$ AS THE BASE**" provides an improved protocol for the amination of aryl halides containing acidic functional groups, such as phenolic –OH, alcohol, acetanilide, amide or an enolizable ketone. The use of $LiN(SiMe_3)_2$ as the base instead of NaO-*t*-Bu was important for this transformation. Other amide bases tested were also effective. Possible roles of these bases in making this reaction to work in the presence of aforementioned functional groups are also discussed.

The sixth chapter titled "**APPLICATION OF A NEW BICYCLIC TRIAMINOPHOSPHINE LIGAND IN Pd-CATALYZED BUCHWALD-HARTWIG AMINATION REACTIONS OF ARYL CHLORIDES, BROMIDES, AND IODIDES**" discusses the synthesis and application of a new bicyclic triaminophosphine ligand, $P(i\text{-}BuNCH_2)_3CMe$, in the Buchwald-Hartwig amination reaction of aryl halides. The scope and limitations of this ligand as well as the stereoelectronic differences that exist between this ligand and the proazaphosphatrane, $P(i\text{-}BuNCH_2CH_2)_3N$, is presented in this chapter.

The seventh chapter titled "**SYNTHESIS OF *N*-ARYL-AZA-CROWN ETHERS VIA Pd-CATALYZED AMINATION REACTIONS OF ARYL CHLORIDES WITH AZA-CROWN ETHERS**" presents our results on the synthesis of *N*-aryl-aza-crown ethers using amination technology. The method uses $P(i\text{-}BuNCH_2CH_2)_3N$ and $P(i\text{-}BuNCH_2)_3CMe$ as the ligand. A variety of aryl chlorides, as well as bromides and iodides, were coupled with the aza-crown ethers. The applicability of Buchwald's ligand with aryl chlorides is also shown in this case.

The eighth chapter titled "**$Pd_2(dba)_3$/$P(i\text{-}BuNCH_2CH_2)_3N$-CATALYZED STILLE CROSS-COUPLING OF ARYL CHLORIDES**" details our exploration into the palladium-catalyzed Stille cross-coupling of aryl chlorides with organotin reagents. A systematic investigation into the effect of various proazaphosphatranes and additives on the

coupling efficiency is discussed. Notably, this catalyst system is only the second general method developed to date for the Stille reactions of aryl chlorides.

The ninth chapter titled "**HIGHLY ACTIVE PALLADIUM CATALYSTS SUPPORTED BY BULKY PROAZAPHOSPHATRANE LIGANDS FOR STILLE CROSS-COUPLING: COUPLING OF VINYL CHLORIDES, ROOM TEMPERATURE COUPLING OF ARYL BROMIDES, COUPLING OF ARYL TRIFLATES, AND SYNTHESIS OF STERICALLY HINDERED BIARYLS**" significantly expands the scope of Stille reactions using $P[(PhCH_2)NCH_2CH_2]_3N$ and $P[(PhCH_2NCH_2CH_2)_2(i\text{-}BuNCH_2CH_2N)]N$ in addition to $P(i\text{-}BuNCH_2CH_2)_3N$ as the ligand. This chapter thus deals with the Stille reactions of aryl and vinyl chlorides and aryl triflates. Additionally, room temperature Stille couplings of aryl bromides and synthesis of tri- and tetra-*ortho*-substituted biaryls are also discussed.

The tenth chapter titled "**LIGAND-, COPPER-, AND AMINE-FREE SONOGASHIRA REACTION OF ARYL IODIDES AND BROMIDES WITH TERMINAL ALKYNES**" discusses our discovery that the Sonogashira reaction of aryl iodides and activated aryl bromides with terminal alkynes can be performed at room temperature without the need of a phosphine ligand, a copper cocatalyst, or an amine base, three ingredients, one or more of which is generally required in Sonogashira reaction! A systematic screening of various bases (organic and inorganic) reveal the usefulness of tetrabutylammonium acetate in the aforementioned reaction. Possible explanations for the effectiveness of this base are also provided.

The eleventh chapter titled "**Pd/P(i-BuNCH$_2$CH$_2$)$_3$N: AN EFFICIENT CATALYST FOR SUZUKI CROSS-COUPLING OF ARYL BROMIDES AND CHLORIDES WITH ARYLBORONIC ACIDS**" focuses on the application of proazaphosphatranes as ligands in yet another important sp^2 carbon-carbon bond forming reaction, namely, the Suzuki reaction. Optimization of reaction parameters (ligand, base, solvent, temperature) and several examples of the coupling reaction are presented in this chapter.

Finally, the thesis ends with the twelfth chapter titled "**GENERAL CONCLUSIONS**" which summarizes the findings of chapters 2-11. It also provides some new ideas and the challenges associated with them for the improvement of some of the reactions discussed in

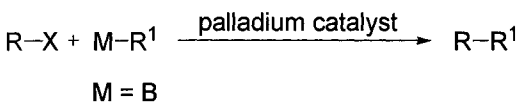
these chapters. Lastly, a few new research areas in which proazaphosphatranes can be utilized as the ligand are outlined.

Introduction

The importance of transition metal-catalyzed reactions in modern organic synthesis is well known and can be easily judged by the sheer number of reviews published in the field.[1] Among various transition metals, palladium has played a leading role in developing fundamentally new methods of building carbon-carbon and carbon-heteroatom bonds.[2] The popularity of the use of palladium in these reactions stems in part due to its tolerance of many functional groups, its air- and moisture-stability, and its wide availability.

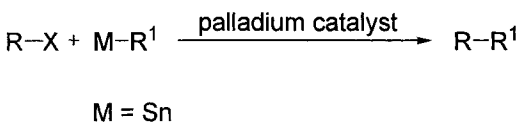
Palladium-catalyzed cross-coupling reactions are generally understood to be the reaction of aryl or vinylic halides (or halide equivalents, such as triflates) with a suitable organometallic nucleophile.

Suzuki



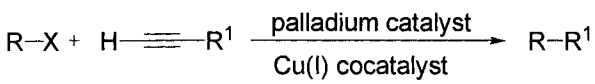
(1)

Stille



(2)

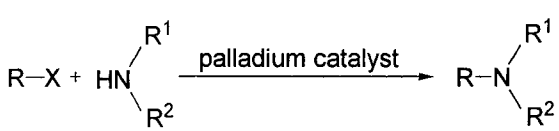
Sonogashira



(3)

R = aryl or vinylic; R^1 = alkyl, aryl, vinylic; X = Br, I , OTf, Cl

Buchwald-Hartwig Amination

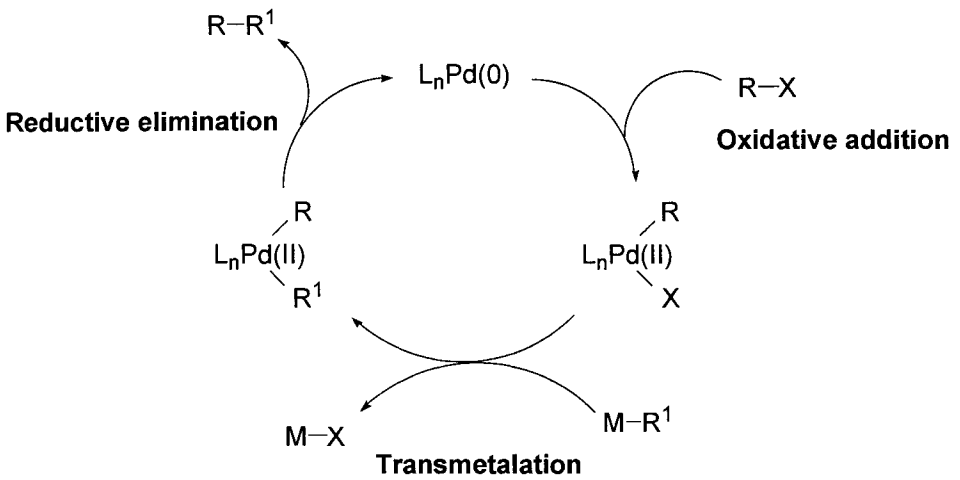


(4)

While palladium-catalyzed cross-coupling reactions, such as the Suzuki[3] (or Suzuki-Miyaura) cross-coupling of organoboron compounds (eq 1), the Stille[4] reaction of organostannanes (eq 2), and the Sonogashira[5] coupling of acetylenes (eq 3) have become the most general and selective carbon-carbon bond forming processes, the Buchwald-Hartwig[6] amination (eq 4) has recently emerged as an extremely powerful tool for carbon-heteroatom (C-N) bond formation. It should be noted that although this reaction does not involve any organometallic nucleophile (using instead an amine in that role) it is regarded as a cross-coupling reaction for the reason discussed in the next paragraph.

The aforementioned cross-coupling reactions, including Buchwald-Hartwig amination, are closely related catalytic processes in that they share most of the mechanistic characteristics, although some differences exist in the activation of the organometallic nucleophile. The generally accepted mechanism for these cross-coupling reactions is depicted in Scheme 1.[7] The first step in the catalytic cycle is the oxidative addition of the organic halide to a Pd(0) complex to give the RPd(II)(L_n)X intermediate, which undergoes transmetalation with an organometallic nucleophile (M-R^1) to give a RPd(II)(L_n)R^1 intermediate, which on reductive elimination provides the desired coupled product and regenerates the Pd(0) catalyst.

Scheme 1. General Mechanism for Palladium-Catalyzed Cross-Coupling Reactions



L = Ligand, generally a phosphine

It should now be emphasized that ancillary ligands (depicted as L in Scheme 1) around the palladium center are all-important for the stability, activity, and selectivity of the palladium catalyst. These ligands are used to stabilize the metal center and to tune the electronic properties and steric crowding around the metal.

Apart from the palladium-catalyzed cross-coupling reactions depicted in eqs 1-4, those involving organomagnesium[8] (Kumada, eq 5), organozinc[9] (Negishi, eq 6), and organosilicon[10] (Hiyama, eq 7) compounds as organometallic partners are also widely used and follow the mechanistic pathway described in Scheme 1.

Kumada

(5)

Negishi

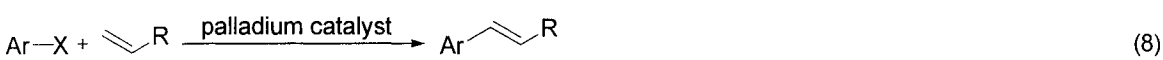
(6)

Hiyama

(7)

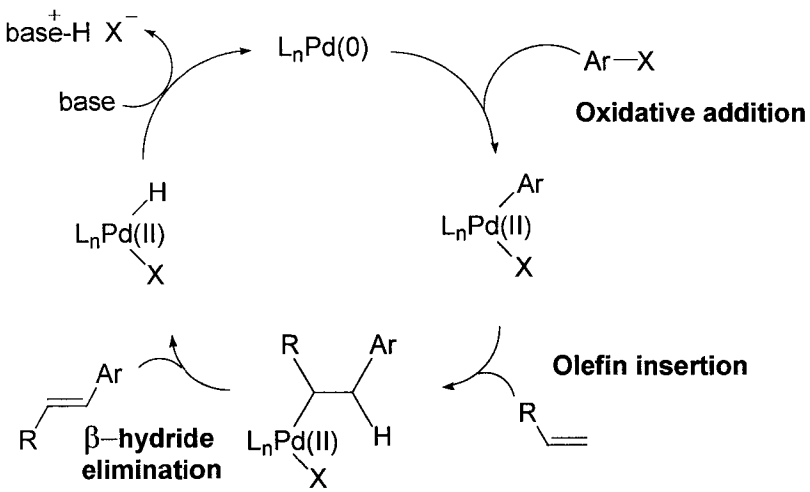
Similarly, the reaction of aryl or vinylic halides and triflates with olefins (the Heck reaction,[11,12] eq 8) is also one of the most important carbon-carbon bond forming processes available to the synthetic organic chemist. However, the mechanism[12] of this reaction is distinct from that of cross-coupling reactions and only the first step of the catalytic cycle (oxidative addition) is the same (Scheme 2).

Heck



(8)

Scheme 2. Mechanism for the Heck Reaction



It is worth mentioning here that since the focus of the research presented in this thesis is on reactions described in eqs 1-4, henceforth emphasis will be placed on these reactions exclusively.

Survey of Phosphine Ligands

Among various ligands available, phosphines are frequently used in Pd-catalyzed cross-coupling reactions, although non-phosphine ligands are now increasingly finding wide-spread use. In this section, a wide array of phosphine ligands will be introduced along with their properties where appropriate.

1. Triarylphosphines

In the synthetic community, PPh_3[13,14] is the most widely used phosphine because of its relatively higher degree of stability toward oxidation. Bulky P(*o*-tol)$_3$,[15] introduced by Heck in his pioneering work on the arylation of olefins,[16] is also an especially effective ligand and was successfully used by Kosugi and Buchwald as the "first generation" ancillary ligand in amination reactions (see the section "**Buchwald Hartwig Amination Reaction**" in this chapter).

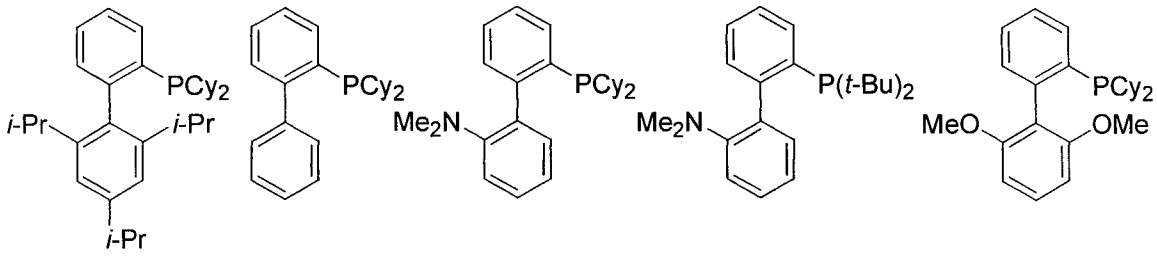
2. Trialkylphosphines

More electron-donating alkylphosphines, such as PCy_3, have also been used successfully in cross-coupling reactions, such as Suzuki,[17] Buchwald-Hartwig amination,[18] and Stille[19] reactions. These electron-rich phosphines accelerate the oxidative addition step. Furthermore, very bulky and highly electron-rich P(*t*-Bu)$_3$ was found to be a very important and versatile ligand, especially for cross-coupling reactions of aryl chlorides.[20] Interestingly, this ligand has been neglected for a long time because it was believed that bulkiness inhibits coordination of reactants. Now it is well understood that strongly electron-donating P(*t*-Bu)$_3$ accelerates the oxidative addition of aryl chlorides, because oxidative addition is nucleophilic in nature. Also, its bulkiness assists facile reductive elimination, as well as formation of the mono-ligated palladium(0) complex [L_1Pd(0)], which is now considered to be the actual catalytic species in palladium-catalyzed cross-coupling reactions.[21] Unfortunately, trialkylphosphines are somewhat air-sensitive. Thus, P(*t*-Bu)$_3$ cannot be readily handled in air because of the ease with which it undergoes oxidation and hence is pyrophoric. However, its phosphonium salt [HP(t-Bu)$_3$]BF_4 is an air-stable precursor from which the desired phosphine can be liberated by treatment with a weak base present in the reaction mixture. Fu and co-workers have shown the versatility of this approach in various Pd-catalyzed cross-coupling reactions.[22]

3. Biphenyl-based phosphine ligands (Buchwald's ligands)

Recently, Buchwald has introduced a family of phosphine ligands with a biphenyl backbone (Scheme 3), commonly referred to as Buchwald's ligands. These phosphines are excellent ligands for C-C,[23] C-N,[24] and C-O[25] bond-forming reactions of aryl chlorides. The effectiveness of these ligands is believed to be due to a unique combination of steric and electronic properties. Their electron-rich nature promotes oxidative addition. Their steric bulk facilitates reductive elimination and formation of a monophosphine intermediate [L_1Pd(0)], thus promoting reactivity. Recent studies have also provided evidence for an interaction between the π–system of the ortho aromatic group on these ligands and the unoccupied metal *d*-orbital, thus stabilizing the catalyst through ligand chelation.[26]

Scheme 3. Buchwald's ligands

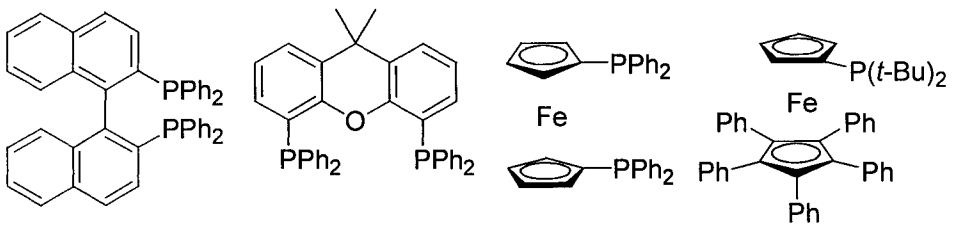


1 **2** **3** **4** **5**

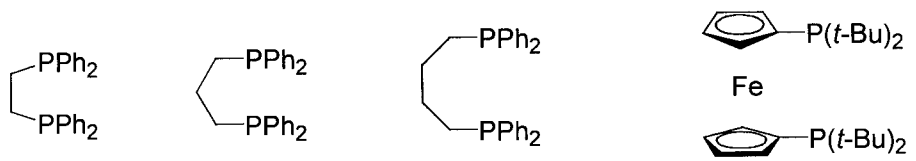
4. Bidentate phosphines

Bidentate phosphines, such as DPPE [1,2-bis(diphenylphosphino)ethane],[27] DPPP [1,3-bis(diphenylphosphino)propane],[28] DPPB [1,4-bis(diphenylphosphino)butane],[29] DPPF [1,1'-bis(diphenylphosphino)ferrocene],[30] and BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][31] are routinely employed in palladium-catalyzed reactions (Scheme 4). In addition, chiral bidentate ligands have been utilized to induce asymmetric reactions.[32]

Scheme 4. Chelating phosphines



6, BINAP **7, Xantphos** **8, DPPF** **9, Q-phos**



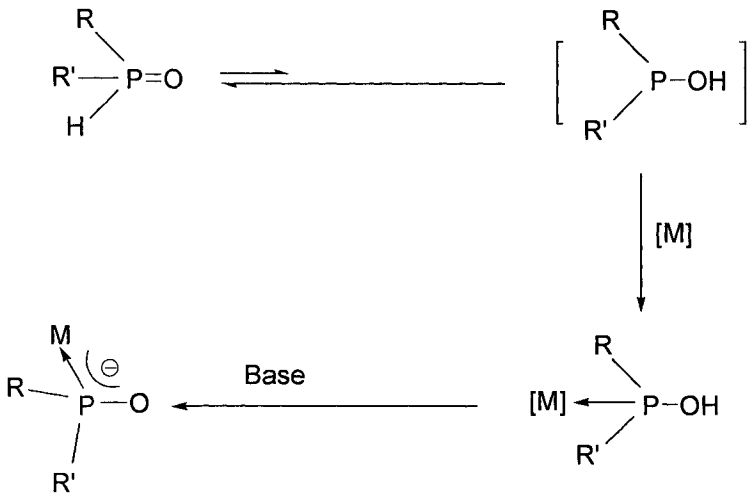
10, DPPE **11, DPPP** **12, DPPB** **13, D*t*BPF**

5. Phosphinous acids

Recently, Li[33] reported that air-stable phosphine oxides [RR'P(O)H] in the presence of transition metals undergo tautomerization to the less stable phosphinous acids [RR'POH],

which subsequently coordinate to Pd centers through phosphorus atoms to form Pd phosphinous acid complexes, which are deprotonated by the base present in the reaction to yield electron-rich, anionic palladium-phosphane complexes, which behave as active catalysts in a variety of palladium-catalyzed cross-coupling reactions.

Scheme 5.



It is now clear from the "**Survey of Phosphine Ligands**" section that attributes that are important and common for the activity of the phosphine ligands can be summarized as follows:

(i) these ligands are electron-rich;

(ii) they are sterically hindered; and

(iii) they are robust and versatile.

We felt that these three criteria were easily met by proazaphosphatranes; a class of compounds of considerable interest to our group. Prior to the start of our research program on palladium-catalyzed cross-coupling reactions in 2000, our group was more focused on the use of proazaphosphatranes (strong bases) as catalysts, as well as stoichiometric reagents, in various organic transformations. Its use as an ancillary ligand for palladium had not previously been explored. At the time I joined Prof. Verkade's group in early 2000, one of his postdoctoral fellows, Dr. Muthukaman Nagarajan, started working on palladium-catalyzed Buchwald-Hartwig amination reactions with the intention of using

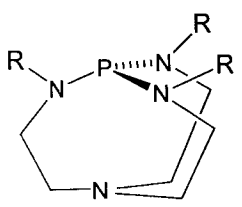
proazaphosphatranes as non-ionic bases (instead of NaO-*t*-Bu). The idea was to increase the functional group compatibility of the aforementioned reaction, since base-sensitive functionalities, such as ester, nitro, and ketone groups, were not compatible with the ionic base NaO-*t*-Bu. This proposal was never realized. We then decided to explore the ligand properties of proazaphosphatranes in Pd-assisted cross-couplings, a decision that has led to considerable success.

6. Proazaphosphatranes – a bicyclic triaminophosphine

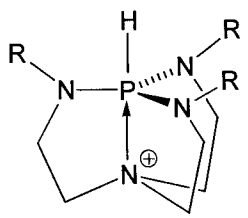
Since 1989, when the first proazaphosphatrane was synthesized in our laboratories,[34] a variety of proazaphosphatranes have been synthesized,[35] a considerable number of which have become valuable in an ever-growing list of organic transformations.[35] Several of these compounds have become commercially available from Aldrich Chemical Co., Strem Chemicals, and Digital Specialities.

Proazaphosphatranes (**14**) are bicyclic and exceedingly strong nonionic Bronsted and Lewis bases, which, unlike all of the commonly utilized non-ionic bases (including phosphazenes), become protonated on their phosphorus atom to form azaphosphatranes (**15**) rather than on one of their nitrogen atoms. The pK_a values for **15** are about 32-34 units in CH_3CN.[36] The strong basicity of these compounds has been attributed to their ability to undergo facile and unique transannulation from their bridgehead nitrogen to the phosphorus atom (Scheme 6, cation **15**), as has been verified by X-ray crystallographic experiments.[37]

Scheme 6.



14
Proazaphosphatrane

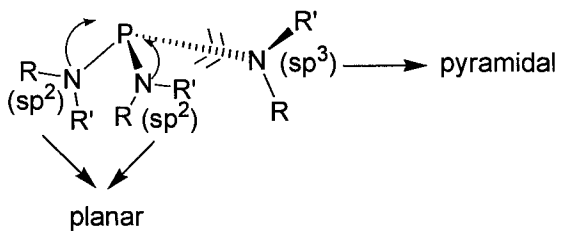


15
Azaphosphatrane

It is now important to understand the difference in the electronic and steric natures of acyclic triaminophosphines, such as $P(NMe_2)_3$ (HMPT) and bicyclic proazaphosphatranes **14**, since

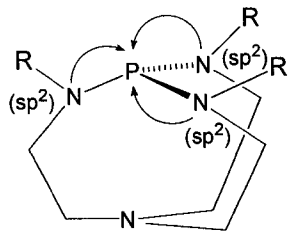
these property differences will be exploited in their use as a ligand in palladium-catalyzed cross-coupling reactions.

Stereoelectronic differences between proazaphosphatranes and their acyclic analogues. Triaminophosphines are electron-rich phosphine ligands because of their strong σ–donor capability. This is ascribed to the donation of lone-pair electron density from nitrogen to phosphorus, making the latter more electron-rich. Acyclic triaminophosphines have one long P-N bond with a pyramidal nitrogen and two short P-N bonds with planar nitrogens.[38] This has been verified by X-ray crystal structures of triaminophosphines, as well as of their metal complexes.[39]



The differences in the geometries around nitrogen render the lone-pair electron donation process somewhat complicated, as only the planar nitrogens have their lone-pair orbitals properly aligned with empty orbitals on phosphorus to make the electron-donation effective, whereas the pyramidal nitrogen's lone-pair sp^3 orbital is anti to the phosphorus sp^3 lone pair making lone-pair electron donation from the pyramidal nitrogen ineffective. In fact, this nitrogen merely acts as an electron-withdrawing substituent and therefore reduces the overall basicity of the acyclic triaminophosphine.

Surprisingly, and in contrast to acyclic triaminophosphines, all three nitrogens adjacent to phosphorus are virtually planar in proazaphosphatranes,[37] as has been verified by X-ray means, and thus are able to contribute their lone-pair electron-density to phosphorus, thereby augmenting its basicity. This effect has its origin in the cage framework of proazaphosphatranes. It is also interesting that the geometry of the $N(CH_2)_3$ nitrogen is planar, owing to van der Waals interactions among the methylene protons adjacent to the axial nitrogen.



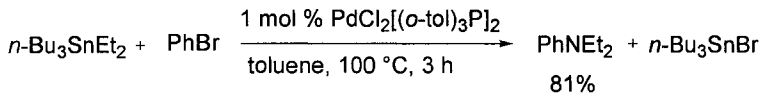
As explained earlier, the basicity of proazaphosphatranes is further enhanced owing to their capability to undergo transannulation (cation **15**). It is important to note that acyclic triaminophosphines lack this basicity enhancement feature.

Literature Survey

In this section, a survey of the literature is carried out individually on Suzuki, Stille, Sonogashira, and Buchwald-Hartwig amination reactions. This survey will focus on important progress made in these reactions in the last decade, particularly aryl bromides, chlorides, and iodides.

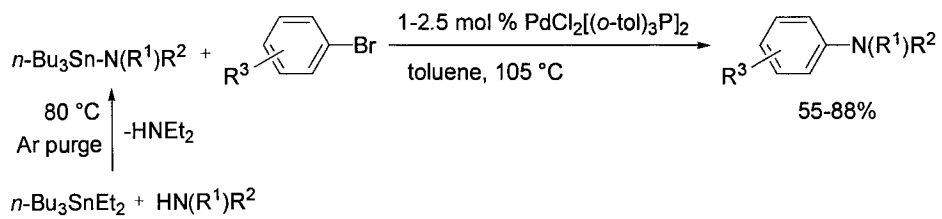
1. Buchwald-Hartwig Amination Reaction

The palladium-catalyzed coupling of aryl halides (or halide equivalents, such as triflates) with amines in the presence of a suitable base represents a powerful tool for the synthesis of compounds containing the *N*-aryl moiety.[6] Aromatic amines are ubiquitous in the pharmaceutical[40] and agrochemical[41] industries. They have also found applications in diverse areas ranging from conducting polymers[42] in material science to ligands[43] for asymmetric homogeneous chemistry. Among the coupling reactions discussed so far, amination chemistry is the most recent. Although this chemistry was independently developed by the Hartwig group at Yale and the Buchwald group at MIT in the early 1990's, the foundation was laid a decade earlier by Migita and co-workers, who in 1983 reported that in the presence of $PdCl_2[(o\text{-tol})_3P]_2$ as the catalyst, aryl bromides coupled with (*N*,*N*-diethylamino)tri-*n*-butylstannane to afford *N*,*N*-diethylaniline (eq 9).[44] Curiously, aryl iodides did not react under these conditions.



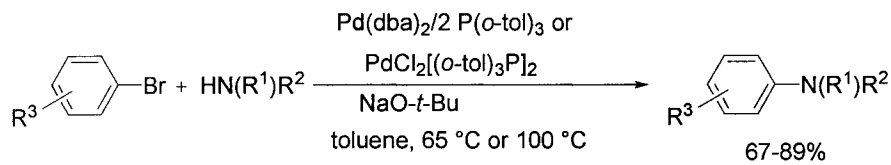
(9)

In 1994, at the outset, Buchwald and Guram realized the practical limitation of this protocol, namely, that the aminostannanes are typically not commercially available and are both thermally and moisture-sensitive, and that the methodology was not readily extendable to other amine types. The solution they put forward was to prepare aminostannanes in situ utilizing transamination reactions. Thus, by employing (*N*,*N*-diethylamino)tri-*n*-butylstannane as a general precursor to aminostannanes, they were able to improve and generalize Migita's protocol for the formation of aniline derivatives (eq 10).[45] They also noted that $PdCl_2L_2$ catalysts (L_2 = $(PPh_3)_2$, DPPF or $Ph_2P(CH_2)_3PPh_2$) containing ligands other than P(*o*-tol)$_3$ are not effective, affording only trace amounts of the desired arylamine. The drawback of this method, however, was the necessity to employ stoichiometric amounts of toxic tin reagents.



(10)

The tin-free amination reaction of aryl bromides was demonstrated simultaneously by both Buchwald and Hartwig. They showed that amines can be directly employed provided NaO-*t*-Bu (Buchwald, eq 11)[46] or $LiN(SiMe_3)_2$ (Hartwig, eq 12)[47] was used as a base. They also observed the formation of side-product (Ar-H) resulting from reduction of the starting aryl bromide in these reactions. The proposed mechanism of this transformation is shown in Scheme 7.



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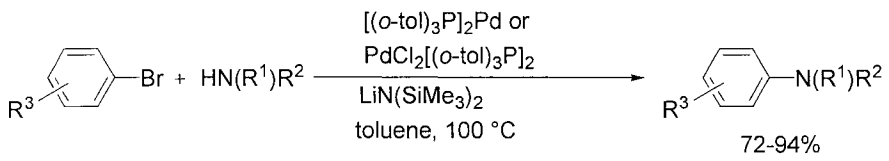
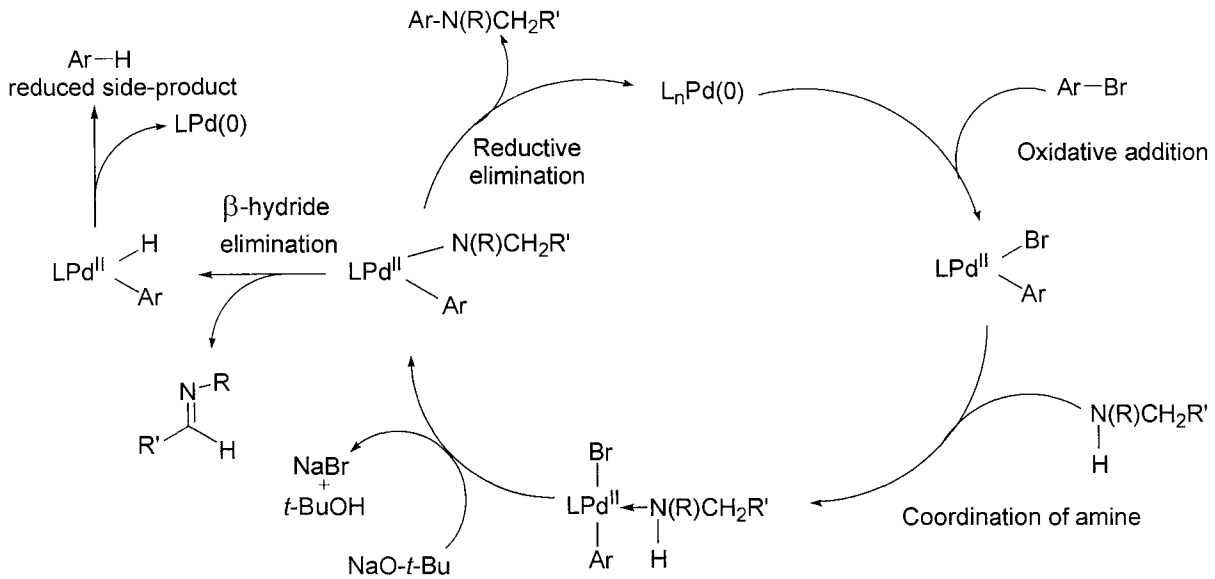
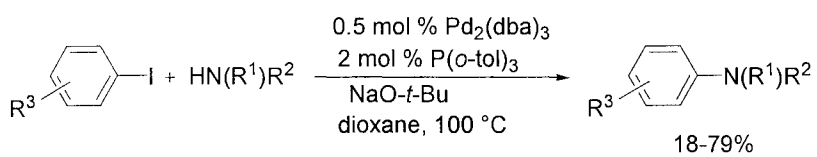


(12)

Scheme 7. Proposed Mechanism for the Pd-Catalyzed Amination Reaction using P(*o*-tol)$_3$ as the Ligand

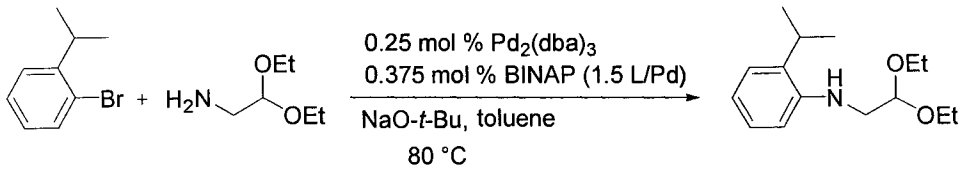


Some of the limitations encountered using the monodentate ligand P(*o*-tol)$_3$ under these conditions were (i) reactions of primary amines and acyclic secondary amines were problematic, (ii) halopyridines were not effective, (iii) aryl iodides (and chlorides) were not suitable substrates, and (iv) some reactions required higher quantities of catalyst. A solution for amination of aryl iodides was achieved by Buchwald in 1996, when he reported for the first time the palladium-catalyzed amination of aryl iodides using P(*o*-tol)$_3$ as the ligand and $Pd_2(dba)_3$ as the palladium precursor (eq 13).[48] Dioxane as solvent was the key to the success of this technique since toluene, THF, DMF, and DME provided only incomplete conversions.



(13)

A more general solution to the aforementioned problems was developed independently by Hartwig and Buchwald with the use of chelating ligands such as BINAP[49] (eq 14) and DPPF[50] (eq 15). In many cases, especially with primary amines, dramatic improvements in the yield were seen. The amination of both aryl iodides and bromides proceeded efficiently.



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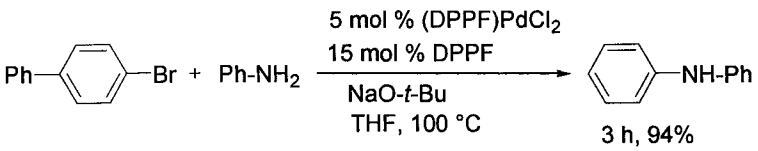
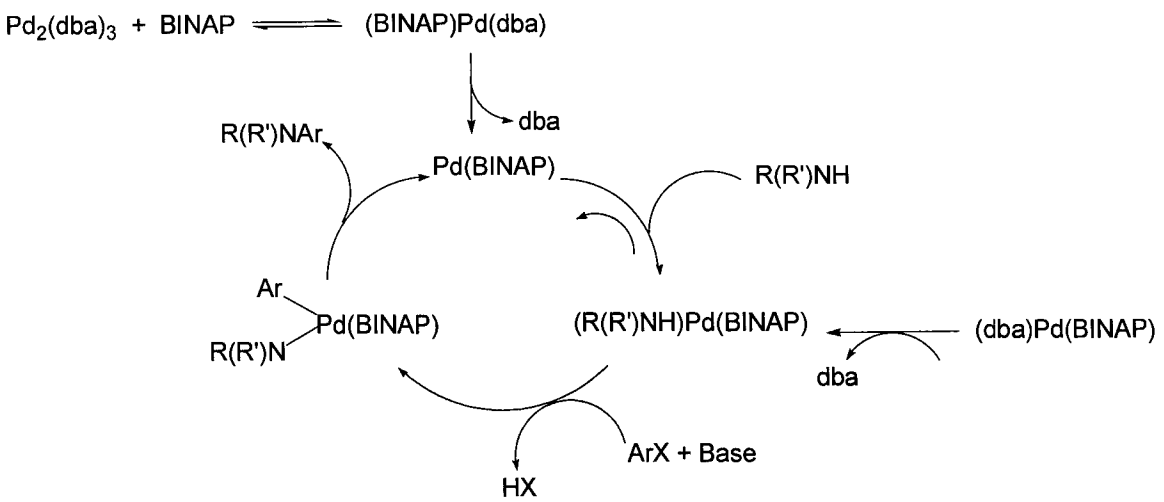


(15)

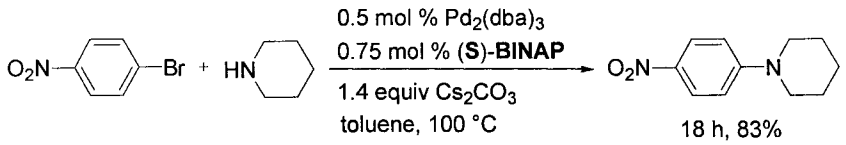
In general, BINAP was found to be a more general ligand than DPPF. Mechanistically, the catalytic cycle for the amination reaction using BINAP or DPPF differs with that for P(*o*-tol)$_3$ as the ligand, in that the key intermediates have two phosphorus atoms from the chelating ligand bound to the Pd. The catalytic cycle proposed by Buchwald for BINAP as the chelating ligand is shown in Scheme 8.[51] The route involves coordination of the amine to the Pd(BINAP) catalyst prior to oxidative addition of the aryl bromide. The three-coordinate palladium intermediate (R(R')NH)Pd(BINAP) thus formed would be more electron-rich and would accelerate the oxidative addition process.

Scheme 8. Proposed Mechanism for BINAP/$Pd_2(dba)_3$-Catalyzed Amination Reaction



The efficiency of chelating ligands, BINAP[52] in particular, is believed to be due to the combination of several factors: (i) the formation of a tight chelate due to rigidity of the binaphthyl backbone and the small bite angle of BINAP (92.7 °) inhibiting the formation of catalytically inactive palladium bis(amine)aryl halide complexes (ii) the large size of BINAP disfavors double arylation of primary amine and promotes reductive elimination to form the arylamine product, and (iii) the rate of *β*–hydride elimination of the aryl amido intermediate is slow compared to reductive elimination.

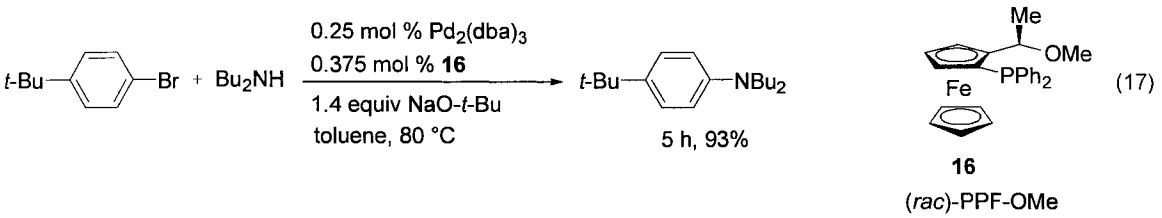
With BINAP as the ligand,[52] the mild base Cs_2CO_3 can also be employed in-place of the strong base NaO-*t*-Bu, allowing base-sensitive functional groups such as esters, nitriles, nitro, and enolizable ketones to participate in the amination reactions (eq 16). It should be noted that both racemic and enantiomeric pure forms of BINAP were effective ligands.



(16)

Halopyridines also reacted efficiently with amines to afford aminopyridines. Acyclic secondary amines such as di-*n*-butylamine, were ineffective with the BINAP system,

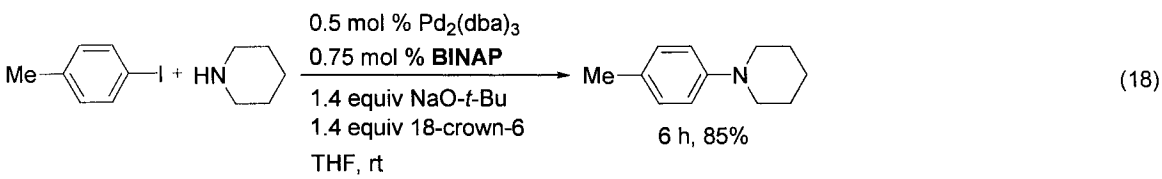
however. In 1997, Buchwald reported a highly effective Hayashi-type ferrocenyl derived phosphine ligand (**16**) for the arylation of this class of amines (eq 17).[53] This ligand probably



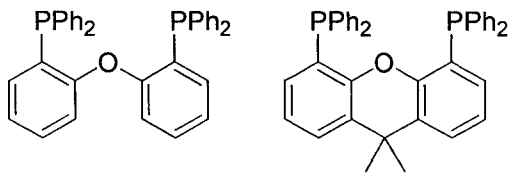
acts as a chelating ligand (chelation of palladium center through oxygen and phosphorus of the ligand); a postulate that is supported by X-ray analysis. However, this catalyst system was not effective with primary amines including unhindered anilines, although sterically hindered aniline reacted efficiently.

Later Buchwald found that by changing the base to Cs_2CO_3 in the above system, substrates bearing methyl and ethyl esters, aldehydes, enolizable ketones, and nitro groups can be coupled.[54]

Furthermore, Buchwald later discovered that BINAP in combination with 18-crown-6 promotes the room temperature coupling of aryl iodides with amines (eq 18).[55]



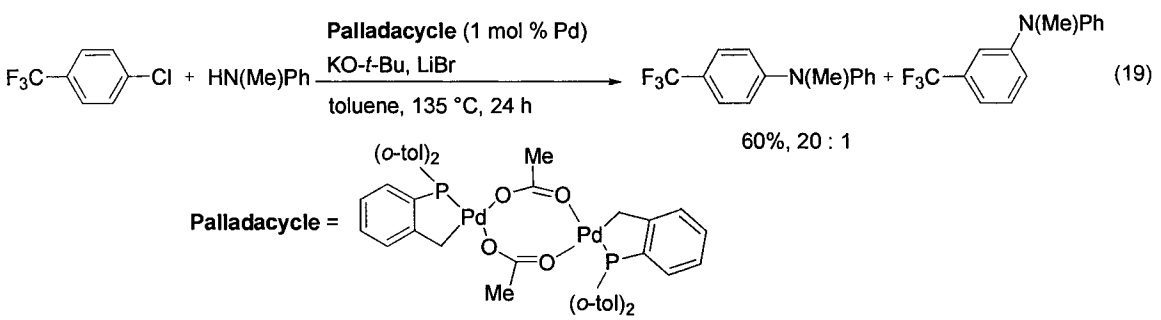
In 1998, Buchwald also developed the chemistry of DPEphos ([bis(2-diphenylphosphino)phenyl]) ether (**17**) as a chelating ligand in palladium-catalyzed amination reactions of aryl bromides with primary anilines.[56] It is worth mentioning that van Leeuwen introduced a Xantphos ligand (**18**) in 1999, which is similar in structure to DPEphos, for the amination reactions of aryl bromides.[57]

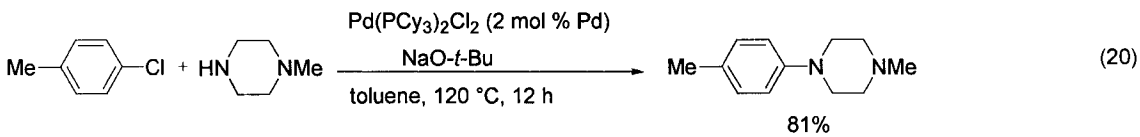


17 DPEphos

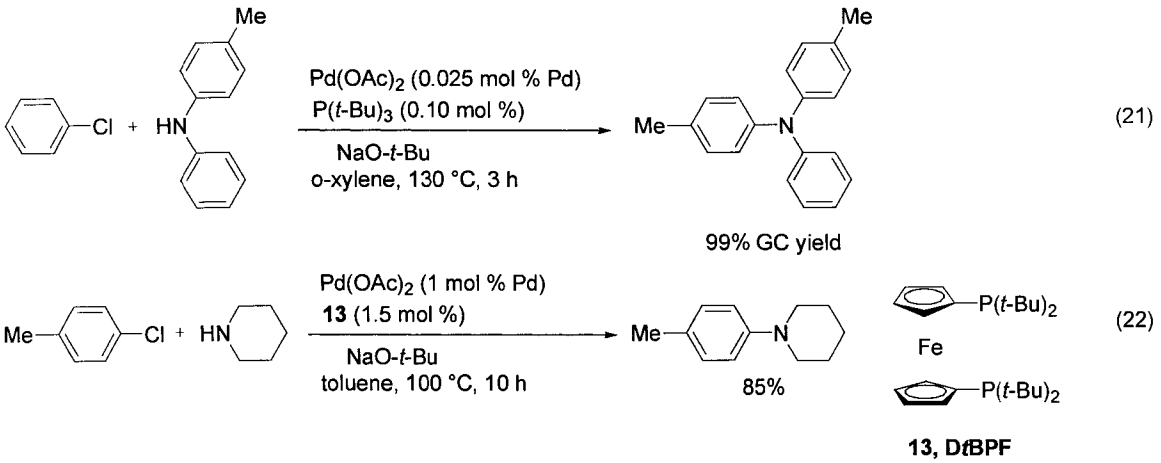
18 Xantphos

In 1997, Beller and co-workers found that the amination of electron-poor (activated) aryl chlorides can be performed using a palladacycle catalyst at higher temperatures (135 °C), in the presence of LiBr with KO-*t*-Bu as the base (eq 19).[58] In the same year, Reddy and Tanaka noted that aryl chlorides can be coupled with secondary amines in good yield using $Pd(PCy_3)_2Cl_2$ as the catalyst (eq 20).[59]

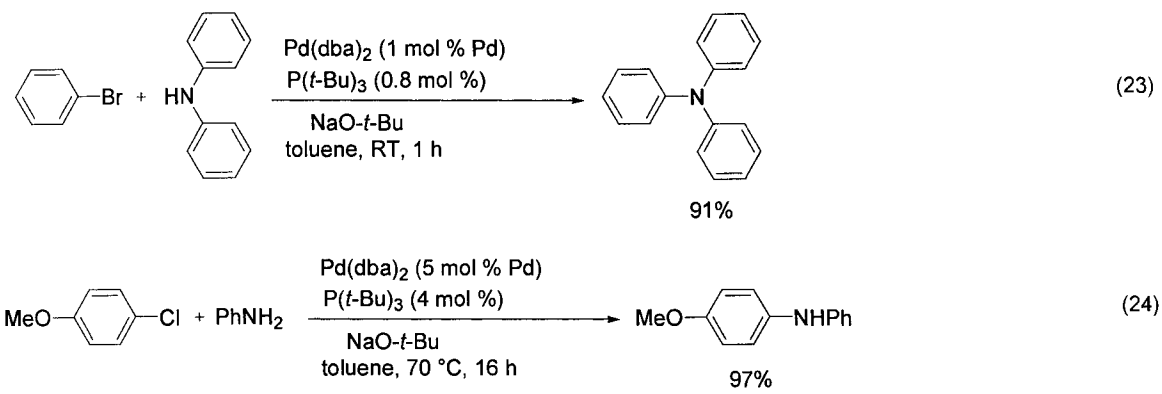




In 1998, Yamamoto, Nishiyama, and Koie of the Tosoh Corporation reported for the first time the use of the highly electron-rich and sterically hindered monodentate phosphine ligand, $P(t\text{-Bu})_3$, in amination reactions.[60] Notably, using $P(t\text{-Bu})_3$ as the ligand, they were able to couple electron-neutral (unactivated) chlorobenzene with *N*-(3-methylphenyl)aniline in 99% GC yield at 130 °C (eq 21). Later that year, Hartwig demonstrated the usefulness of bulky ligand **13** in amination reactions of unactivated aryl chlorides (eq 22).[61]

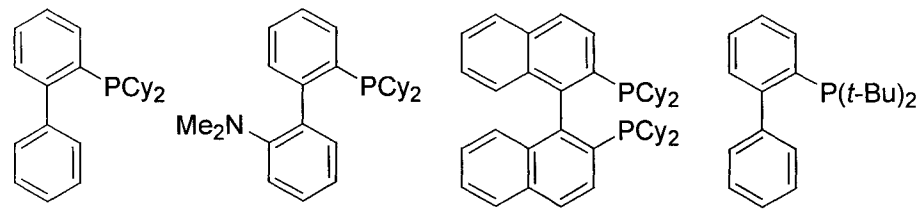


In 1999, taking advantage of the above finding from the workers at Tosoh Corporation, Hartwig and co-workers discovered that while the amination of aryl bromides can be performed at room temperature, the amination of aryl chlorides can be conducted at much lower temperatures (70 °C to rt) using P(*t*-Bu)$_3$ as the ligand (eqs 23 and 24).[62] They noted that maintaining the Pd to ligand ratio of 1:0.8 was important for the success of these reactions. The amination reaction proceeded even in the presence of mild bases such as Cs_2CO_3 or K_3PO_4. They also extended the scope of the amination reaction to the formation of *N*-arylazoles and *N*-arylcarbamates.[62]

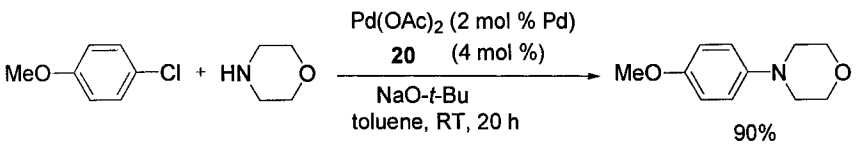


Buchwald reported the use of new biphenyl-based electron-rich phosphine ligands (**2**, **3**, **19**, and **20**) in amination reactions of aryl chlorides, bromides, and iodides. Initially, the catalyst system was based on ligands **3** and **19**.[63] However, the preparation of these ligands required a multistep synthesis. Later, they discovered that palladium complexes supported by simple

phosphines **2** and **20** are efficient catalysts for the amination reaction of a wide variety of aryl halides.[24,64a] While ligand **2** is effective for the amination of functionalized substrates or reactions of acyclic secondary amines (eq 25), ligand **20** allows for the room-temperature amination of many aryl chloride and bromide substrates (eq 26).



2 **3** **19** **20**



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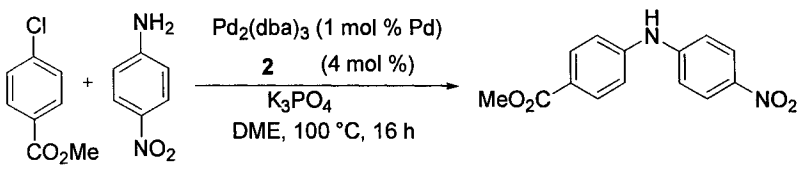
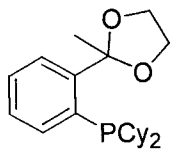


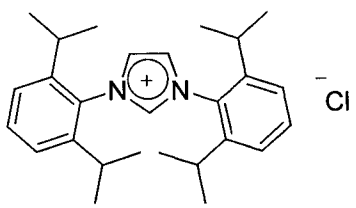
(26)

All types of amines such as acyclic secondary amines, cyclic amines, primary aliphatic amines and primary anilines participated in the process. The scope of these ligands encompasses nearly all of the transformations that can be effected with P(*o*-tol)$_3$, BINAP, PPF-OMe, DPPF and P(*t*-Bu)$_3$. Buchwald also showed that Pd-complexes supported by ligands **2** and **3** provided a general method for the amination of aryl iodides while the Pd-complex supported by ligand **20** afforded only trace amounts of product.[64b] He observed that for certain substrate combinations, van Leeuwen's Xantphos ligand (**18**) proved effective.[64b] In 1999, Guram reported the use of a phenyl-backbone-derived P,O ligand (**21**) in the amination of aryl chlorides.[65]

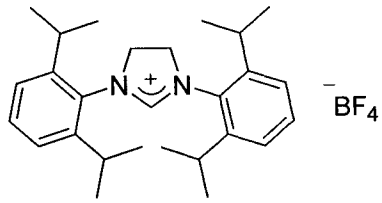


21

A non-phosphine ligand to effect amination reactions was reported by Nolan[66] in 1999 which consisted of nucleophilic unsaturated N-heterocyclic carbenes (**22**) as phosphine analogues. He demonstrated that sterically hindered versions of these ligands, such as the chloride salt of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**23**), are effective for the amination of aryl chlorides at elevated temperatures. Hartwig, later showed that the room temperature amination reactions of aryl chlorides can be performed by using saturated carbene ligand instead.[67]

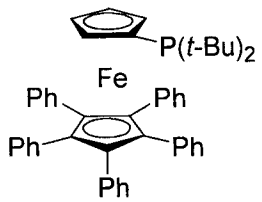


22
(unsaturated carbene)



23
(saturated carbene)

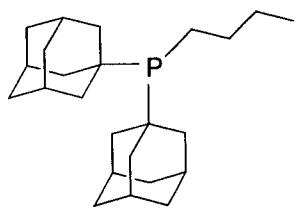
In 2002, Hartwig and co-workers prepared a new air-stable and sterically hindered monophosphine ligand (Q-phos, **9**) in two steps from ferrocene and have shown that it generates a highly active catalyst for amination reactions.[68]



Q-phos

9

Beller in 2002 reported the application of di(1-adamantyl)-*n*-butylphosphine (**24**) as the ligand in amination reactions of unactivated aryl chlorides.[69]

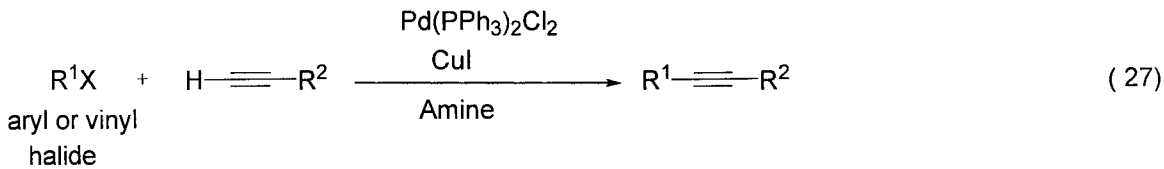


24

Amination reactions have also been performed under aqueous conditions. For example, Hartwig and co-workers have developed conditions that allow the use of KOH and NaOH in the presence of a phase-transfer catalyst (cetyltrimethylammonium bromide, $C_{16}H_{33}NMe_3Br$), 1 equiv of water, $Pd[P(t\text{-}Bu)_3]_2$ as the catalyst, and toluene as a cosolvent, in the amination of aryl bromides and chlorides.[70] Buchwald has shown that if ligand **1** is used, the amination reactions can be done in water as a solvent using no cosolvent.[71] Furthermore, the use of ligand **1** significantly expands the substrate scope of Pd-catalyzed aromatic amination, tolerating functional groups such as amides, carboxylic acids, aliphatic amines, and acetanilides that were not compatible with earlier reported catalyst systems.[71]

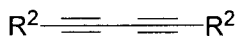
2. Sonogashira Reaction

The reaction of aryl or vinyl halides (or halide equivalents) with terminal alkynes gives arylalkynes or conjugated enynes respectively, which are important intermediates for the assembly of bioactive natural products and new materials.[72] This reaction, known as the Sonogashira reaction,[5,73] is usually catalyzed by a palladium-phosphine complex and is co-catalyzed by Cu(I) in the presence of an amine as the solvent and the base (eq 27). The role of Cu(I) is generally believed to form copper acetylide in situ which then transmetalates with palladium.



(27)

However, such copper acetylides are prone to undergo Glaser-type oxidative dimerization,[74] when exposed to air or an oxidant, giving byproducts (alkyne dimer, **25**)

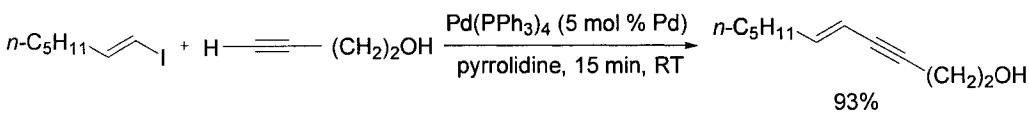


25

which are generally difficult to separate from the desired products. Furthermore, the copper acetylide is a potentially explosive material. In recent years, several reports have appeared dealing with the aforementioned issues by performing the Sonogashira reaction under copper-free conditions.

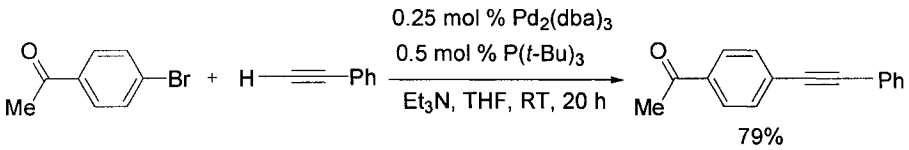
Because my research on Sonogashira reactions focused on copper-free (as well as amine- and phosphine-free) conditions, only important contributions in the field of copper-free Sonogashira reactions will be discussed in the introduction to this transformation.

Performing Sonogashira reactions without the use of a Cu(I) cocatalyst has been observed previously. One of the earliest reports appeared in 1993 by Linstrumelle, wherein he reported that (*E*)-1-iodo-1-heptene coupled with 3-butyn-1-ol to give the desired enyne in 93% isolated yield at room temperature in pyrrolidine using 5 mol % of $Pd(PPh_3)_4$ as the catalyst (eq 28).[75] Notably, the reaction was complete in 15 min. However, when phosphine-free palladium precursors such as $Pd(OAc)_2$ and $PdCl_2(PhCN)_2$ were employed, the reaction proceeded more sluggishly (22 h, 55-57%). The reaction of an iodobenzene also proceeded at room temperature while bromobenzene required an elevated temperature (80 °C).



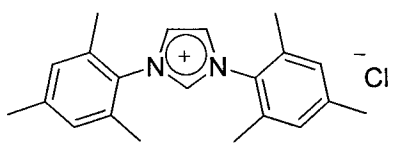
(28)

In 1996, Sinou described the reaction of aryl or vinyl halides (Br, I) with terminal alkynes at room temperature using $Pd(OAc)_2$ and PPh_3 in the presence of Et_3N and Bu_4NHSO_4 but without Cu(I), the so-called Jeffrey's conditions.[76] Herrmann, in 2000, reported the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system for a copper-free Sonogashira reaction of aryl bromides at room temperature (eq 29).[77] Et_3N was used as the base as well as the solvent although THF

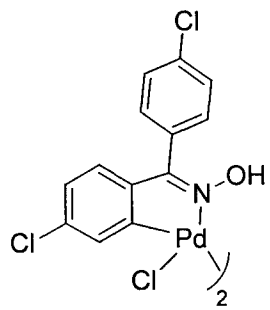


(29)

could also be used as the solvent. In the same year, Mori and co-workers showed that the copper-free Sonogashira reaction can be carried out in the presence of silver(I) oxide (Ag_2O) as an activator and $Pd(PPh_3)_4$ as the catalyst at 60 °C in THF.[78] They also demonstrated the usefulness of tetrabutylammonium fluoride (TBAF) and tetrabutylammonium hydroxide (TBAOH) as activators in these reactions.[78] In 2002, Ryu reported the Sonogashira reaction of aryl iodides with terminal acetylenes in an ionic liquid, namely, [BMIm][PF_6], using $PdCl_2(PPh_3)_2$ as the catalyst, *i*-Pr_2NH as the base at 60 °C in the absence of a copper salt.[79] In 2002, Nolan disclosed a palladium/imidazolium salt catalyst system (**26**) to effect Sonogashira reactions of aryl bromides under copper-free conditions using Cs_2CO_3 as the base in *N*,*N*-dimethylacetamide solvent at 80 °C.[80] In the same year, Nájera and co-workers reported a copper- and amine-free Sonogashira reaction of aryl iodides using a phosphine-free oxime-derived palladacycle (**27**) as the catalyst and tetrabutylammonium acetate as the base in NMP at 110 °C.[81] Notably, a very low catalyst loading of 0.1 mol % Pd was employed in this study.



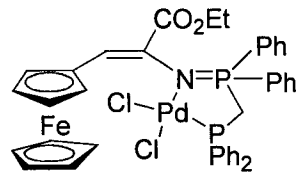
26
(imidazolium salt)



27
(oxime palladacycle)

In 2003, Leadbeater developed a rapid copper-free Sonogashira reaction of aryl iodides and activated aryl bromides by employing the traditional catalyst $Pd(PPh_3)_2Cl_2$ and excess piperidine as the base at 70 °C.[82] The reactions proceeded to completion in 10 min. In 2004,

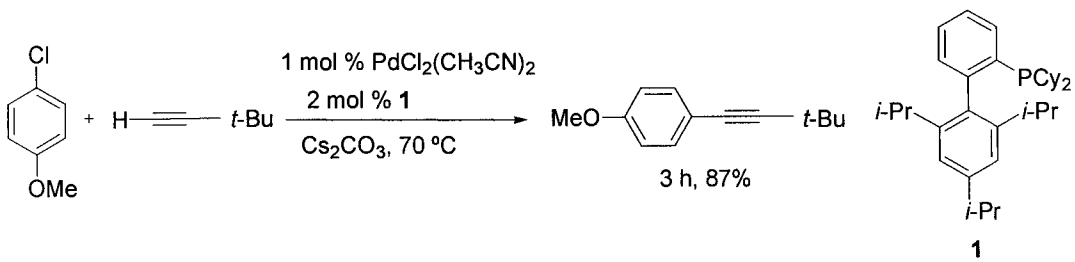
Soheili and co-workers at Merck developed a copper-free Sonogashira reaction of aryl bromides at room temperature under slightly modified conditions from those of Fu and Buchwald[83] and Herrmann[77] by using the $(AllylPdCl)_2/P(t\text{-}Bu)_3$ catalyst system in the presence of DABCO (or piperidine) as the base in an acetonitrile solvent.[84] Arques and Molina showed that by using ferrocene-based phosphinimine-phosphine ligand (**28**), a copper- and amine-free Sonogashira reaction of aryl iodides and activated aryl bromides can be performed at 110 °C using very low palladium loadings (0.1 mol %).[85]



28

(phosphinimine-phosphine)

More recently, an impressive contribution to this field came from Buchwald's group where he showed that the Sonogashira reaction of aryl chlorides can be performed under copper- and amine-free conditions with the use of a $[PdCl_2(CH_3CN)_2]$/**1** catalyst system (eq 30).[86]



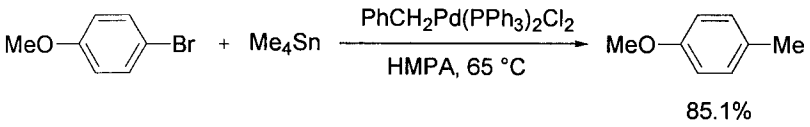
(30)

1

3. Stille Reaction

The palladium-catalyzed Stille reaction is an extremely powerful method for the coupling of aryl or vinyl halides (or halide equivalents) with organostannanes.[4,20] The pioneering work of Stille and co-workers led to the development of this important carbon-carbon bond-forming reaction (eq 31).[87] Due to its versatility and functional group tolerance, it is frequently used

in the total synthesis of large polyfunctional molecules for the coupling of complex subunits.[88]

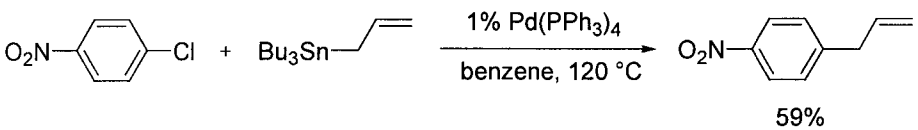


(31)

In this introduction to the Stille reaction, emphasis will be placed on reactions of aryl chlorides, the main focus of my research on this transformation.

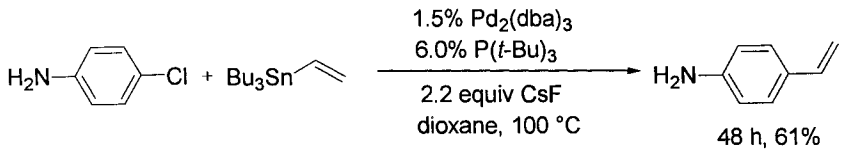
Among aryl halides, aryl bromides and iodides have found broad utility as electrophilic coupling partners in the Stille reaction. Until recently, cheaper and more widely available but less reactive aryl chlorides have remained elusive in this reaction. In contrast, great success has been achieved in the Stille reaction of heteroaryl chlorides such as chloro-substituted pyridines, pyradizines, pyrimidines, pyrazines, thiadiazoles, triazines, quinolines, isoquinolines, quinolones, quinazolines, benzothiazoles, purines, β-carbolines, phenanthrolines, and quinoxalines.[20]

Examples of Stille reactions of aryl chlorides were rare prior to the flurry of reports in the late 1990's and early 2000. The first example with an aryl chloride was reported by Migita and co-workers in 1977, in which they coupled highly activated 1-chloro-4-nitrobenzene with allyltributyltin in 59% yield using 1 mol % of $Pd(PPh_3)_4$ at 120 °C (eq 32).[89]



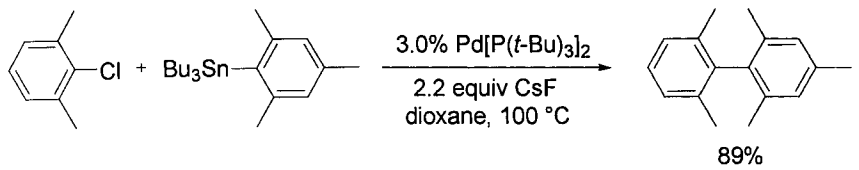
(32)

It is ironical that, given the importance of the Stille reaction in organic synthesis, it took more than 20 years for researchers to devise a general method for the Stille cross-coupling of aryl chlorides. Thus, in 1999, Fu,[90] in his pioneering studies, reported the first mild, effective, and general palladium-catalyst supported by the highly electron-rich and bulky P(*t*-Bu)$_3$ ligand for the Stille cross-coupling of electronically diverse aryl chlorides at 100 °C (eq 33).



(33)

A key aspect of this report was the use of the fluoride-activation strategy. Accordingly, taking advantage of the fact that tin is fluorophilic[91] and that hypervalent organotin species are more reactive than their tetravalent precursors, Fu demonstrated that the presence of CsF as an additive was essential for the reaction to proceed in high yield.[90] Subsequently, in 2002, Fu expanded the scope of the Stille reaction to the formation of sterically hindered (tetra-*ortho*-substituted) biaryls using $Pd[P(t\text{-}Bu)_3]_2$ as the catalyst in the presence of a fluoride additive (eq 34) and to the room temperature coupling of aryl bromides without any fluoride additive (eq 35). Certain activated aryl chlorides also reacted satisfactorily although a fluoride additive was required for these reactions.[92]



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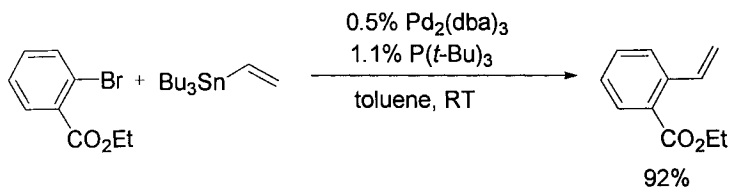
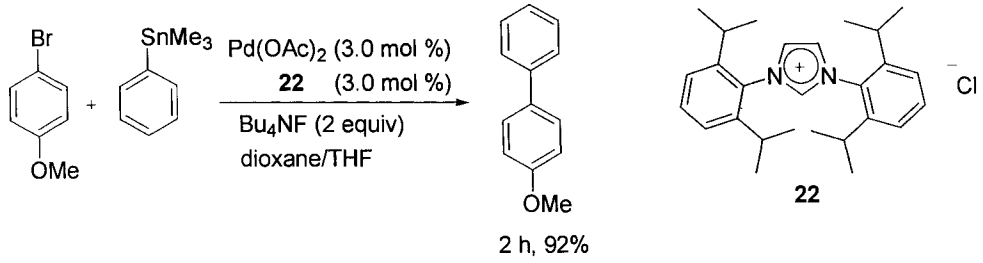


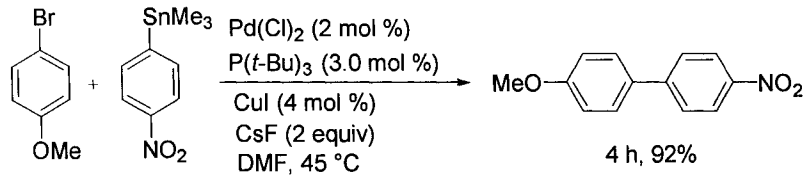
(35)

In 2001, Nolan reported the palladium/imidazolium salt (**22**) catalyst system for the Stille reaction of aryl bromides and activated aryl chlorides at elevated temperatures (80-100 °C) (eq 36).[93] For unactivated and deactivated aryl chlorides, only poor to moderated yields of the desired couled product were obtained.



(36)

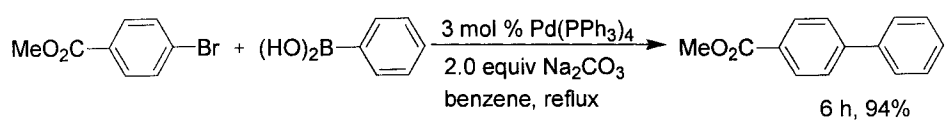
In 2002, Choudary described a layered double-hydroxide-supported nanopalladium catalyst for the Stille reaction of aryl chlorides, including electron-rich examples which operate under mild conditions (50 °C).[94] Stille reactions of aryl chlorides and bromides in water at 135 °C using palladium-phosphinous acid complexes was reported by Wolf in 2003.[95] Interestingly, the amine Cy_2NMe was used as an additive instead of a fluoride source. More recently, in 2004, Baldwin and co-workers demonstrated that the combination of CuI and CsF can significantly enhance the Stille reaction.[96] They found that while the $PdCl_2/P(t\text{-}Bu)_3$/CuI/CsF system in DMF is effective for the Stille coupling of aryl bromides (eq 37), aryl iodides work very well with the $Pd(PPh_3)_4$/CuI/CsF system.



(37)

4. Suzuki Cross-Coupling Reactions

The palladium-catalyzed Suzuki reaction of aryl and vinyl halides/triflates with a boronic acid nucleophile is a powerful method for the construction of C-C bonds.[3,97] Although first introduced by Suzuki in 1981 (eq 38),[98] it remains an extremely popular reaction as evidenced by its methodological development over the last several years and its use in natural product syntheses.[99]

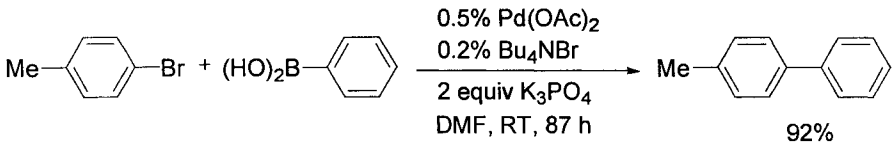


(38)

The popularity of this coupling process stems in part because of the nontoxic nature, commercial availability and air- and moisture stability of boronic acids. This reaction is typically carried out in the presence of base, the role of which is to render the boronic acid sufficiently reactive to undergo transmetalation with palladium by the formation of a higher-coordinate and more reactive "boronate" complex. The presence of base is essential because in its absence no reaction occurs. Common inorganic bases such as Na_2CO_3, $NaHCO_3$, Tl_2CO_3, K_3PO_4, CsF, Cs_2CO_3, and KF are usually employed. Phosphine-based palladium catalysts such as $Pd(PPh_3)_4$ are generally used, although in some instances, especially with activated aryl bromides and iodides, it is possible to achieve the desired coupling by using palladium catalysts without a phosphine ligand such as $Pd(OAc)_2$ and $Pd_2(dba)_3$. While aryl bromides, iodides and triflates are commonly used as the coupling partner aryl chlorides are unreactive under these coupling conditions.

The low reactivity of aryl chlorides is usually attributed to their aversion to oxidatively add to Pd(0) species (the first step of the catalytic cycle) because of the large bond dissociation energy of the C-Cl bond (i.e., bond dissociation energies for Ph-X: Cl: 96 kcal/mol; Br: 81 kcal/mol; I: 65 kcal/mol). Since aryl chlorides are cheap and widely available compared with their bromide and iodide counterparts, their failure to participate in the case of unactivated and deactivated aryl chlorides in this synthetically important reaction was considered an impediment and a major challenge to researchers working in this area. However, in recent years, the use of electron-rich and sterically hindered ligands (both phosphines and non-phosphines) has led to the renaissance of this reaction. The following survey of the Suzuki reaction is thus aimed at summarizing some of the important advances appeared in the literature in recent years.

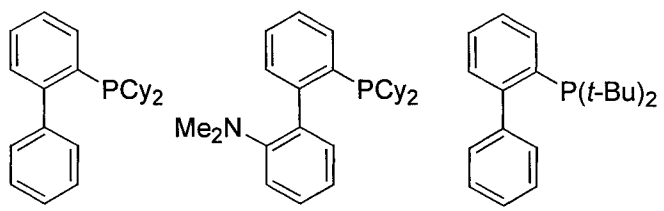
In 2000, Dupont's group in Brazil reported that simple $Pd(OAc)_2$ in combination with the additive Bu_4NBr and base K_3PO_4 in DMF effectively promotes the Suzuki cross-coupling of aryl bromides (electron-rich, -neutral, and -poor) and aryl chlorides (electron-poor only) with phenylboronic acid in high yield (eq 39).[100]



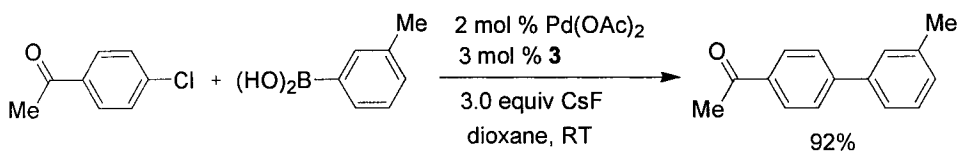
(39)

This discovery has two important implications: (i) no added phosphine (or non-phosphine, for that matter) ligands are necessary in the case of the Suzuki reaction of more reactive aryl bromides and activated aryl chlorides, and (ii) to develop highly active palladium catalysts, ligands had to be developed to accommodate electron-neutral and electron-rich aryl chlorides coupling partners. However, it is important to note that all but one example reported were with phenylboronic acids.[100] Thus it should not come as a surprise that any change in the electronics of the boronic acid might decrease the catalyst activity and to develop a "truly" general palladium catalyst system, several combinations of substrates must be tested.

The first palladium catalyst (based on ligand **3**) for the Suzuki reaction of electron-rich and electron-deficient aryl chlorides was reported by Buchwald in 1998 which proceeded at room temperature or under relatively mild conditions (eq 40).[101] However, the synthesis of this ligand required 4 steps from commercially available starting materials.

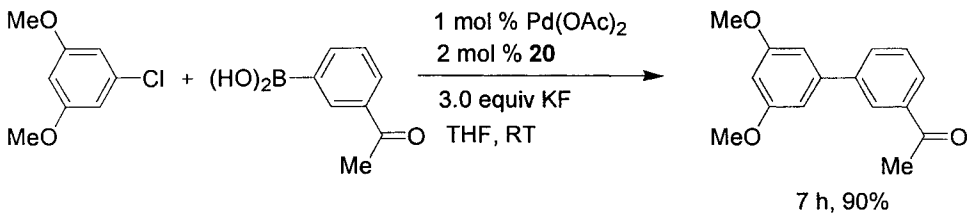


2 **3** **20**



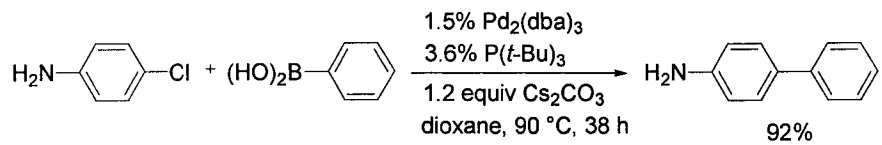
(40)

Subsequently, it was shown that catalysts based on ligands **2** and **20** were also highly effective for the Suzuki coupling of aryl chlorides and bromides (eq 41).[102,103]



(41)

In contrast to **3**, **2** and **20** could be synthesized in a single step. In the same year, Fu demonstrated that the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system with Cs_2CO_3 as the base couples electronically diverse aryl chlorides with a wide variety of arylboronic acids at 80-90 °C to give biaryls in excellent yields (eq 42).[104] Later in 2000, Fu discovered that Suzuki cross-couplings of activated aryl chlorides could be carried out at room temperature if KF was used as the base (eq 43).[105] In this study, it was also shown that aryl bromides could be coupled at room temperature and sterically hindered biaryls could be synthesized in high yields under mild conditions.[105]



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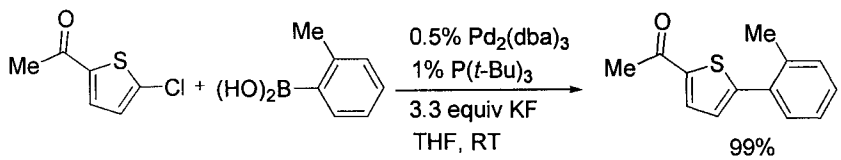
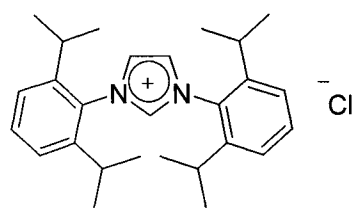


(43)

In 1999, Nolan reported that the palladium catalyst supported by N-heterocyclic carbene imidazolium salt **26** allows the Suzuki cross-coupling of aryl chlorides with arylboronic acids at 80 °C (eq 44).[106] In subsequent studies, he found that imidazolium salt **22** also generates a highly active palladium catalyst for the Suzuki coupling of aryl chlorides.[107]



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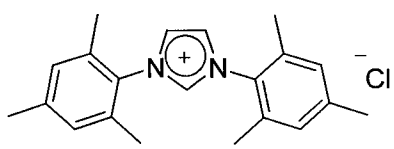
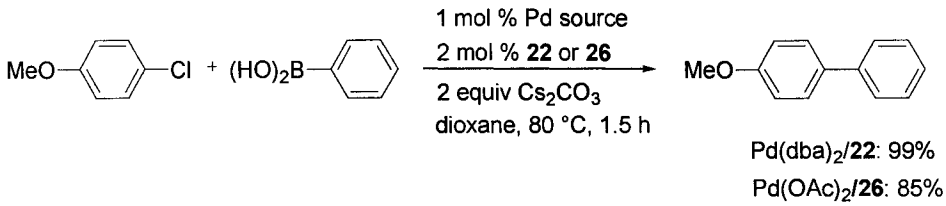
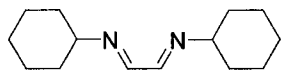


26



(44)

Nolan also developed a highly efficient Suzuki reaction based on simple diazabutadiene ligand **29** for the coupling of aryl bromides at 80 °C (eq 45).[108] Some of the features given for to its effectiveness are strong σ–donor and π-acceptor properties as well as its chelating nature.



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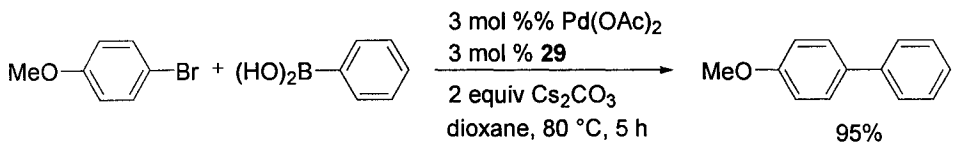
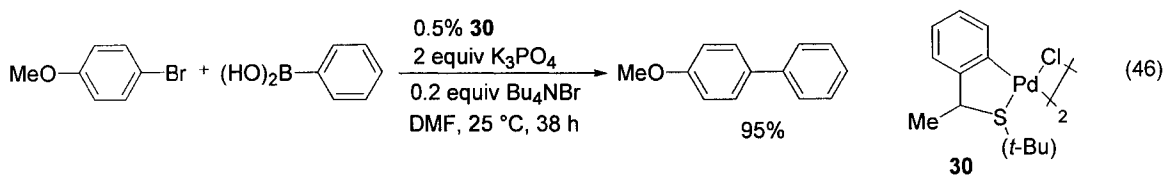


(45)

In 2000, Dupont and Monteiro demonstrated the efficacy of the sulfur-containing palladacycle **30** in the Suzuki cross-coupling of aryl bromides at room temperature (eq 46).[109] This phosphine-free catalyst was also effective for the coupling of activated aryl chlorides although at elevated temperatures (130 °C).

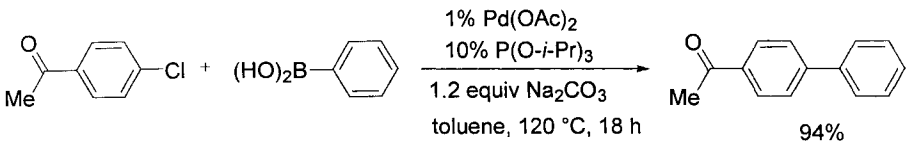


30

(46)

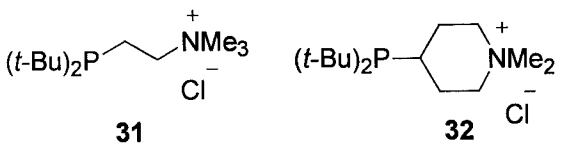
The work of Beller in 2000 showed that $Pd(OAc)_2$ in combination with sterically hindered phosphites [$P(O\text{-}i\text{-}Pr)_3$ or $P(O\text{-}2,4\text{-}t\text{-}BuC_6H_3)_3$] are highly efficient catalysts for the coupling of aryl bromides and activated aryl chlorides with phenylboronic acid at 120 °C (eq 47).[110] The use of NaOH or Na_2CO_3 as the base was crucial. Since phosphites are generally believed to be considerably less electron-rich than phosphines due to the high electronegativity of

oxygen, Beller's finding is quite remarkable and holds considerable promise in palladium catalysis since phosphites are cheaper and more stable toward oxygen than phosphines.

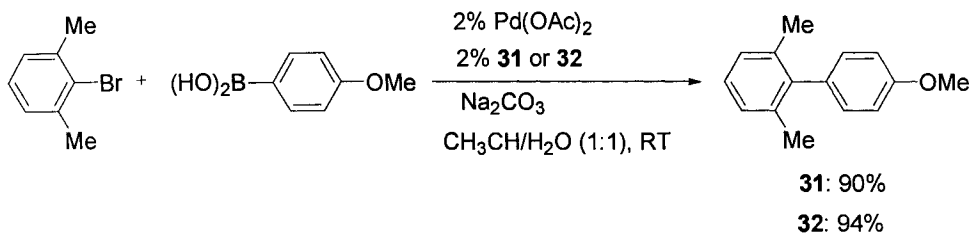


(47)

In 2001, Shaughnessy developed the first room-temperature aqueous-phase Suzuki couplings of aryl bromides using sterically demanding water-soluble alkylphosphines **31** and **32** (eq 48).[111]

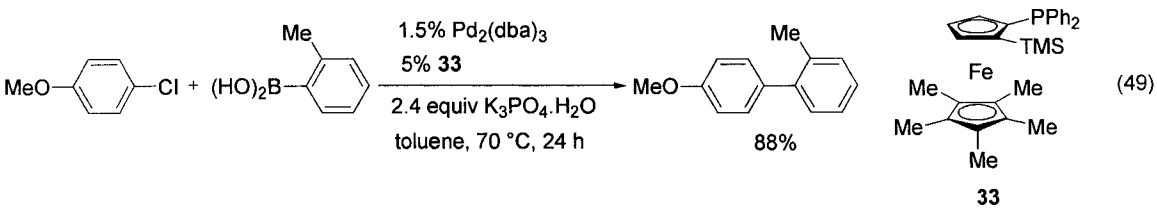


31 **32**



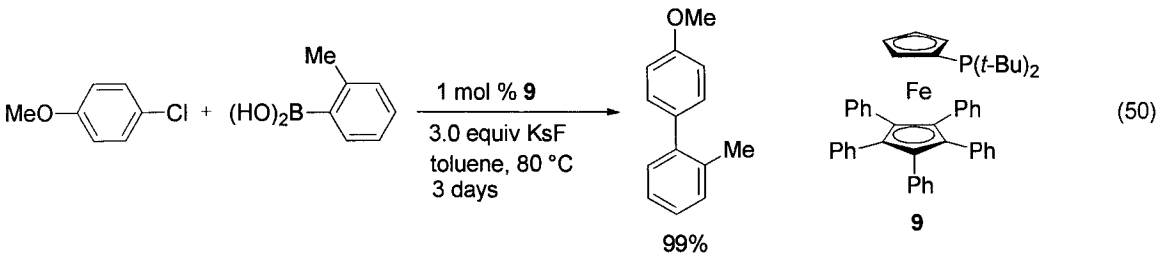
(48)

Both ligands **31** and **32** provided highly active catalysts. The authors suggested that these catalysts would prove useful in solution-phase combinatorial library synthesis, among other applications. In the same year, in a report somewhat paralleling that of Beller's on phosphites, a surprising but highly effective palladium catalyst bearing a triarylphosphine ligand **33** for the Suzuki couplings of aryl chlorides was described by Fu.[112] Noteworthily, unactivated and deactivated aryl chlorides coupled with arylboronic acids under relatively mild conditions (70 °C) while activated aryl chlorides reacted at room temperature (eq 49).



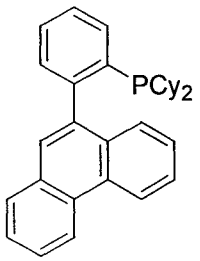
(49)

In 2002, Hartwig reported the Suzuki cross-coupling of aryl bromides and chlorides with arylboronic acids using Q-phos (**9**) as the ligand (eq 50).[68]



(50)

In an elegant work reported in 2002, Buchwald described the synthesis of challenging sterically hindered biaryls via Suzuki coupling using phenanthrene-based ligands **34** and **35** (eqs 51 and 52).[113] Tetra-*ortho*-substituted biaryls with substituents such as methyl, primary alkyl, phenyl and alkoxy groups were readily synthesized in good yields. For the Suzuki coupling of aryl halides possessing an electron-withdrawing group at the *ortho*-position, catalysts based on **34** and **35** were not suitable. For the coupling of this class of substrates, DPEphos (**17**) was employed as the ligand (eq 53).[113] In this case, the inclusion of freshly activated 4 Å molecular sieves was found to be beneficial. The high activity of **34** and **35** was probably due to the stabilization of the active species by an unusual π-coordination of the phenanthrene moiety with the palladium center, as indicated by a crystallographic analysis of a complex of **34** and Pd(0).[113]



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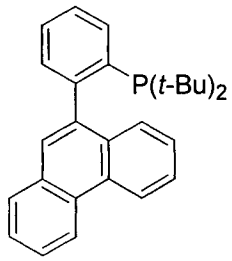

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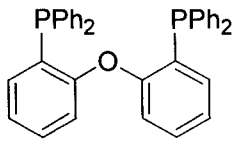
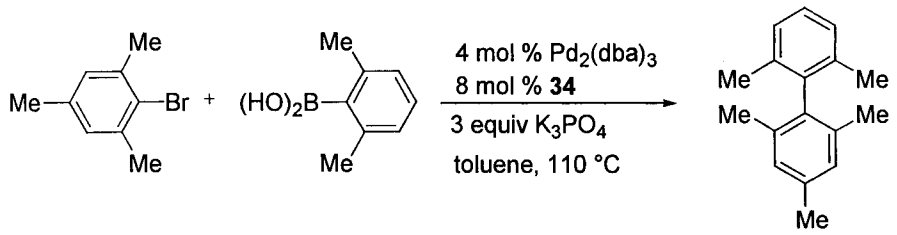


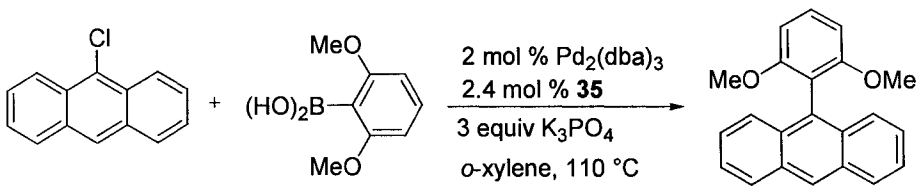
17

DPEphos



82%

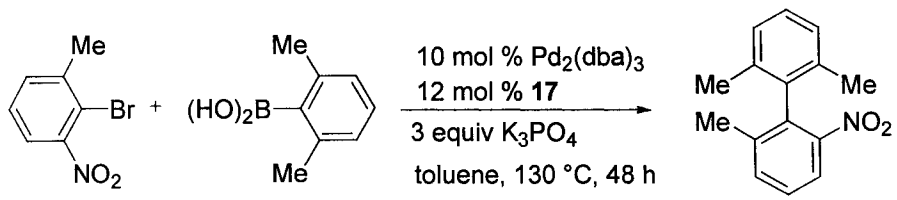
(51)



93%

93%

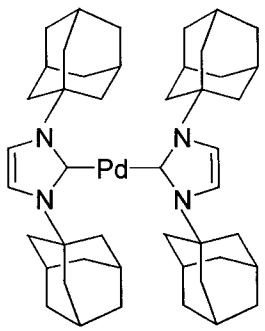
(52)



69%

(53)

Following Buchwald's work, Hermann described a well-defined Pd(0)-complex **36** containing the N-heterocyclic carbene ligand shown for the Suzuki cross-coupling of aryl chlorides at room temperature (eq 54).[114] *Ortho*-substituted aryl chlorides or boronic acids were not suitable substrates with this catalyst system, however.



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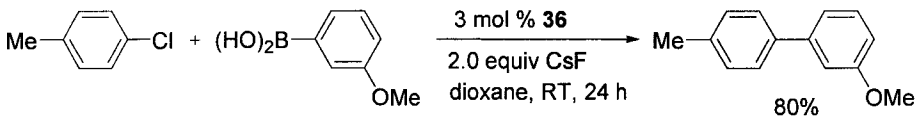
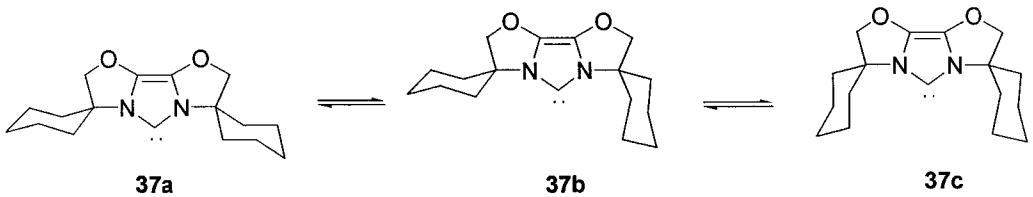
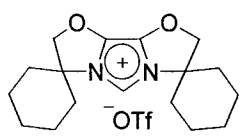


(54)

In 2003, Glorius and co-workers developed a highly efficient catalyst system based on the N-heterocyclic carbene **37** (prepared from the imidazolim salt **38**) for the Suzuki cross-coupling of sterically hindered biaryls at room temperature (eq 55).[115] They argued that **37**, due to its flexible steric bulk, could exist as the three different conformers **37a**, **37b**, and **37c**. While conformation **37a** with the coordinated Pd(0) would be expected to undergo oxidative addition and facilitate transmetalation, conformations **37b** and **37c** would favor a monocarbene Pd species and enhance reductive elimination.[115] Using this catalyst system, di-*ortho*-substituted biaryls could be obtained in good to excellent yields.



37a **37b** **37c**



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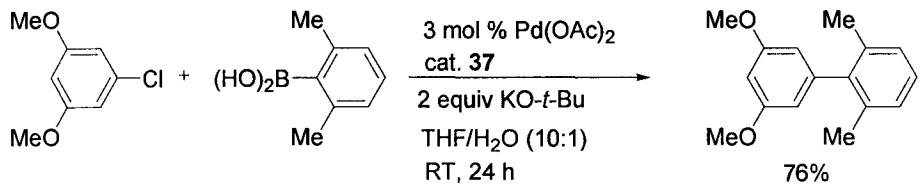
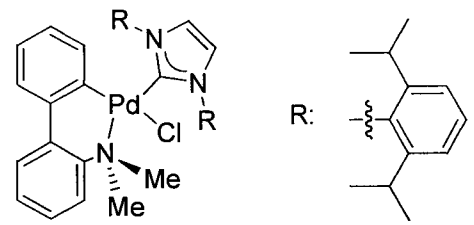


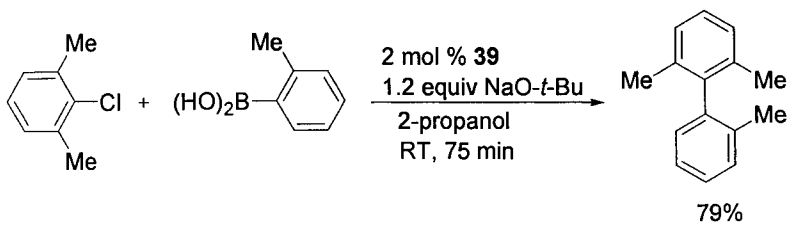
(55)

37 was prepared from: **38** (3.1 mol %), KH (6.25 mol %), KO-*t*-Bu (0.67 mol %) in THF

A more general catalyst system for the Suzuki coupling of sterically hindered aryl chlorides proceeding at room temperature was reported by Nolan later that year who combined the palladacycle framework with the N-heterocyclic carbene to generate a highly active catalyst **39** providing various di- and tri-*ortho*-substituted biaryls in excellent yields in a short period of time (45-120 min) (eq 56).[116] Notably, the reaction uses technical-grade 2-propanol as the solvent. It was further noted that the aryl chloride must be added slowly to prevent its dehalogenation in a side-reaction.[116]

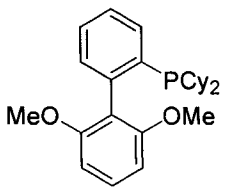


39



79% (56)

In 2004, Buchwald reported a highly general catalyst system for the Suzuki cross-coupling of aryl bromides and chlorides (eqs 57-59).[117] The catalyst, based on ligand **5**, allows coupling of sterically hindered substrates, operates at very low palladium loadings (down to 0.003 mol % Pd for ArCl and 0.0005 mol % Pd for ArBr), permits room temperature Suzuki coupling of aryl chlorides (including sterically hindered ones) and tolerates the coupling of heteroaryl chlorides. The exceptional catalyst activity and lifetime is believed to be due to: (i) the two methoxy groups which increase the electron density in the biaryl backbone, and (ii) the lone pairs on the oxygen which could interact with the palladium metal and stabilize intermediate complexes. In fact, the X-ray crystal structure of the **5**/Pd(0)dba complex shows an unusual Pd(0) η^1–arene interaction (mainly a π-interaction) with the ipso carbon on the benzene ring.[117]



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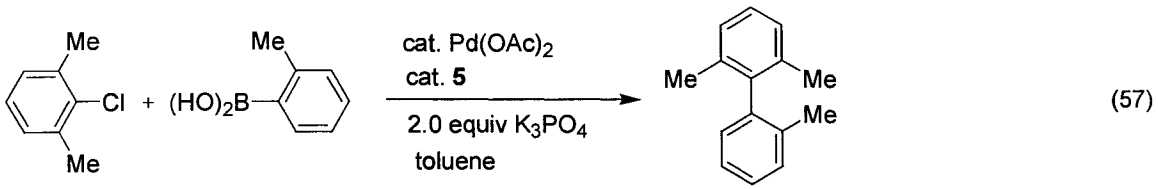


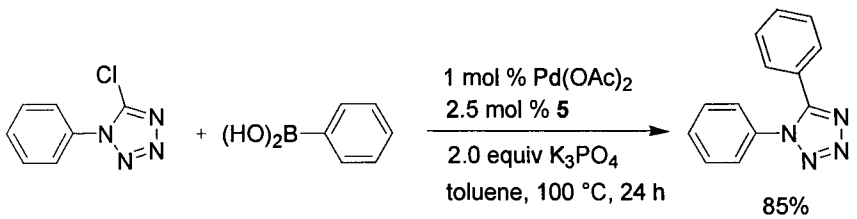
(57)

(a) 0.02 mol % Pd, 0.1 mol % **5**, 100 °C, 20 h: **97%**

(b) 0.2 mol % Pd, 0.5 mol % **5**, 90 °C, 12 min: **98%**

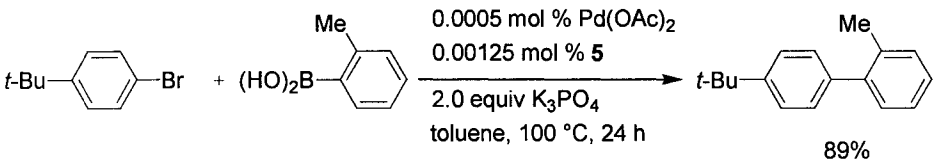
(c) 0.5 mol % Pd, 0.5 mol % **5**, RT, 3 h: **90%**

For RT conditions, THF was used instead of toluene and H_2O (0.6 equiv) was also added



85%

(58)



89%

(59)

Conclusions

In summary, this introduction chapter is an attempt to provide a brief overview of important palladium-catalyzed coupling transformations, namely, Buchwald-Hartwig amination, Sonogashira, Stille, and Suzuki reactions. As seen, for each of these reactions, the optimization of various reaction parameters is of utmost importance for achieving good success. This has not only led to the development of a plethora catalyst systems, but it also has made it difficult for researchers to decide which of these catalysts systems would work in his/her chemistry which might be entirely different from the examples appearing in the publications.

References

1. For recent reviews on transition-metal catalyzed reactions, (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048. (d) Skoda-Foldes, R.; Kollar, L. *Chem. Rev.* **2003**, *103*, 4095. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

2. For reviews on organopalladium chemistry: (a) Negishi, E.-i. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley and Sons: New York, 2002; Vols. 1 and 2. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1996**, *161*, 129. (c) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley and Sons: New York, 1995. (d) Tsuji, J. *J. Organomet. Chem.* **1986**, *300*, 281. (e) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (f) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: New York, 1980.

3. For reviews on the Suzuki reaction, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Suzuki, A. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

4. For reviews on the Stille reaction, see: (a) Fugami, K.; Kosugi, M. *Top. Curr. Chem.* **2002**, *219*, 87. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

5. For reviews on the Sonogashira reaction, see: (a) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (b) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (c) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002.

6. For reviews on the Buchwald-Hartwig amination reaction, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (d) Wolfe, J. P.; Wagaw,, S.; Marcoux, J.-F.; Buchwald,

S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (f) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

7. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

8. (a) Yamamura, M.; Moritani, I.; Murahashi, S.-i. *J. Organomet. Chem.* **1975**, *91*, C39. For a review of the Kumada reaction, see: (b) Negishi, E.-i. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

9. Erdik, E. *Tetrahedron* **1992**, *48*, 9577. Also see ref. 8b.

10. (a) Hiyama, T. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471.

11. (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

12. For recent reviews of the Heck reaction, see: (a) Whitecombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

13. Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

14. Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

15. Heck, R. F. *Org. React.* (N.Y.) **1982**, *27*, 345.

16. For a recent application, see: Yoshida, M.; Sugimoto, K.; Ihara, M. *Org. Lett.* **2004**, *6*, 1979.

17. (a) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4120. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

18. Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.

19. Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Chem. Commun.* **2002**, 2608.

20. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

21. (a) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794. (b) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598. (c) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.

22. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

23. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

24. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413.

25. Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

26. (a) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7856. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336.

27. Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9453.

28. Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3*, 295.

29. Beller, M.; Krotz, A.; Baumann, W. *Adv. Synth. Catal.* **2002**, *344*, 517.

30. Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519.

31. Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704.

32. Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

33. (a) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (b) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (c) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643.

34. Lensink, C.; Xi, S.-K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478.

35. For reviews, see: (a) Verkade, J. G.; Kisanga, P. B. *Tetrahedron* **2003**, *59*, 7819. (b) Verkade, J. G. Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3. (c) Verkade, J. G. *Top. Curr. Chem.* **2003**, *223*, 1. (d) Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233. (e) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483.

36. Kisanga, P. B.; Verkade, J. G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431.

37. Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69

38. (a) Clarke, M. L.; Holliday, G. L.; Slawin, A. M. Z.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2002**, 1093. (b) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721. (c) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065.

39. (a) Molloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696. (b) Cowley, A. H.; Lattman, M.; Stricklen, P. M.; Verkade, J. G. *Inorg. Chem.* **1982**, *21*, 543. (c) Romming, C.;

Songstad, J. *Acta Chem. Scand., Ser. A* **1980**, *34*, 365. (d) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1979**, *33*, 187.

40. Negwer, M. In *Organic-Chemical Drugs and their Synonyms: (An International Survey)*, 7th ed.; Akademie Verlag GmbH: Berlin, 1994.

41. Montgomery, J. H. In *Agrochemicals Desk Reference: Environmental Data*; Lewis Publishers: Chelsea, MI 1993.

42. D'Aprano, G.; Leclerc, M.; Zotti, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33.

43. Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.

44. Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

45. Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

46. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348.

47. Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

48. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

49. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

50. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

51. Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104.

52. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

53. Marcoux, J-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568.

54. Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.

55. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

56. Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.

57. Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789.

58. Beller, M.; Riermeier, T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073.

59. Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.

60. Nishiyama, M. Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

61. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.

62. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

63. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

64. (a) Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.

65. (a) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. Petersen, J. L. *Organometallics* **1999**, *18*, 1840. (b) Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237.

66. (a) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (b) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307.

67. Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

68. Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

69. Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chemical* **2002**, *182-183*, 515.

70. Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.

71. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

72. (a) Paterson, I.; Davies, R. D.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603. (b) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110. (c) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (d) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605.

73. (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Takahashi, K.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

74. (a) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320. (b) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 42.

75. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

76. Nguefack, J-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* **1996**, *37*, 5527.

77. Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679.

78. Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.

79. Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.

80. Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.

81. Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365.

82. Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653.

83. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.

84. Soheili, S.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191.

85. Arques, A.; Auñon, D.; Molina, P. *Tetrahedron Lett.* **2004**, *45*, 4337.

86. Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.

87. (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

88. (a) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 9468. (b) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.;Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830.

89. Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301.

90. Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed. Engl.* **1999**, *38*, 2411.

91. *Chemistry of Tin*; Smith, P. J., Ed.; Blackie Academic & Professional: New York, 1998.

92. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

93. Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

94. Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127.

95. Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551.

96. Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.

97. (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Chem. Rev. 2002, 102, 1359. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9663.

98. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

99. (a) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (b) Goa, K. L.; Wagstaff, A. J. *Drugs* **1996**, *51*, 820.

100. Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199.

101. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

102. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

103. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

104. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387.

105. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

106. Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *2*, 2053.

107. Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866.

108. Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077.

109. Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881.

110. Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830.

111. Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757.

112. Liu, S-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408.

113. Yin, J.; Rainka, M. P.; Zhang, X-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

114. Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363.

115. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690.

116. Navarro, O.; Kelly, R. A.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194.

117. Walker, S. D.; Barder, T. E.; Martinelli, Buchwald, S. L. *Angew. Cem., Int. Ed.* **2004**, *43*, 1871.

CHAPTER 2. P(*i*-BuNCH$_2$CH$_2$)$_3$N: AN EFFECTIVE LIGAND IN THE PALLADIUM-CATALYZED AMINATION OF ARYL BROMIDES AND IODIDES

A paper published in *The Journal of Organic Chemistry*

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Abstract

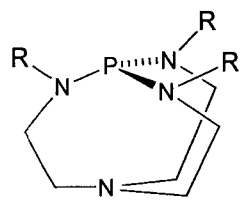
It is shown that the bicyclic triaminophosphine P(*i*-BuNCH$_2$CH$_2$)$_3$N serves as an effective ligand for the palladium-catalyzed amination of a wide array of aryl bromides and iodides. Other bicyclic or acyclic triaminophosphines, even those of similar basicity and/or bulk, were inferior.

Introduction

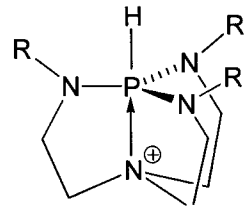
Palladium-catalyzed amination reactions are fundamentally important organic transformations that have received tremendous attention over the past few years.[1] Elegant work by Hartwig,[2] Buchwald,[3] and others[4] has led to significant improvements in amination methodology since its discovery by Migita and co-workers in 1983.[5] Most of the reported methods employ electron-rich phosphine ligands,[6] possessing either a ferrocene[7] or a biphenyl backbone,[8] or bulky nucleophilic N-heterocyclic carbenes (sometimes referred to as "phosphine mimics").[4a,c,9] Chelating phosphines such as 1,1'-bis(diphenylphosphino)ferrocene (DPPF)[2a] and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)[3b,10] have been demonstrated to exhibit improved catalytic activity in this type of transformation. Although room-temperature amination reactions are known,[8] the range of substrate combinations that can be employed at this temperature are rather limited, whereas reactions performed at 80 °C or higher accommodate a wide variety of substrates.

Although triaminophosphines, and particularly P(NMe$_2$)$_3$, have often been used to ligate transition metals, to the best of our knowledge there have been no reports of the use of such ligands in Pd-catalyzed amination chemistry. This may be partly due to the diminished electron-donating capability of acyclic triaminophosphines compared with

trialkylphosphines, as was recently rationalized by Woollins.[11] The reduced Lewis basicity of triaminophosphines is believed to arise from differences in the geometries of their nitrogens. X-ray crystal structures of free tris(dialkylamino)phosphines and their transition metal complexes[12,13] reveal that phosphorus bears two nearly planar nitrogens and one pyramidal nitrogen. While the two planar nitrogens are capable of donating electron density to phosphorus via their unhybridized lone pairs (which are roughly perpendicular to the phosphorus lone pair) the pyramidal nitrogen simply acts as an electron-withdrawing atom since its more sp^3-hybridized lone pair is oriented anti to the phosphorus lone pair.



1a R = Me
2a R = Et
3a R = *i*-Pr
4a R = *i*-Bu
5a R = *neo*-Pent
6a R = 4-Pyridyl



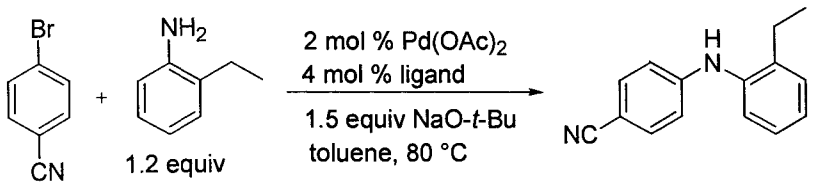
1b R = Me
2b R = Et
3b R = *i*-Pr
4b R = *i*-Bu
5b R = *neo*-Pent
6b R = 4-Pyridyl

As part of our own effort to understand and exploit the stereoelectronic properties of tris(dialkylamino)phosphines, we reasoned that by rendering the backbone of the triaminophosphine quite rigid in a bicyclic framework in which all three nitrogens would be geometrically and conformationally very similar[14] to the two planar electron-donating nitrogens in tris(dialkylamino)phosphines, we could significantly enhance the basicity of such phosphines and thus facilitate oxidative addition to the metal. Furthermore, the electronic and steric influences in such ligands could be easily tailored by introducing suitable organic substituents at each PN_3 nitrogen to impart the desired steric bulk which could assist in the reductive elimination step. In addition to these advantages possessed by pro-azaphosphatranes of types **1a-6a**, such bicyclic systems also feature the potential for basicity enhancement via transannulation of the bridgehead nitrogen's lone pair to the phosphorus as in **1b-6b**[15] some of which we recently showed possess pK_a values of approximately 33 in acetonitrile.[16] Compounds of type **1** have proven to be exceedingly

useful nonionic bases and catalysts for a variety of useful transformations during the last 10 years.[17] Herein we show that commercially available **4a** is an excellent ligand in the palladium-catalyzed aminations of aryl bromides and iodides.

Results and Discussion

For our optimization studies, we selected the $Pd(OAc)_2$/L-catalyzed amination of 4-bromobenzonitrile with 2-ethylaniline in toluene as a model reaction (reaction 1). Initial reactions with **1a** and **2a** as ligands were disappointing, providing only a trace amount of N-arylated product (Table 1, entries 1 and 2). Since ligand steric hindrance can improve



(1)

TABLE 1. Screening of Triaminophosphine Ligands for the Reaction Shown in Eq 1[a]

entry	ligand	yield (%)[b]	entry	ligand	yield (%)[b]
1	**1a**	15	6	**6a**	0
2	**2a**	5	7	**$P(NMe_2)_3$**	10[c]
3	**3a**	0	8	**$P(NEt_2)_3$**	11[c]
4	**4a**	97	9	**$P[N(i\text{-}Bu)_2]_3$**	15[c]
5	**5a**	30			

[a] Control experiments show that either in the absence of a Pd source or in the absence of the bicyclic triaminophosphine ligand **4**, no reaction was observed. [b] Isolated yields (average of two runs). [c] 15% of hydrodehalogenated arene was isolated.

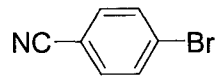
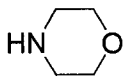
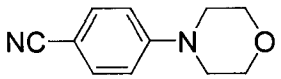
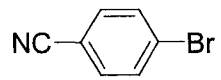
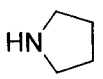
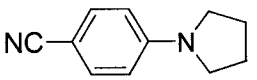
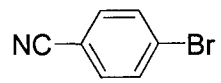
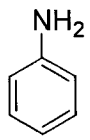
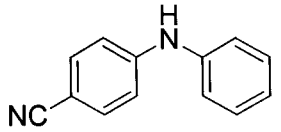
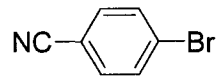
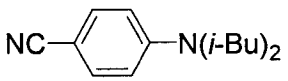
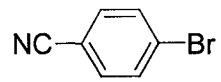
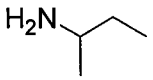
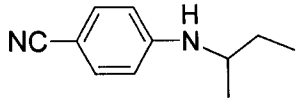
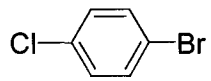
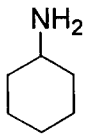
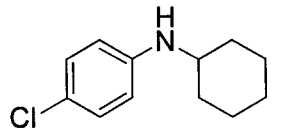
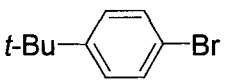
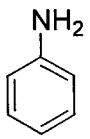
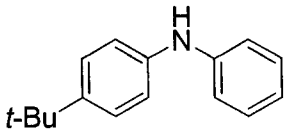
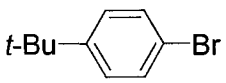
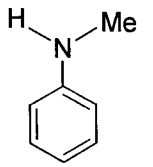
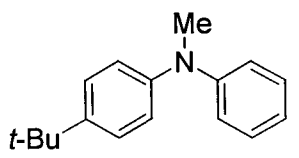
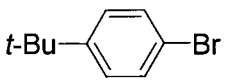
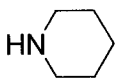
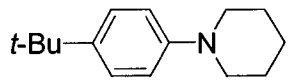
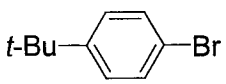
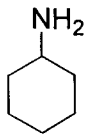
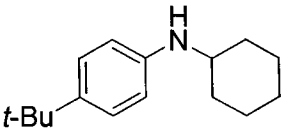
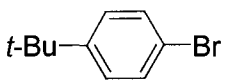
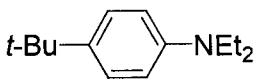
catalytic performance,[18] the more bulky bicyclic triaminophosphines **3a** and **4a** were employed in this reaction. Although ligand **3a** was not effective, it was gratifying to find that, with **4a** (a colorless liquid), the desired amination product was isolated in 97% yield (Table 1, entry 4). Interestingly, further increases in ligand steric hindrance (**5a** and **6a**) proved ineffective (Table 1, entries 5 and 6). The inefficiency of ligand **3a** might be due to the fact that it does not provide sufficient steric bulk since the Me groups on the *i*-Pr substituents are turned outward and away when the Pd is coordinated to phosphorus, a conformation that is also present in the solid-state structure of the free ligand and its protonated form.[14] Although

5a could be assumed to be at least as efficient as **4a**, if not more so, it appears that, after a point achieved in **4a**, additional steric hindrance becomes detrimental to catalyst activity. Thus, **4a** presumably possesses a unique balance of stereoelectronic influences that optimize activity of the catalyst system. As expected, the relatively electron-poor acyclic triaminophosphine ligands $P(NR_2)_3$ (R = Me, Et, *i*-Bu) gave very poor yields with incomplete conversion (Table 1, entries 7-9).

The best results were obtained in aminations performed at 80 °C in toluene using NaO-*t*-Bu[19] as a base and a catalyst system generated in situ from 2 mol % $Pd(OAc)_2$ and 4 mol % of **4a**. With optimized conditions in hand, the scope of this catalytic process was examined with various aryl bromides and iodides, and the results are summarized in Tables 2 and 3, respectively. As seen in Table 2, the Pd/**4a** catalyst system efficiently catalyzed the cross-coupling reaction of electronically diverse aryl bromides with a variety of amines. Thus, electron-poor (e.g., 4-bromobenzonitrile), electron-neutral (e.g., 4-*tert*-butylbromobenzene), and electron-rich (e.g., 4-bromoanisole) aryl bromides coupled smoothly with various anilines (primary and secondary) to afford the N-arylated products in excellent yields (Table 2, entries 3, 7, 8, 17, and 18). Secondary cyclic amines were also efficiently arylated. For example, morpholine and pyrrolidine reacted with 4-bromobenzonitrile to give the desired products in high yields (Table 2, entries 1 and 2). Similarly, piperidine coupled with 4-*tert*-butylbromobenzene and 4-bromoanisole in good to excellent yields (Table 2, entries 9 and 19). It may be noted that the piperidine coupling reaction gave a large amount of reduced side products with a very active Pd/BINAP catalyst system.[10]

The Pd/**4a** catalyst system was also effective for primary aliphatic amines that were branched at the αposition. For instance, cyclohexylamine reacted with 4-*tert*-butylbromobenzene to produce the N-arylated product in 89% yield (Table 2, entry 10). Moreover, sterically hindered 2-bromotoluene reacted cleanly with cyclohexylamine (Table 2, entry 16). A slightly lower yield was obtained with electron-poor 4-bromochlorobenzene (Table 2, entry 6). A catalyst loading of 5 mol % allowed the reaction of 4-bromobenzonitrile with *sec*-butylamine (Table 2, entry 5). However, the reaction of long-chain primary alkylamines such as *n*-hexylamine with aryl bromides usually gave less than 50% yield of the desired product

TABLE 2. Palladium/**4a**-Catalyzed Amination of Aryl Bromides[a]

entry	aryl bromide	amine	product	yield (%)[b]
1				99
2				96
3				99
4		$(i\text{-Bu})_2NH$		70[c]
5				65[c]
6				70
7				99
8				93
9				82
10				88
11		Et_2NH		57[c]

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.2 mmol of amine, 1.5 mmol of NaO-*t*-Bu, 2.0 mol % $Pd(OAc)_2$, 4.0 mol % **4a**, 5 mL of toluene, 80 °C, 9-15 h. Reaction times have not been minimized. [b] Isolated yields (average of two runs). [c] 5.0 mol % $Pd(OAc)_2$ was used. [d] 3.0 mol % $Pd(OAc)_2$ was used.

TABLE 2. Continued

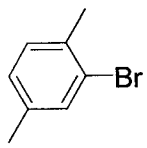
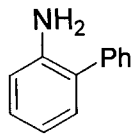
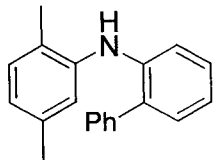
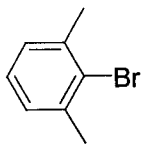
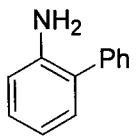
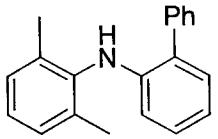
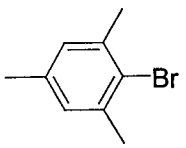
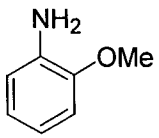
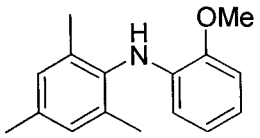
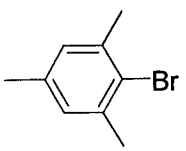
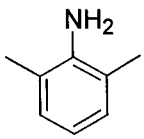
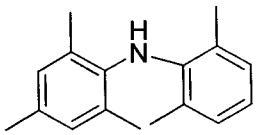
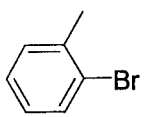
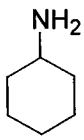
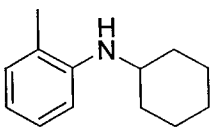
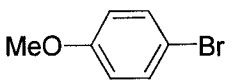
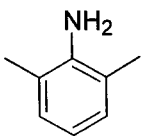
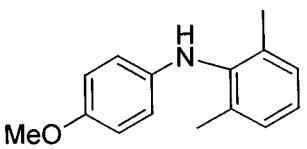
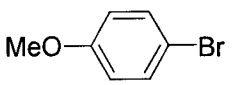
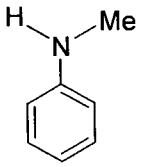
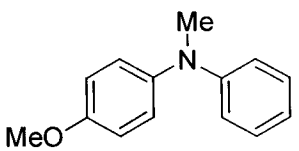
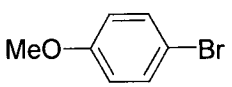
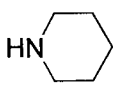
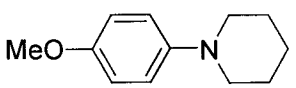
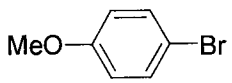
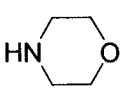
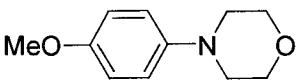
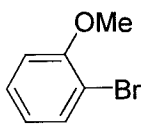
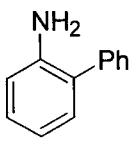
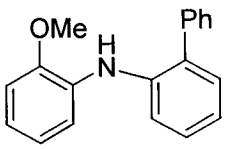
entry	aryl bromide	amine	product	yield (%)[b]
12				99
13				94
14				99
15				99
16				84[d]
17				97
18				91
19				92
20				95
21				93

TABLE 2. Continued

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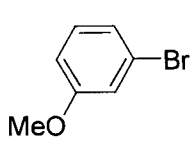
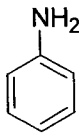
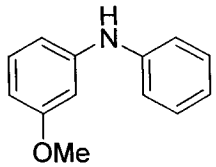
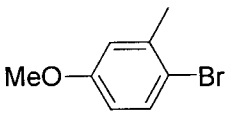
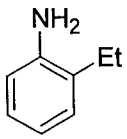
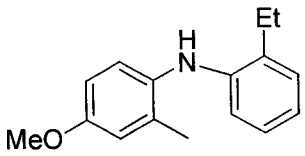
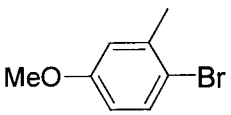
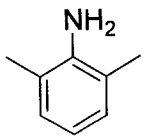
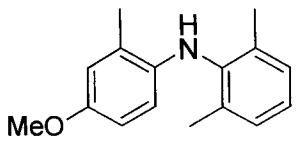
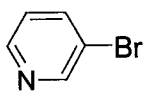
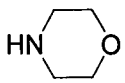
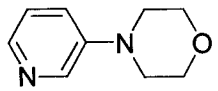
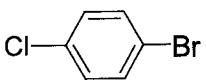
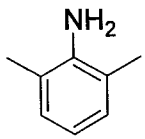
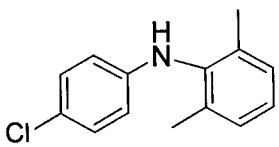
22				96
23				96
24				98
25				89
26				90

even when greater quantities of catalyst and/or longer reaction times were employed. The main side products were the diarylated amine, which may be attributed to the formation of a catalytically inactive bis(primary amine)palladium(II) complex,[20] and the hydrodehalogenated arene, resulting from β-hydride elimination. Reactions of acyclic secondary amines with aryl bromides also occurred (in moderate yields) although they required the use of 5 mol % $Pd(OAc)_2$. Thus, 4-bromobenzonitrile and 4-*tert*-butylbromobenzene reacted with diisobutylamine and diethylamine, respectively, to form the corresponding N-aryl product (Table 2, entries 4 and 11, respectively).

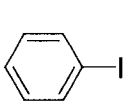
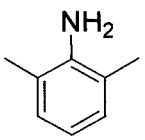
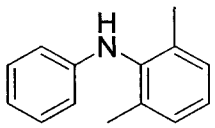
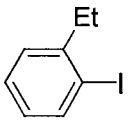
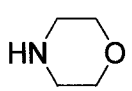
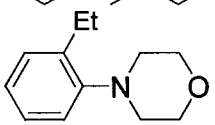
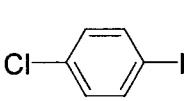
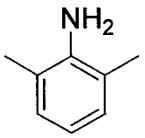
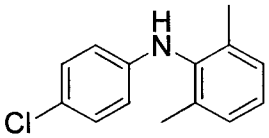
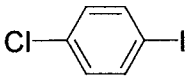
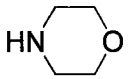
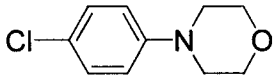
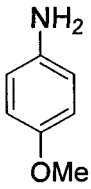
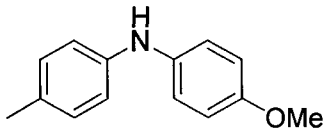
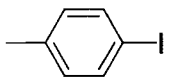
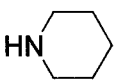
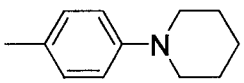
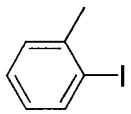
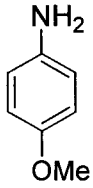
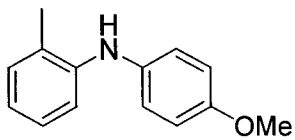
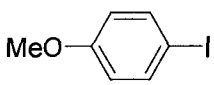
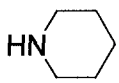
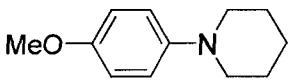
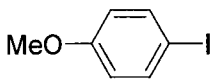
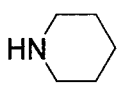
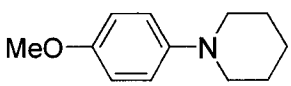
Steric hindrance on either coupling partner was well tolerated, often giving the desired product in almost quantitative yield. For example, mono and di-*ortho*-substituted aryl bromides reacted with 2-aminobiphenyl to give excellent yields of the desired product (Table 2, entries 12 and 13). Particularly noteworthy is the reaction of 2-bromomesitylene with 2,6-

dimethylaniline, which afforded the tetra-*ortho*-substituted arylamine product in 99% isolated yield (Table 2, entry 15). With DPEphos (bis[2-(diphenylphosphino)phenyl] ether), *rac*-BINAP, or DPPF as a ligand,[21] the analogous reaction involving 2-bromo-*m*-xylene and 2,6-diisopropylaniline required much higher catalyst loading (5 mol % Pd) and a reaction temperature of 100 °C (20 °C higher than that reported in the present work).

Our protocol was equally effective for aryl bromides possessing substituents at various positions (Table 2, entries 21-24). The reaction of an heteroaryl bromide with morpholine also proceeded well (Table 2, entry 25).

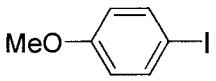
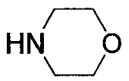
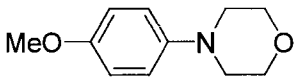
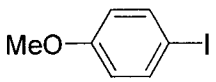
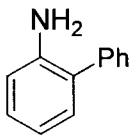
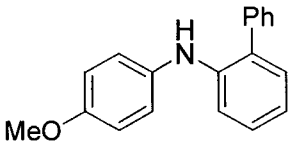
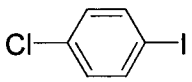
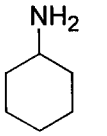
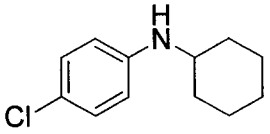
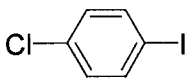
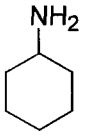
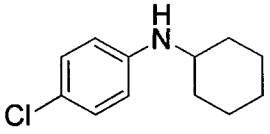
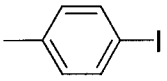
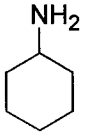
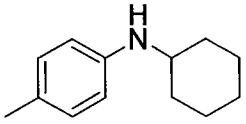
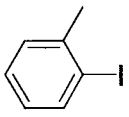
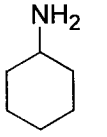
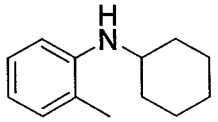
Next, we investigated amination reactions of extensively used and easy obtainable aryl iodides (Table 3). With the $Pd(OAc)_2$/**4a** catalyst system, electronically neutral aryl iodides readily combined with anilines (Table 3, entries 1, 5, and 7) and secondary cyclic amines (Table 3, entries 2 and 6). Slightly lower yields of arylamines were achieved with electron-deficient aryl iodides (Table 3, entry 3) owing to formation of reduced arene side products. Electron-rich aryl iodides were also suitable substrates (Table 3, entries 10 and 11). Although $Pd(OAc)_2$ was used as a palladium source for most reactions, reactions of electron-rich aryl iodides usually proceeded well when $Pd_2(dba)_3$ was employed (Table 3, compare entries 8 and 9). The reaction of aryl iodides with primary aliphatic amines and acyclic secondary amines did not proceed to completion even with higher catalyst loading (5 mol % Pd) and longer reaction times. However, cyclohexylamine did react with aryl iodides although in moderate yields (Table 3, entries 12-15) when a slightly higher catalyst loading (4 mol % Pd) was employed to permit the reaction to go to completion. In general (as can be seen from Tables 2 and 3) aryl iodides provided lower yields of the arylamine product compared with their bromide counterparts, the former being more prone to β-hydride elimination leading to formation of hydrodehalogenation product.

TABLE 3. Palladium/**4a**-catalyzed Amination of Aryl Iodides[a]

entry	aryl iodide	amine	product	yield (%)[b]
1				99
2				96
3				90[c]
4				89
5				90
6				78
7				95
8				56
9				75[d]

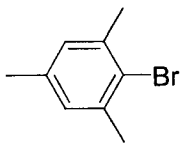
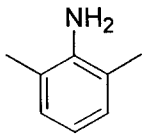
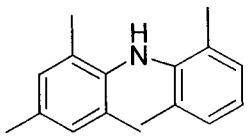
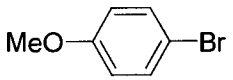
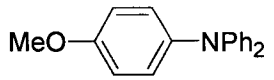
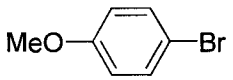
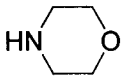
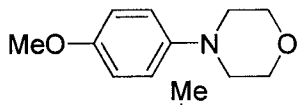
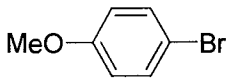
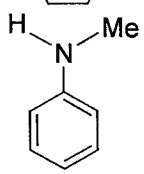
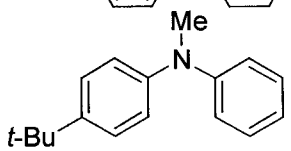
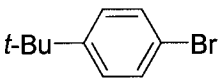
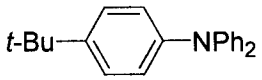
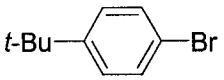
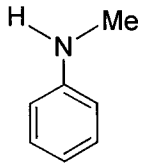
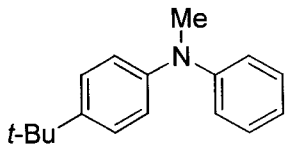
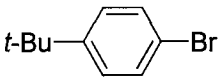
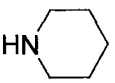
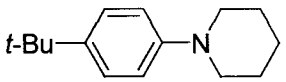
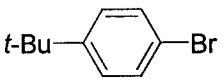
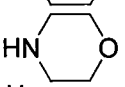
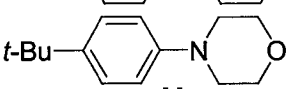
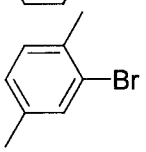
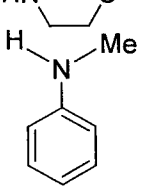
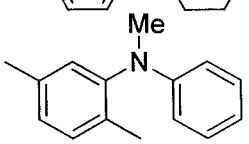
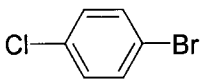
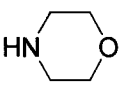
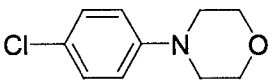
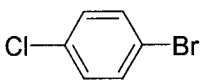
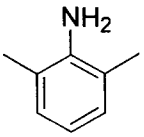
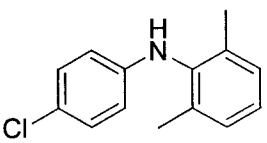
[a] Reaction conditions: 1.0 mmol of aryl iodide, 1.2 mmol of amine, 1.5 mmol of NaO-*t*-Bu, 2.0 mol % $Pd(OAc)_2$, 4.0 mol % of ligand **4a**, 5 mL of toluene, 80 °C, 9-12 h. Reaction times have not been minimized. [b] Isolated yields (average of two runs). [c] 10% of hydrodehalogenated arene was isolated. [d] 2.0 mol % of $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$ was used. [e] 4.0 mol % of $Pd(OAc)_2$ was employed.

TABLE 3. Continued

entry	aryl iodide	amine	product	yield (%)[b]
10				79
11				75[d]
12				43
13				51[e]
14				59[e]
15				62[e]

We also carried out amination reactions at a low catalyst loading (0.5 mol % Pd, Table 4),[22] and most of these reactions were complete in <22 h. The sterically hindered arylamine in entry 1 was formed in excellent yield (94%). Secondary cyclic amines were generally also efficiently arylated, often giving improved results over those obtained using either Pd/BINAP or Buchwald's catalyst sytem. For example, the reaction of 1-bromo-4-*tert*-butylbenzene with piperidine using 0.5 mol % Pd/**4a** afforded the desired product in 92% yield while Buchwald's catalyst system utilizing (*o*-biphenyl)PCy_2 as a ligand with 0.5 mol % Pd gave an 86% yield.[8] Similarly, the aforementioned substrate and morpholine were coupled in 99%

TABLE 4. Amination of Aryl Bromides Using Pd/**4a** at Low Catalyst Loading[a]

entry	aryl bromide	amine	product	yield (%)[b]
1				94
2		Ph_2NH		95
3				93
4				91
5		Ph_2NH		96
6				94
7				92
8				99
9				61
10				50
11				87

[a] 0.5 mol % $Pd(OAc)_2$; 1 mol % ligand **4a**. [b] Isolated yields.

isolated yield using 0.5 mol % Pd/**4a** while the Pd/BINAP catalyst system gave a 93% yield when the reaction was run neat.[10] Additionally, *N*-methylaniline, which is often a problematic substrate for the Pd/BINAP catalyst system, was also cleanly arylated (Table 4).

It appears that the catalytic system comprising $Pd(OAc)_2$ and ligand **4a** is the most effective catalyst reported to date for the reaction of sterically hindered arylbromides and anilines. Moreover, the scope of Pd/**4a** catalyst system exceeds (for the examples discussed above) or generally equals that of Pd/BINAP, Pd/(*o*-biphenyl)PCy_2, or Pd/(*o*-biphenyl)$P(t\text{-Bu})_2$.

Because arylamines are industrially important synthetic targets, a crucial requirement for viability of an industrial process to synthesize them using palladium technology is ligand cost. In this regard it is worth mentioning that **4a** at \$50.50/5 g is cheaper than racemic BINAP, $P(t\text{-Bu})_3$ and (*o*-biphenyl)PCy_2, or (*o*-biphenyl)$P(t\text{-Bu})_2$ by almost a factor of 2, 3, and 5, respectively.[23]

In summary, we have demonstrated that ligand **4a** functions uncommonly efficiently in amination reactions. Various aryl bromides and iodides were readily coupled with a range of amines, including primary and secondary anilines, cyclic secondary amines, primary amines branched at the αposition, and (with limited success) acyclic secondary amines. Good to excellent yields were obtained with the vast majority of substrate combinations. Several salutary features of **4a** are (a) commercial availability, (b) optimum steric effects provided by the *i*-butyl groups, and (c) electron-richness of the phosphorus arising from the donating capability of all three virtually planar nitrogens adjacent to the phosphorus, as well as the possibility for augmented basicity of the phosphorus arising from transannular bonding between the bridgehead nitrogen and the phosphorus atom. Both of these basicity-enhancing stereoelectronic influences are lacking in acyclic triaminophosphines, which we have shown behave poorly under our reaction conditions. Finally, we believe that the comparatively very low price of ligand **4a**, compared with other phosphine ligands usually employed in amination reactions, enhances its appeal. An exploration of aryl chloride aminations using our approach is underway.

Experimental Section

General Experimental Conditions. All reactions were performed under an atmosphere of argon in oven-dried glassware. Toluene was collected from a solvent purification system and stored over 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, unless otherwise noted. Thin-layer chromatography (TLC) was

performed using commercially prepared 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Silica gel 60 (9385, 230-400 mesh) was used for column chromatography. Melting points were determined in unsealed capillary tubes and are uncorrected. The reported yields are isolated yields and are the average of two runs. All commercially available reagents were used as received. Ligands **1a-6a** were prepared according to our previously reported procedures[15] (although ligands **1a**, **3a**, and **4a** are commercially available from Aldrich).

General Procedure for Aminating Aryl Bromides and Iodides. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (2 mol %) and NaO-*t*-Bu (1.5 mmol) inside a nitrogen-filled glovebox. The flask was capped with a rubber septum and removed from the glovebox. Aryl halide (1.0 mmol), amine (1.2 mmol), and toluene (5 mL) were then successively added. The flask was placed in an 80 °C oil bath, and the reaction mixture was stirred until the starting material had been completely consumed as judged by TLC. The mixture was cooled to room temperature and adsorbed onto silica gel. The crude product was purified by column chromatography. The presence of hydrodehalogenated product in some of the preparations was verified by TLC using authentic samples for comparison.

***N*-(*p*-Cyanophenyl)-2-ethylaniline**: white solid, mp 63-64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.43 (d, 2H, J = 7.9 Hz), 7.32 (d, 1H, J = 6.7 Hz), 7.25-7.19 (m, 3H), 6.77 (d, 2H, J = 8.8 Hz), 5.90 (s, 1H), 2.59 (q, 2H, J = 4.7 Hz), 1.20 (t, 3H, J = 6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ149.9, 139.1, 137.5, 133.8, 129.7, 127.1, 126.1, 125.1, 120.3, 114.2, 100.5, 24.5, 14.5. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.08; H, 6.30; N, 12.61. Found: C, 81.00; H, 6.38; N, 12.27.

***N,N*-Diisobutyl-4-cyanoaniline**: white solid, mp 71-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 2H, J = 9.0 Hz), 6.61 (d, 2H, J = 9.1 Hz), 3.21 (d, 4H, J = 7.4 Hz), 2.14-1.98 (m, 2H), 0.92 (d, 12H, J = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ150.9, 133.6, 121.0, 112.0, 96.6, 60.1, 26.5, 20.4. Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.26; H, 9.56; N, 12.17. Found: C, 78.10; H, 10.01; N, 12.25.

***N*-(*4-tert*-Butylphenyl)cyclohexylamine**: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.25-7.19 (m, 2H), 6.58-6.56 (m, 2H), 3.28-3.21 (m, 1H), 2.05 (d, 2H, J = 12.1 Hz), 1.80-1.65 (m, 3H), 1.41-

1.15 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ145.2, 139.7, 126.2, 113.0, 52.1, 33.8, 31.8, 26.2, 25.2, 16.5. Anal. Calcd for $C_{16}H_{25}N$: C, 83.11; H, 10.82; N, 6.06. Found: C, 83.21; H, 10.56; N, 5.92.

2,5-Dimethyl-2'-phenyldiphenylamine: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.51-7.35 (m, 5H), 6.77 (d, 1H, J = 2.57), 5.42 (s, 1H), 2.29 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ141.4, 141.2, 139.3, 136.7, 130.84, 129.5, 129.1, 128.7, 127.6, 126.1, 123.1, 120.3, 120.1, 116.8, 21.4, 17.6. Anal. Calcd for $C_{20}H_{19}N$: C, 87.91; H, 6.96; N, 5.13. Found: C, 87.88; H, 6.73; N, 5.38.

2,6-Dimethyl-2'-phenyldiphenylamine: white solid, mp 101-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.63 (d, 2H, J = 7.3 Hz), 7.54 (t, 2H, J = 6.7 Hz), 7.43 (t, 1H, J = 7.0 Hz), 7.23 (d, 1H, J = 6.7 Hz), 7.16-7.12 (m, 4H), 6.85 (t, 1H, J = 7.0 Hz), 6.27 (d, 1H, J = 8.2 Hz), 5.32 (s, 1H), 2.23 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ143.3, 139.7, 138.4, 136.3, 130.4, 129.6, 129.1, 128.7, 128.6, 127.7, 127.5, 126.0, 117.9, 111.7, 18.5. Anal. Calcd for $C_{20}H_{19}N$: C, 87.91; H, 6.96; N, 5.13. Found: C, 87.79; H, 6.66; N, 5.45.

Acknowledgment

The authors are grateful to the National Science Foundation for research support. We also thank Dr. G. K. Jnaneshwara for providing a sample of **4a**.

Supporting Information Available

Spectra of previously unknown compounds and references for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org. The ^{1}H and ^{13}C NMR spectra for the compounds prepared and references for known compounds are available in the appendix A in this thesis. To avoid duplication of spectra some of the ^{1}H and ^{13}C NMR spectra also appear in appendices B and D.

References

1. (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic synthesis*; John Wiley & Sons: Chichester, England, 1995. For a general review of palladium-catalyzed aryl aminations, see: (b) Wolfe, J. P. Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem.*

Res. **1998**, *31*, 805. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 805. (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

2. (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. Also see ref 9.

3. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (c) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560. (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (e) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

4. (a) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (b) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163. (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (d) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *Organometallics* **1999**, *18*, 1840. (e) Artamkina, G. A.; Ivushkin, V. A.; Beletskaya, P. *Russ. J. Org. Chem.* **1970**, *35*, 1797. (f) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169. (g) Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600.

5. Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

6. (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K, H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

7. (a) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.

8. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. See also ref 4d and references therein.

9. Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

10. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

11. (a) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065. (b) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721.

12. (a) Molloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696. (b) Xi, S. K.; Schmidt, H.; Lensink, C.; Kim, S.; Wintergrass, D.; Daniels, L. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1990**, *29*, 2214. (c) Socol, S. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 88. (d) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1980**, *34*, 365. (e) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1979**, *33*, 187.

13. For a discussion of the electronic structure of tris(dialkylamino)phosphines, see: Cowley, A. H.; Lattman, M.; Stricklen, P. M.; Verkade, J. G. *Inorg. Chem.* **1982**, *21*, 543.

14. An X-ray structural study of **3a** showed that the bonding environment around the PN_3 nitrogen is rather planar, the sum of angles being 354.9, 356.6, and 357.5° (Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69).

15. See: (a) Kisanga, P.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467 and references therein. (b) Liu, X.; Verkade, J. G. Manuscript in preparation.

16. Kisanga, P. B.; Verkade, J, G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431.

17. Verkade, J. G. In New Aspects of Phosphorus Chemistry II. *Top. Curr. Chem.* Majoral, J. P., Ed. **2002**, *233*, 1.

18. Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626.

19. Weaker bases such as Cs_2CO_3, CsF, K_3PO_4, K_2CO_3, and NaOH failed to promote coupling.

20. Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.

21. Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.

22. The reaction of 1-chloro-4-iodobenzene with morpholine using the Pd/**4a** catalyst system (0.5 mol % Pd) gave an 85% yield of the desired product. The general protocol for the amination of aryl iodides using Pd/**4a** at such a low catalyst loading has not yet been fully scoped.

23. Ligand **4a**: $50.50 (5 g, Aldrich). Racemic BINAP: $90.60 (5 g, Aldrich). P(*t*-Bu)$_3$: $148.00 (5 g, Aldrich). 2-(Di-*tert*-butylphosphino)biphenyl or 2-(dicyclohexylphosphino)biphenyl: $99.00 (2 g, Strem).

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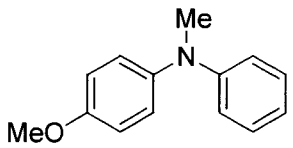
Reference 1c should read Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

In entry 4 in Table 4, the correct structure of the product is



Page 55, paragraph 2 in this thesis. The price of ligand **4a** [P(*i*-BuNCH$_2$CH$_2$)$_3$N] is noted as \$50.50/5 g, a figure taken from the Aldrich catalogue circulated at that time (2002). However, that price was later discovered to be a misprint. Thus the entire paragraph, including ref 23, should be disregarded. For the current price of ligand **4a**, readers should consult a recent catalog.

CHAPTER 3. P[N(*i*-Bu)CH_2CH_2)$_3$N: A VERSATILE LIGAND FOR THE Pd-CATALYZED AMINATION OF ARYL CHLORIDES

A paper published in the *Organic Letters*

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Abstract

Palladium-catalyzed amination reactions of aryl chlorides with amines proceeded in the presence of the bicyclic triaminophosphine P[N(*i*-Bu)CH_2CH_2]$_3$N to afford the corresponding arylamines in good to excellent yields. Electron-poor, electron-neutral, and electron-rich aryl chlorides all participated with equal ease.

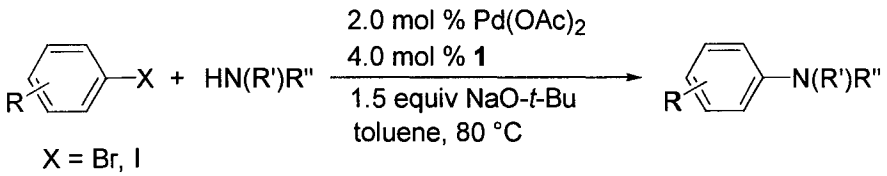
Published Manuscript

The Pd-catalyzed amination of aryl halides (or halide equivalents) has emerged as a powerful tool for the synthesis of substituted anilines in recent years.[1] Though less reactive, aryl chloride substrates are highly desirable compared with their bromide and iodide counterparts in terms of cost and availability. The relatively low reactivity of aryl chlorides has been attributed to their aversion to oxidatively adding to Pd(0) species because of the large dissociation energy (402 KJ/mol at 298 K)[2] of the C-Cl bond. Recently, much progress has been made in the development of catalysts capable of utilizing aryl chlorides as substrates in aryl amination processes.[3] Most of these catalyst systems employ bulky electron-rich alkylphosphines or N-heterocyclic carbenes as ligands, presumably facilitating the oxidative addition of otherwise unreactive aryl chlorides.

Although triaminophosphines (e.g., P[NMe_2]$_3$) are well known, they have not been studied (prior to our previous studies[4,5]) in these cross-coupling reactions. This may be partly due to the diminished electron-donating capability of acyclic triaminophosphines (associated with their pseudo C_2 symmetry) compared with trialkylphosphines, as has been rationalized by Woollins recently.[6] We reasoned, however, that triaminophosphines could function as ligands if their framework were made fairly rigid but strain-free in a bicyclic (approximately

C_{3v}) structure, thus enhancing the lone pair electron density at phosphorus.[7] In accordance with this rationale, we were able to demonstrate that commercially available ligand **1**[8] in combination with $Pd(OAc)_2$ is a highly efficient catalytic system for the amination of aryl bromides and iodides (Scheme 1).[4] Additionally, we have demonstrated the unusually high activity of ligand **1** in Suzuki cross-couplings of aryl bromides and chlorides with arylboronic acids.[5]

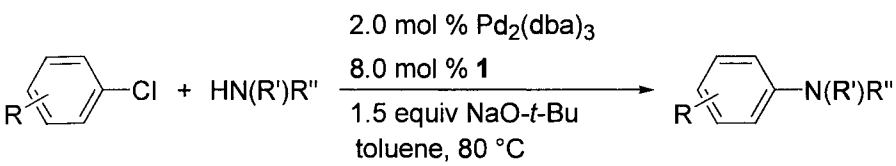
Scheme 1. General Conditions Used for the Amination of Aryl Bromides and Iodides



In this contribution, we show that ligand **1** is also effective in the amination of aryl chlorides, thus identifying it as one of the very few ligands that efficiently facilitate amination reactions of aryl chlorides as well as those of aryl iodides and bromides.

The general conditions employed for the amination of aryl chlorides are summarized in Scheme 2. For anilines and cyclic secondary amines, $Pd_2(dba)_3$ as a palladium precursor instead of $Pd(OAc)_2$ in combination with **1** was found to be useful. Also, a slightly higher catalyst loading (4 mol % Pd) was required to obtain good to excellent yields of the arylamine products. However, the $Pd(OAc)_2$/**1** catalyst system proved to be advantageous over $Pd_2(dba)_3$/**1**, for primary amines, and an acyclic secondary amine.

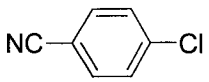
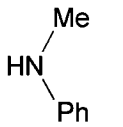
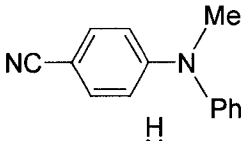
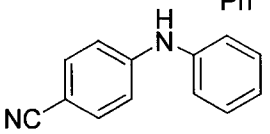
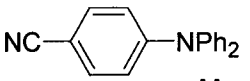
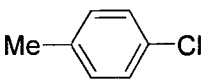
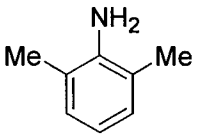
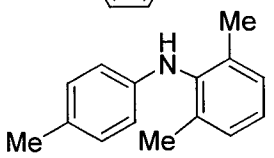
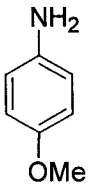
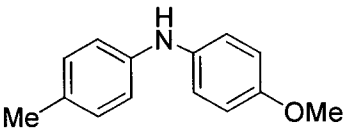
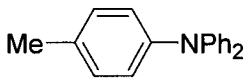
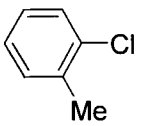
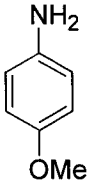
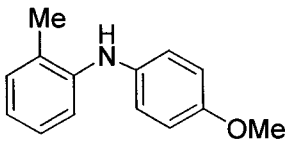
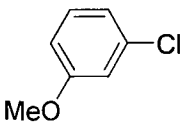
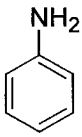
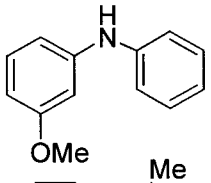
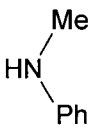
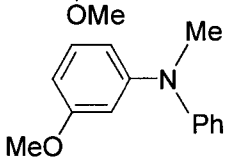
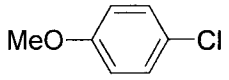
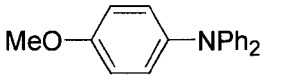
Scheme 2. General Conditions Used in the Present Study for the Amination of Aryl Chlorides



As shown in Tables 1 and 2, electronically diverse aryl chlorides can be coupled to a variety of amines in the presence of **1** and $Pd_2(dba)_3$. Both primary and secondary anilines were efficiently coupled with electron-poor, electron-neutral, and electron-rich aryl chlorides (Table 1). *ortho*-Substitution of the aryl chloride had a rather minor effect in cross-coupling

efficiency. For example, while the reaction of 4-chlorotoluene with *p*-anisidine proceeded in 99% yield (entry 5, Table 1), the analogous reaction with 2-

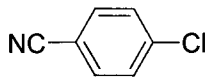
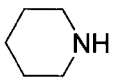
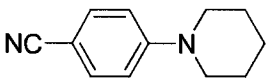
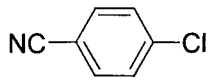
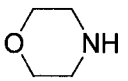
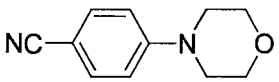
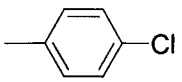
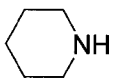
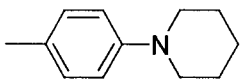
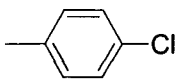
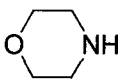
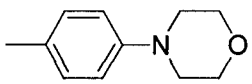
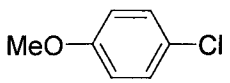
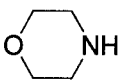
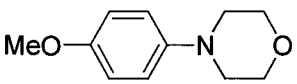
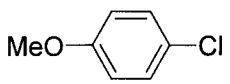
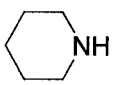
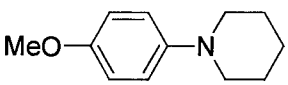
Table 1. Amination of Aryl Chlorides with Anilines[a]

entry	chloride	amine	product	yield (%)[b]
1				88
2		$PhNH_2$		90
3		Ph_2NH		94[c]
4				87
5				99
6		Ph_2NH		88[c]
7				87
8				98
9				95
10		Ph_2NH		91[c]

[a] Conditions: 1.0 equiv of aryl chloride, 1.2 equiv of amine, 1.5 equiv of NaO-*t*-Bu, 2.0 mol % $Pd_2(dba)_3$, 8.0 mol % ligand **1**, 5 mL of toluene, 80 °C. [b] Isolated yields (average of at least two runs). [c] Performed with 4.0 mol % $Pd_2(dba)_3$.

chlorotoluene gave an 87% yield (entry 7, Table 1) of the corresponding product. The reactions of sterically hindered and less nucleophilic diphenylamine, required a higher catalyst loading (8 mol % Pd). Secondary cyclic amines were also readily coupled, and the amination products were obtained in high yields (entries 1-6, Table 2). In most cases, hydrodehalogenated arenes, resulting from competitive β-hydride elimination,[9] were the side products (<3%).

Table 2. Amination of Aryl Chlorides with Cyclic Secondary Amines[a]

entry	chloride	amine	product	yield (%)[b]
1				90
2				94
3				86
4				95
5				89
6				87

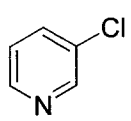
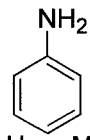
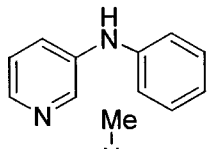
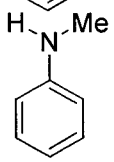
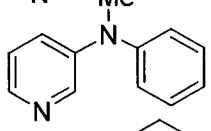
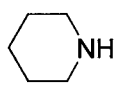
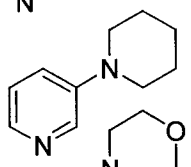
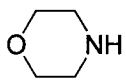
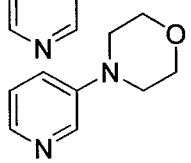
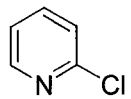
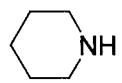
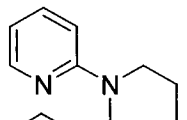
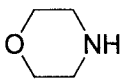
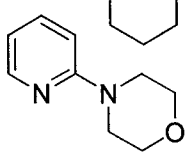
[a] Conditions are identical to those used in Table 1. [b] Isolated yields (average of two runs).

Notably, the reactions of chloropyridines also proceeded without difficulty with the $Pd_2(dba)_3$/**1** catalyst system, giving rise to the desired products in good yields (Table 3). Generally, monodentate ligands [e.g., $(o\text{-tol})_3P$] are considered to be unsuitable for this class of substrates because they can compete with the pyridine substrates for palladium to form catalytically inactive *trans*-bis(pyridyl)palladium species.[10] However, the electron-richness of ligand **1** inhibits such side reactions.

With 4 mol % $Pd_2(dba)_3$, coupling of more recalcitrant amines (e.g., primary and acyclic secondary amines) was facilitated and the corresponding substituted anilines were obtained

in moderate to good yields. For the aforementioned amines, 5 mol % $Pd(OAc)_2$ was found to give results comparable to those with $Pd_2(dba)_3$ (8 mol % Pd), and therefore the former palladium compound was employed (Table 4) for the remainder of the study. The reaction of cyclohexylamine, a cyclic primary amine, was especially efficient under

Table 3. Amination of Chloropyridines[a]

entry	chloride	amine	product	yield (%)[b]
1				53
2				89
3				88
4				90
5				87
6				83

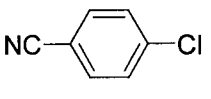
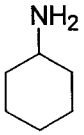
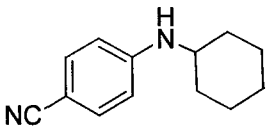
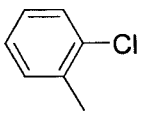
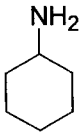
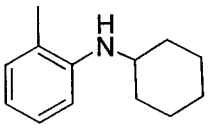
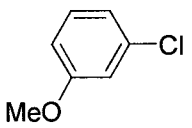
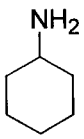
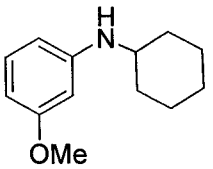
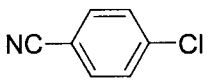
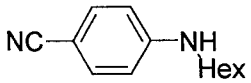
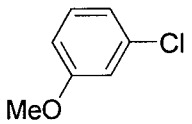
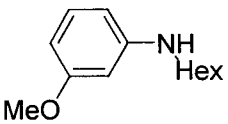
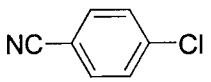
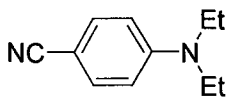
[a] Conditions are identical to those used in Table 1. [b] Isolated yields (average of two runs).

these conditions, allowing a diverse group of aryl chlorides to be successfully employed (entries 1-3, Table 4). While reasonable yields were obtained for the coupling of 4-chlorobenzonitrile and 3-chloroanisole with a long-chain primary aliphatic amine (*n*-hexylamine, entries 4 and 5, Table 4), the reaction of the acyclic secondary amine, diethylamine, proceeded only with an electron-poor aryl chloride (entry 6, Table 4).

For the reactions discussed in Table 4, we also observed the formation of hydrodehalogenated side products.

Although, in all cases, some of the reaction components were assembled inside a glovebox (i.e., NaO-*t*-Bu, a suitable Pd precursor and solid aryl chloride), we have found that its use is not an absolute requirement. Yields were very similar when all the reaction components were assembled outside a glovebox using standard Schlenk techniques. However, we recommend storing moisture-sensitive NaO-*t*-Bu in a desiccator if a glovebox is not available. Although ligand **1** is unusually stable to oxidation, it was stored in a closed container under an inert atmosphere.

Table 4. Amination of Aryl Chlorides with Primary Amines and an Acyclic Secondary Amine[a]

entry	chloride	amine	product	yield (%)[b]
1				90
2				91
3				63
4		*n*-HexNH$_2$		49
5		*n*-HexNH$_2$		43
6		Et_2NH		56

[a] Conditions: 1.0 equiv of aryl chloride, 1.4 equiv of amine, 1.5 equiv of NaO-*t*-Bu, 5.0 mol % $Pd(OAc)_2$, 10.0 mol % ligand **1**, 5 mL of toluene, 80 °C. [b] Isolated yields (average of at least two runs).

Triaminophosphine **1** is the first member of a new class of phosphines shown to be an effective ligand in palladium-assisted C-N bond-forming reactions. Although the use of **1**

requires higher loading than trialkylphosphines and also the use of a strong base (NaO-*t*-Bu), its low cost compared with other well-known ligands and its considerable ability to effect aminations of a broad spectrum of substrates favors it as a ligand of choice. Further, the effectiveness of **1** in promoting palladium-catalyzed coupling of amines with aryl chlorides as well as bromides and iodides broadens the utility of this compound beyond its well established use as a strong nonionic base in stoichiometric and base-catalyzed reactions.[11] Although we presently do not have a clear understanding of the origin of the exceptional reactivity of our Pd/**1** catalyst system, our working hypothesis is that the effectiveness of ligand **1** arises from two factors: (a) phosphorus electron richness stemming from pseudo C_{3v} symmetry and possible N→P transannulation, thus enhancing the oxidative addition step, and (b) steric bulk provided by the *iso*-butyl groups, thus promoting the reductive elimination step. Studies underway are aimed at further optimization of the stereoelectronic properties of triaminophosphine ligands in metal-assisted reactions.

Acknowledgment

The authors are grateful to the National Science Foundation for grant support.

Supporting Information Available

Experimental procedures and references for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org. This is also available in the appendix B in this thesis.

References

1. For reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

2. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

3. For representative examples of aryl chloride aminations, see: (a) Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2002**, *3494*, 1. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.;

Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (e) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (f) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *Organometallics* **1999**, *18*, 1840. (g) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K, H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (h) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (i) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (j) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807. (k) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *39*, 22367.

4. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

5. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

6. (a) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065. (b) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721.

7. For discussions of the electronic structure of tris(alkylamino)phosphines, see: (a) Cowley, A. H.; Lattman, M.; Stricklen, P. M.; Verkade, J. G. *Inorg. Chem.* **1982**, *21*, 543. (b) Molloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696. (c) Xi, S. K.; Schmidt, H.; Lensink, C.; Kim, S.; Wintergrass, D.; Daniels, L. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1990**, *29*, 2214. (d) Socol, S. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 88. (e) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A.* **1980**, *34*, 365. (f) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A.* **1979**, *33*, 187.

8. 2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undec-ane, Aldrich cat. no. 56,588-1.

9. Based on TLC. For a proposed reaction mechanism, see (a) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12950. (b) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (c) Also see refs 1a-d.

10. Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

11. Verkade, J. G. *Top. Curr. Chem.* **2002**, *233*, 1.

CHAPTER 4. SCOPE AND LIMITATIONS OF $Pd_2(dba)_3$/P(*i*-$BuNCH_2CH_2)_3N$-CATALYZED BUCHWALD-HARTWIG AMINATION REACTIONS OF ARYL CHLORIDES

A paper published in *The Journal of Organic Chemistry*

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Abstract

Proazaphosphatrane ligands in combination with $Pd_2(dba)_3$ generate highly active catalysts for Buchwald-Hartwig amination of aryl chlorides. In particular, commercially available P(*i*-$BuNCH_2CH_2)_3N$ is a highly general and efficient ligand, allowing the coupling of an electronically diverse set of aryl chlorides, including chloropyridines, with a wide variety of amines using 1 mol % of Pd at 100 °C. Either a 1:1 or 2:1 ratio of ligand to Pd was found to be effective. This catalyst system performs exceptionally well for sterically hindered substrates, even with only 0.25 mol % of Pd. It is shown that NaOH can also be used as the base (instead of NaO-*t*-Bu) allowing functionalized substrates to participate in these reactions.

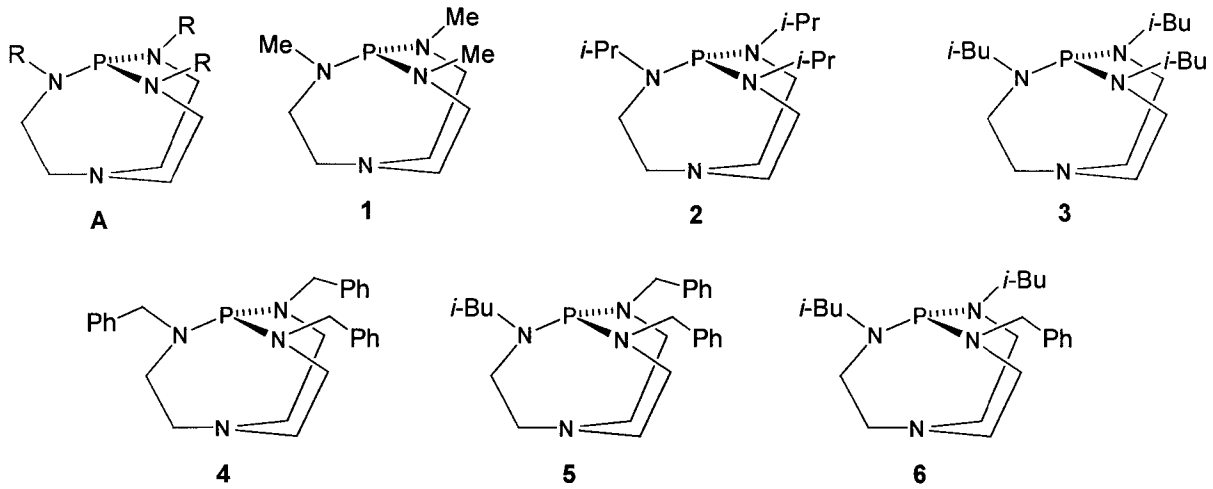
Introduction

Over the past decade, one of the foremost accomplishments in the field of catalysis has been the discovery of the palladium-catalyzed carbon-nitrogen bond forming process commonly known as the Buchwald-Hartwig amination reaction.[1-3] This process generally involves the coupling of aryl halides with amines mediated by a suitable palladium complex as a catalyst to afford aryl amines which often are important intermediates in organic synthesis and which occur within the molecular framework of several natural products,[4] dendrimers,[5] ligands,[6-8] and advanced materials.[9] A major impetus to this field was provided by the ability to activate notoriously unreactive but relatively cheap aryl chlorides. Not surprisingly, a plethora of palladium catalyst systems, featuring a palladium-bound ligand, are now accessible for accomplishing the aforementioned transformation involving aryl chlorides. Typically, electronically rich sterically hindered ligands belonging to the trialkylphosphine,[10-13]

ferrocenyl dialkylphosphine,[14] aryldialkylphosphine,[15-17] heterocyclic carbene,[18-20] palladacycle,[21-23] or phosphinous acid[24] classes have been investigated in these reactions.

Over the past few years, part of our research effort has focused on the design, synthesis, and application of proazaphosphatranes of type **A** to organic methodology.[25] Recently, we have focused on the use of **A** as an ancillary ligand in palladium-mediated coupling reactions. In this regard, we have successfully demonstrated that in contrast to **1** and **2**, the commercially available proazaphosphatrane **3** is highly active in Suzuki,[26] Buchwald-Hartwig amination,[27-29] *alpha*-arylation,[30,31] and Stille[32] reactions. We have also developed a novel triaminophosphine ligand, $P(i\text{-}BuNCH_2)_3CMe$, which is structurally similar to **3**, for Buchwald-Hartwig amination reactions.[33] A particular notable feature of this ligand is that, in contrast to **3**, it allows weak base such as Cs_2CO_3 to function in amination reactions.

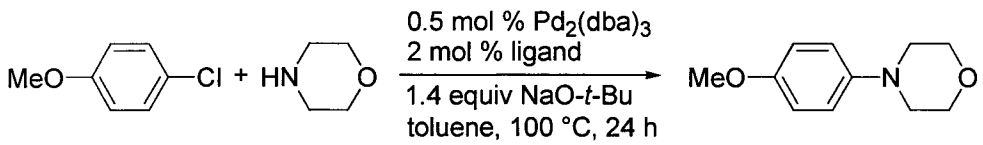
In a recent communication, we reported that by using 2 mol % of $Pd_2(dba)_3$ (4 mol % Pd) and 8 mol % **3** (2L/Pd), a wide array of aryl chlorides can be coupled with a variety of amines at 80 °C.[28] We believed that the level of catalyst loading (4 mol %) used in laboratory-scale experiments in our protocol might render larger scale experiments overly costly in view of the cost of the precious metal catalyst. We speculated that these reactions could be conducted with decreased catalyst loading albeit at higher temperature. Further, since the appearance of our preliminary report on the amination of aryl chlorides employing **3** as an ancillary ligand,[28] we have synthesized three new proazaphosphatranes with benzyl as well as a combination of *iso*-butyl and benzyl substituents on the PN_3 nitrogens, namely **4**, **5**, and **6**. Our previous studies on Pd/proazaphosphatrane-catalyzed reactions have revealed that the *iso*-butyl group on the PN_3 nitrogen is particularly important for catalyst activity presumably providing a propitious balance of steric and electronic parameters.[26-32] However, recent results from our laboratories on Stille reactions catalyzed by proazaphosphatranes[32] have shown that ligands **4** and **5** also generate quite active palladium catalysts for the coupling of aryl chlorides with organotin compounds. Thus we also wished to explore the usefulness of ligands **4**, **5**, and **6** in amination reactions of aryl chlorides. Here we give a full account of our studies on $Pd_2(dba)_3$/**3**-catalyzed Buchwald-Hartwig amination reactions of aryl chlorides.[34]



Results and Discussion

Ligand screening. To test the feasibility of the above notions, we initially conducted the reaction of 4-chloroanisole with morpholine at 100 °C, as shown in entry 3 of Table 1. To our delight, using a 0.5 mol % of $Pd_2(dba)_3$ in combination with 2 mol % of ligand **3** (corresponding to a four-fold decrease in the catalyst loading from our original protocol)

Table 1. Effect of Proazaphosphatrane Ligands on Pd-Catalyzed Amination of 4-Chloroanisole with Morpholine



entry	ligand	yield (%)[a]
1	**1**	10
2	**2**	31
3	**3**	88
4	**4**	<5
5	**5**	47
6	**6**	86

[a] Isolated yields (average of two runs).

this reaction indeed proceeded smoothly to afford the desired product in 88% isolated yield after 24 h. When $Pd(OAc)_2$ was used as the palladium precursor, this reaction was substantially slower and was not complete in 24 h perhaps because of the induction period required for the reduction of Pd(II) to the catalytically active Pd(0) species.

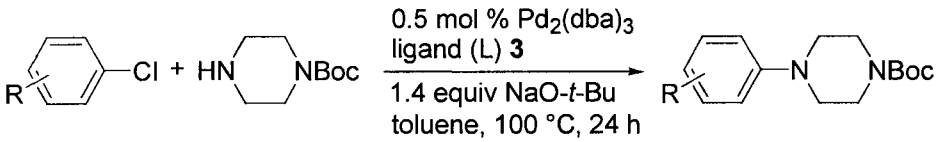
Encouraged by these results, we evaluated the efficacy of various proazaphosphatranes in the same screening reaction. Five additional ligands in addition to **3** were screened in this study. The results, provided in Table 1 demonstrate that variations of the PN_3 nitrogen substituents can have significant impact on catalyst activity. Thus the ligand containing three *iso*-butyl groups (**3**) is much more effective than those with three methyl (**1**), *iso*-propyl (**2**) or benzyl groups (**4**). Interestingly, ligand **4** performed very poorly in the screening reaction whereas it was quite successfully employed in Stille reactions of aryl chlorides.[32] On the other hand, ligand **5** containing one *iso*-butyl and two benzyl groups led to the formation of an appreciable quantity of the amination product. Surprisingly, ligand **6**, containing two *iso*-butyl groups and one benzyl group, afforded the desired amination product in 86% isolated yield which is comparable to that obtained with ligand **3** (entries 4 and 6, Table 1). These results indicate that catalyst activity is more strongly dependent on the number of *iso*-butyl groups on the PN_3 nitrogens than might have been expected. We now attempt to rationalize the differences in the activities of ligands **1-6**.

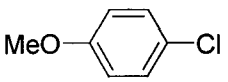
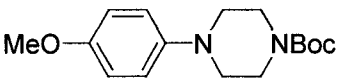
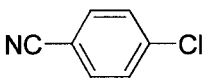
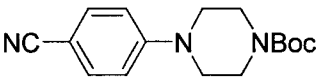
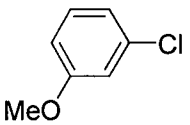
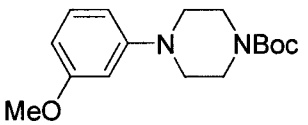
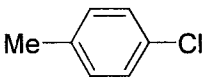
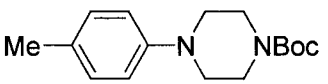
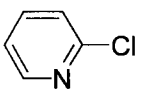
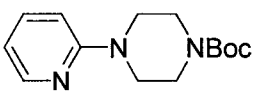
A coordinatively unsaturated monophosphine Pd(0) complex is generally accepted as the catalytically active species in palladium-catalyzed cross-coupling reactions and a three coordinate monophosphine-ligated arylpalladium halide (an example of which was isolated) has been proposed to form after the oxidative addition step.[35] Formation of such complexes is usually favored by sterically hindered ligands. We believe that although ligands **1** and **2** are electronically rich, they lack sufficient steric bulk to form/stabilize monophosphine-ligated PdL species. In contrast, we believe that ligands **3** and **6** (and to some extent ligand **5**) possess a striking balance of electron-richness and steric bulk needed for the generation of active catalyst. In this regard, however, our attempts to isolate a Pd-**3** complex have so far failed. Although, we presently do not have a satisfactory explanation for the ineffectiveness of ligand **4**, one possibility is that the electron rich palladium center of the Pd(0)-**4** complex undergoes intramolecular aromatic C-H bond activation (cyclometalation). Of the three

generally accepted mechanistic pathways for such activation (namely, electrophilic metallation, oxidative addition, and the formation of an agostic intermediate[36]) the first option seems unlikely because such a process would involve electrophilic attack of Pd(0) on an ipso carbon of a benzene ring. At this point we are unable to choose between the remaining two possibilities, both of which could be expected to lead to a catalytically inactive species.

Scope of the $Pd_2(dba)_3$/3-Catalyzed Amination Reactions of Aryl Chlorides. Having successfully demonstrated the viability of the $Pd_2(dba)_3$/**3**-catalyzed amination reactions of 4-chloroanisole with morpholine under low palladium loadings, experiments were conducted to determine the scope and limitations of the aforementioned catalyst system. The results are collected in Tables 1-9. The *N*-aryl piperazine moiety is embedded in several pharmacologically interesting targets such as ligands of serotonin (5-HT)-receptors,[37] antifungals,[38] antivirals,[39] antibacterials,[40] and cholesterol ester transfer protein inhibitors.[41] Table 2 summarizes our results on the coupling of various aryl and heteroaryl chlorides with *N*-Boc-protected piperazines. It was shown previously that the ratio of ligand to palladium is an important reaction parameter in palladium-assisted cross-coupling reactions. For example, while the 1:1 ratio of P(*t*-Bu)$_3$ to Pd furnishes a very active catalyst in Suzuki cross-coupling reactions, the use of a 2:1 ratio renders the catalyst inactive.[40] Under the conditions of reduced catalyst loading we report here, either a 1:1 or 2:1 ratio of **3** to Pd generates a very active catalyst that allows coupling of electron-rich, electron-neutral, and electron-poor aryl chlorides. For example, the reaction of 4-chloroanisole with *N*-Boc-protected piperazine gave the expected product in 99% yield (entry 1) with a 2:1 ratio of **3** to Pd, and the use of a 1:1 ratio was equally effective, furnishing the product in 97% yield (entry 2). Notably, the reaction of 2-chloropyridine also proceeded cleanly (entry 7).

Table 2. $Pd_2(dba)_3$/**3**-Catalyzed Amination of Aryl Chlorides with *N*-Boc-piperazine

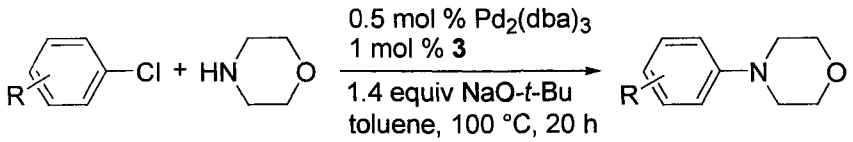


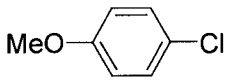
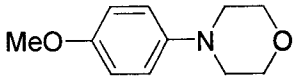
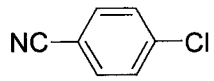
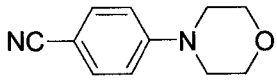
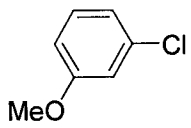
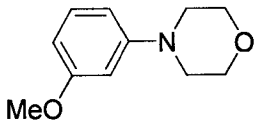
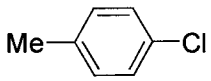
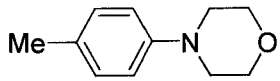
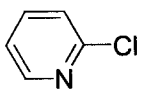
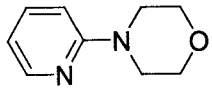
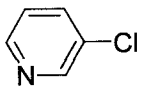
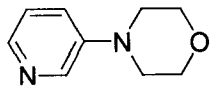
entry	chloride	L/Pd	product	yield (%)[a]
1		2		99
2		1		97
3		2		90
4		2		96
5		2		95
6		1		94
7		1		92

[a] Isolated yields (average of two runs).

We have also established that under the reduced catalyst loading conditions described here, a broad spectrum of aryl chlorides can be coupled with morpholine (Table 3). Using a 1:1 ratio of **3** to Pd, yields of the coupled products were 90% or better except in the case of 4-chlorotoluene (entry 4). Interestingly, the coupling of activated 4-chlorobenzonitrile proceeded in slightly lower yield than that of deactivated 4-chloroanisole owing to the observation of more hydrodehalogenation occurring in the former case. It is also possible that coordination of the nitrile group with the alkali metal of the base might also be responsible for the lower yield, as has been observed by Hartwig.[14]

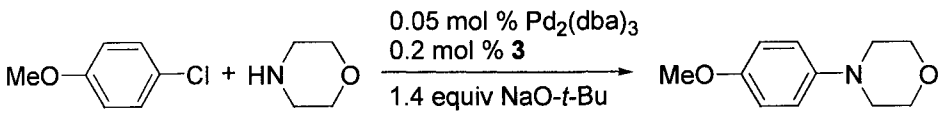
Table 3. $Pd_2(dba)_3$/**3**-Catalyzed Amination of Aryl Chlorides with Morpholine



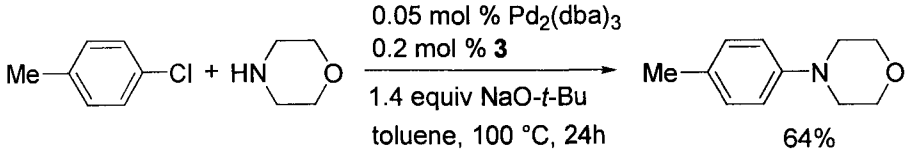
entry	chloride	product	yield (%)[a]
1			92
2			90
3			95
4			89
5			98
6			88[b]

[a] Isolated yields (average of two runs). [b] 1.5 mol % of $Pd_2(dba)_3$ was employed.

Reactions of the ortho-substituted aryl chlorides 2-chlorotoluene and 2-chloroanisole with morpholine occurred in low yield (<40%). Although deactivated 3-chloropyridine was a suitable substrate, it was necessary in this case to use 1.5 mol % of $Pd_2(dba)_3$ (3 mol % Pd) in combination with 3 mol % of **3**.



(1)

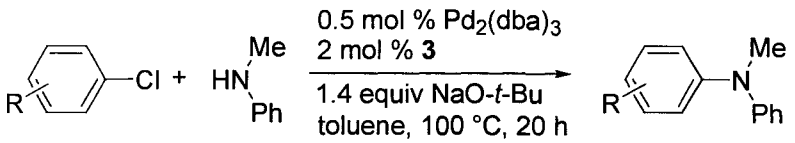


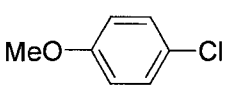
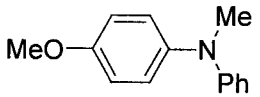
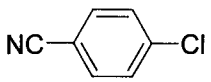
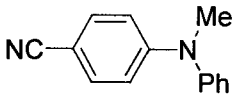
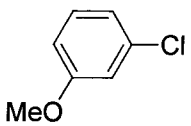
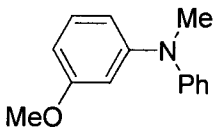
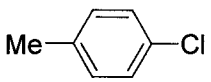
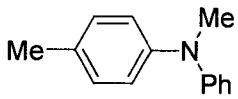
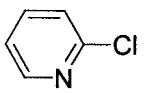
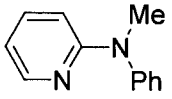
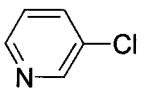
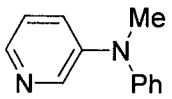
(2)

We observed that for certain substrate combinations, catalyst loading can be lowered to 0.1 mol % of Pd to give the desired products in reasonable yields. For example, using 0.05 mol % of $Pd_2(dba)_3$ and 0.2 mol % of **3**, the coupling of deactivated 4-chloroanisole with morpholine proceeded in 20 % isolated yield after 24 h (eq 1) whereas the reaction of electron-neutral 4-chlorotoluene with morpholine afforded the desired product in 64% isolated yield (eq 2).

Results from the coupling of various aryl chlorides with the secondary aniline *N*-methylaniline are summarized in Table 4. Chloropyridines as well as electron-poor, electron-neutral and electron-rich aryl chlorides all reacted to afford good to excellent product yields. The scope of the reaction of aryl chlorides with diphenylamine is illustrated in Table 5. In many of the reactions examined, we employed both a 1:1 and a 2:1 ratio of **3** to Pd. Although no general correlation of the reactivity of aryl chlorides with these ratios emerged, it is interesting to note that some aryl chlorides coupled in higher yields when a 1:1 ratio of **3** to Pd was employed while others reacted more successfully with a 2:1 ratio. For example, the reaction of electron-rich 4-chloroanisole with diphenylamine afforded the corresponding product in 89% yield (entry 2, Table 5) with a 1:1 ratio of **3** to Pd as compared to a 71% yield (entry 1, Table 5) when a 2:1 ratio of **3** to Pd was used. The coupling of electron-neutral 4-chlorotoluene occurred in higher yield with a 2:1 ratio of **3** to Pd (compare entries 6 and 7, Table 5). *o*-Chlorotoluene also reacted with diphenylamine in excellent yields (entries 11 and 12, Table 5).

Table 4. $Pd_2(dba)_3$/**3**-Catalyzed Amination of Aryl Chlorides with *N*-Methylaniline

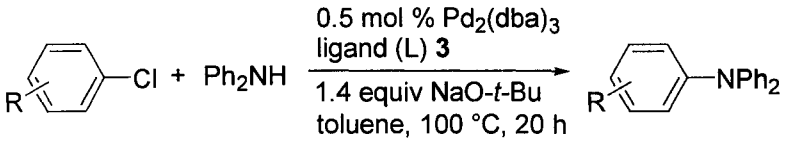


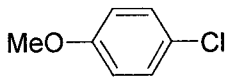
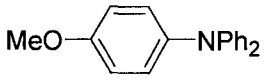
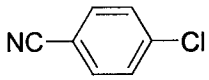
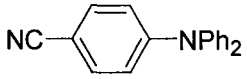
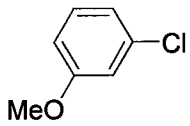
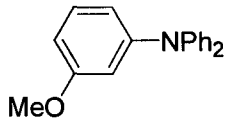
entry	chloride	product	yield (%)[a]
1			95
2			89
3			86[b]
4			88[b]
5			98
6			80

[a] Isolated yields (average of two runs). [b] A 1:1 ratio of **3** to Pd was used.

Results of reactions of aryl chlorides with simple anilines to provide diarylamines are given in Table 6. Substituted anilines as well as aniline itself could be arylated with electronically diverse aryl chlorides. These reactions proceeded best with 1 mol % of $Pd_2(dba)_3$ while the reaction was much slower when 0.5 mol % of $Pd_2(dba)_3$ was employed. As revealed in this table, the presence of an ortho-substituent on the aryl chloride had no deleterious effect and in fact, coupling occurred in nearly quantitative yield (entry 12, Table 6). We also examined amination reactions of aryl chlorides with sterically hindered 2,6-dimethylaniline (Table 7). Only 1 mol % of Pd was sufficient for these couplings to occur in high yields.

Table 5. $Pd_2(dba)_3$/**3**-Catalyzed Amination of Aryl Chlorides with Diphenylamine



entry	chloride	L/Pd	product	yield (%)[a]
1		2		71
2		1		89
3		2		92
4		2		92
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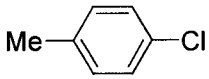
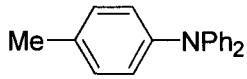
6		2		98
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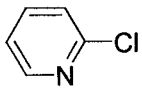
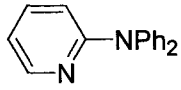
8		2		98
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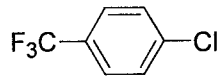
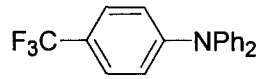
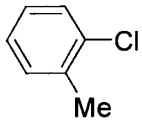
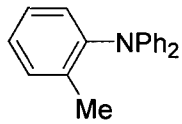
10		1		99
11		2		99
12		1		94

[a] Isolated yields (average of two runs).

Interestingly, the reaction of 2-chloro-*m*-xylene with 2,6-dimethylaniline provided tetra-ortho-substituted diarylamine in 89% isolated yield at 100 °C in the presence of only 0.5 mol % Pd (entry 5, Table 7). Remarkably, when the catalyst loading was lowered to 0.25 mol % of Pd, the desired coupling product was still obtained in high (85%) isolated yield (entry 6, Table 7). Although the aforementioned reaction is quite challenging, the result obtained is not totally surprising. Mechanistically, such a class of substrates would involve a highly hindered aryl amidopalladium intermediate of type ArNPd(L)Ar', for which the product-forming reductive elimination step would be expected to be facile in the presence of a bulky

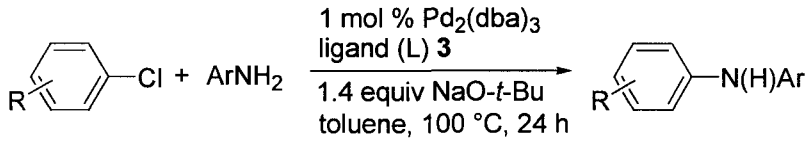
ligand such as **3** owing to relief of strain.[43] Comparison of our yield with yields previously reported for the same reaction conducted at 120 °C over 20 h using 0.5 mol % of Pd in the presence of the ligands PCy_3[13] (96%) and $DMAPPAd_2$ [di(1-adamantyl)-3-(*N*,*N*-dimethylamino)propylphosphine][13] (96%) revealed that the activity of these ligands are comparable to that of **3** (95%, entry 7, Table 7). However, catalysts based on $PhPCy_2$ (90%), P(*t*-Bu)$_3$[13] (77%), (*o*-biphenyl)PCy_2[13] (42%), and $BuPCy_2$[13] (78%) were inferior to the $Pd_2(dba)_3$/**3** catalyst system.

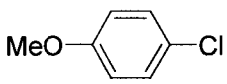
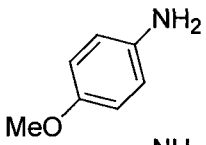
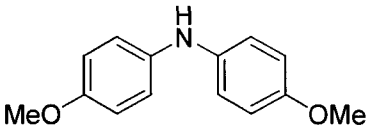
It is well known that reactions of acyclic secondary amines and primary aliphatic amines with aryl chlorides are not commonplace in amination chemistry. Nevertheless, catalysts bearing (*o*-biphenyl)P(*t*-Bu)$_2$,[15] Q-phos (di-*tert*-butylphosphino pentaphenylferrocene),[14] P(*t*-Bu)$_3$,[11] *n*-$BuPAd_2$ [di(1-adamantyl)-*n*-butylphosphine],[13] 2-(2'-dicyclohexylphosphinophenyl)-2-methyl-1,3-dioxolane,[17] and unsaturated imidazolium[20] as ligands did allow such couplings in good to excellent yields. We have also investigated the efficacy of **3** in the arylation of these amines (Table 8). In the examples presented in this table, the use of $Pd(OAc)_2$ as a precatalyst instead of $Pd_2(dba)_3$ was found to be beneficial. For cyclohexylamine and dibutylamine (representative members of cyclic hindered primary aliphatic amines and acyclic secondary amines, respectively) it was necessary to increase catalyst loading to 3 mol % of Pd in order to achieve the coupling products in good yields. These slightly modified conditions were effective for the amination of 4-chlorobenzonitrile, 4-chlorotoluene, and even the strongly electron-donating methoxide substituent in the meta-position of chlorobenzene with cyclohexylamine, providing the corresponding products in 65-67% yield (entries 1, 2, and 4, Table 8). Under these conditions no diarylation product was observed. Reactions of hindered aryl halides with hindered primary aliphatic amines often proceed in high yields as compared with unhindered systems because of reduced formation of hydrodehalogenation side-product. In accord with this observation, we found that the coupling of 2-chlorotoluene with cyclohexylamine also occurred in high yield (entry 3, Table 8). Reactions of the unhindered primary aliphatic amine *n*-hexylamine required 6 mol % of Pd and still the reaction proceeded in only moderate yield (entries 5 and 6, Table 8) owing to significant hydrodehalogenation and diarylation. Attempts to minimize diarylation side products by using 1.5-2 equivalents of *n*-hexylamine (relative to aryl chloride) were not

successful. Acceptable yields were obtained for the arylation of dibutylamine with aryl chlorides possessing electron-poor or electron-neutral groups. Unfortunately, reactions of electron-rich 4-chloroanisole with primary aliphatic amines and acyclic secondary amines were inefficient.

We also briefly examined the use of NaOH[20,44] as the stoichiometric base in $Pd_2(dba)_3$/**3**-catalyzed amination reactions of aryl chlorides (Table 9). Although these reactions were slower than those with NaO-*t*-Bu, probably because of the poor solubility of NaOH in toluene, the reaction did provide good to excellent product yields and it did not require a phase-transfer catalyst. In contrast, Hartwig's use of alkali metal hydroxides (NaOH and KOH) as bases in amination reactions did require a phase-transfer catalyst.[44] Our protocol was applicable to aryl chlorides bearing base-sensitive functional groups, such as nitro and enolizable ketones, and required 2 mol % of palladium. These substrates were not compatible when strongly basic NaO-*t*-Bu was used as the stoichiometric base. The electron-rich aryl chloride 4-chloroanisole was also amenable to our protocol. Cyclic secondary amines, the secondary aniline diphenylamine, and aniline were suitable substrates. For the reaction of 4-chloroanisole with aniline, the catalyst loading had to be increased to 2 mol % of $Pd_2(dba)_3$ in order to obtain the desired product in good yield (entry 9, Table 9). In a singular case, we found that the desired reaction occurred even in the presence of added water and a phase-transfer catalyst. Thus, the reaction of 1-chloro-4-nitrobenzene with diphenylamine proceeded in 87% isolated yield in the presence of NaOH, H_2O, **3** (cat.) $Pd_2(dba)_3$ (cat.), and Bu_4NBr (cat.) (entry 3, Table 9). It should be noted that palladium-catalyzed amination reactions using NaOH or KOH as bases have also been performed in aqueous media in the absence of a phase-transfer reagent and with or without the use of a co-solvent.[16,45]

Table 6. $Pd_2(dba)_3$/**3**-Catalyzed Amination of Aryl Chlorides with Simple Anilines



entry	chloride	amine	L/Pd	product	yield (%)[a]
1			2		78
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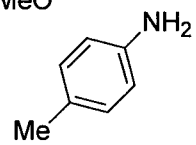
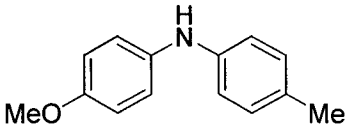
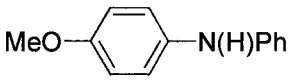
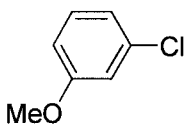
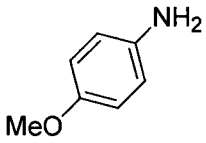
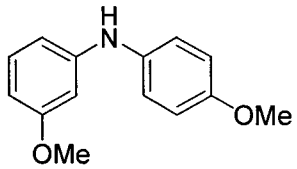
3			2		78
4		$PhNH_2$	2		84
5			2		72
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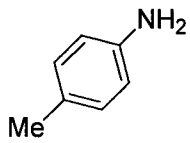
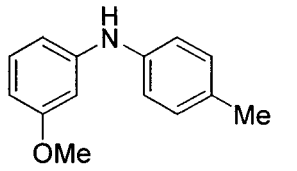
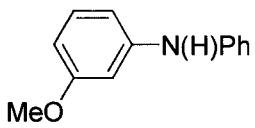
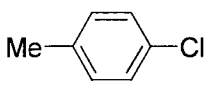
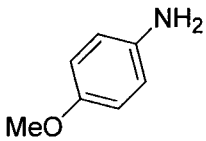
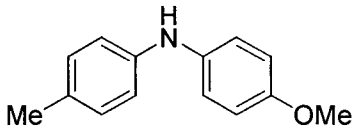
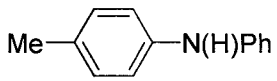
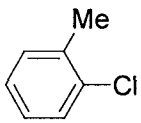
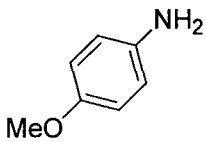
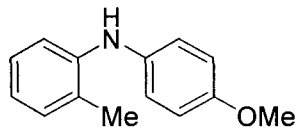
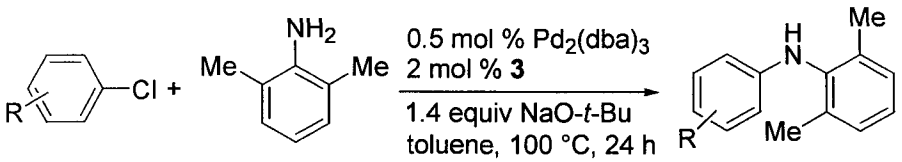
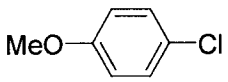
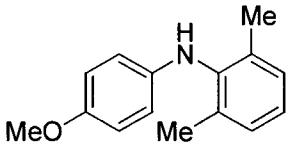
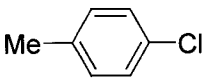
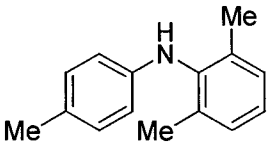
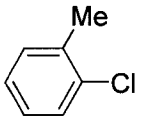
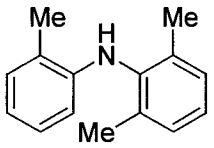
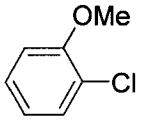
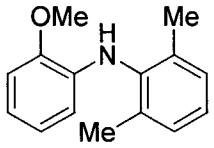
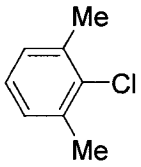
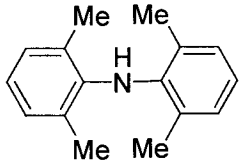
7			1		86
8			2		84
9		$PhNH_2$	2		86
10			2		84
11		$PhNH_2$	2		86
12			2		99

[a] Isolated yields (average of two runs).

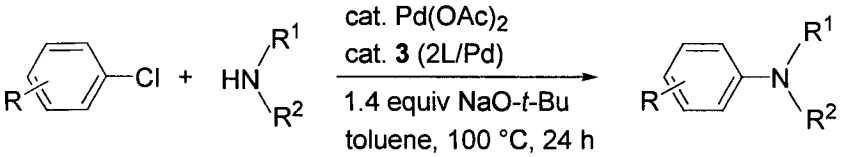
Table 7. $Pd_2(dba)_3$/**3**-Catalyzed Amination of Aryl Chlorides with Sterically Hindered 2,6-Dimethylaniline

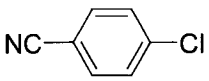
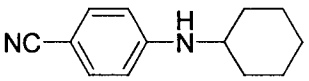
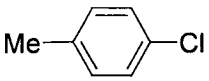
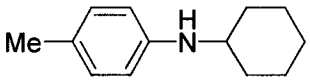
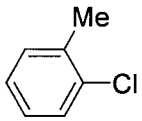
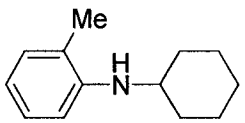
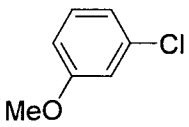
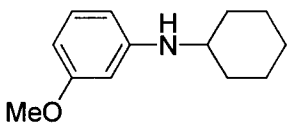
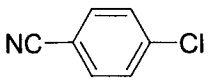
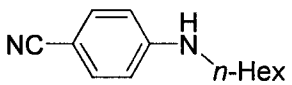
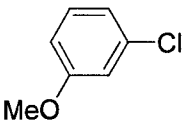
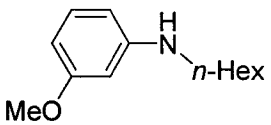
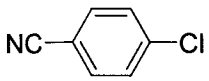
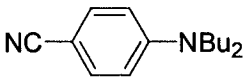
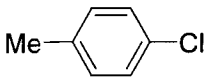
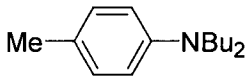


entry	chloride	product	yield (%)[a]
1			86
2			88
3			94
4			85
5			89[b]
6			85[c]
7			95[d]

[a] Isolated yields (average of two runs). [b] 0.25 mol % of $Pd_2(dba)_3$ and 1 mol % of **3** was employed. [c] 0.125 mol % of $Pd_2(dba)_3$ and 0.5 mol % of **3** was employed. [d] The reaction was conducted at 120 °C for 20 h.

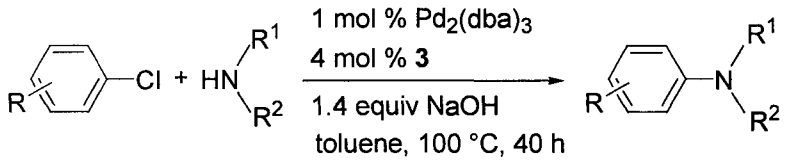
Table 8. $Pd(OAc)_2$/**3**-Catalyzed Amination of Aryl Chlorides with Aliphatic Amines

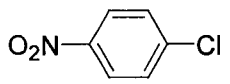
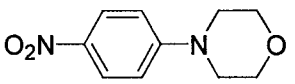
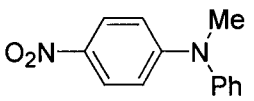
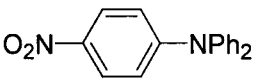
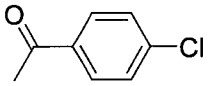
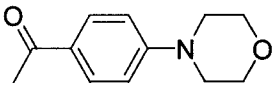
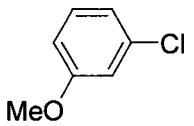
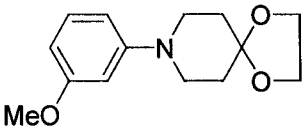
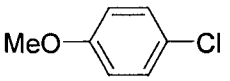
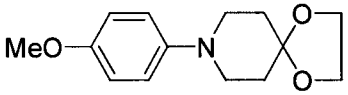
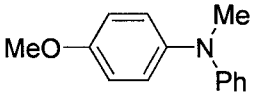
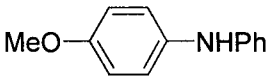


entry	chloride	mol % Pd	product	yield (%)[a]
1		3		67
2		3		67
3		3		87
4		3		65
5		6		68
6		6		68
7		3		66
8		3		55

[a] Isolated yields (average of two runs).

Table 9. $Pd_2(dba)_3$/**3**-Catalyzed Amination of Aryl Chlorides using NaOH as the Base



entry	chloride	product	yield (%)[a]
1			>99
2			92
3			90
4			87[b]
5			95
6			91
7			89
8			98
9			82[c]

[a] Isolated yields (average of two runs). [b] 1.4 equiv of H_2O and 0.2 equiv of Bu_4NBr was also added to the reaction. [c] 2 mol % of $Pd_2(dba)_3$ was employed.

A comment on assembly of the reaction components. Except for the screening of the ligands, for which the glove-box (Table 1) was used, weighing of the reaction components (palladium catalyst precursor, base, and solid substrates) was carried out in air (Tables 2-9) and standard Schlenk-line techniques were employed. When moisture-sensitive NaO-*t*-Bu was employed, small quantities of it in a vial were removed from the glove-box (where the

bottle of NaO-*t*-Bu was stored) and then weighed in air for the reaction. Because ligand **3** is air- and moisture-sensitive, we prepared a stock solution of it in toluene (2 mM) and stored it under argon outside the glove-box.

Conclusions

By building on our previous findings, we have shown that more economical protocols for palladium-catalyzed Buchwald-Hartwig amination reactions of aryl chlorides can be developed using commercially available ligand **3**. We have determined that the *iso*-butyl group on the PN_3 nitrogens of the proazaphosphatrane framework is important for maximizing activity of the proazaphosphatrane/$Pd_2(dba)_3$ catalyst system, but that ligand **6**, with two *iso*-butyl groups and one benzyl group on PN_3 nitrogens, also functions as a potent ligand in this system. The $Pd_2(dba)_3$/**3** combination allows coupling of electronically diverse aryl chlorides with an array of amines to proceed in high yields. The majority of these reactions were conducted using 1 mol % of Pd. For the reaction of 2-chloro-*m*-xylene with 2,6-dimethylaniline, catalyst loading can be lowered to as little as 0.25 mol % of Pd without significantly compromising product yield. Either a 1:1 or 2:1 ratio of L:Pd was found to be effective in this reaction. The $Pd_2(dba)_3$/**3** catalyst system also permitted amination reactions to occur (although slowly) in the presence of NaOH as the stoichiometric base, with aryl functional groups such as nitro and enolizable ketone being tolerant to these conditions.

Experimental Section

General Considerations: All reactions were performed under an atmosphere of argon in oven-dried glassware. Toluene was collected from a Grubbs type solvent purification system and stored over 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates and visualized with short wavelength UV light (254 nm). The yields reported are isolated yields and are the average of at least two runs. All commercially available reagents were used as received. All compounds described in Tables 1-9 are known in the literature and were characterized by comparing their ^1H and ^{13}C

NMR or MS to the previously reported data. In all cases, the comparisons were very favorable.

General Procedure for the Screening of Ligands (Table 1): An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (0.5 mol %) and NaO-*t*-Bu (1.4 mmol) inside a nitrogen-filled glove-box. Ligands that were solids, namely, **1**, **4,** and **5** (2 mol %) were also added at this time. The flask was capped with a rubber septum and removed from the glove-box. This cycle was repeated three times. Ligands that were liquids, namely, **2**, **3**, and **6** (2 mol %) were then added via syringe from a stock solution (2 mM in toluene). Morpholine (1.2 mmol), 4-chloroanisole (1.0 mmol) and toluene (3 mL) were then successively added by syringe. The reaction mixture was heated at 100 °C for 24 after which the mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

General Procedure for the $Pd_2(dba)_3$/3-Catalyzed Amination Reactions of Aryl Chlorides (Tables 2-7): An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (x mol %, see Tables 2-7) and NaO-*t*-Bu (1.4 mmol) in air. Amine (1.2 mmol) and aryl chloride (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **3** (x-2x mol %, see Tables 2-7) was then added via syringe from a stock solution (2 mM in toluene). Aryl chloride (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol) and toluene (3 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (20-24 h). The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

General Procedure for the $Pd(OAc)_2$/3-Catalyzed Amination Reactions of Aryl Chlorides with Aliphatic Amines (Table 8): An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (3-6 mol %) and NaO-*t*-Bu (1.4 mmol) in air. Amine (1.2 mmol) and aryl chloride (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **3** (6-12 mol %) was then added via syringe from

a stock solution (2 mM in toluene). Aryl chloride (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol) and toluene (3 mL) were then successively added by syringe. The reaction mixture was heated at 100 °C until the starting material had been completely consumed as judged by TLC (24 h). The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

General Procedure for the $Pd_2(dba)_3$/3-Catalyzed Amination Reactions of Aryl Chlorides using NaOH as the Base (Table 9): An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (1 mol %) and NaOH (1.4 mmol) in air. Amine (1.2 mmol) and aryl chloride (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **3** (4 mol %) was then added via syringe from a stock solution (2 mM in toluene). Aryl chloride (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol) and toluene (3 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (40 h). The mixture was subsequently cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

Acknowledgment

We are grateful to the Aldrich Chemical Co. for their generous support of this study by supplying research samples. The National Science Foundation is gratefully acknowledged for financial support of this work in the form of a grant. The authors also thank Dr. Weiping Su for the supply of ligands **4**, **5**, and **6** and Dr. M. Nagarajan (RanBaxy, New Delhi, India) formerly in our group for his preliminary experiments.

Supporting Information Available

Experimental details, references for known compounds, and copies of ^{1}H and ^{13}C NMR spectra for all the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org. This is also available in the appendix C in this thesis.

References

(1) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

(2) (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (c) Wolfe, J. P.; Wagaw,, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(3) (a) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.

(4) (a) Beland, F. A.; Kadlubar, F. F. *Handbook of Experimental Pharmacology, Carcinogenesis and Mutagenesis*; Grove, Springer, Verlag: Heidelberg, 1990. (b) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028. (c) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112.

(5) Louie, J.; Hartwig, J. F.; Fry, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 11695.

(6) Westmoreland, I.; Munslow, I. J.; O'Shaughnessy, P. N.; Scott, P. *Organometallics* **2003**, *22*, 2972.

(7) Greco, G. E.; Popa, A. I.; Schrock, R. R. *Organometallics* **1998**, *17*, 5591.

(8) Furstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5229.

(9) Huyskens, F. L.; Huyskens, P. L.; Persoons, A. P. *J. Chem. Phys.* **1998**, *108*, 8161.

(10) Nishiyama, M. Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

(11) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(12) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.

(13) Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chemical* **2002**, *182-183*, 515.

(14) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

(15) Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(16) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(17) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. Petersen, J. L. *Organometallics* **1999**, *18*, 1840.

(18) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229.

(19) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

(20) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.

(21) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H-U. *Angew. Chem. Int. Ed.* **2002**, *41*, 3668.

(22) Zim, D. Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413.

(23) Bedford, R. B.; Blake, M. E. *Adv. Synth. Catal.* **2003**, *345*, 1107.

(24) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677.

(25) Ligands **1**, **2**, and **3** are commercially available from Aldrich and Strem Chemicals. (a) For recent reviews, see: Verkade, J. G. *Top. Curr. Chem.* **2002,** *233,* 1. (b) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 7819.

(26) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

(27) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

(28) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

(29) Urgaonkar, S.; Verkade, J. G. *Adv. Synth. Catal.* **2004**, *346*, 611.

(30) You, J.; Verkade, J. G. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 5051.

(31) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.

(32) (a) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421. (b) Su, W.; Urgaonkar, S.; Mclaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.,* in press.

(33) Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

(34) Our preliminary studies of Pd/**3**-catalyzed aminations of aryl chlorides were recently communicated, see ref 28.

(35) Stambuli, J. P.; Buhl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346.

(36) Vigalok, A.; Milstein, D. *Acc. Chem. Res.* **2001**, *34*, 798.

(37) Broekkamp, C. L. E.; Leysen, D. B.; Peeters, W. M. M.; Pinder, R. M. *J. Med. Chem.* **1995**, *38*, 4615.

(38) Hepperle, M.; Eckart, J.; Gala, D. *Tetrahedron Lett.* **1999**, *40*, 5655.

(39) Hagibara, M.; Kashiwase, H.; Katsube, T.; Kimura, T.; Komai, T.; Momota, K.; Ohmine, T.; Nishigaki, T.; Kimura, S.; Shimada, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3063.

(40) Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374.

(41) Xia, Y.; Mirzai, B.; Chackamannil, S.; Czamiecki, M.; Wang, S.; Clemmons, A.; Ahn, H.-S.; Boykow, G. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 919.

(42) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(43) For mechanistic studies, see: (a) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. (b) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905. (c) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618 and references cited therein. Also, see ref 35.

(44) For the use of alkali metal hydroxides as bases in amination chemistry, see: Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.

(45) Wüllner, G.; Jänsch, H.; Kannenberg, S.; Schubert, F.; Boche, G. *Chem. Commun.* **1998**, 1509.

CHAPTER 5. PALLADIUM/PROAZAPHOSPHATRANE-CATALYZED AMINATION OF ARYL HALIDES POSSESSING A PHENOL, ALCOHOL, ACETANILIDE, AMIDE OR AN ENOLIZABLE KETONE FUNCTIONAL GROUP: EFFICACY OF $LiN(SiMe_3)_2$ AS THE BASE

A paper published in the *Advanced Synthesis and Catalysis*

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Abstract

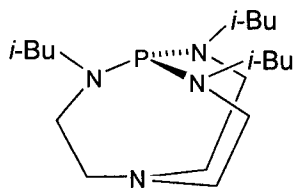
A commercially available catalyst system comprising $Pd(OAc)_2$ or $Pd_2(dba)_3$ and the proazaphosphatrane ancillary ligand $P(i\text{-}BuNCH_2CH_2)_3N$ (**1**) for the amination of aryl halides substituted with a phenol, alcohol, acetanilide, amide or ketone group containing an enolizable hydrogen is described. The reaction is performed in the presence of $LiN(SiMe_3)_2$ as the base. Other bases tested were either less effective or completely non-functional.

Introduction

Lithium bis(trimethylsilyl)amide [$LiN(SiMe_3)_2$] is a well known sterically hindered non-nucleophilic base that has played an increasingly important role in organic synthesis.[1] In one such application, Hartwig recently employed $LiN(SiMe_3)_2$ as the base in the palladium-catalyzed reaction of aryl halides with amines.[2] In 1997, Brüning reported that $LiN(SiMe_3)_2$ can be utilized as a nitrogen source (nucleophile) in palladium-catalyzed aminations of allyl chloride.[3] Building on this observation, Hartwig, in 2001, demonstrated the use of $LiN(SiMe_3)_2$ as an ammonia equivalent for the $Pd(dba)_2/P(t\text{-}Bu)_3$-catalyzed conversion of aryl halides to anilines.[4] Later that year, Buchwald used $Pd_2(dba)_3$ and (*o*-biphenyl)PCy_2 for the same transformation.[5] More recently, Buchwald[6] showed the utility of $LiN(SiMe_3)_2$ as a base for amination reactions of aryl halides possessing substituents such as acetanilide, alcohol, and phenol; functional groups that were not compatible with either the original protocol utilizing NaO-*t*-Bu as the base or with the modified procedure wherein weaker bases such as K_3PO_4 or Cs_2CO_3 were employed. The inefficient amination reactions using these

bases when the aforementioned functional groups were present may be due to binding of the deprotonated species to the palladium with resulting deactivation of the catalyst. This reaction inefficiency may also be due to the ineffectiveness of the commonly employed ligands to support such transformations as is indicated in a recent report by Buchwald wherein amination reactions of aryl halides substituted by amide and acetanilide functional groups were accomplished with the use of a sterically hindered biaryl monophosphine ligand.[7]

Our recent investigation of palladium-catalyzed reactions (*e.g.*, Suzuki,[8] amination,[9] and *alpha*-arylation[10]) led us to the discovery of a new bicyclic triaminophosphine ligand, namely, **1** (2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane, a member of the proazaphosphatrane class of compounds[11]) for these transformations (Figure 1).



1

Figure 1. Bicyclic triaminophosphine ligand

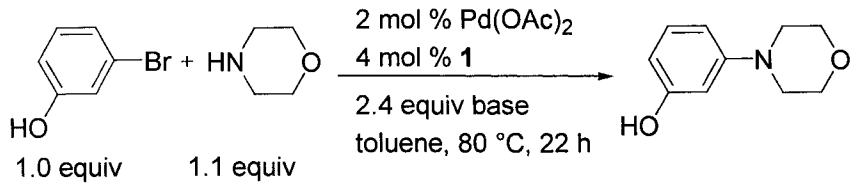
In the case of aryl amination reactions, the Pd/**1** catalyst system, in combination with NaO-*t*-Bu as the base, displays very high activity for the coupling of aryl halides with amines.[9] However, there were limitations for the types of functional groups that can be present in the substrates. Thus, the conversion of substrates possessing amide, alcohol, phenol, and ketone substituents into desired products proved difficult. The use of a weaker base, such as Cs_2CO_3, failed to promote this reaction. Following the report of Buchwald that $LiN(SiMe_3)_2$ functions as an unique base for the aforementioned substrate types,[6] we were interested in its application to amination reactions catalyzed by **1**/Pd. Here we report the results of that study.

Results and Discussion

We first examined the coupling of 3-bromophenol with morpholine using 2 mol % of $Pd(OAc)_2$ and 4 mol % of ligand 1 in the presence of various bases in toluene at 80 °C (Table 1). As expected, bases such as NaO-*t*-Bu, LiO-*t*-Bu and Cs_2CO_3 afforded either trace or undetectable amounts of the desired coupled product (Table1, entries 1-3).

However, the combination of LDA (1.0 equiv) and NaO-*t*-Bu (1.4 equiv) provided a good yield of the product (Table 1, entry 4). Here, initial deprotonation of the acidic proton

Table 1. Survey of bases



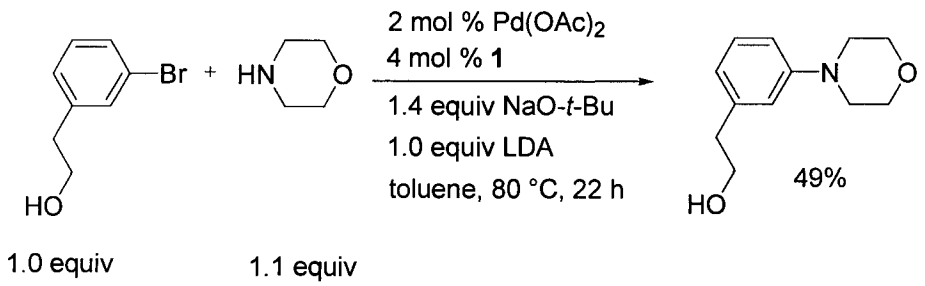
entry	base	yield[a] (%)
1	NaO-*t*-Bu	trace
2	Cs_2CO_3	nr[c]
3	LiO-*t*-Bu	nr[c]
4	NaO-*t*-Bu[b]	80
5	$LiN(SiMe_3)_2$	92
6	$KN(SiMe_3)_2$	85
7	$NaN(SiMe_3)_2$	88

[a] Isolated yields (average of two runs).

[b] 1.0 equiv of LDA was also added.

[c] nr = no reaction.

from the phenol by an equivalent of LDA would be followed by typical palladium-catalyzed amination chemistry[12] with NaO-*t*-Bu playing the role of the base. Changing the base to a commercially available solution of $LiN(SiMe_3)_2$ in THF resulted in a higher yield of the product (Table 1, entry 5). Other silylamide bases such as $KN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ were also effective in providing good yields (Table 1, entries 6 and 7). Isolation of the product was readily achieved by direct loading of the reaction mixture onto a silica gel column for chromatography. It was further determined that the LDA/NaO-*t*-Bu system could also be used in the coupling of aryl bromides possessing a primary alcohol functionality (Scheme 1).



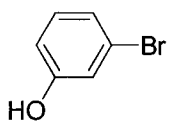
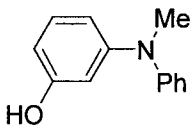
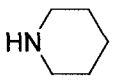
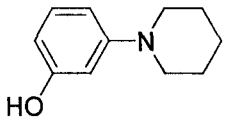
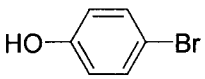
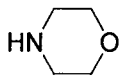
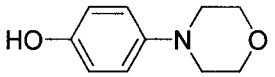
Scheme 1.

Although the protocol involving the combination of LDA and NaO-*t*-Bu as the deprotonating agent and the base, respectively, was effective for bromophenols, its utilization in the reactions of 4-bromobenzamide, 4'-bromoacetanilide, and 4'-bromoacetophenone yielded undetectable amounts of the desired product. These results are in accord with those of Buchwald's group, except in the case of 4'-bromoacetanilide, wherein the LDA/NaO-*t*-Bu protocol was also effective in their hands.[6]

From the above results it is clear that lithium bis(trimethylsilyl)amide is a highly effective base in amination reactions using the **1**/Pd catalyst system. In examining the scope of this methodology, it was found that functionalities such as phenol, alcohol, amide, keto, and acetanilide were compatible (Table 2). Although a standard palladium loading of 2 mol % was used for aryl bromides, some substrate combinations gave good to excellent yields even with substantially lower catalyst loadings. For example, while the reaction of 4-bromophenol with *N*-methylaniline and with morpholine in the presence of 2 mol % of palladium afforded 95% (Table 2, entry 6) and 83% (Table 2, entry 3) yields of the desired products, respectively, these reactons also occurred with about equal efficiency with 1 mol % of Pd (92% and 75%, respectively) as well as with 0.5 mol % of Pd (88% and 72%, respectively) as is seen in entries 7, 4, 8 and 5, respectively, of Table 2. Similarly, the amination of 4'-bromoacetanilide with *N*-methylaniline and with morpholine proceeded in high yields even with low palladium loadings (Table 2, entries 14-19). Reactions of bromoacetophenone were slightly less effective and required longer reaction times (Table 2, entries 21-24). Aryl bromides possessing a primary alcohol substituent were also transformed into the desired product in acceptable yields (Table 2, entries 12 and 13) and the amination of 4-bromobenzamide was also achieved in high yield (Table 2, entry 25). This protocol was also

successful when *N*-BOC-piperazine was used as the coupling partner, leading to the formation of a highly functionalized aryl amine (Table 2, entry 33).

Table 2. Pd/P(i-Bu$NCH_2CH_2)_3$N-Catalyzed Amination of Aryl Bromides and Chlorides[a]

entry	aryl halide	amine	mol % Pd	product	time (h)	yield[b](%)
1			2		20	95
2			2		27	88
3			2		22	83
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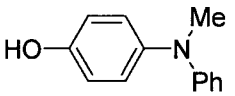
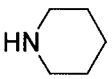
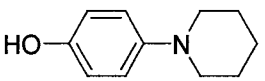
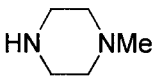
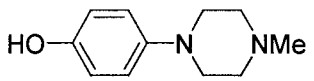
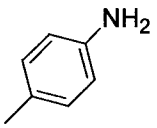
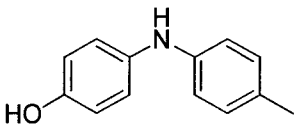
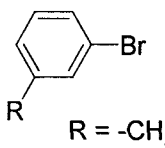
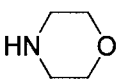
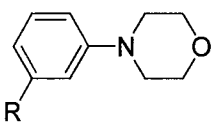
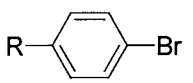
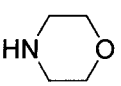
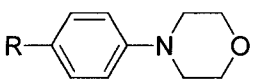
5			0.5		22	72
6			2		23	95
7			1		23	92
8			0.5		23	88
9			2		28	82
10			1		20	76
11			2		28	78
12			2		25	60
	R = -CH_2CH_2OH					
13			2		26	73

[a] Conditions: 1.0 equiv of aryl halide, 1.1 equiv of amine, cat. $Pd(OAc)_2$, cat. ligand **1** (2L/Pd), 2.4 equiv of $LiN(SiMe_3)_2$ (1M in THF), 80 °C. Reaction times have not been minimized.

[b] Isolated yields (average of two runs).

[c] $Pd_2(dba)_3$ was used in place of $Pd(OAc)_2$.

[d] The reaction was carried out at 100 °C.

Table 2. Continued

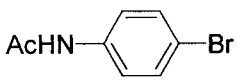
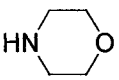
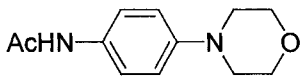
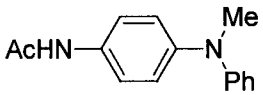
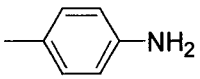
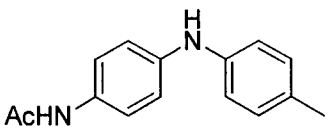
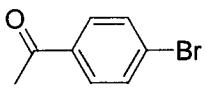
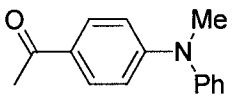
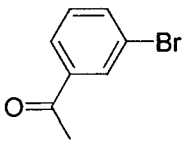
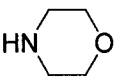
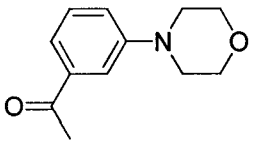
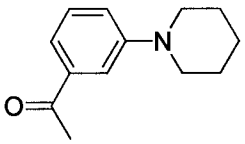
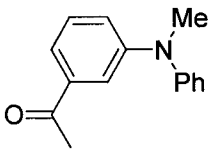
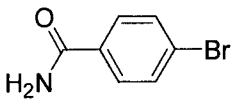
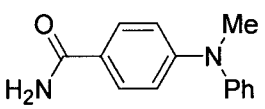
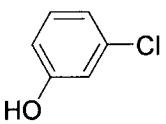
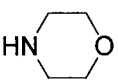
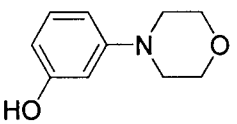
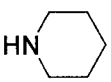
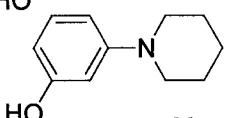
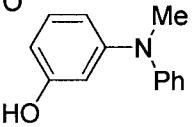
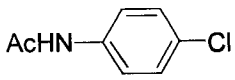
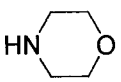
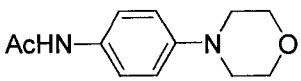
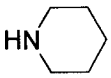
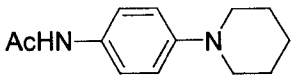
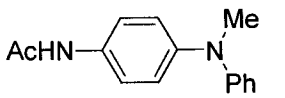
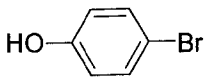
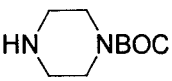
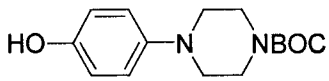
entry	aryl halide	amine	mol % Pd	product	time (h)	yield[b](%)
14			2		24	94
15			1		24	85
16			0.5		24	85
17			2		24	95
18			1		24	92
19			0.5		24	79
20			2		28	78
21			2		30	65
22			2		30	88
23			2		32	60
24			2		29	89
25			2		20	93
26			4		29	97[c,d]
27			4		31	66[c,d]
28			4		24	97[c,d]

Table 2. Continued

entry	aryl halide	amine	mol % Pd	product	time (h)	yield[b](%)
29			4		32	82[c,d]
30			4		32	80[c]
31			4		34	52[c,d]
32			4		28	95[c,d]
33			2		20	72

We were pleased to find that aryl chlorides were also suitable substrates, although a higher catalyst loading (4 mol % Pd) and reaction temperature (100 °C) were necessary (Table 2, entries 26-32). In these reactions, $Pd_2(dba)_3$ was more effective as a palladium source than $Pd(OAc)_2$. In one case, the reaction proceeded in good yield even at 80 °C. Thus 4'-chloroacetanilide reacted with morpholine at 100 °C and at 80 °C, providing 82% and 80% yields of the desired product, respectively (Table 2, entries 29 and 30).

Although the **1**/Pd catalyst system is quite general, several limitations were encountered which are summarized as follows: (a) the reaction proceeded sluggishly when the functional groups amide, acetanilide, alcohol, ketone or phenol were present in the amine component; (b) the amination reactions of aryl halides substituted with these groups at the *ortho* position yielded none of the desired product; and (c) primary amines and acyclic amines were not compatible under these conditions.

In all the reactions presented here, a commercially available solution of $LiN(SiMe_3)_2$ in THF (1M) was used for convenience. Interestingly, when solid $LiN(SiMe_3)_2$ was used with toluene as the only solvent, reactions proceeded slowly and provided inferior yields compared with reactions carried out with THF[13] and toluene as a binary solvent system. This observation may stem from the insolubility of the lithium alkoxide or lithium enolate formed during the the reaction in toluene. Furthermore, additional experiments showed that $KN(SiMe_3)_2$ can be

substituted for $LiN(SiMe_3)_2$, although lower yields were usually observed. Here also, THF as a co-solvent was essential because when toluene was used as the sole solvent, a precipitate was observed.

The exceptional activity displayed by silylamide bases, especially $LiN(SiMe_3)_2$,[14] might be due to deprotonation of the substrate with resultant formation *in situ* of a covalently bound lithium which acts as a protecting group that inhibits coordination of an alcohol or amide group to palladium. The highly aggregated state and tight ion pairing which is a characteristic of lithium alkoxides, might provide some degree of stability to such intermediates,[15] even at the elevated temperatures used in our protocol. Another factor in the efficacy of silylamide bases in these reactions is the possible formation of a silylated alcohol or silylated amide intermediate via migration of a trimethylsilyl (TMS) group from the silylamide base to the alcohol or amide, thus protecting the oxygen or nitrogen, respectively, from coordination to the palladium. On the basis of the experiments discussed herein, it may be concluded that the latter option is favored with the amide, acetanilide, and ketone functionality because these functional groups are compatible with $LiN(SiMe_3)_2$ but not with the LDA/NaO-*t*-Bu system. Because the LDA/NaO-*t*-Bu base system as well as silylamide bases are effective in the case of an aryl halide bearing an alcohol or phenol functionality, two types of oxygen protection may be operating. Thus protection via covalent binding (Li^+) or ion pairing (Na^+, K^+) may be occurring, or TMS protection may be at play.

Conclusion

In summary, we have demonstrated the utility of $LiN(SiMe_3)_2$ as a base in Pd/**1**-catalyzed aminations of aryl chlorides and bromides containing a relatively acidic functional group, namely, a phenol, an alcohol, an amide, an acetanilide or a ketone possessing enolizable hydrogens. This new catalyst system (wherein the ligand **1** is also commercially available[16]) significantly expands the repertoire of methodologies enabling such transformations.

Experimental Section

General Considerations: All reactions were performed under an atmosphere of argon in oven-dried glassware. Toluene was collected from a Solvent Purification System and stored

over 4 Å molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, unless otherwise noted. The yields reported are isolated yields and are the average of at least two runs. All commercially available reagents were used as received. Although ligand **1** is commercially available,[16] we synthesized it according to our previously reported procedure.[17] For convenience, a stock solution of **1** in toluene (2 mM) was prepared and stored under argon. All products in Tables 1 and 2 are known in the literature and were characterized by comparing their ^{1}H and ^{13}C NMR or mass spectra to the previously reported data. In all cases, the comparisons were very favorable.

General procedure for the coupling of aryl halides with amines

An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ or $Pd_2(dba)_3$ (x mol %, see Table 2), amine (1.2 mmol) and aryl bromide (1.0 mmol). The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **1** (2x mol %, see Table 2), $LiN(SiMe_3)_2$ solution (1M in THF) (2.3 mmol) and toluene (5 mL) were then successively added by syringe. The reaction mixture was heated at the temperature indicated in Table 1 and reaction progress was monitored by TLC. After completion of the reaction, the crude reaction mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

***N*-(3-Hydroxyphenyl)-morpholine[18] (product in Table 1 and Table 2, entry 26)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.09 (m, 1H), 6.50-6.47 (m, 1H), 6.36-6.34 (m, 2H), 6.23 (bs, 1H), 3.86 (m, 4H), 3.11 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 152.9, 130.4, 108.4, 107.5, 103.3, 67.0, 49.5.

3-Hydroxy-*N*-methyl-diphenylamine[19] (Table 2, entries 1 and 28) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 2H), 7.15-7.04 (m, 4H), 6.48-6.40 (m, 2H), 5.10 (bs, 1H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 150.8, 149.0, 130.3, 129.6, 122.7, 122.6, 111.7, 107.8, 106.2, 40.6.

***N*-(3-Hydroxyphenyl)-piperidine[20] (Table 2, entries 2 and 27)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11-7.06 (m, 1H), 6.55-6.51 (m, 1H), 6.36-6.29 (m, 2H), 5.76 (bs, 1H), 3.09-3.05 (m, 4H), 1.72-1.53 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 153.6, 130.2, 109.4, 107.1, 104.4, 51.0, 25.7, 24.4.

***N*-(4-Hydroxyphenyl)-morpholine[6] (Table 2, entries 3, 4 and 5)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86-6.75 (m, 4H), 4.99 (bs, 1H), 3.87 (m, 4H), 3.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 145.8, 118.4, 116.2, 67.2, 51.2.

4-Hydroxy-*N*-methyl-diphenylamine[6] (Table 2, entries 6, 7 and 8) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.22 (m, 2H), 7.09-7.06 (m, 2H), 6.86-6.83 (m, 5H), 5.45 (bs, 1H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 150.0, 142.7, 129.3, 12.6, 118.8, 116.6, 116.2, 40.8.

***N*-(4-Hydroxyphenyl)-piperidine[21] (Table 2, entry 9)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89-6.69 (m, 4H), 5.09 (bs, 1H), 3.01 (s, 4H), 1.73-1.53 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 146.6, 119.6, 116.0, 53.0, 26.2, 24.3.

***N*-(4-Hydroxyphenyl)-piperazine[22] (Table 2, entry 10)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 6.82-6.68 (m, 4H), 3.10-3.08 (m, 4H), 2.66-2.65 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 145.0, 119.0, 116.4, 55.3, 50.7, 46.1.

***N*-(4-Hydroxyphenyl)-*p*-toluidine[23] (Table 2, entry 11)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06-6.96 (m, 4H), 6.87-6.76 (m, 4H), 5.30 (bs, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 142.6, 137.0, 130.0, 129.7, 121.6, 116.9, 116.3, 20.8.

2-(3-Morpholin-4-yl-phenyl)-ethanol[6] (Table 2, entry 12) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.19 (m, 1H), 6.79-6.73 (m, 3H), 3.86-3.80 (m, 6H), 3.16-3.13 (t, J = 4.8 Hz, 4H), 2.81 (t, J = 6.6 Hz, 2H), 2.03 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 139.8, 129.6, 120.9, 116.7, 114.0, 67.1, 63.8, 49.6, 39.8.

2-(4-Morpholin-4-yl-phenyl)-ethanol[6] (Table 2, entry 13) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.12 (m, 2H), 6.88-6.86 (m, 2H), 3.86-3.78 (m, 6H), 3.13-3.12 (m, 4H), 2.81-2.76 (m, 2H), 1.81 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 130.2, 130.0, 116.3, 67.2, 64.0, 49.8, 38.5.

***N*-(4'-Morpholin-4-yl-phenyl)-acetanilide[24] (Table 2, entries 14, 15, 16, 29 and 30)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.9 Hz, 2H), 7.21 (bs, 1H), 6.88 (d, J = 8.9 Hz, 2H), 3.87-3.83 (m, 4H), 3.11-3.09 (m, 4H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 148.5, 130.8, 121.8, 116.5, 67.1, 50.0, 24.6.

***N*-[(4'-(*N*-phenyl-*N*'-methylamino)-phenyl]-acetanilide[6] (Table 2, entries 17, 18, 19 and 32)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (bs, 1H), 7.43-7.40 (m, 2H), 7.27-7.22 (m, 2H), 7.00-

6.88 (m, 5H), 3.27 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 149.3, 145.8, 132.5, 129.4, 122.2, 121.9, 120.8, 119.4, 40.6, 24.5.

***N*-[4'-(4-Methyl-phenyl)-amino]-acetanilide[6] (Table 2, entry 20)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (bs, 1H), 7.36-7.33 (m, 2H), 7.07-7.04 (m, 2H), 6.95-6.91 (m, 4H), 5.65 (bs, 1H), 2.29 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 141.0, 140.7, 131.2, 130.7, 130.1, 122.2, 118.4, 118.0, 24.5, 20.9.

4'-(*N*-phenyl-*N*'-methylamino)-acetophenone[25] (Table 2, entry 21) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.44-7.38 (m, 2H), 7.26-7.20 (m, 3H), 6.77-6.74 (m, 2H), 3.37 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 152.9, 147.5, 130.4, 130.1, 127.3, 126.4, 125.9, 113.6, 40.5, 26.4.

3'-(Morpholin-4-yl-)-acetophenone[26] (Table 2, entry 22) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.31 (m, 3H), 7.11-7.07 (m, 1H), 3.86-3.82 (m, 4H), 3.20-3.16 (m, 4H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 151.7, 138.2, 129.5, 120.5, 114.6, 67.0, 49.3, 27.0.

3'-(Piperidin-4-yl-)-acetophenone[27] (Table 2, entry 23) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.50 (m, 1H), 7.38-7.28 (m, 2H), 7.14-7.10 (m, 1H), 3.22-3.18 (m, 4H), 2.57 (s, 3H), 1.74-1.67 (m, 4H), 1.62-1.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 152.5, 138.1, 129.3, 121.3, 119.5, 115.4, 67.0, 50.6, 27.0, 25.9, 24.4.

3'-(*N*-phenyl-*N*'-methylamino)-acetophenone[6] (Table 2, entry 24) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.55 (m, 1H), 7.48-7.44 (m, 1H), 7.35-7.27 (m, 3H), 7.15-7.03 (m, 4H), 3.36 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 149.6, 148.7, 138.5, 129.8, 129.4, 123.5, 122.7, 120.6, 117.6, 40.6, 27.0.

4-(*N*-phenyl-*N*'-methylamino)-benzamide[28] (Table 2, entry 25) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (m, 2H), 7.41-7.35 (m, 2H), 7.20-7.18 (m, 3H), 6.81-6.78 (m, 2H), 6.04 (bs, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 152.1, 147.8, 130.0, 129.0, 125.7, 125.3, 122.6, 114.6, 40.4.

***N*-(4'-Piperidin-4-yl-phenyl)-acetanilide[29] (Table 2, entry 31)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (bs, 1H), 7.35 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 3.09-3.06 (m, 4H), 2.10 (s, 3H), 1.72-1.65 (m, 4H), 1.58-1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 149.6, 130.2, 121.8, 117.2, 51.3, 26.1, 24.5, 24.4.

***N-tert*-Butoxycarbonyl-4-(4-hydroxyphenyl)-piperazine[30] (Table 2, entry 33)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84-6.75 (m, 5H), 3.58-3.55 (m, 4H), 2.98-2.94 (m, 4H), 1.48 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 151.2, 145.2, 119.5, 116.2, 80.5, 51.4, 28.7.

Acknowledgements

We thank the Aldrich Chemical Company for their generous support of this study by supplying research samples. The National Science Foundation is gratefully acknowledged for financial support of this work in the form of a grant.

References

[1] a) H. J. Reich, J. H. Rigby, in *Handbook of Reagents for Organic Synthesis, Acidic and Basic Reagents*, John Wiley & Sons, Chichester, **1999**, pp. 221; b) T. L. Rathman, *Chem. Spec.* **1989**, *9*, 300; c) M. W. Rathke, *J. Am. Chem. Soc.* **1970**, *92*, 3222.

[2] J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609.

[3] J. Brüning, *Tetrahedron Lett.* **1997**, *38*, 3187.

[4] S. Lee, M. Jørgensen, J. F. Hartwig, *Org. Lett.* **2001**, *3*, 2729.

[5] X. Huang, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3417.

[6] M. C. Harris, X. Huang, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 2885.

[7] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.

[8] S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Tetrahedron Lett.* **2002**, *43*, 8921.

[9] a) S. Urgaonkar, M. Nagarajan, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 452; b) S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Org. Lett.* **2003**, *5*, 815.

[10] a) J. You, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 8003; b) J. You, J. G. Verkade, *Angew. Chem. Int. Ed.* **2003**, *42*, 5051.

[11] For recent reviews, see: a) J. G. Verkade, *Top. Curr. Chem.* **2002**, *233*, 1; b) P. B. Kisanga, J. G. Verkade, *Tetrahedron* **2003**, *59*, 7819.

[12] For reviews, see: a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; b) J. F. Hartwig, in *Modern Amination Methods*, (Ed.: A. Ricci) Wiley-VCH, Weinheim, **2000**; c) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125; d) J. P. Wolfe, S.

Wagaw, J. -F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805; e) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 805; f) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.

[13] The reaction in THF alone as the solvent also furnished the desired product but in only moderate yields compared with the toluene-THF solvent system.

[14] Similar speculations were also made by Buchwald, see ref. 6.

[15] B. L. Lucht, B. D. Collum, *Acc. Chem. Res.* **1999**, *32*, 1035 and references cited therein.

[16] Ligand **1** is available from Aldrich and Strem Chemicals.

[17] P. B. Kisanga, J. G. Verkade, *Tetrahedron* **2001**, *57*, 467.

[18] L. Shi, M. Wang, C. Fan, F. Zhang, Y. Tu, *Org. Lett.* **2003**, *5*, 3515.

[19] S. Kimura, T. Kobayashi, S. Ishige, *Ger. Offen.* 2049527, **1971**; *Chem. Abstr.* **1971**, *75*, 22500.

[20] M. Skowronska-Ptasainska, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1985**, *50*, 2690.

[21] K. L. Holland, T. A. Morris, P. J. Nava, M. Zabic, *Tetrahedron* **1999**, *55*, 7441.

[22] M. S. Egbertson, L. M. Turchi, G. D. Hartman, W. Halczenko, D. B. Whitman, J. J. Perkins, A. E. Krause, N. Ihle, D. A. Claremon, *PCT Int. Appl.* 9412181, **1994**; *Chem. Abstr.* **1994**, *122*, 315098.

[23] K. Wedemeyer, S. Boehm, *Ger. Offen.* 2024859, **1981**; *Chem. Abstr.* **1981**, *95*, 6770.

[24] J. B. Christensen, N. Schioedt, K. Bechgaard, T. Buch-Rasmussen, *Acta Chem. Scand.* **1996**, *50*, 1013.

[25] G. Wüllner, H. Jänsch, S. Kannenberg, F. Schubert, G. Boche, *Chem. Commun.* **1998**, *15*, 1509.

[26] M. P. Terpugova, Y. I. Amosov, I. L. Kotlyarevskii, R. N. Myasnikova, *Izvestiya Akademii Nauk SSR, Seriya Khimicheskaya* **1976**, *3*, 665; *Chem. Abstr.* **1976**, *85*, 21256.

[27] L. Doub, J. S. Kaltenbronn, D. Schweiss, *US Patent* 2954734, **1976**; *Chem. Abstr.* **1976**, *85*, 108683.

[28] C. A. Willoughby, K. T. Chapman, *Tetrahedron Lett.* **1996**, *37*, 7181.

[29] G. Goto, H. Yukimasa, M. Miyamoto, *Eur. Pat. Appl.* 449195, **1991**; *Chem. Abstr.* **1991**, *116*, 128671.

[30] K. Ogata, K. Ito, T. Sakaue, Y. Inoue, *PCT Int. Appl.* 2002032883, **2002**; *Chem. Abstr.* **2002**, *136*, 325570.

Supporting Materials

The ^{1}H NMR spectra for the reaction products are available in the appendix D in this thesis.

CHAPTER 6. APPLICATION OF A NEW BICYCLIC TRIAMINOPHOSPHINE LIGAND IN Pd-CATALYZED BUCHWALD-HARTWIG AMINATION REACTIONS OF ARYL CHLORIDES, BROMIDES, AND IODIDES

A paper published in *The Journal of Organic Chemistry*

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Abstract

The new bicyclic triaminophosphine ligand P(*i*-BuNCH$_2$)$_3$CMe (**3**) has been synthesized in three steps from commercially available materials and its efficacy in palladium-catalyzed reactions of aryl halides with an array of amines has been demonstrated. Electron-poor, electron-neutral, and electron-rich aryl bromides, chlorides, and iodides participated in the process. The reactions encompassed aromatic amines (primary or secondary) and secondary amines (cyclic or acyclic). It has also been shown that the weak base Cs_2CO_3 can be employed with ligand **3**, allowing a variety of functionalized substrates (e.g., those containing esters and nitro groups) to be utilized in our amination protocols. This ligand provides a remarkably general, efficient, and mild palladium catalyst for aryl iodide amination. Although **3** is slightly air and moisture sensitive, easy procedures can be adopted that avoid the need of a glovebox. Comparisons of the efficacy of **3** in these reactions with that of the proazaphosphatrane P(*i*-BuNCH$_2$CH$_2$)$_3$N (**2**) reveal that in addition to the opportunity for transannulation in **2** (but not in **3**), other significant stereoelectronic contrasts exist between these two ligands which help account for differences in the activities of the Pd/**2** and Pd/**3** catalytic systems.

Introduction

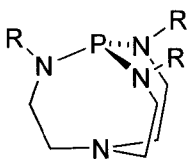
The synthesis of arylamines from amines and aryl halides (or halide equivalents such as tosylates and triflates) using palladium methodology has enjoyed considerable importance in the literature,[1] primarily owing to the fact that arylamines possess a diverse range of potential

applications in the pharmaceutical,[2] dye,[3] agricultural,[4] and polymer[5] industries. Aryl amines have also been demonstrated to be useful as ligands for transition metals.[6]

The palladium catalyzed process for the synthesis of arylamines has several advantages over commonly employed approaches such as nucleophilic aromatic substitution, Ullmann coupling,[7] reductive amination, and nitration followed by reduction. Advantages include better functional group compatibility, a one-step reaction, ready availability of starting materials from a myriad of commercial sources and relatively mild reaction conditions. The palladium-catalyzed cross-coupling of aryl halides and amines to generate arylamines was first studied by Migita[8] and subsequently developed by Buchwald and Hartwig.[1] The pioneering work of these investigators led to remarkable advances in our understanding of fundamental aspects of these reactions.[9] One such aspect is the proper choice of ligand that can stabilize catalytically active Pd(0) complexes. Lloyd-Jones recently noted, "Often unpredictably, the choice of ligand in Pd-catalyzed reactions can make surprisingly little difference or can open up new avenues".[10]

The variety of effective ligands that have been introduced for Pd-catalyzed amination reactions can be classified in terms of the three generations over which they have evolved. First generation catalyst systems included monodentate phosphines [e.g., P(*o*-tol)$_3$][11] while chelating bidentate phosphines such as BINAP[12] or DPPF[13] comprise second generation catalyst systems that greatly improved the scope of amination reactions. Further improvements came with the advent of electron-rich sterically hindered third generation phosphines such as P(*t*-Bu)$_3$[14] and *o*-(biphenyl)P(*t*-Bu)$_2$.[15] Non-phosphine ligands, such as *N*-heterocyclic carbenes (saturated as well as unsaturated) can also be considered to belong to this generation.[16] Third generation catalysts permitted the use of otherwise notoriously unreactive but cheaper aryl chlorides as substrates in amination reactions.

In recent years our explorations of the chemistry of proazaphosphatranes of type **1**, first synthesized in our laboratories, have shown them to be exceedingly potent catalysts, promoters and strong nonionic stoichiometric bases that facilitate a variety of useful organic transformations.[17] More recently, we discovered that commercially available **2** is a highly active ligand in Suzuki[18] and Buchwald-Hartwig amination reactions of aryl halides, including those of aryl chlorides.[19,20]



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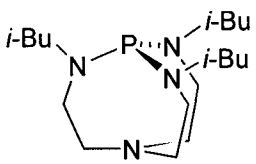
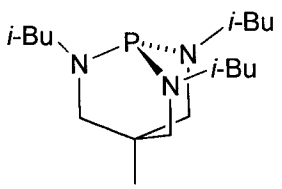


2



3

We believed that the unusually high activity of **2** in Suzuki and Buchwald-Hartwig amination reactions was due primarily to a) the electron-donating capability of the three planar PN_3 nitrogens, b) a desirable degree of bulk provided by the *iso*-butyl groups, and c) potential transannulation from the bridgehead nitrogen's lone pair to phosphorus.[18] Thus in contrast, acyclic triaminophosphines [e.g., $P(NMe_2)_3$ or $P(N\textit{i}\text{-}Bu_2)_3$] were shown to be very ineffective ligands in amination reactions partly because the phosphorus in these triaminophosphines is not sufficiently electron-rich owing to a departure of the conformation of these molecules from a C_{3v} arrangement of the $P(NC_2)_3$ moiety in which the unhybridized lone pair orbital on each nitrogen lies tangential to a circle whose plane is perpendicular to and contains the three-fold axis at its center.[21,22]

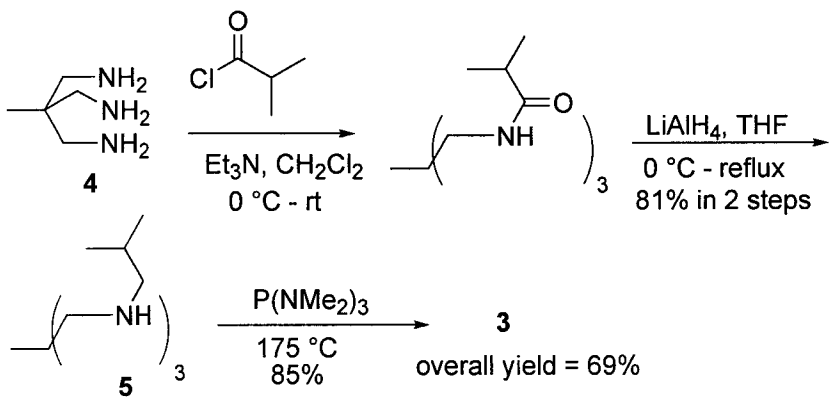
In view of the efficiency of ligand **2** in Buchwald-Hartwig amination reactions,[19,20] its bicyclic nature prompted us to speculate whether ligand **3** could also be employed in these reactions, since the two ligands are structurally quite similar. The three PN nitrogens in proazaphosphatranes such as **2** have virtually planar geometries and those in **3** can be assumed to be have the same property. Because **3** is a liquid (see below) that did not crystallize well at low temperature, the determination of its molecular structure by X-ray means was precluded. Such a study reported by us for the oxide analogue $OP(MeNCH_2)_3CMe$ revealed nearly perfect C_{3v} symmetry with a sum of the angles around the nitrogens of 357°.[23] As in this derivative of **3**, the three PN nitrogens in **3** are also capable of providing electron density to the phosphorus, thereby electronically enriching the $Pd(0)L_n$ complex for oxidative addition with aryl halides. In addition, the bulky *iso*-butyl groups in **3** would facilitate reductive elimination. Importantly, however, ligand **3** (unlike **2**) lacks the possibility for basicity enhancement through transannulation. Thus utilization of **3** as a ligand could potentially provide insight regarding the importance of transannulation in the activity of **2**. In this article, we describe the synthesis of a new ligand **3**, which though structurally

similar to **2**, has quite different stereoelectronic properties. Here we also present the utility of **3** in Pd-catalyzed Buchwald-Hartwig amination reactions of aryl chlorides, bromides and iodides and we provide a rationale for differences in the activity of the Pd/**3** and Pd/**2** systems.

Results and Discussion

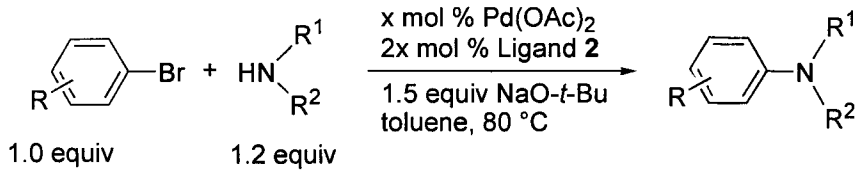
Synthesis of ligand 3. The triaminophosphine ligand **3** was synthesized from triamine **4** as summarized in Scheme 1. Although commercially available,[24] **4** can be easily prepared in three high-yield steps from cheaper and commercially available 1,1,1-*tris*(hydroxymethyl)ethane.[25] Treatment of triamine **4** with isobutyryl chloride followed by $LiAlH_4$ reduction resulted in the formation of *tri-iso*-butyl substituted amine **5** in 81% yield in two steps. Ring closure of **5** to **3** was achieved by heating the former in the presence of $P(NMe_2)_3$ at 175 °C for 48 h to afford **3** as a colorless liquid in 85% yield and in 69% overall yield from **4**. Ligand **3** was unambiguously characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy as well as elemental analysis (see Experimental Section). Remarkably, ^{31}P NMR spectroscopic monitoring of **3**, kept in the air for 40 h, revealed that about 90% of **3** remained unchanged. Interestingly, $P(t\text{-}Bu)_3$, a highly effective ligand for wide variety of Pd-catalyzed cross-coupling reactions,[26] including amination reactions, has been shown to be destroyed in air within 2 h.[15b] Although **3** showed a high degree of air and moisture stability, we recommend that it be stored under argon.

SCHEME 1



Catalytic activity of 3 in aryl bromide amination reactions. Our initial test of the efficacy of **3** in Pd-catalyzed amination reactions involved aryl bromides with NaO-*t*-Bu as the base. We were intrigued to discover that conditions developed for the amination reactions that employed **2** as the ligand[27] also worked for ligand **3**. The general reaction conditions for the coupling reaction are described in Scheme 2 and results are provided in Table 1.

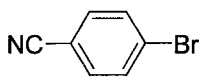
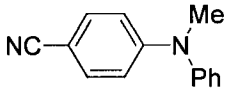
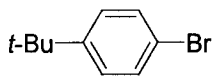
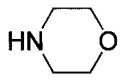
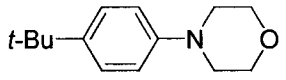
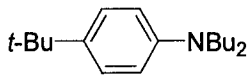
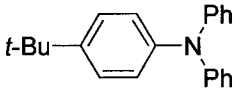
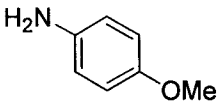
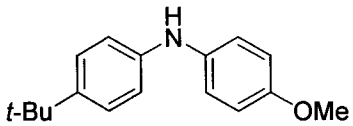
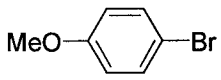
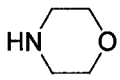
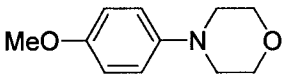
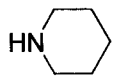
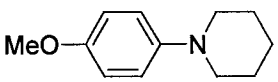
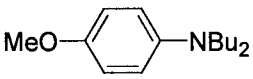
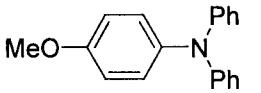
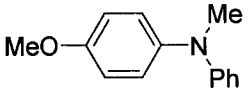
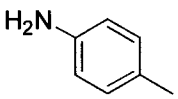
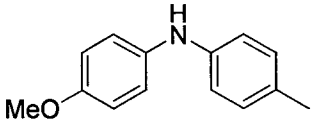
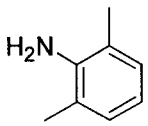
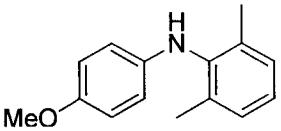
SCHEME 2



For the majority of substrates, 0.5 mol % Pd was sufficient to achieve high yields of arylamines, and most of these reactions were completed in less than 20 h. No attempts were made to optimize reaction times. Electron-poor, electron-neutral, and electron-rich aryl bromides, including, bromopyridines, were readily aminated with the $Pd(OAc)_2$/**3** catalyst system. Primary anilines with *ortho*-substituents and secondary anilines were efficiently coupled at 80 °C. As was the case with the $Pd(OAc)_2$/**2** catalyst system, amination reactions of highly sterically hindered substrates using $Pd(OAc)_2$/**3** also proceeded exceedingly well (entry 13, Table 1).[19] Hydrodehalogenation side products were detectable in most cases by TLC. The $Pd(OAc)_2$/**3** catalyst system was also effective for the arylation of cyclic secondary amines (entries 2, 6, 7 and 14, Table 1). Di-*n*-butylamine (a member of a normally difficult class of substrates) was also cleanly coupled, giving the desired product in very good to acceptable yields. For this class of amines, 2 mol % Pd was needed (entries 3, 8 and 15, Table 1). This result contrasts that observed when ligand **2** was employed, namely, that reactions of acyclic secondary amines proceeded in only moderate yields (57-70%) and required 5 mol % Pd.[19]

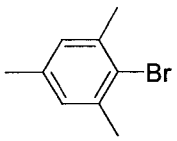
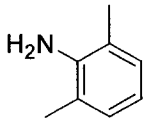
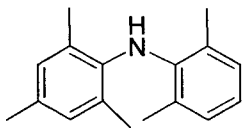
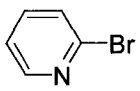
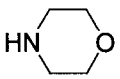
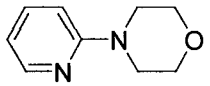
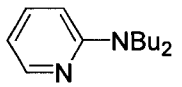
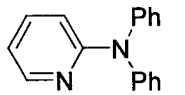
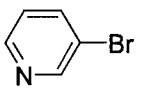
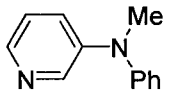
Unfortunately, long-chain (*n*-hexylamine) or branched primary aliphatic amines (cyclohexylamine) did not react cleanly under our conditions.

TABLE 1. Pd/**3**-Catayzed Amination of Aryl and Heteroaryl Bromides[a]

Entry	Bromide	Amine	mol % Pd	Product	Yield (%)[b]
1			0.5		96
2			0.5		93
3		Bu_2NH	2		95
4		Ph_2NH	1		94[c]
5			2		78[c]
6			1		92
7			0.5		67
8		Bu_2NH	2		73
9		Ph_2NH	2		95[c]
10			0.5		92
11			2		77[c]
12			2		93

[a] Conditions: 1.0 equiv of aryl bromide, 1.2 equiv of amine, 1.5 equiv of NaO-*t*-Bu, cat. $Pd(OAc)_2$, cat. Ligand **3** (2L/Pd), 3 mL of toluene, 80 °C, 15-20 h. Reaction times have not been optimized. [b] Isolated yields. [c] Reaction was performed at 100 °C. [d] $Pd_2(dba)_3$ used in place of $Pd(OAc)_2$.

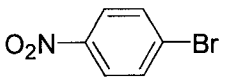
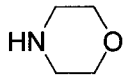
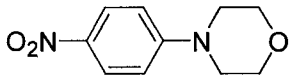
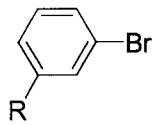
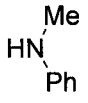
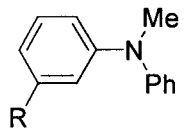
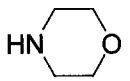
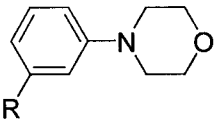
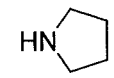
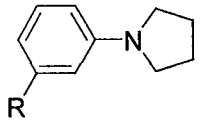
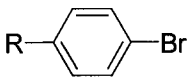
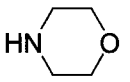
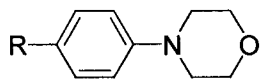
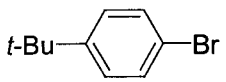
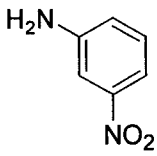
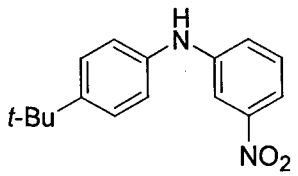
TABLE 1. Continued

Entry	Bromide	Amine	mol % Pd	Product	Yield (%)[b]
13			0.5		96
14			0.5		93
15		Bu_2NH	2		88
16		Ph_2NH	4		87[c,d]
17			5		84[d]

Although primary anilines without an *ortho*-substituent reacted poorly using the **3**/Pd catalyst system at 80 °C, a reaction temperature of 100 °C allowed efficient coupling of this class of anilines. For example, the reaction of 4-bromoanisole with *p*-toluidine proceeded to completion using 2 mol % $Pd(OAc)_2$ and 4 mol % **3** at 100 °C, affording the desired product in 77% yield (entry 11, Table 1). Similarly, 4-*tert*-butylbromobenzene coupled with *p*-anisidine to give a 78% yield of product (entry 5, Table 1).

Although the above protocol is reasonably useful, it involves the use of NaO-*t*-Bu as the base, thus rendering the conditions ineffective for aryl halides containing base-sensitive functional groups. After surveying a range of bases, we were pleased to find that the weaker base Cs_2CO_3 could also be employed in the presence of the Pd/**3** catalyst system, and examples of amination reactions demonstrating the use of this base are reported in Table 2. In most cases these reactions proceeded successfully at 80 °C with 1 mol % $Pd(OAc)_2$ and 2 mol % **3**. It is worth noting that by contrast, alkylphosphine catalysts [biphenyl- or ferrocenyl-based, or P(*t*-Bu)$_3$] generally require heating up to 100 °C for the amination of functionalized aryl bromides.[14a,15b,28]

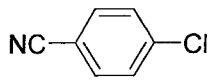
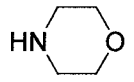
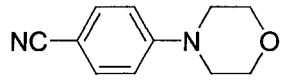
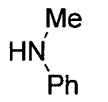
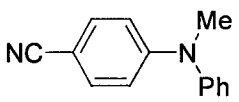
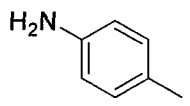
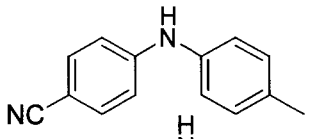
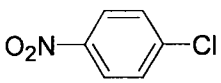
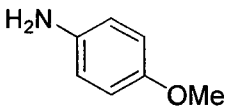
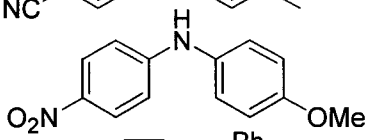
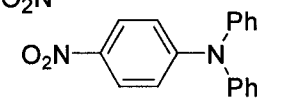
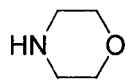
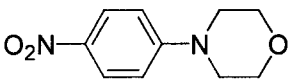
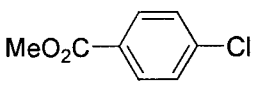
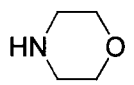
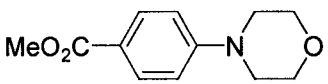
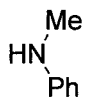
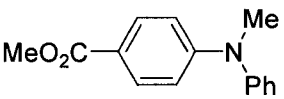
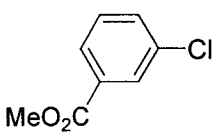
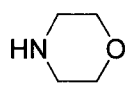
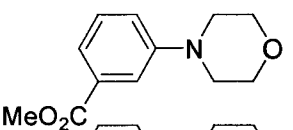
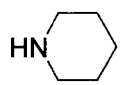
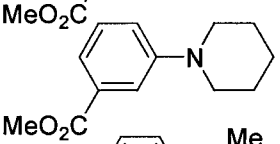
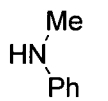
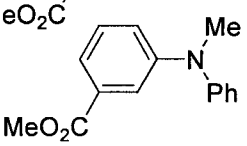
TABLE 2. $Pd(OAc)_2$/**3**-Catalyzed Amination of Functionalized Aryl Bromides[a]

Entry	Bromide	Amine	Product	Yield (%)[b]
1				95
2				97
3				92[c]
4				42[c]
5				85[c]
6				61[d]

[a] Conditions: 1.0 equiv of aryl bromide, 1.2 equiv of amine, 1.5 equiv of Cs_2CO_3, 1.0 mol % $Pd(OAc)_2$, 2.0 mol % Ligand **3** (2L/Pd), 3 mL of toluene, 80 °C, 15-20 h. Reaction times have not been optimized. [b] Isolated yields. [c] R = CO_2Me. [d] Reaction was performed at 100 °C.

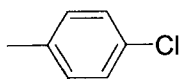
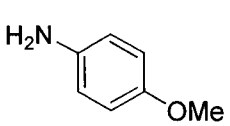
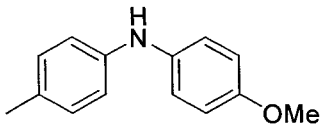
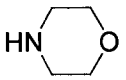
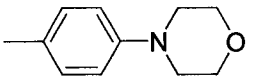
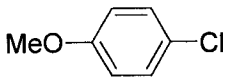
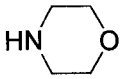
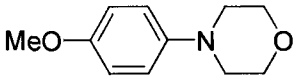
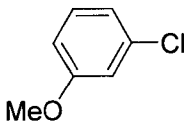
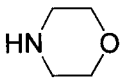
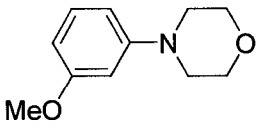
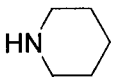
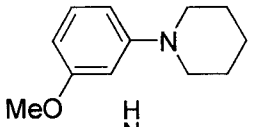
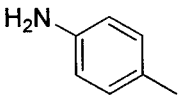
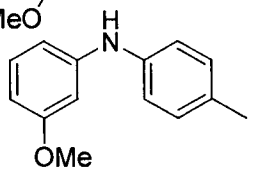
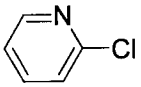
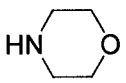
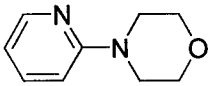
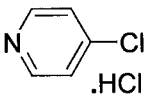
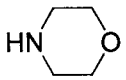
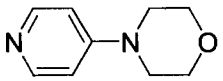
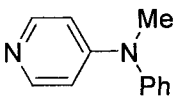
Catalytic activity of 3 in aryl chloride amination reactions. The utilization of aryl chlorides in Pd-catalyzed cross-coupling reactions is important from a commercial as well as an academic standpoint. Consequently, a significant proportion of recent papers on amination reactions have focused on the use of aryl chlorides as substrates. The results of our investigations of such couplings using the Pd/**3** catalyst system are summarized in Table 3. We found that a higher catalyst loading (4 mol % Pd) and a reaction temperature of 110 °C was needed to drive the reactions to completion. In a control experiment, the reaction of activated 4-chloronitrobenzene with morpholine in toluene at 110 °C gave

TABLE 3. Pd/**3**-Catalyzed Amination of Aryl Chlorides[a]

Entry	Chloride	Amine	Product	Yield (%)[b]
1				91[d]
2				93[c]
3				97[c]
4				97[c]
5		Ph_2NH		92[c]
6				97[c]
7				98[c,d]
8				85[c]
9				77[c]
10				70[c]
11				92[c]

[a] Conditions: 1.0 equiv of aryl chloride, 1.2 equiv of amine, 1.5 equiv of NaO-*t*-Bu, 2.0 mol % $Pd_2(dba)_3$, 8.0 mol % Ligand **3** (2L/Pd), 3 mL of toluene, 110 °C, 24 h. Reaction times have not been optimized. [b] Isolated yields. [c] Cs_2CO_3 used in place of NaO-*t*-Bu. [d] $Pd(OAc)_2$ used in place of $Pd_2(dba)_3$.

TABLE 3. Continued

Entry	Chloride	Amine	Product	Yield (%)[b]
12				77[c]
13				70
14				52
15				55
16				64[c]
17				69[c]
18				87[c]
19				85[d]
20				84[d]

no desired product in the presence of Cs_2CO_3. A similar experiment conducted with 4 mol % of $Pd(OAc)_2$ without any added ligand resulted in the formation of only a trace amount of product after 36 h. Among the solvents tested (toluene, THF, dioxane, and DME) toluene was found to be the most effective. Either $Pd(OAc)_2$ or $Pd_2(dba)_3$ can be used as the palladium(0) precursor. As expected, the best yields were obtained with aryl chlorides possessing electron-withdrawing groups, but electron-neutral and electron-rich aryl chlorides provided good to moderate yields of desired product. Cyclic secondary amines, secondary

anilines, primary anilines, and diphenyl amine participated well in our amination process. In contrast to aryl chloride aminations involving ligand **3**, those using ligand **2** can be performed at a lower temperature (80 °C) providing good to excellent yields with electronically diverse systems.[20]

Catalytic activity of 3 in aryl iodide amination reactions. Although more reactive, aryl iodides usually provide lower yields than their bromide counterparts in such reactions. Catalyst systems that have been described in the literature involve toxic additives such as 18-crown-6,[29] higher catalyst loading (up to 5 mol %),[13] lack of generality,[16b] and the use of the strong base (NaO-*t*-Bu).

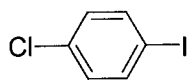
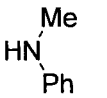
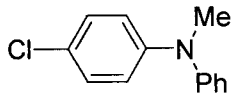
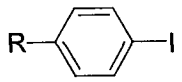
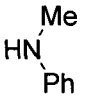
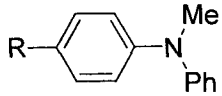
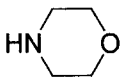
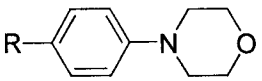
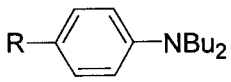
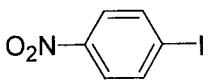
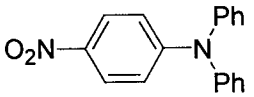
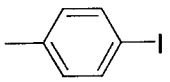
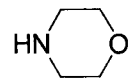
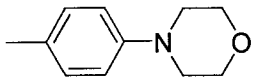
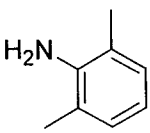
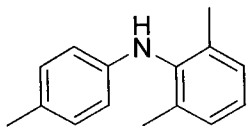
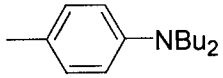
Recently, Buchwald's group has reported an efficient procedure for the coupling of aryl iodides with amines using biphenyl-based phosphine ligands and Xantphos, a chelating bisphosphine.[30] Although their procedure was effective when NaO-*t*-Bu was the base, reactions involving Cs_2CO_3 had several disadvantages. Firstly, higher temperatures were required to achieve good yields (100 °C or 120 °C). Secondly, co-solvents (Et_3N or *t*-BuOH) were needed for rate enhancements. Thirdly, secondary acyclic amines and diarylamines were problematic. The single case of a reaction involving an acyclic secondary amine that was described utilized electronically favored 4-iodobenzophenone as a substrate and that reaction required 5 mol % Pd loading. Since the appearance of that report, we described a Pd catalyst system utilizing ligand **2** for the amination of aryl iodides[19] which though attractive, utilized the strong base (NaO-*t*-Bu) which limits substrate scope. Thus a catalyst system that can achieve a higher degree of versatility for aryl iodide aminations would be desirable.

By an extension of our amination experiments that gave promising results with aryl bromides and chlorides, we found that the $Pd(OAc)_2$/**3** catalyst system, in combination with Cs_2CO_3 as the base, allowed a variety of aryl iodides to couple successfully with amines at 80 °C (20-40 °C lower than the literature reports).

Exceptions to this approach were the reactions where primary aniline lacking an *ortho*-substituent was used as a coupling partner. For unfunctionalized substrates, NaO-*t*-Bu was also able to function as the base. For activated aryl iodides and for one example of a deactivated aryl iodide, 0.5 mol % of Pd led to excellent yields of diarylamines (entries 1, 2, 3 and 11, Table 4). The use of 2 mol % of Pd allowed the reaction of unactivated and

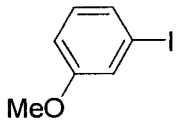
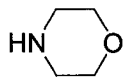
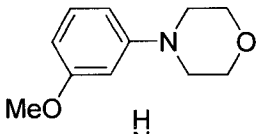
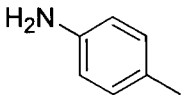
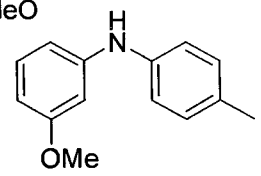
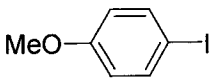
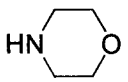
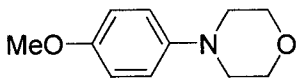
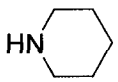
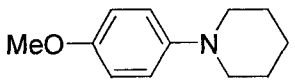
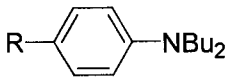
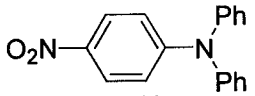
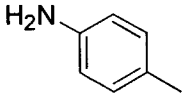
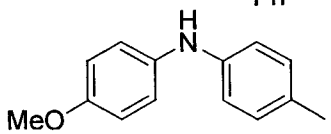
deactivated aryl iodides to occur in good yields (entries 6, 7, 11 and 12, Table 4). As observed with aryl bromides, reactions of aryl iodides with primary anilines lacking an *ortho*-substituent required the use of a somewhat higher reaction temperature (entries 10 and 15, Table 4). Reactions of an acyclic secondary amine with aryl iodides also occurred at 80 °C (entries 4, 8 and 13, Table 4). Reactions of diphenylamine also proceeded smoothly at 100 °C with the Pd/**3** catalyst system when Cs_2CO_3 was employed (entries 5 and 14, Table 4). As with aryl bromides, reactions of aryl iodides with primary aliphatic amines gave poor results when Cs_2CO_3 or NaO-*t*-Bu was employed as the base. Notwithstanding this limitation, it appears that the Pd/**3** catalyst system utilizing Cs_2CO_3 as the base is the most efficient, general and mild catalytic combination reported to date for the amination of aryl iodides.

TABLE 4. $Pd(OAc)_2$/**3**-Catalyzed Amination of Aryl Iodides[a]

Entry	Iodide	Amine	mol % Pd	Product	Yield (%)[b]
1			0.5		96
2			0.5		93[c]
3			0.5		93[c]
4		Bu_2NH	2		90[c]
5		Ph_2NH	1		80[d]
6			2		77
7			2		97
8		Bu_2NH	2		80

[a] Conditions: 1.0 equiv of aryl iodide, 1.2 equiv of amine, 1.5 equiv of Cs_2CO_3, cat. $Pd(OAc)_2$, cat. ligand **3** (2L/Pd) 3 mL of toluene, 80 °C, 15-20 h. Reaction times have not been optimized. [b] Isolated yields. [c] R = CO_2Et. [d] Reaction was performed at 100 °C.

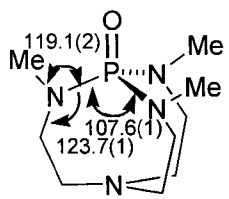
TABLE 4. Continued

Entry	Iodide	Amine	mol % Pd	Product	Yield (%)[b]
9			0.5		83
10			2		75[d]
11			0.5		96
12			2		77
13		Bu_2NH	5		60
14		Ph_2NH	4		83[d]
15			2		71[d]

Salient features of a convenient reaction protocol. Although ligand **3** is slightly moisture and air-sensitive, easy procedures can be adopted that avoid the need for a glove box. A stock solution of **3** was prepared in toluene, and the appropriate amount was collected using a syringe. NaO-*t*-Bu and Cs_2CO_3 were stored inside the glove box and were removed (in small amounts) to the outside just before the use. Thus, for all the reactions presented in this paper, aryl halide (if solid), amine (if solid), base and palladium acetate were weighed in air in a Schlenk flask. The flask was then evacuated and purged with argon three times. Ligand **3** was then added via syringe and also aryl halides and amines (if liquids). However, it was determined that the order of addition of reagents was not important.

Stereoelectronic comparisons of ligands 2 and 3. The difference in reactivity between **2** and **3** in palladium-catalyzed aryl halide aminations can be attributed to the presence of interesting contrasts in their stereoelectronic properties. Because of the greater constraint in

the bicyclic smaller cage framework of **3** relative to **2**, steric protection of the phosphorus in the former by the isobutyl groups may well be diminished substantially. This suggestion is supported by the PNC_{exo} bond angle of 119.1(2)° in **6**[31] and 126.3(2)° in **7**.[23] We believe that a similar difference in PNC_{exo} bond angles exists between the trivalent



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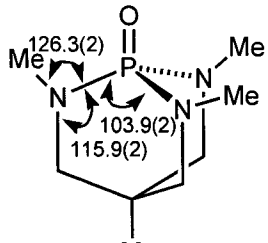
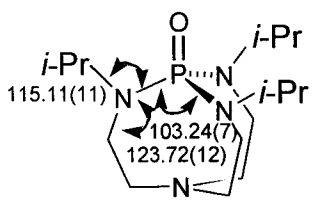


7 Me

phosphorus ligands **2** and **3**, although structural data are available only for **8**[32] which is an analogue of **2**. Thus the average of the PNC_{exo} bond angles in **8** [115.11(11)°] represents a ca 4° decrease from that in **6** owing to narrowing of the NPN bond angle in **8**, while the PNC_{cage} angle remains quite constant in both compounds. A similar decrease in PNC_{exo} angle from **7** to **3** can be expected for the same reason. Support for the suggestion that the PNC_{cage} angle remains quite constant upon oxidation (or coordination) of the phosphorus, emanates from a comparison of the structural metrics of **9**[33] and **10**[34] in which opening of the OPO bond angle from **10** to **9** does not greatly affect the POC angle.



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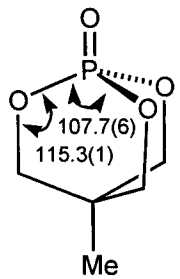

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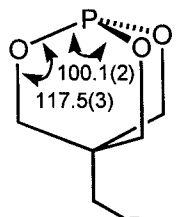

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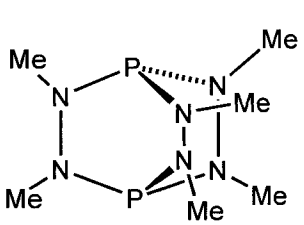
Although the structures of **11**[35] and **12**[36] have been obtained by crystallographic means, the standard deviations for the metrics of interest in **11** are too large (3 to 4°) to make a useful comparison for our purposes. For crystallographic metric differences to be significant, we believe they should be outside 3 x esd values. As expected on the foregoing discussion, the NPN [103.7(2)°] and PNN [113.6(3)°] bond angles in **12** are similar to their counterparts in **7**.[37]



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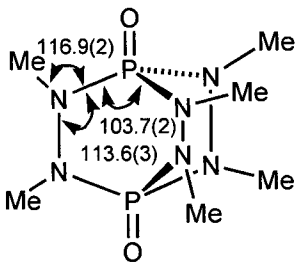

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It thus appears that any opening of the NPN bond angle in **2** or **3** upon coordination to the palladium(II) center in the oxidative addition intermediate would result mainly in widening of the PNC_{exo} angle by perhaps comparable amounts in each ligand, thereby reducing steric hindrance to coordination. The smaller steric encumbrance of the phosphorus in **3** compared with that in **2** (stemming from the larger PNC_{exo} angle in the former) would enhance the donor capability of the phosphorus of **3**, thereby favoring the oxidative addition step. The greater constraint in **3** also confers on it a more rigid C_{3v} symmetry that maximizes electron donation from each PN_3 nitrogen lone pair to the phosphorus,[38] whereas in **2**, conformational inversion around the molecular axis between extreme C_3 conformations mitigates such electron donation. Thus in the absence of transannulation in **2**, **3** can be assumed to be the more basic ligand based on its larger PNC_{exo} angle and its conformational rigidity.

The idea that the basicity of ligand **3** is greater than that of untransannulated **2**, but less than that of transannulated **2** can be used to rationalize observed differences in the activities of these ligands in palladium assisted aminations of aryl halides. In the case of aryl bromides and iodides, the scope of such reactions supported by the Pd/**3** system appears at first glance to be quite similar to that facilitated by the Pd/**2** system. However, the scope is actually greater for the Pd/**3** system because substrates bearing base-sensitive substituents are much better tolerated. As with aryl bromides and iodides, the Pd/**3** system is also effective in catalyzing aminations of aryl chlorides possessing base-sensitive substituents. This advantage can be rationalized on the basis of the more weakly basic nature of **3** compared with **2** if transannulation of **2** in the oxidative addition intermediate of these aryl halides (Figure 1) is occurring to some significant degree.[39] The relatively poor σ-donor ability of **3** compared with transannulated **2** in the arylPd(II)amine(X) complex (Figure 1) allows the amine to bind

more tightly when **3** is the ligand, thus rendering the N-H proton more acidic, consequently enabling a relatively weak base such as Cs_2CO_3 to function. It should be noted that attempts to isolate an oxidative addition intermediate with **3** or with **2** (or sterically less hindered analogues of the latter) have thus far failed.

The general and substantial increase in activity of the Pd/**2** system relative to the Pd/**3** system in aminations of aryl chlorides not bearing base-sensitive substituents, suggests that **2** transannulates to a greater extent in the corresponding aryl chloride than in aryl bromide or aryl iodide oxidative addition intermediates, owing to the presence of a more electronegative halide on the aryl chloride oxidative addition intermediate. This intermediate is thus stabilized by enhanced phosphorus atom basicity[33] in **2** through enhanced transannulation in this ligand.

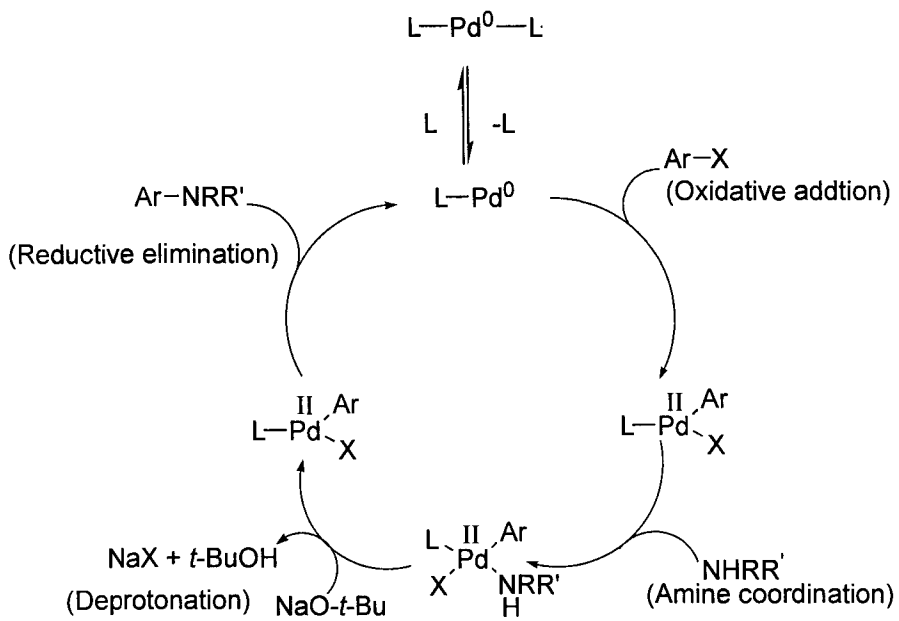

Figure 1. Outline of the Catalytic Cycle for Buchwald-Hartwig Amination Reactions.

In summary, the new bicyclic triaminophosphine ligand **3**, which was synthesized in three facile steps, generates a very active and broadly useful Pd catalyst system for Buchwald-Hartwig amination reactions. Couplings of an electronically diverse array of aryl halides with amines are realized in good to excellent yields. In addition, the use of Cs_2CO_3 in the presence of ligand **3** in these reactions permits aryl chlorides, bromides and iodides with base-sensitive

functional groups to be aminated efficiently. It appears that though the basicity of **3** is greater than that of untransannulated **2** this relationship can be reversed on coordination of these ligands in their respective Pd(II) oxidative addition intermediates arising from aryl halides. Although it has been shown that significant versatility can be achieved in the amination of aryl bromides and iodides using the Pd/**3** catalyst system, there are limitations to our protocol. Thus aminations of aryl chlorides require higher catalyst loading and a reaction temperature of 110 °C, and primary alkyl amines (normal or branched chain) do not function well as reagents. The same is true for the Pd/**2** system except that the reactions can be carried out at 80 °C.

Experimental Section

General Considerations: All reactions were performed under an atmosphere of argon in oven-dried glassware. Toluene was collected from a Solvent Purification System and stored over 4 Å molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates and visualized with short wavelength UV light (254 nm). Silica gel 60 (9385, 230-400 mesh) was used for column chromatography. The yields reported are isolated yields and are the average of at least two runs. All commercially available reagents were used as received. For convenience, a stock solution of **3** in toluene (2 mM) was prepared and stored under argon. All compounds described in Tables 1-4 are known in the literature and were characterized by comparing their ^{1}H and ^{13}C NMR or mass spectra to the previously reported data. In all cases, the comparisons were very favorable.

Synthesis of Bicyclic Ligand 3.

Isobutyryl chloride (80.0 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise to a mixture of *tris*(2-aminomethyl)ethane **4** (20.0 mmol) and triethylamine (80.0 mmol) in 40 mL of dry CH_2Cl_2 at 0 °C. The mixture was stirred at room temperature overnight. After filtering the precipitate that formed, the filtrate was concentrated on a rotary evaporator and then diluted with water (30 mL). The product was extracted with EtOAc (3 x 100 mL) and then the organic layers were combined, dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a slurry which was used in the next step without further purification. The

slurry (18.0 mmol, as crude product) in 50 mL of dry THF was added dropwise to a solution of $LiAlH_4$ (126.0 mmol) in 200 mL of dry THF over a period of 30 min. The mixture was then refluxed for three days after which it was cooled to 0 °C. Fifty mL of a 10 % KOH solution in water was then added and the mixture was again heated to reflux for 4 h. The white precipitate that had formed was filtered, washed with hot THF (3 x 100 mL) and the filtrates were then combined. THF was removed under reduced pressure and the crude product obtained was distilled under vacuum to afford **5** in 81% yield from **4** as a colorless oil (bp: 78-80 °C/200 mTorr). ^{1}H NMR ($CDCl_3$) δ 0.86 (d, 21 H, J = 6.7 Hz), 1.53 (broad s, 3H), 1.65 (m, 3H), 2.33 (d, 6H, J = 6.6 Hz), 2.50 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.8, 28.3, 38.4, 58.6, 59.3. Anal. Calcd. for $C_{17}H_{39}N_3$: C, 71.58; H, 13.68; N, 14.74. Found: C, 71.71; H, 13.30; N, 14.66.

tris(2-*i*-Butylaminomethyl)ethane **5** (8.8 mmol) and $P(NMe_2)_3$ (9.0 mmol) were charged to a 50 mL flask under Ar. The flask was placed in a 175 °C oil bath and the reaction mixture was stirred for three days at that temperature. The crude material obtained was distilled under vacuum to afford **3** in 85% yield (overall yield from **4**, 69%) as a colorless oil (bp: 80-82 °C/200 mTorr). ^{1}H NMR (C_6D_6) δ 0.58 (s, 3H), 0.88 (d, 18H, J = 6.6 Hz), 1.70 (m, 3H), 2.46 (d, 6H, J = 3.1 Hz), 2.62 (m, 6H). ^{13}C NMR (C_6D_6) δ 20.4, 22.6, 27.0 (d, J = 11.0 Hz), 34.3 (d, J = 1.6 Hz), 59.8 (d, J = 4.0 Hz), 61.6 (d, J = 25.0 Hz). ^{31}P NMR (C_6D_6) δ 81.6. Anal. Calcd. for $C_{17}H_{36}N_3P$: C, 65.17; H, 11.50; N, 13.42. Found: C, 64.27; H, 11.70; N, 13.64.

$Pd(OAc)_2$/3-Catalyzed Amination of Aryl and Heteroaryl Bromides (Table 1). *General Procedure:* An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (x mol %, see Table 1) and NaO-*t*-Bu (1.5 mmol). Amine (1.2 mmol) and aryl bromide (1.0 mmol) were also added at this time, if they were solids. The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **3** (2x mol %, see Table 1) was then added via syringe from a stock solution. Aryl bromide (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol) and toluene (3 mL) were then successively added by syringe. The reaction mixture was heated at the temperature indicated in Table 1 until the starting material had been completely consumed as judged by TLC (15-20 h). The mixture was then cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

$Pd(OAc)_2$/3-Catalyzed Amination of Functionalized Aryl Bromides (Table 2). *General Procedure:* An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (x mol %, see Table 2) and Cs_2CO_3 (1.5 mmol). Amine (1.2 mmol) and aryl bromide (1.0 mmol) were also added at this time, if they were solids. The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **3** (2x mol %, see Table 2) was then added via syringe from a stock solution. Aryl bromide (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol) and toluene (3 mL) were then successively added by syringe. The reaction mixture was heated at a temperature indicated in Table 2 until the starting material had been completely consumed as judged by TLC (15-20 h). The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography using a mixture of hexanes and ethyl acetate as eluent.

$Pd(OAc)_2$ or $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl chlorides (Table 3). *General Procedure:* An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ or $Pd_2(dba)_3$ (x mol %, see Table 3) and NaO-*t*-Bu (1.5 mmol) or Cs_2CO_3 (1.5 mmol). Amine (1.2 mmol) and aryl chloride (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **3** (2x mol %, see Table 3) was then added via syringe from a stock solution. Aryl chloride (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol) and toluene (3 mL) were then successively added by syringe. The reaction mixture was heated at 110 °C until the starting material had been completely consumed as judged by TLC (24 h). The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

$Pd(OAc)_2$/3-Catalyzed Amination of Aryl Iodides (Table 4). *General Procedure:* An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (x mol %, see Table 4) and NaO-*t*-Bu (1.5 mmol) or Cs_2CO_3 (1.5 mmol). Amine (1.2 mmol) and aryl iodide (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated and then flushed with argon. This cycle was repeated three times. Ligand **3** (2x mol %, see Table 4) was then added via syringe from a stock solution. Aryl iodide (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol) and toluene

(3 mL) were then successively added by syringe. The reaction mixture was heated at a temperature indicated in Table 4 until the starting material had been completely consumed as judged by TLC (15-20 h). The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography (hexanes/ethyl acetate as eluent).

Acknowledgment

The authors thank the National Science Foundation for financial support in the form of a grant.

Supporting Information Available

^{1}H and ^{13}C NMR spectra for all compounds, references for products in Tables 1-4, and ^{31}P NMR spectra fro ligand **3**. Thiis material is available free of charge via the Internet at http://pubs.acs.org. This is also available in the appendix E in this thesis.

References

1. (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 805. (f) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046.

2. Beland, F. A.; Kadlubar, F. F. *Handbook of Experimental Pharmacology, Carcinogenesis and Mutagenesis*; Grove, Springer, Verlag: Heidelberg, Germany, 1990.

3. Waring, D. R.; Hallas, G. *The Chemistry and Application of Dyes*; Plenum: New York, 1990.

4. *CRC Handbook of Pesticides*; Milne, G. W. A., Ed.; CRC Press: Boca Raton, FL, 1994.

5. (a) Mukundan, T. *Macromol. Mater. Eng.* **2002**, *287*, 442. (b) Skotheim, T. A.; Elsenbaumer, R. L.; Reynolds, J. R. *Handbook of Conducting Polymers*, 2nd ed.; Marcel Dekker: New York, 1997.

6. (a) Westmoreland, I.; Munslow, I. J.; O'Shaughnessy, P. N.; Scott, P. *Organometallics* **2003**, *22*, 2972. (b) Greco, G. E.; Popa, A. I.; Schrock, R. R. *Organometallics* **1998**, *17*, 5591.

7. For recent work on copper-catalyzed Ullmann coupling, see: (a) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (c) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791.

8. Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

9. For mechanistic studies, see: (a) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. (b) Stambuli, J. P.; Buhl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346. (c) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905. (d) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618 and references therein.

10. Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953.

11. (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348.

12. (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (b) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359. (c) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

13. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

14. (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

15. (a) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413. (b) Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

16. (a) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (d) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307.

17. For a recent review, see: Verkade, J. G. *Top. Curr. Chem.* **2002**, *233*, 1.

18. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

19. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

20. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

21. (a) Molloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696. (b) Xi, S. K.; Schmidt, H.; Lensink, C.; Kim, S.; Wintergrass, D.; Daniels, L. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1990**, *29*, 2214. (c) Socol, S. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 88. (d) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1980**, *34*, 365. (e) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1979**, *33*, 187.

22. For a discussion of the electronic structure of tris(dialkylamino)phosphines, see: Cowley, A. H.; Lattman, M.; Stricklen, P. M.; Verkade, J. G. *Inorg. Chem.* **1982**, *21*, 543.

23. Clardy, J. C.; Kolpa, R. L.; Verkade, J. G. *Phosphorus* **1974**, *4*, 133.

24. Available from Fluka.

25. Fleischer, E. B.; Gebala, A. E.; Levey, A.; Tasker, P. A. *J. Org. Chem.* **1971**, *36*, 3042.

26. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

27. Reactions were also performed with the trimethyl and triisopropyl analogues of ligand **2**. For the reaction shown in Table 1, entry 6, the trimethyl analogue provided less than 20% yield whereas triisopropyl analogue yielded 62% of the coupled product with 2 mol % of Pd in both cases.

28. Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

29. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

30. Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.

31. Tang, J.-S.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931.

32. Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69.

33. Nimrod, D. M.; Fitzwater, D. R.; Verkade, J. G. *J. Am Chem. Soc.* **1968**, *90,* 2780.

34. Milbrath, D. S.; Springer, J. P.; Clardy, J. C.; Verkade, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 5493.

35. Vandoorne, W.; Hunt, G. W.; Perry, R. W.; Cordes, A. W. *Inorg. Chem.* **1971**, *10*, 2591.

36. Gilje, J. W.; Seff, K. *Inorg. Chem.* **1972**, *11*, 1643.

37. However, the PNC angle in **12** [116.9(2) °] is considerably smaller than this angle in **7**, which may be associated with the observation that the nitrogens in **12** are not planar. See ref 35.

38. (a) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065. (b) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721.

39. The existence of variable degrees of transannulation in adducts of proazaphosphatranes has been documented from crystallographic data. See ref 17.

ERRATUM SUBMITTED TO THE JOURNAL OF ORGANIC CHEMISTRY

Reference 1e is incorrect. It should read: Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

CHAPTER 7. SYNTHESIS OF *N*-ARYL-AZA-CROWN ETHERS VIA Pd-CATALYZED AMINATION REACTIONS OF ARYL CHLORIDES WITH AZA-CROWN ETHERS

A paper published in the *Tetrahedron*

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Abstract

The $Pd_2(dba)_3$/P(*i*-$BuNCH_2CH_2)_3N$ (**1**) catalyst system effectively catalyzes the coupling of aza-crown ethers with electronically diverse aryl chlorides, affording *N*-aryl-aza-crown ethers in good yields. The $Pd_2(dba)_3$/P(*i*-$BuNCH_2)_3CMe$ (**2**) catalyst system containing the more constrained bicyclic triaminophosphine is useful for aryl chlorides possessing base-sensitive ester, nitro, and nitrile functional groups.

1. Introduction

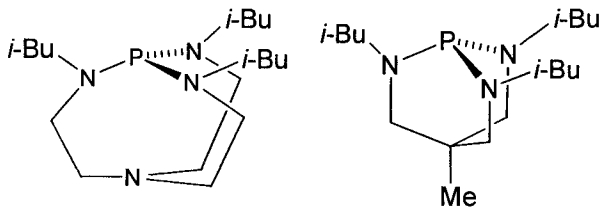
The chemistry of *N*-aryl-aza-crown ether derivatives is attracting significant interest because of the utility of these compounds in synthesizing fluoroionophores in which, for example, a fluorescent aryl moiety is covalently linked to the nitrogen of an aza-crown ether.[1] These molecules can serve as sensitive and selective sensors of cations by binding them in the crown ether, thereby modifying the intensity and/or the energy of the signal of the fluorophore. Pyridine-functionalized aza-crown ethers have also been used as a scaffold for self-assembly in supramolecular chemistry.[2] Traditional approaches to the preparation of *N*-aryl-aza-crown ethers include nucleophilic aromatic substitution of activated aryl halides with aza-crown ethers under high pressure conditions,[3] or manipulation of functional groups on aniline precursors.[4] However, these approaches suffer from one or more of the following problems that impede accessibility to this important class of compounds: stringent conditions, multiple step syntheses, low yields, and limited substrate scope.

In recent years, palladium-catalyzed Buchwald-Hartwig amination reactions of aryl halides with amines have emerged as a method of choice for C-N bond forming processes.[5-7] In this

respect, Witulski et al.[8] have developed a Pd/PPh_3 and a $Pd/P(o\text{-tol})_3$ catalyst system for the coupling of aryl and heteroaryl bromides with aza-crown ethers. However, this method was limited to electron-poor aryl and heteroaryl bromides. Interestingly, the use of $P(t\text{-Bu})_3$,[7] a popular ligand for Pd-catalyzed amination reactions, gave inferior results probably because of its steric bulk.

An improvement to the above protocol was described by Zhang and Buchwald[9] who achieved cross-coupling of aryl bromides with aza-crown ethers using a catalyst system comprised of $Pd_2(dba)_3$ and biphenyl-based monophosphine ligands with NaO-*t*-Bu as the base. Although electronically diverse and also *ortho*-substituted aryl bromides could be employed in these reactions, limitations still existed. For example, the authors noted that poor yields of *N*-aryl-aza-crown ethers were obtained when weak bases such as Cs_2CO_3 or K_3PO_4 were used in place of NaO-*t*-Bu, thus precluding the introduction of various base-sensitive functional groups into the aryl substrate. A particularly important apparent limitation was that no examples employing aryl chlorides as the coupling partner were reported. Aryl chlorides are cheaper and are available in wider diversity than bromides or iodides, and their applicability in coupling with aza-crown ethers would constitute a significant advance, especially since aza-crown ethers are currently quite expensive. We report here a general and efficient method for the synthesis of *N*-aryl-aza-crown ethers via a palladium-catalyzed amination reaction of aryl chlorides that occurs in the presence of bicyclic triaminophosphine ligands **1** and **2**.

Our recent explorations in palladium-catalyzed cross coupling reactions have established that electron-rich and commercially available proazaphosphatrane **1** (Fig. 1), first synthesized in our laboratories, serves as an excellent ligand in Suzuki,[10] Buchwald-Hartwig amination,[11] Stille,[12] and *alpha*-arylation[13] reactions. Notoriously unreactive aryl chlorides can also be employed in these transformations. We have also developed a new bicyclic triaminophosphine ligand **2** (Fig. 1) for which we have demonstrated utility in Buchwald-Hartwig amination reactions.[14] It was noted that ligand **2** is especially useful for substrates with functionalities that require a weak base such as Cs_2CO_3.

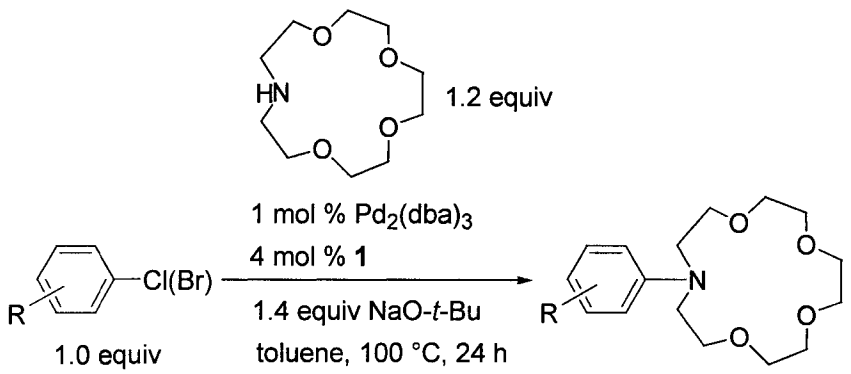


1 2

Figure 1. Bicyclic Triaminophosphine Ligands

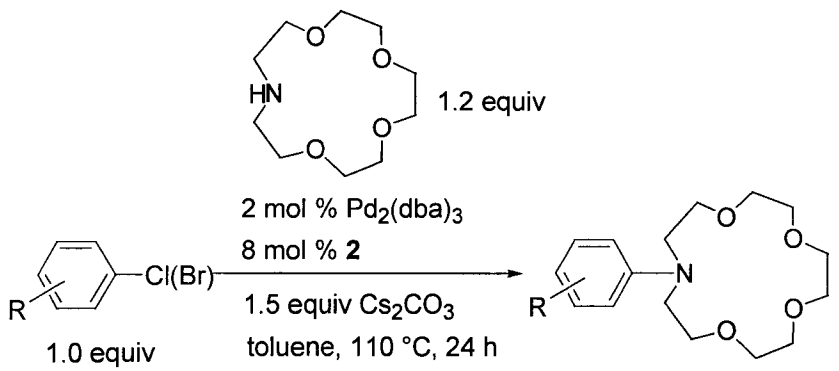
2. Results and discussion

We initially investigated the coupling of commercially available 1-aza-15-crown-5 with aryl chlorides. After brief experimentation, we established that a variety of aryl chlorides can be coupled with 1-aza-15-crown-5 using 1 mol% $Pd_2(dba)_3$ and 4 mol% ligand **1** in toluene at 100 °C (Scheme 1) in the presence of NaO-*t*-Bu as the base.



Scheme 1. Conditions for $Pd_2(dba)_3$/**1**-Catalyzed Synthesis of N-Aryl-Aza-Crown Ethers

Not surprisingly, aryl chlorides possessing an ester, nitro or nitrile group did not fare well in this approach. For these substrates, however, conditions developed by us utilizing **2** as the ligand in the presence of the mild base Cs_2CO_3 proved to be gratifyingly efficacious (Scheme 2).

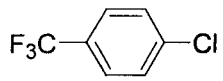
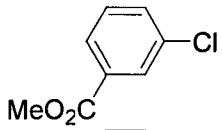
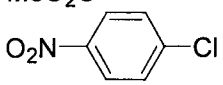
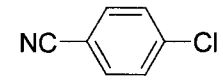
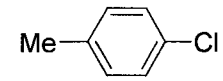
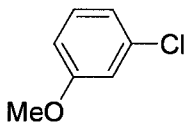
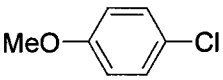
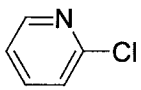
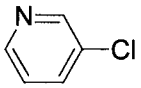
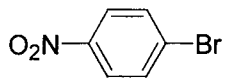
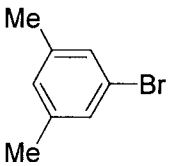


Scheme 2. Conditions for $Pd_2(dba)_3$/**2**-Catalyzed Synthesis of N-Aryl-Aza-Crown Ethers Possessing Base-Sensitive Functional Groups

The potential and scope of this methodology is illustrated in Table 1 by the reaction of a variety of aryl chlorides and bromides with 1-aza-15-crown-5. It is seen in this table that electronically diverse aryl chlorides as well as bromides can be coupled successfully in good to excellent yields with the aza-crown ether. Using the $Pd_2(dba)_3$/**1** catalyst system (2 mol% Pd), electron-poor 4-chlorobenzotrifluoride afforded the desired product in 86% yield (entry 1). Electron-neutral 4-chlorotoluene also reacted efficiently (80% product yield, entry 5). Electron-rich 4-chloroanisole, a more challenging substrate, also functioned as a substrate, providing the desired *N*-aryl-aza-crown ether in moderate yield (50%, entry 7). The *meta*-substituted aryl chloride, 3-chloroanisole also coupled, giving a 66% product yield (entry 6). Notably, 2-chloropyridine and less reactive 3-chloropyridine were also successfully coupled (entries 8 and 9). The coupling shown in entry 9 is particularly impressive, because to date, no catalyst system has been reported for the coupling of 3-halopyridines with aza-crown ethers. Under these conditions, electron-neutral and electron-rich aryl bromides also participated in the process (entries 11-13).

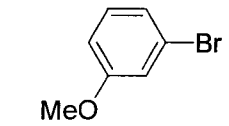
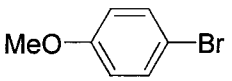
As mentioned earlier, the $Pd_2(dba)_3$/**2** catalyst system in the presence of the weak base Cs_2CO_3 was employed (4 mol% Pd) for substrates with base-sensitive functional groups. Thus, methyl-3-chlorobenzoate (73%, entry 2), 4-chloronitrobenzene (81%, entry 3), 4-chlorobenzonitrile (56%, entry 4), and 4-bromonitrobenzene (87%, entry 10) were all aminated under our standard conditions. For the reaction of 4-bromonitrobenzene, however, 2 mol% of Pd was sufficient for the coupling to occur in high yield.

Table 1. $Pd_2(dba)_3$/**1** or **2**-Catalyzed Synthesis of *N*-Aryl-Aza-Crown Ethers from Aryl Chlorides

entry	aryl halide	ligand	mol % Pd	base	yield (%)[a]
1		**1**	2	NaO-*t*-Bu	80[b]
2		**2**	4	Cs_2CO_3	73[c]
3		**2**	4	Cs_2CO_3	81[c] (79)[d]
4		**2**	4	Cs_2CO_3	56[c]
5		**1**	2	NaO-*t*-Bu	80[b]
6		**1**	2	NaO-*t*-Bu	66[b] (61)[d]
7		**1**	2	NaO-*t*-Bu	50[b]
8		**1**	2	NaO-*t*-Bu	76[b]
9		**1**	2	NaO-*t*-Bu	51[b]
10		**2**	2	Cs_2CO_3	87[c]
11		**1**	2	NaO-*t*-Bu	82[b] (81)[d]

[a] Isolated yields (average of two runs).
[b] For reaction conditions, see Scheme 1.
[c] For reaction conditions, see Scheme 2.
[d] Yields in parenthesis refer to the same reaction performed without the use of glove-box (see text).

Table 1. Continued

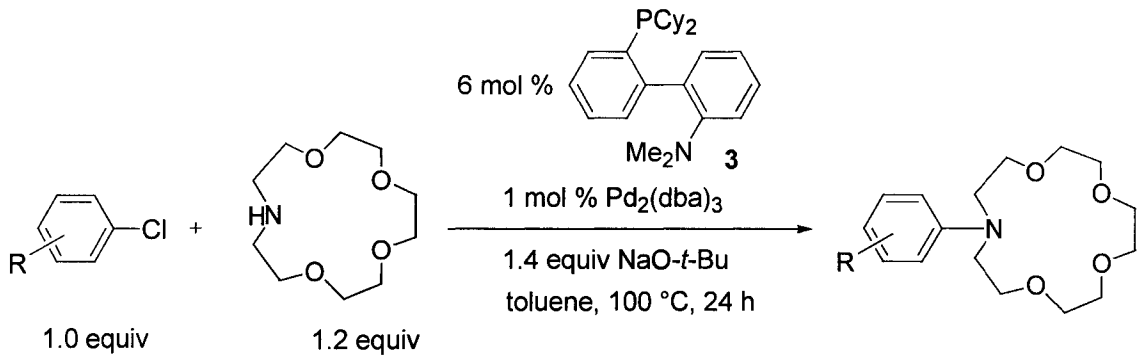
entry	aryl halide	ligand	mol % Pd	base	yield (%)[a]
12		**1**	2	NaO-*t*-Bu	68[b]
13		**1**	2	NaO-*t*-Bu	60[b]

Although ligands **1** and **2** are slightly air- and moisture-sensitive, they can be easily handled without the need for a glove-box using standard Schlenk techniques. Because of the moisture sensitivity of NaO-*t*-Bu and Cs_2CO_3, these reagents were stored and weighed inside the glove-box. However, we have established that the weighing of the aforementioned reagents inside the glove-box is not an absolute requirement. Thus when a sample of one of these reagents was taken from material stored inside the glove-box and weighed outside the glove-box with manipulations carried out using Schlenk techniques, amination reactions proceeded with almost equal efficiency (see parenthesized yields in entries 3, 6, and 11 of Table 1). The same procedure was also applied to other ingredients, that is, $Pd_2(dba)_3$, aryl chloride, toluene, and aza-crown ether.

The present methodology is not without its limitations, however. For example, *ortho*-substituted aryl chlorides did not couple with 1-aza-15-crown-5 to an appreciable extent and *ortho*-substituted aryl bromides provided only trace amounts of products.

We have also applied a biphenyl based aminophosphine ligand **3** (Buchwald's ligand) to synthesize the target compounds from aryl chlorides (Table 2). Using the protocol of Buchwald [i.e., 1 mol% of $Pd_2(dba)_3$ and 6 mol% of **3** (3L/Pd)], 4-chloroanisole and 4-chlorotoluene efficiently reacted with 1-aza-15-crown-5, affording the desired products in 61% (entry 1, Table 2) and 79% yields (entry 2, Table 2), respectively. However, when aryl chlorides with functional groups such as nitro and ester were employed in the presence of Cs_2CO_3 as the base, the corresponding products were obtained in only poor yields (entries 3 and 4, Table 2). As demonstrated above, the coupling of these substrates can be best carried out using ligand **2**.

Table 2. Synthesis of *N*-Aryl-Aza-Crown Ethers from Aryl Chlorides using Buchwald's Protocol

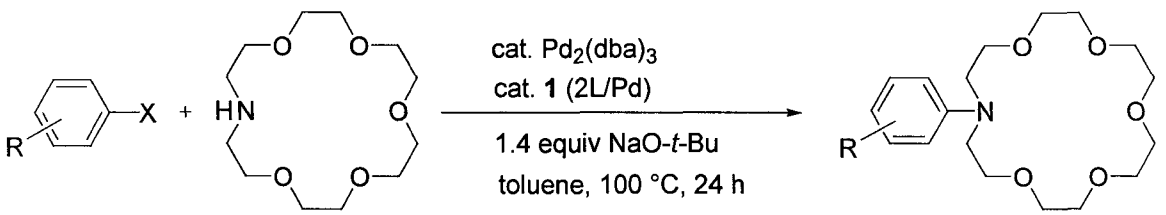


entry	R	yield (%)[a]
1	4-OMe	61
2	4-Me	79
3	4-NO_2	44[b,c]
4	3-CO_2Me	26[b,c]

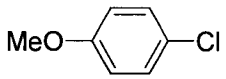
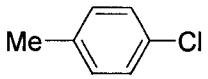
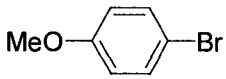
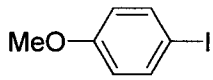
[a] Isolated yields (average of two runs).
[b] 2 mol % of $Pd_2(dba)_3$ and 12 mol % of **3** were used.
[c] Cs_2CO_3 was used as the base.

We have extended our methodology based on the $Pd_2(dba)_3$/**1** catalyst system to the arylation of a second aza-crown ether, namely, 1-aza-18-crown-6 and the results are summarized in Table 3. Using unactivated and deactivated aryl chlorides, bromides, and iodides, yields obtained were in the range of 51-55% (entries 1-4). For an aryl iodide, only 1 mol % of Pd was used.

Table 3. $Pd_2(dba)_3$/**1**-Catalyzed Coupling of Aryl Halides with 1-Aza-18-crown-6



1.0 equiv 1.2 equiv

entry	aryl halide	mol % Pd	yield (%)[a]
1		2	51
2		2	52
3		1.8	54
4		1	55

[a] Isolated yields (average of two runs).

3. Conclusions

The synthesis of various *N*-aryl-aza-crown ethers was readily achieved via palladium-catalyzed amination of aryl chlorides, bromides, and iodides in which the catalyst system consists of $Pd_2(dba)_3$ and one of the bicyclic triaminophosphine ligands **1** or **2**, the choice depending on the nature of the aryl substrate. Using this approach, the reaction is tolerant of a variety of functional groups. To the best of our knowledge, our protocol is the first reported for coupling aryl chlorides with aza-crown ethers. We have also demonstrated the utility of Buchwald's ligand in the reactions involving aryl chlorides.

4. Experimental

4.1. General methods

$Pd_2(dba)_3$, NaO-*t*-Bu, and Cs_2CO_3 were purchased from Aldrich and used without further purification. Toluene was collected from a Grubbs type solvent purification system. All other

reagents were commercially available and were used as received. Ligands **1**[15] and **2**[14] were prepared according to previously reported procedures, although **1** is commercially available from Aldrich and Strem Chemicals. For convenience, stock solutions of **1** and **2** in toluene (2 mM) were prepared and stored under argon. All reactions were performed under an atmosphere of argon in oven-dried glassware. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, unless otherwise noted. Elemental analyses were performed by Desert Analytics (Tucson, Arizona, USA). Mass spectra were recorded on a Kratos MS 50 instrument. The yields reported are isolated yields and are the average of two runs.

4.2. General procedure for the coupling of aryl halides with aza-crown ethers using the $Pd_2(dba)_3$/1 or $Pd_2(dba)_3$/2 catalyst system (Tables 1 and 3)

An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (0.5-2 mol%, see Tables 1 and 3), an appropriate aza-crown ether (1.2 mmol), and NaO-*t*-Bu (1.4 mmol) or Cs_2CO_3 (1.5 mmol) inside a glovebox. If the aryl halide (1.0 mmol) was a solid, it was also added at this time. The flask was capped with a rubber septum and removed from the glove box. Ligand **1** or **2** (2-8 mol%) was then added via syringe from a stock solution (2 mM in toluene). Aryl halide (if a liquid, 1.0 mmol) and toluene (3 mL) were then successively added via syringe. The reaction mixture was heated at the temperature indicated (see Tables 1 and 3) for 24 h. The mixture was then cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography using initially 10% ethyl acetate/hexanes and then ethyl acetate as eluents.

4.3. General procedure for the coupling of aryl chlorides with 1-aza-15-crown-5 using Buchwald's catalyst system (Table 2)

Inside a glovebox, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (1 mol%), 1-aza-15-crown-5 (1.2 mmol), ligand **3** (6 mol%), and NaO-*t*-Bu (1.4 mmol). The flask was capped with a rubber septum and removed from the glove box. Then aryl chloride (1.0 mmol) and toluene (3 mL) were successively added via syringe and the reaction mixture was heated at 100 °C for 24 h. The mixture was cooled to

room temperature, adsorbed onto silica gel and then purified by column chromatography using initially 10% ethyl acetate/hexanes and followed by ethyl acetate as eluents.

4.4. References for known compounds and Spectroscopic data for unknown compounds

4.4.1. *N*-(4-Trifluoromethylphenyl)-1-aza-15-crown-5 (Table 1, entry 1). The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.2. *N*-(3-Carbomethoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.19 (m, 3H), 6.85-6.82 (m, 1H), 3.86 (s, 3H), 3.76-3.58 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 147.8, 131.3, 129.4, 117.0, 116.0, 112.3, 71.5, 70.4, 70.3, 68.6, 52.7, 52.2. HRMS *m/z* Calcd for $C_{18}H_{27}NO_6$: 353.18384. Found: 353.18430. Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.19; H, 7.65. Found: C, 61.34; H, 7.81.

4.4.3. *N*-(4-Nitrophenyl)-1-aza-15-crown-5 (Table 1, entries 3 and 10). The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[8a]

4.4.4. *N*-(4-Cyanophenyl)-1-aza-15-crown-5 (Table 1, entry 4). The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[16]

4.4.5. *N*-(4-Methylphenyl)-1-aza-15-crown-5 (Table 1, entry 5 and Table 2, entry 2). The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[17]

4.4.6. *N*-(3-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entries 6 and 12). The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.7. *N*-(4-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entries 7 and 13, and Table 2, entry 1). The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.8. *N*-(2-Pyridinyl)-1-aza-15-crown-5 (Table 1, entry 8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 3.5 Hz, 1H), 7.34 (t, J = 7.1 Hz, 1H), 6.49-6.42 (m, 2H), 3.72-3.57 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 148.0, 137.2, 111.6, 106.0, 71.4, 70.4, 70.2, 69.3, 51.2. HRMS *m/z* Calcd for $C_{15}H_{24}N_2O_4$: 296.17361. Found: 296.17410. Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.81; H, 8.11. Found: C, 60.67; H, 8.31.

4.4.9. *N*-(3-Pyridinyl)-1-aza-15-crown-5 (Table 1, entry 9). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.05 (m, 1H), 7.90 (d, J = 4.3 Hz, 1H), 7.09-7.06 (m, 1H), 6.94-6.92 (m, 1H), 3.74-3.55

(m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 137.3, 134.2, 123.8, 118.2, 71.5, 70.5, 70.2, 68.4, 52.5. HRMS *m/z* Calcd for $C_{15}H_{24}N_2O_4$: 296.17361. Found: 296.17410. Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.81; H, 8.11. Found: C, 60.98; H, 7.97.

4.4.10. *N*-(3,5-Dimethylphenyl)-1-aza-15-crown-5 (Table 1, entry 11). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.11. *N*-(4-Methoxyphenyl)-1-aza-18-crown-6 (Table 3, entries 1, 3, and 4). ^1H NMR (300 MHz, $CDCl_3$): δ 6.82-6.70 (m, 4H), 3.74-3.56 (m, 27H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 142.4, 115.1, 114.4, 71.03, 70.99, 70.8, 69.0, 56.0, 52.4. HRMS *m/z* Calcd for $C_{19}H_{31}NO_6$: 369.21514. Found: 369.21580. Anal. Calcd for $C_{19}H_{31}NO_6$: C, 61.79; H, 8.40. Found: C, 61.63; H, 8.33.

4.4.12. *N*-(4-Methylphenyl)-1-aza-18-crown-6 (Table 3, entry 2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 3.70-3.56 (m, 24H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.0, 130.0, 125.2, 112.1, 71.1, 71.08, 71.0, 70.9, 69.1, 51.7, 20.4. HRMS *m/z* Calcd for $C_{19}H_{31}NO_5$: 353.22022. Found: 353.22100. Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.59; H, 8.78. Found: C, 64.67; H, 8.67.

Acknowledgements

We thank the Aldrich Chemical Co. for their generous support of this study by supplying research samples. The National Science Foundation is gratefully acknowledged for financial support of this work in the form of a grant.

References and notes

1. (a) Lohr, H.-G.; Vogtle, F. *Acc. Chem. Res.* **1985**, *18*, 65. (b) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515.

2. Chi, K-W.; Addicott, C.; Stang, P. J. *J. Org. Chem.* **2004**, *69*, 2910.

3. (a) Matsumoto, K.; Hashimoto, M.; Toda, M.; Tsukube, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2497. (b) Ciobanu, M.; Matsumoto, K. *Liebigs Ann.* **1997**, 623.

4. (a) Crochet, P.; Malval, J.-P.; Lapouyade, R. *Chem. Commun.* **2000**, 289. (b) Hirano, T.; Kikuchi, K.; Urano, Y.; Higuchi, T.; Nagano, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1052. (c)

Lednev, I. K.; Hester, R. E.; Moore, J. N. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 1551. (d) Liu, R. C. W.; Fung, P.-S.; Xue, F.; Mak, T. C. W.; Ng, D. K. P. *J. Chem. Res. (S)* **1998**, 414.

5. (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (c) Wolfe, J. P.; Wagaw,, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

6. (a) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

7. (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

8. (a) Witulski, B. *Synlett* **1999**, 1223. (b) Witulski, B.; Zimmerman, Y.; Dacros, V.; Desvergne, J.-P.; Bassani, D. M.; Bouas-Laurent, H. *Tetrahedron Lett.* **1998**, *39*, 4807. (c) Witulski, B.; Weber, M.; Bergstrasser, U.; Desvergne, J.-P.; Bassani, D. M.; Bouas-Laurent, H. *Org. Lett.* **2001**, *3*, 1467.

9. Zhang, X.-X.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 8027.

10. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

11. (a) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452. (b) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815. (c) Urgaonkar, S.; Verkade, J. G. *Adv. Synth. Catal.* **2004**, *346*, 611.

12. (a) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421. (b) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.*, in press.

13. (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (b) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.

14. Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

15. Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467.

16. Letard, J. F.; Lapouyade, R.; Rettig, W. *Pure Appl. Chem.* **1993**, *65*, 1705.

17. Lu, Xiaoming; Zhong, Ruifa; Liu, Shuncheng; Liu, Yu. *Polyhedron* **1997**, *16*, 3865.

Supporting Materials

The ^{1}H NMR spectra for all reaction products and ^{13}C NMR spectra for unknown reaction products are available in the appendix F in this thesis.

CHAPTER 8. $Pd_2(dba)_3$/P(*i*-BuNCH$_2$CH$_2$)$_3$N-CATALYZED STILLE CROSS-COUPLING OF ARYL CHLORIDES

A paper published in the *Organic Letters*

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Abstract

The $Pd_2(dba)_3$/P(*i*-BuNCH$_2$CH$_2$)$_3$N (**1d**) catalyst system is highly effective for the Stille cross-coupling of aryl chlorides with organotin compounds. This method represents only the second general method for the coupling of aryl chlorides. Other proazaphosphatranes possessing benzyl substituents also generate very active catalysts for Stille reactions. Noteworthy features of the method are: (a) commercial availability of ligand **1d**, (b) the wide array of aryl chlorides that can be coupled, and (c) applicability to aryl, vinyl, and allyl tin reagents.

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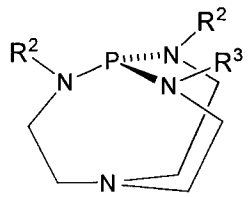
The palladium-catalyzed Stille cross-coupling of aryl halides (or halide equivalents) with organotin reagents is an important C-C bond-forming reaction that has found wide application in organic synthesis.[12] Until recently, this method was handicapped by the need to use aryl bromides or iodides as the reaction partner. Unlike the case with other Pd-catalyzed processes (e.g., Suzuki[3] and Buchwald-Hartwig amination[4] reactions) where a myriad of catalyst systems allow coupling of economically attractive but notoriously unreactive aryl chlorides, the same is not true with the Stille coupling of aryl chlorides.[5] However, significant progress was achieved recently. For example, Fu,[6] in his pioneering studies, disclosed a palladium-catalyst based on sterically hindered electron-rich P(*t*-Bu)$_3$ for the Stille cross-coupling of aryl chlorides. This method, although general, requires a highly air-sensitive and pyrophoric ligand that requires special handling techniques. Although the air-stable Pd[P(*t*-Bu)$_3$]$_2$[7] complex was recommended as an alternative to $Pd_2(dba)_3$/P(*t*-Bu)$_3$ for this process, its high cost is a deterrent to its widespread use. On the other hand, P(*t*-Bu)$_3$

has recently become commercially available as the air-stable precursor $[(t\text{-Bu})_3PH]BF_4$.[8] Nolan[9] reported a Pd/N-heterocyclic carbene system for the Stille reaction of aryl chlorides. However, this protocol provided good yields only for electron-deficient aryl chlorides. For electron-neutral and electron-rich aryl chlorides, only poor to moderate yields were obtained. In an elegant work, Choudary reported a layered double-hydroxide-supported nanopalladium catalyst for the Stille reaction of aryl chlorides, including electron-rich aryl chlorides under mild conditions (50 °C).[10] However, the generality of the process remains to be determined. More recently, the Stille reaction of aryl chlorides in water utilizing palladium-phosphinous acid complexes was described by Wolf.[11] This methodology required very high temperatures (135-140 °C); no examples involving electron-rich aryl chlorides were reported, and important functional groups such as esters and aldehydes were not compatible. Therefore, catalyst systems with both a higher degree of stability and activity (preferably commercially available) that can effect Stille coupling of aryl chlorides are highly desirable.

Previous work in our laboratories has established that a bicyclic proazaphosphatrane[12] bearing *iso*-butyl (**1d**) groups on the PN_3 nitrogens is a highly effective ligand for several Pd-catalyzed cross-coupling reactions of aryl halides, including those of aryl chlorides.[13] We report herein a general and efficient method for the Stille coupling of aryl chlorides with organotin reagents utilizing **1d** as the ancillary ligand. Additionally, we show that proazaphosphatranes possessing groups other than *iso*-butyl on the PN_3 nitrogens can also generate a highly active palladium catalyst for the Stille reaction of aryl chlorides.



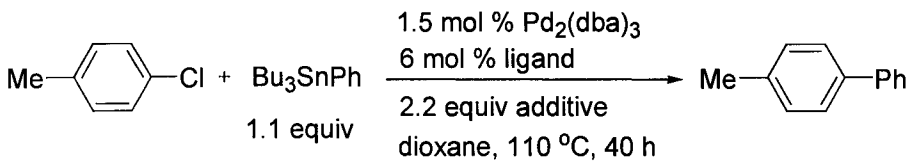
1a: R^1, R^2, R^3 = Me; **1b:** R^1, R^2, R^3 = *i*-Pr
1c: R^1, R^2 = *i*-Pr, R^3 = Bn; **1d:** R^1, R^2, R^3 = *i*-Bu
1e: R^1, R^2 = *i*-Bu, R^3 = Bn; **1f:** R^1, R^2 = Bn, R^3 = *i*-Bu
1g: R^1, R^2, R^3 = Bn; **1h:** R^1, R^2, R^3 = Piv

Figure 1. Proazaphosphatrane Ligands

For optimization of reaction conditions, Stille coupling of electron-neutral 4-chlorotoluene with phenyltributyltin in dioxane at 110 °C was chosen as a model reaction. Both Fu's[6] and Nolan's[9] studies on the Stille reaction have revealed the importance of a fluoride source in activating organotin compounds for the transmetalation step. Thus, we also tested various

fluoride additives. As shown in Table 1, employing CsF as a fluoride source and ligands with either smaller substituents on the PN_3 nitrogens (**1a** and **1b**) or a large substituent (**1h**) did not afford the desired coupling product in appreciable amounts (entries 1, 2, and 11). Interestingly, changing one PN_3 substituent of **1b** to benzyl led to a dramatic increase in the product yield (**1c**, entry 3). Expectedly, **1d** with *iso*-butyl groups on PN_3 nitrogens generated a very active catalyst, providing the desired biphenyl in 84% isolated yield (entry 4). The salutary effect of the benzyl group on catalytic activity was also evident in ligands **1e-g**, which also effectively promoted the Stille reaction (entries 7, 9, and 10). Although it is not presently clear what the origin of the beneficial influence of the benzyl group is on the activity of the catalyst, one possibility is that this group stabilizes the active palladium catalyst through the interaction of its aromatic π-orbitals with empty d-orbitals on

Table 1. Screening of Proazaphosphatrane Ligands and Fluoride Additives



entry	ligand	additive	yield (%)[a]
1	**1a**	CsF	<2
2	**1b**	CsF	21
3	**1c**	CsF	42
4	**1d**	CsF	84
5	**1d**	KF	37
6	**1d**	Me_4NF	92
7	**1e**	CsF	89
8	**1e**	Me_4NF	96
9	**1f**	CsF	91
10	**1g**	CsF	92
11	**1h**	CsF	<2

[a] Isolated yields (average of two runs).

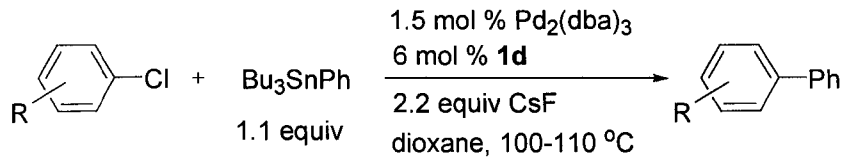
palladium.[14] Another possibility is that the benzyl group (like *iso*-butyl) possesses the unique balance of stereoelectronic influences required for catalytic activity in this reaction.

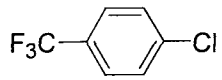
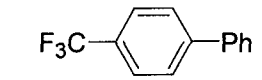
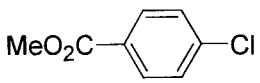
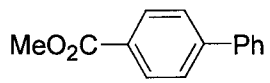
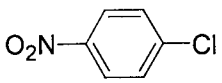
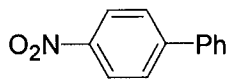
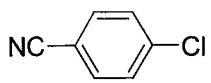
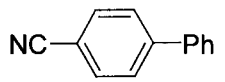
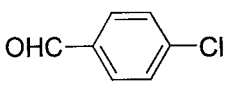
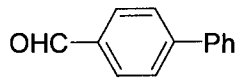
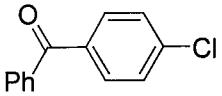
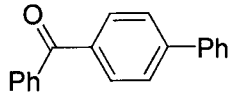
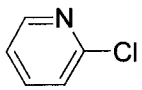
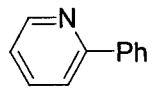
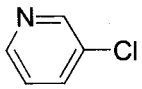
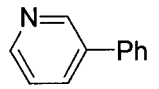
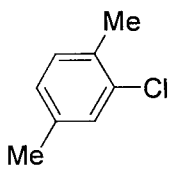
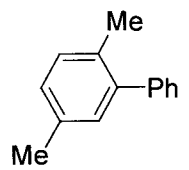
Further optimization of the fluoride additives (entries 4-8) established the efficacy order to be Me_4NF > CsF >> KF, which probably results from their decreasing solubilities in the solvent used. We chose to use the $Pd_2(dba)_3$/**1d**/CsF catalyst system for evaluating the scope of our protocol, due to the commercial availability of **1d**[15] and the lower cost of CsF compared with Me_4NF.

As demonstrated in Tables 2 and 3, the $Pd_2(dba)_3$/**1d**/CsF catalyst system is remarkably general, high-yielding, and tolerant of a range of functionalities.[16] Thus, reactions of activated or deactivated aryl chlorides with phenyltributyltin provided excellent yields, as did reactions of chloropyridines. The method is compatible with a trifluoromethyl (Table 2, entry 1), ester (Table 2, entry 2), nitro (Table 2, entry 3), cyano (Table 2, entry 4), aldehyde (Table 2, entry 5), or ketone (Table 2, entry 6) functional group. Even reactions of ortho-substituted aryl chlorides occurred in high yields (Table 2, entries 9-11). As seen in entries 12 and 13 of this table, the use of the more soluble fluoride additive Me_4NF provided a higher yield of the desired product than did CsF.

The scope of the $Pd_2(dba)_3$/**1d**/CsF catalyst system was further extended to reactions of aryl chlorides with vinyltin and allyltin reagents (Table 3). Electron-poor (Table 3, entries 1 and 2), sterically hindered (Table 3, entries 3-5), and electron-rich (Table 3, entries 6-10) aryl chlorides can be efficiently coupled, although for the reaction of electron-rich 4-chloroanisole with tributyl(vinyl)tin, the $Pd_2(dba)_3$/**1e**/Me_4NF catalyst system resulted in a higher yield of the desired product (compare entries 6-8). Interestingly, reactions of aryl chloride with allyltributyltin afforded the desired allylation product along with its regioisomer. For example, for electron-deficient aryl chlorides, the desired allylation product was obtained as a minor isomer (Table 3, entry 2), whereas electron-neutral and electron-rich aryl chlorides gave the desired Stille product as the major isomer (Table 3, entries 5 and 9).

Table 2. Stille Cross-Coupling of Aryl Chlorides with Phenyltributyltin



entry	aryl chloride	time (h)	product	yield (%)[a]
1		30		96[b]
2		24		95[b]
3		30		86[b]
4		24		96[b]
5		30		89[b]
6		30		93[b]
7		36		85
8		36		99
9		36		90

[a] Isolated yields (average of two runs). [b] Reaction was carried out at 100 °C. [c] Me_4NF was used in place of CsF.

Table 2. Continued

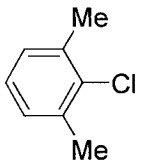
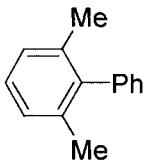
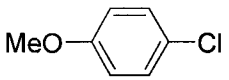
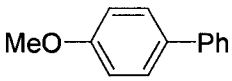
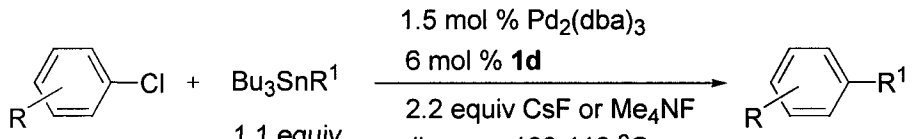
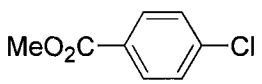
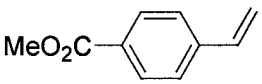
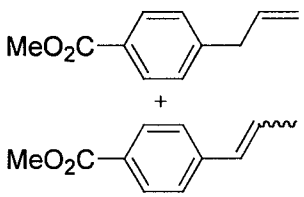
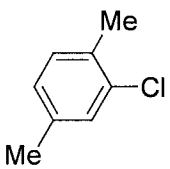
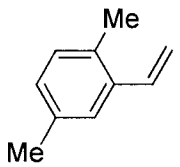
entry	aryl chloride	time (h)	product	yield (%)[a]
10		48		95
11		48		98[c]
12		48		71
13		48		90[c]

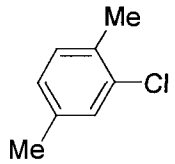
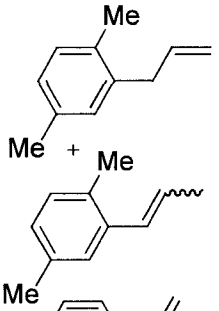
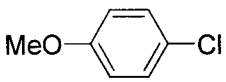
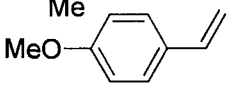
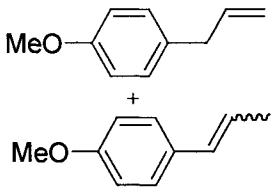
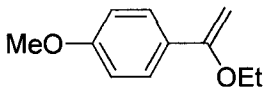
Table 3. Stille Cross-Coupling of Aryl Chlorides with Vinyl and Allyl Tin Reagents



entry	aryl chloride	time (h)	product	yield (%)[a]
1		32		93[b]
2		32		98 (1:4)[b,c]
3		40		34
4		40		72[d]

[a] Isolated yields (average of two runs). [b] Reaction was carried out at 100 °C. [c] The ratio represents that of the desired allylation product to its conjugated regioisomer. The ratio was determined by NMR spectroscopy. Isolated yields are for the mixture of regioisomers. [d] Me_4NF was used in place of CsF. [e] 1.5 equiv of tin reagent was used. [f] Ligand **1e** was employed.

Table 3. Continued

entry	aryl chloride	time (h)	product	yield (%)[a]
5		40		95 (15:2)[c]
6		48		23
7		48		53[d,e]
8		48		89[d,e,f]
9		48		94 (7:1)[c]
10		48		97

In summary, we have discovered that members of a family of proazaphosphatrane ligands in combination with $Pd_2(dba)_3$ generate very active palladium catalysts for the Stille cross-coupling of aryl chlorides with organotin compounds,[17] furnishing desired products in high yields. The methodology is compatible with functional groups such as an ester, nitro, trifluoromethyl, keto, cyano, and aldehyde. We believe that the range of Pd-catalyzed cross-couplings that can be accomplished with triaminophosphine **1d** renders this ligand a suitable alternative to alkylphosphines, giving additional impetus to our exploration of this class of compounds in metal-catalyzed reactions.

Acknowledgment

We thank the Aldrich Chemical Co. for their generous support of this study by supplying research samples. The National Science Foundation is gratefully acknowledged for financial support of this work in the form of a grant.

Supporting Information Available

Experimental details and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org. While experimental details are available in the appendix G in this thesis, ^{1}H and ^{13}C NMR spectra are available in the appendix H (pertaining to Chapter 9) to avoid duplication of spectra.

References

1. For reviews on Stille cross-coupling reaction, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **2002**, *41*, 4176.

2. For applications of the Stille reaction in natural product synthesis, see: (a) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443. (b) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46. (c) Boger, D. L.; Ichikawa, S.; Jiang, H. *J. Am. Chem. Soc.* **2000**, *122*, 12169.

3. For leading references to Suzuki couplings of aryl chlorides, see: (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **1998**, *37*, 3387. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (d) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540. (e) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (f) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (g) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (h) Urgaonkar, S.; Nagarajan, M. Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

4. For leading references to Buchwald-Hartwig amination reactions of aryl chlorides, see: (a) Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (c) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (d) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (e) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics* **1999**, *18*, 1840. (f) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (g) Reddy, N. P.; Tanaka, M.; *Tetrahedron Lett.* **1997**, *38*, 4807. (h) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

5. For Pd-catalyzed Stille reactions of activated aryl chlorides, see: Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301. See also refs 1b and 1c.

6. (a) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **1999**, *38*, 2411. (b) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

7. Available from Strem Chemicals.

8. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

9. Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

10. Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2003**, *124*, 14127.

11. Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551.

12. For recent reviews, see: (a) Verkade, J. G. *Top. Curr. Chem.* **2002**, *233*, 1. (b) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 7819. (c) Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta*, in press.

13. (a) Urgaonkar, S. Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452. (b) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (c) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003. Also see refs 3h and 4h.

14. For Pd-arene interactions in palladium complexes, see: (a) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7816. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336. (c) Yin, J.; Rainka, M. P.; Zhang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

15. Ligand **1d** is commercially available from Aldrich and Strem Chemicals.

16. **General Procedure.** An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (1.5 mol %) and CsF or Me_4NF (2.2 mmol) inside a glovebox. If the aryl chloride (1.0 mmol) was a solid, it was also added at this time. The flask was capped with a rubber septum and removed from the glovebox. Ligand **1** (6.0 mol %) was then added via syringe from a stock solution (2 mM in dioxane). Aryl chloride (if a liquid, 1.0 mmol), tin reagent (1.1 mmol), and dioxane (2 mL) were then successively added via syringe. Under a positive pressure of argon, the flask was sealed with a Teflon screw-cap, and then the reaction mixture was heated at the temperature indicated (see Tables 1-3) until the starting material had been completely consumed as judged by TLC. The mixture was then cooled to room temperature, diluted with ether or acetone, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

17. Further studies on the Stille reaction of aryl chlorides with various substituted aryl tin reagents are ongoing and will be reported in due course.

ERRATUM SUBMITTED TO ORGANIC LETTERS

Reference 10 is incorrect. It should read: Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127.

CHAPTER 9. HIGHLY ACTIVE PALLADIUM CATALYSTS SUPPORTED BY BULKY PROAZAPHOSPHATRANE LIGANDS FOR STILLE CROSS-COUPLING: COUPLING OF VINYL CHLORIDES, ROOM TEMPERATURE COUPLING OF ARYL BROMIDES, COUPLING OF ARYL TRIFLATES, AND SYNTHESIS OF STERICALLY HINDERED BIARYLS

A paper published in the *Journal of The American Chemical Society*

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Abstract

A family of proazaphosphatrane ligands [$P(RNCH_2CH_2)_2N(R'NCH_2CH_2)$: R = R' = *i*-Bu, **1**; R = Bz, R' = *i*-Bu, **3**; R = R' = Bz, **4**] for the palladium-catalyzed Stille reactions of aryl chlorides is described. Catalyst derived from ligands **1** and **4** efficiently catalyze the coupling of electronically diverse aryl chlorides with an array of organotin reagents. The catalyst system based on the ligand **3** is active for the synthesis of sterically hindered biaryls (di-, tri-, and tetra-*ortho* substituted). The use of ligand **4** allows room-temperature coupling of aryl bromides and it also permits aryl triflates and vinyl chlorides to participate in Stille coupling.

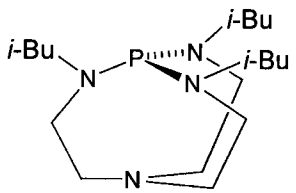
Introduction

The coupling of two sp^2-centered carbons remains an important goal as well as a challenge for synthetic organic chemists. Among various strategies, transition-metal-catalyzed processes, especially those catalyzed by palladium, have made significant contributions to this field.[1] The palladium-catalyzed Stille cross-coupling[2] of aryl halides (or halide equivalents) with organotin reagents is an important C-C bond forming reaction that has found wide application in natural product synthesis,[3] carbohydrate chemistry,[4] and biological research,[5] which in part stems from the ready availability of organotin reagents, their air- and moisture-stability and the excellent functional group tolerance of this approach. Until recently, this method was handicapped by the need to use aryl bromides or iodides as the

reaction partner. Surprisingly, unlike the case with other Pd-catalyzed processes (e.g., Suzuki,[6] Heck,[7] and Buchwald-Hartwig amination[8] reactions) wherein a myriad of catalyst systems allow coupling of economically attractive but notoriously unreactive aryl chlorides, the same is not true for the Stille coupling of aryl chlorides.[9] Here the low reactivity of aryl chlorides has generally been attributed to its reluctance to participate in oxidative addition, the first step of the catalytic cycle. However, significant progress has been achieved recently. For example, Fu,[10] in his pioneering studies, disclosed a palladium-catalyst, based on sterically demanding electron-rich P(*t*-Bu)$_3$ as the supporting ligand, for the Stille cross-coupling of aryl chlorides. This method, although general, employs a highly air-sensitive and pyrophoric ligand that requires special handling. Although air-stable Pd[P(*t*-Bu)$_3$]$_2$ was recommended as an alternative to Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$ for these reactions, its high cost is a deterrent to its widespread use. On the other hand, the air-stable [(*t*-Bu)$_3$PH]BF$_4$,[11] which is now commercially available,[12] can serve as a replacement for P(*t*-Bu)$_3$ via its deprotonation by base to release the free ligand *in situ*. Nolan[13] reported a Pd/N-heterocyclic carbene system for the Stille reaction of aryl chlorides. However, this protocol provided good yields only for activated aryl chlorides. Unactivated and deactivated aryl chlorides afforded only poor to moderate yields. In elegant work, Choudary reported a layered double-hydroxide-supported nanopalladium catalyst for the Stille reaction of aryl chlorides, including electron-rich examples which operate under mild conditions (50 °C).[14] However, the generality of the process remains to be determined. Stille reaction of aryl chlorides in water utilizing palladium-phosphinous acid complexes was described by Wolf.[15] This methodology required quite elevated temperatures (135-140 °C); important functional groups such as esters and aldehydes were not compatible under the conditions employed; and more significantly, no examples involving electron-rich aryl chlorides were reported. More recently, Baldwin found that the PdCl$_2$/P(*t*-Bu)$_3$ catalyst system, in combination with CuI and CsF using DMF as the solvent, facilitates Stille coupling of aryl chlorides at 100 °C.[16] But again, the reaction is effective with electron-deficient aryl chlorides (except for one example reported) and less effective with electron-rich systems (one example reported). Consequently, catalyst systems with a higher degree of stability and activity that can accomplish Stille coupling of electronically diverse aryl chlorides are highly desired.

Proazaphosphatranes,[17] first synthesized in our laboratories, are unusually electron-rich compounds compared with their acyclic counterparts [e.g., $P(NMe_2)_3$] because: (a) the three PN_3 nitrogens in these rigid bicyclic triaminophosphines are quite planar,[18] thus contributing their electron-density to phosphorus thereby making it more electron-rich and (b) transannulation from the bridgehead nitrogen's lone pair to phosphorus could also potentially enhance its basicity. Not surprisingly, acyclic triaminophosphines lack both of these electron-richness enhancement features. It should be noted that the catalytic activity of proazaphosphatranes can be further augmented by the introduction of suitable groups on PN_3 nitrogens.

Previous work in our laboratories has established that a bicyclic proazaphosphatrane[17] bearing *iso*-butyl groups on the PN_3 nitrogens (**1**) is a highly effective ligand for several Pd-catalyzed cross-coupling reactions, including Buchwald-Hartwig amination,[18] Suzuki,[6h] and *alpha*-arylation[19] reactions. Very recently, we reported in a communication that Pd/**1** also serves as a general catalyst for the Stille coupling of aryl chlorides.[20] In this paper, we fully describe our studies of Stille coupling of aryl chlorides as well as of room temperature coupling of aryl bromides.



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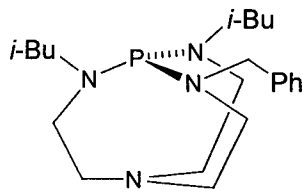

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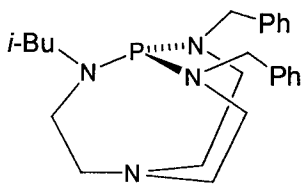

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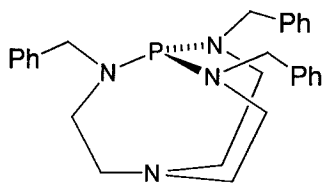


4

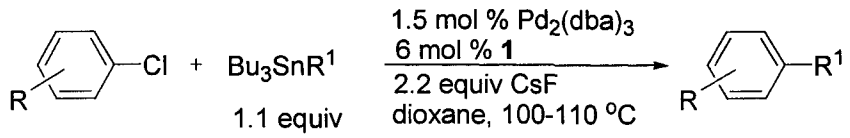
Results and Discussion

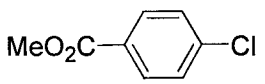
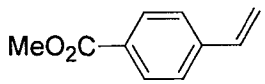
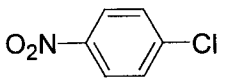
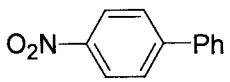
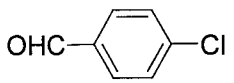
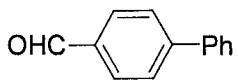
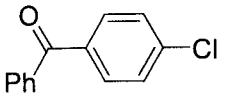
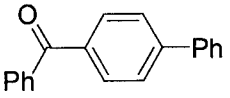
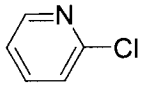
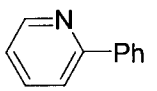
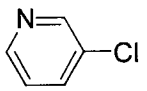
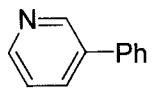
At the outset, we performed experiments to examine the influence of varying the substituents on PN_3 nitrogens on catalyst activity. We discovered that palladium catalysts supported by ligands **2-4**, bearing benzyl as well as a combination of *iso*-butyl and benzyl groups on PN_3

nitrogens, generate more active catalysts for the coupling of 4-chlorotoluene with tributylphenyltin than the one supported by ligand **1**, with ligand **4** functioning as the most effective of all. Activation of the less nucleophilic tin reagent was achieved by the addition of 2.2 equivalents of CsF.[21]

The scope of the palladium-catalyzed Stille reaction of aryl chlorides was explored by using 1.5 mol % of $Pd_2(dba)_3$ and 6 mol % of commercially available ligand **1** (two ligands per palladium) in reactions conducted at 100-110 °C. A selection of pertinent results from our previous communication[20] plus one new example (entry 11) are collected in Table 1. The reaction has a broad scope, tolerating a variety of functional groups (NO_2, CN, CO_2Me, CHO, COPh, and OMe) and substrate steric hindrance. Chloropyridines can also be successfully coupled.

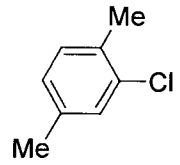
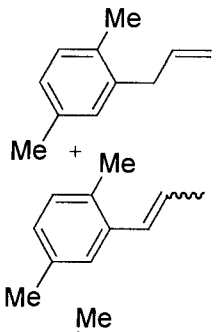
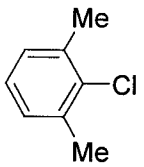
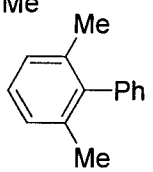
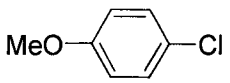
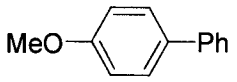
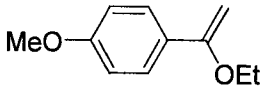
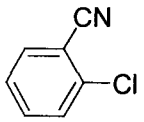
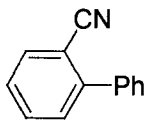
TABLE 1. Stille Cross-Coupling of Aryl Chlorides Catalyzed by $Pd_2(dba)_3$/**1**



entry	aryl chloride	time (h)	product	yield (%)[a]
1		24		93[b]
2		30		86[b]
3		30		89[b]
4		30		93[b]
5		36		85[c]
6		36		99[c]

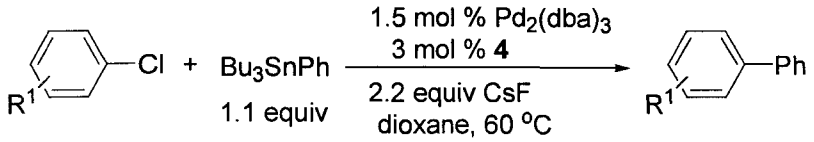
[a] Isolated yields (average of two runs). [b] The reaction temperature was 100 °C. [c] The reaction temperature was 110 °C. [d] The ratio was determined by ^1H NMR spectroscopy.

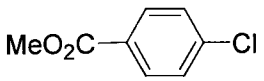
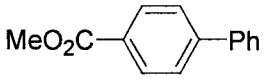
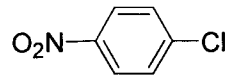
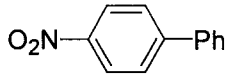
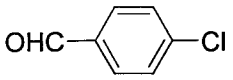
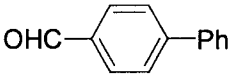
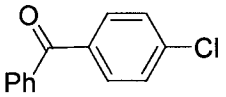
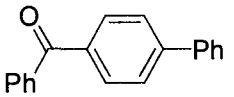
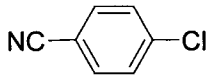
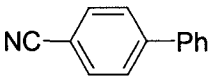
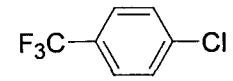
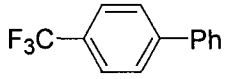
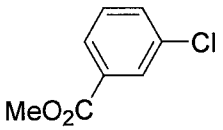
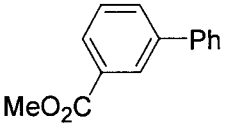
TABLE 1. Continued

entry	aryl chloride	time (h)	product	yield (%)[a]
7		36		95[c] (15:2)[d]
8		48		95[c]
9		48		71[c]
10		48		97[c]
11		48		91[c]

Stille Cross-Coupling using the $Pd_2(dba)_3$/4 Catalyst System: Activated Aryl Chlorides. We were pleased to discover that with **4** as the ligand, the reaction temperature could be decreased to 60 °C without compromising reaction yields in Stille coupling of activated aryl chlorides (Table 2). We also found that the use of a 1:1 (or 1:1.2) ratio of Pd:**4** generated a more active catalyst than a 1:2 ratio. In the presence of CsF as an activator of the organotin reagent, the $Pd_2(dba)_3$/**4** catalyst system catalyzed the Stille reactions of a wide array of activated aryl chlorides, encompassing functional groups such as ester (entries 1 and 7), nitro (entry 2), aldehyde (entry 3), ketone (entry 4), cyano (entry 5), and trifluoromethyl (entry 6), with tributylphenyltin at 60 °C in dioxane. All these reactions afforded excellent yields of the corresponding biaryls.

TABLE 2. Stille Cross-Coupling of Activated Aryl Chlorides Catalyzed by $Pd_2(dba)_3$/**4**



entry	aryl chloride	time (h)	product	yield (%)[a]
1		28		95
2		28		98
3		28		93
4		28		98
5		30		98
6		28		99
7		36		95

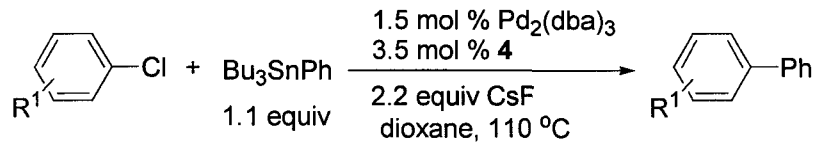
[a] Isolated yields (average of two runs).

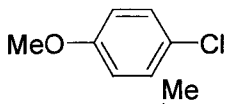
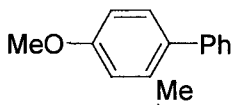
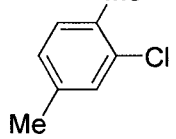
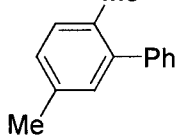
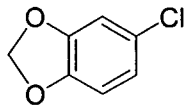
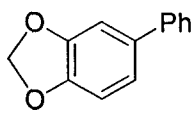
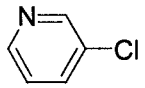
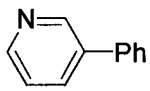
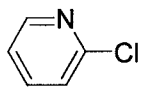
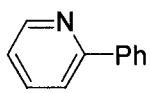
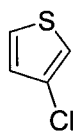
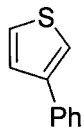
Encouraged by the results obtained using ligand **4** with 1:1 ratio of L to Pd, we reexamined the activity of a palladium catalyst based on ligand **1** using a 1:1 ratio of L to Pd in the Stille process. For activated aryl chlorides, we found that the use of **1** as the ligand gave results comparable to those obtained when ligand **4** was employed. For example, the reaction of 4-chlorobenzonitrile with phenyltributyltin at 60 °C provided the coupling product in 96% yield using $Pd_2(dba)_3$/**1**.

Stille Cross-Coupling using the $Pd_2(dba)_3$/4 Catalyst System: Unactivated, Deactivated, and Hetero Aryl Chlorides. The $Pd_2(dba)_3$/**4** catalyst system was also found to be effective

for the cross-coupling of unactivated and deactivated aryl chlorides with tributylphenyltin at 110 °C (Table 3). For example, the reaction of 4-chloroanisole

TABLE 3. Stille Cross-Coupling of Unactivated, Deactivated and Hetero Aryl Chlorides Catalyzed by $Pd_2(dba)_3$/**4**



entry	aryl chloride	time (h)	product	yield (%)[a]
1		48		87
2		42		85
3		45		90
4		40		97
5		48		64
6		48		69[b]

[a] Isolated yields (average of two runs). [b] 6 mol % of **1** was used.

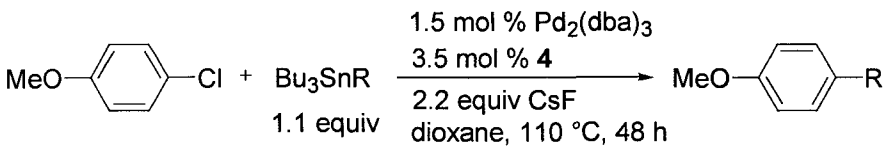
(entry 1), 2-chloro-*p*-xylene (entry 2), and 5-chloro-1,3-benzodioxole (entry 3) with tributylphenyltin all proceeded in high yield at 110 °C using 3 mol % of Pd and 3.5 mol % of **4** (Pd:**4** = 1:1.2). Examples in entries 4-6 demonstrate the viability of heteroaryl chlorides in Stille coupling. Interestingly, the reaction of activated 2-chloropyridine provided only a moderate yield (64%) of product compared with deactivated 3-chloropyridine (97%). It should be noted that several research groups have experienced problems in palladium-catalyzed Heck reactions of 2-halopyridines, presumably owing to formation of an unreactive

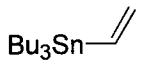
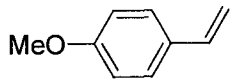
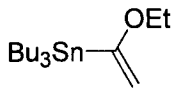
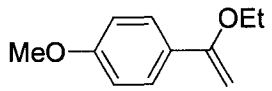
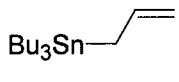
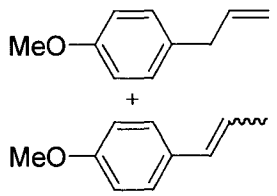
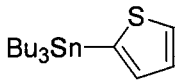
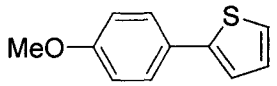
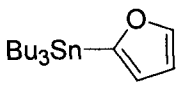
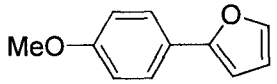
pyridyl-bridged palladium dimer during the course of reaction.[22] Nevertheless, the reaction of 2-chloropyridine occurred in 85% yield with **1** as the ligand when the ratio of Pd to ligand was increased to 1:2 (see Table 1, entry 5). Overall, catalysts based on **1** using a 1:1.2 ratio of L to Pd gave inferior yields for deactivated and unactivated aryl chlorides compared with the catalyst based on **4**.

The coupling of chlorothiophenes is challenging in palladium-based methodologies because of the strong affinity of sulfur for Pd, resulting in catalyst poisoning. Gratifyingly, we found that the $Pd_2(dba)_3$/**1** catalyst system effects Stille coupling of 3-chlorothiophene in respectable yield (Table 3, entry 6). For this substrate, the catalyst based on ligand **4** was less effective. To our knowledge this represents the first example of Stille coupling of chlorothiophenes.

Stille Cross-Coupling using the $Pd_2(dba)_3$/4 Catalyst System: Variation of Organotin Reagents. The scope of the $Pd_2(dba)_3$/**4**/CsF catalyst system was further expanded to include a diverse set of organotin reagents, in which deactivated 4-chloroanisole was chosen as the coupling partner (Table 4). Functionalities on organotin reagents that were successfully coupled using this methodology included vinyl (entries 1 and 2), allyl (entry 3), aryl (Table 3, entry 1), and heteroaryl groups (entries 4 and 5 in Table 4). The results obtained in the latter entries are particularly significant, since very few examples of Stille reactions of aryl chlorides with heteroaryl tin reagents are known. To the best of our knowledge, this is the first time that cross-coupling of an aryl chloride with organotin reagents possessing thiophene and furan moieties has been successfully carried out.

TABLE 4. Stille Cross-Coupling of 4-Chloroanisole with Various Organotin Reagents Catalyzed by $Pd_2(dba)_3$/**4**



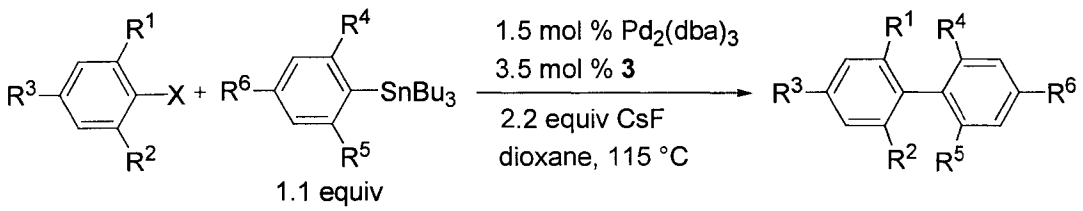
entry	$RSnBu_3$	product (s)	yield (%)[a]
1			57
2			96
3			95 (7:1)[b]
4			67
5			97

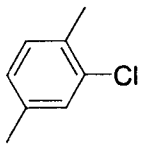
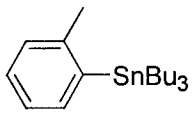
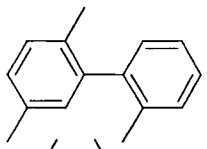
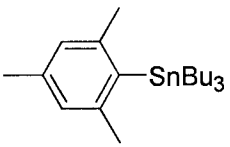
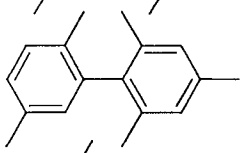
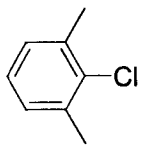
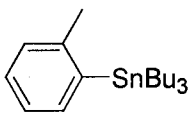
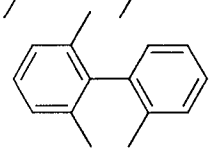
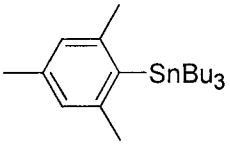
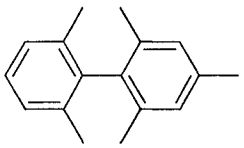
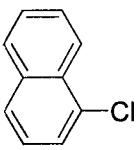
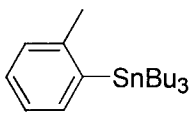
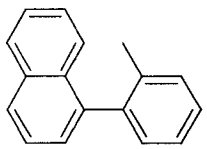
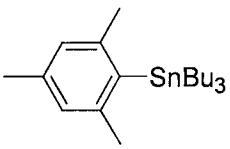
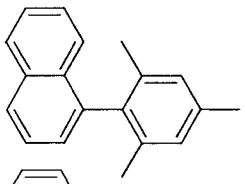
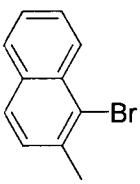
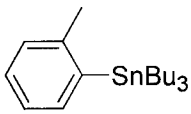
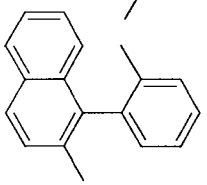
[a] Isolated yields (average of two runs). [b] The ratio was determined by ^1H NMR spectroscopy.

Synthesis of Sterically Hindered Biaryls using the $Pd_2(dba)_3$/3 Catalyst System. An important criterion used to judge the performance of a catalyst system in Pd-catalyzed cross-coupling processes is its ability to generate sterically hindered biaryls. Although great progress has been achieved in closely related Suzuki-Miyaura cross-coupling reactions for synthesizing tri- and tetra-*ortho* substituted biaryls,[23] their efficient production via the Stille reaction has not been rewarding so far except for the catalyst system [$Pd(P(t\text{-}Bu)_3)_2$] reported by Fu.[10b] As a logical extension of our efforts, the synthesis of sterically hindered biaryls via Stille coupling was then examined using proazaphosphatranes as ligands. Disappointingly, the reaction of 2-chloro-*m*-xylene with 2,4,6-trimethylphenyl(tributyl)tin provided only a trace amount of tetra-*ortho* substituted biaryl when **1** was employed as the ligand. However, ligands **2** and **4** afforded a 27% and 61% yield of the desired biaryl, respectively. Subsequently, much to our delight, we found that the introduction of ligand **3** allowed such

cross-coupling to occur in high yield (81%, Table 5, entry 4). The ability of the catalyst system $Pd_2(dba)_3$/**3** to produce sterically hindered biaryls was then explored (Table 5). As seen from this table, the reaction tolerates not only one or two *ortho*-substituents on the aryl halide, but it also tolerates the same steric hindrance on the aryl tin reagent. Excellent yields were obtained in all cases. Even very sterically hindered 2,4,6-triisopropyl bromobenzene can be coupled. For example, the reaction of 2,4,6-triisopropyl bromobenzene with *o*-tolyltributyltin gave an 88% isolated product yield (Table 5, entry 9). To our knowledge, this represents the first example of the synthesis via a Stille reaction of a tri-*ortho*-substituted biaryl bearing *ortho* groups larger than a methyl group.

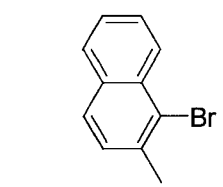
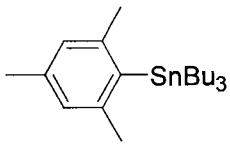
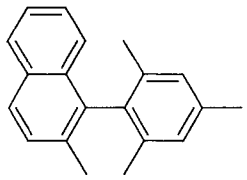
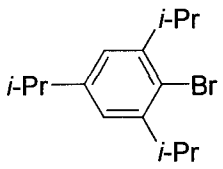
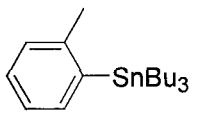
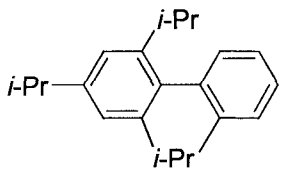
TABLE 5. Synthesis of Sterically Hindered Biaryls *via* Stille Cross-Coupling Catalyzed by $Pd_2(dba)_3$/**3**



entry	aryl halide	stannane	product	yield (%)[a]
1				99
2				88
3				97
4				81
5				98
6				97
7				86

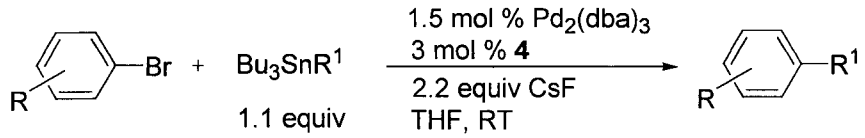
[a] Isolated yields (average of two runs). [b] 3 mol % of $Pd_2(dba)_3$ and 7 mol % of **3** were used.

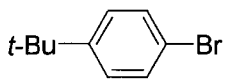
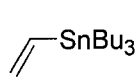
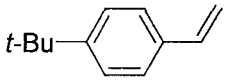
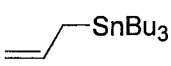
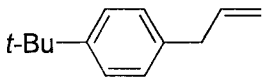
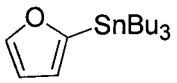
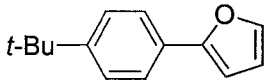
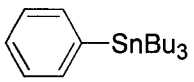
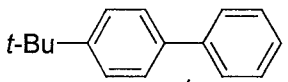
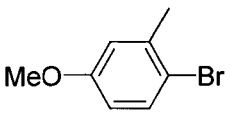
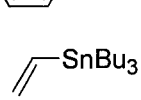
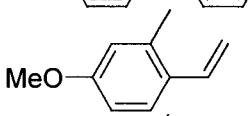
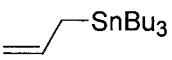
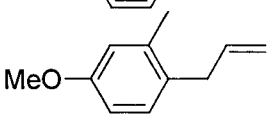
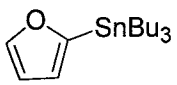
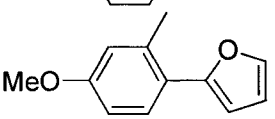
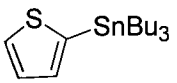
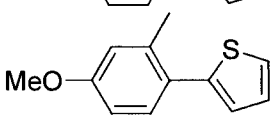
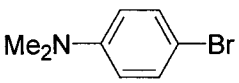
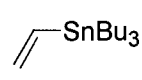
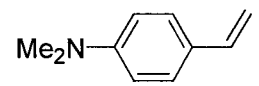
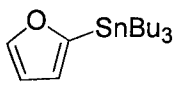
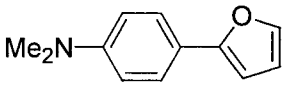
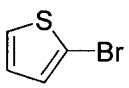
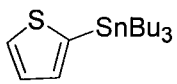
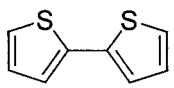
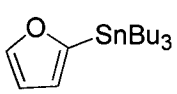
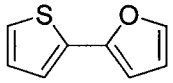
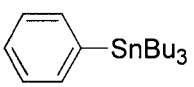
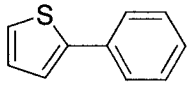
TABLE 5. Continued

entry	aryl halide	stannane	product	yield (%)[a]
8				77
9				88[b]

Stille Cross-Coupling of Aryl Bromides at Room Temperature using the $Pd_2(dba)_3$/4 Catalyst System. We next turned our attention to Stille reactions of aryl bromides. There are numerous reports on Stille reactions of aryl bromides at elevated temperatures,[24] but only one general catalyst system [$Pd_2(dba)_3$/P(*t*-Bu)$_3$] has been described for room temperature reactions.[10b] Initially, we performed room-temperature Stille experiments were using **1** as the ligand. We found that although $Pd_2(dba)_3$/**1**/CsF catalyzes the room-temperature coupling of 4-*tert*-butylbromobenzene and 4-bromo-3-methylanisole with vinyl(tributyl)tin in 91% and 82% yields, respectively, reactions did not proceed to completion in THF even after 21 h. We were pleased to observe, however, that the use of **4** as the ligand leads to a significantly more active catalyst, allowing the reaction to proceed to completion in 10-16 h. For room-temperature Stille couplings, THF was found to be the most effective solvent. The results described in Table 6 demonstrate that $Pd_2(dba)_3$/**4**/CsF enables coupling of electronically and sterically diverse aryl bromides with a broad spectrum of tin reagents at room temperature. Thus, electron-neutral 4-*tert*-butylbromobenzene (Table 6, entries 1-4), *ortho*-substituted and electron-rich 4-bromo-3-methylanisole (entries 5-7), and even very electron-rich 4-*N*,*N*-dimethylaminobromobenzene coupled in excellent yields (entries 9 and 10) at room temperature. However, Stille reactions of substrates containing the thiophene moiety were very slow at room temperature, and mild heating (50 °C) was required for the reactions to proceed to completion (entries 8, 11, 12, and 13). This result may be ascribed to a tendency

TABLE 6. Room Temperature Stille Cross-Coupling of Aryl Bromides Catalyzed by $Pd_2(dba)_3$/**4**

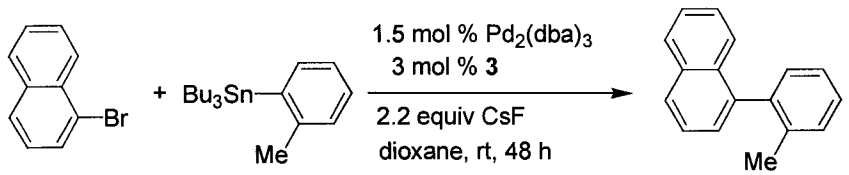


entry	aryl or heteroaryl bromide	stannane	product	yield (%)[a]
1				99
2				87
3				97
4				98
5				97
6				97
7				98
8				99[b]
9				97
10				93
11				99[b]
12				98[b]
13				91[b]

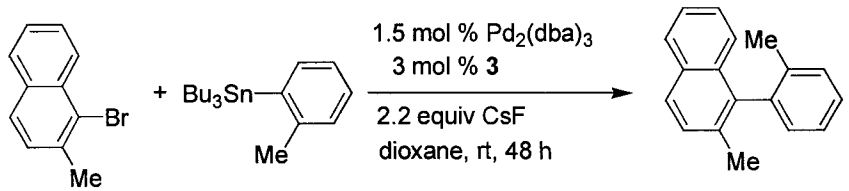
[a] Isolated yields (average of two runs). [b] The reaction temperature was 50 °C.

of the thiophenic sulfur to bind to palladium, thus reducing its activity and/or retarding transmetalation.

Even sterically hindered biaryls could be synthesized at room temperature using ligand **3** (eqs 1 and 2). Equation 2, which depicts the first successful synthesis of a tri-*ortho*-substituted biaryl through a Stille reaction of an aryl bromide at room-temperature, is particularly interesting.

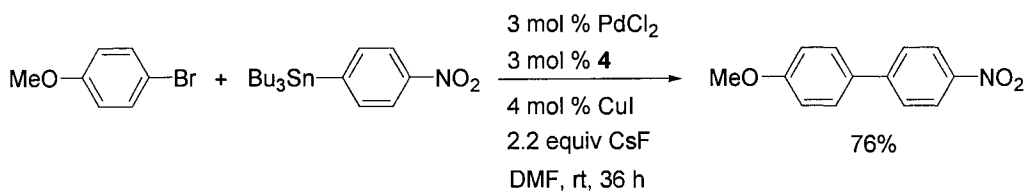


(1)



(2)

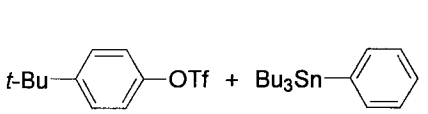
Another challenging coupling of electron-rich 4-bromoanisole with electron-deficient 4-(tributylstannyl)nitrobenzene was also accomplished at room-temperature in good yield (eq 3). Interestingly, the reaction proceeded quite sluggishly using our standard conditions [$Pd_2(dba)_3$/**4**/THF or $Pd_2(dba)_3$/**4**/dioxane]. However, by employing the conditions developed by Baldwin[16] [except that in the present study ligand **4** was employed whereas Baldwin used P(*t*-Bu)$_3$], the desired coupling product was obtained in 76% isolated yield. It should also be noted that in this case, the addition of CuI to the reaction mixture significantly improved the yield because in its absence, only a trace amount of the desired coupled product was obtained. Similar enhancement of a Stille process using a combination of CuI and CsF was observed by Baldwin.[16]



(3)

We also briefly examined the efficacy of aryl triflates as substrates in Stille reactions catalyzed by proazaphosphatrane ligands. We found that aryl triflates are also viable

substrates and again the use of ligand **4** provided the best results (eq 4). The reaction did not proceed to completion with the use of ligand **1** even after 36 h, whereas the use of ligands **2**, **3**, and **4** led to completion within that time.

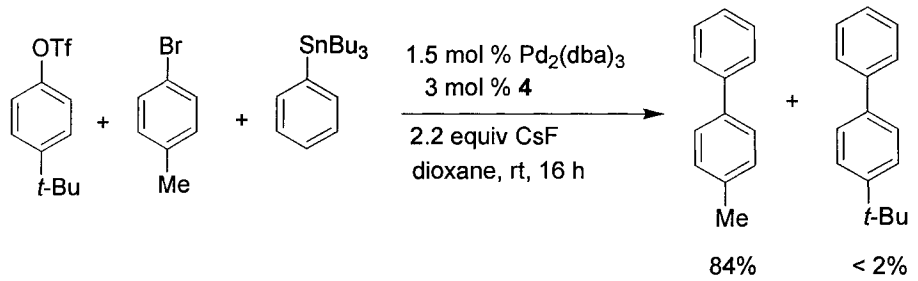


(4)

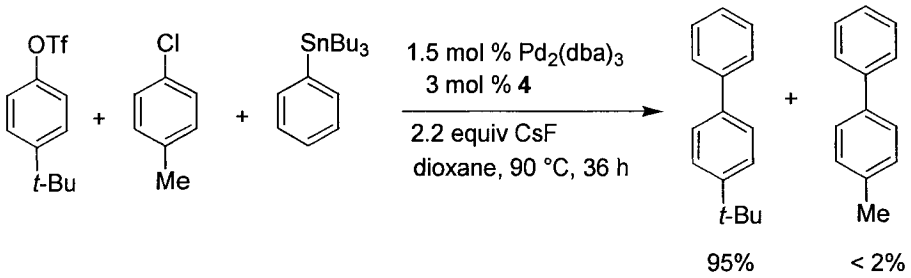
ligand	yield(%)[a]
1	85
2	90
3	94
4	97

[a] Isolated yields.

Competition Experiments for the Order of Reactivity. To determine the order of reactivity of aryl halides and triflates in Stille cross-couplings catalyzed by $Pd_2(dba)_3$/**4**, two competition experiments were conducted as shown in equations 5 and 6. Not surprisingly, it was established that the product obtained was derived almost exclusively from the aryl bromide (eq 5) whereas the competition experiment between aryl chloride and triflate performed at 90 °C revealed that the aryl triflate reacted in preference to the aryl chloride (eq 6). From these two experiments it can be concluded that the order of reactivity under our conditions follows the traditional order: aryl bromide > aryl triflate > aryl chloride.[2] It is worthy of note that this observed reactivity is quite different from the one reported by Fu's group for Stille coupling using P(*t*-Bu)$_3$ as a ligand, which follows the unexpected order: aryl bromide > aryl chloride > aryl triflate.[10b]



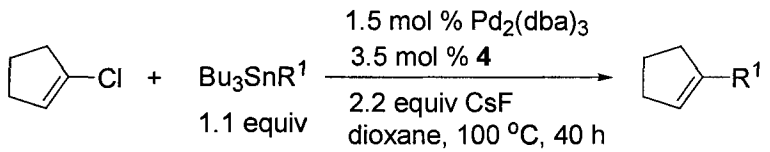
(5)

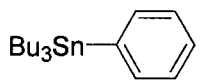
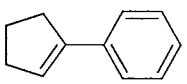
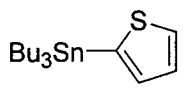
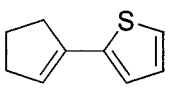
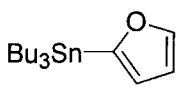
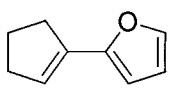


(6)

Stille Cross-Coupling of Vinyl Chlorides using the $Pd_2(dba)_3$/4 Catalyst System. Another challenging Stille reaction involves the use of unactivated vinyl chlorides and not unexpectedly, only one catalyst system ($Pd/P(t\text{-}Bu)_3$)[10b,25] has thus far been reported for the Stille coupling of such substrates. In that report, 3 mol % of $Pd(P(t\text{-}Bu)_3)_2$ was employed as the catalyst and the reaction temperature was 100 °C. We observed that the $Pd_2(dba)_3$/**4** catalyst system was also effective for cross-coupling a vinyl chloride with various tin reagents at 100 °C, affording the corresponding coupled products in excellent yields (Table 7).

TABLE 7. Stille Cross-Coupling of Vinyl Chlorides Catalyzed by $Pd_2(dba)_3$/**4**



entry	tin reagent	product	yield (%)[a]
1			91
2			83
3			93

[a] Isolated yields (average of two runs).

^{31}P NMR Studies. To gain some insights into the mechanism,[26] we investigated the fate of ligand **4** in Stille reactions by ^{31}P NMR spectroscopy. A mixture of **4** (δ 127.9) and $Pd_2(dba)_3$ in a 1:1 ratio at room temperature shows a phosphorus resonance at δ 132.4. We tentatively

assigned this peak to a Pd-**4** complex. We then monitored the reaction of 1-bromo-4-*tert*-butylbenzene with tributylphenyltin in THF at room temperature as well as the reaction of 4-chlorotoluene with tributylphenyltin in dioxane at 110 °C in the presence of ligand **4**. In both cases the same ^{31}P chemical shift at 132.4 ppm was observed as the only major phosphorus-containing species (>90%). These observations suggest that perhaps the Pd-**4** complex (δ 132.4) is the resting state species in the catalytic cycle. Further work in our laboratory is underway to delineate the palladium-species involved in these reactions.

Conclusions

Proazaphosphatrane ligands (**1**, **3**, and **4**) provide general and effective palladium catalysts for Stille transformations. Catalysts utilizing **1** and **4** as the supporting ligand efficiently allow coupling of electronically diverse aryl chlorides with a wide array of organotin reagents. Reactions of sterically hindered substrates are most effectively catalyzed with **3** as the supporting ligand and Stille couplings of aryl bromides are more easily facilitated at room-temperature with ligand **4**. Vinyl chlorides and aryl triflates are also suitable substrates. We believe that a unique balance of unusual electron-richness and steric hindrance is a salient feature of these ligands. The exceptional activity shown by the palladium catalyst supported by ligand **4** may also stem from the possibility that a benzyl group stabilizes the active palladium catalyst through the interaction of its aromatic π-orbitals with empty *d*-orbitals on palladium.[27] Another possibility presently unclear is that subtle stereoelectronic effects may operate to ligate **4** more tightly to the Pd center compared with **1**, thereby maintaining a higher electron density at palladium favoring oxidative addition, while simultaneously inhibiting decomposition of the complex.

Acknowledgment

We thank the Aldrich Chemical Co. for their generous support of this study by supplying research samples. The National Science Foundation is gratefully acknowledged for financial support of this work in the form of a grant.

Supporting Information Available

Experimental details, references for known compounds, complete characterization of unknown compounds, and copies of ^{1}H and ^{13}C for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org. This is also available in the appendix H in this thesis.

References

(1) (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley & Sons: New York, 1995. (c) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, Chapter 4.

(2) For reviews of the Stille reaction, see (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterwoth: London, 1987. (d) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (e) Hassa, J.; Svignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (f) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(3) For recent applications of the Stille reaction in natural product synthesis, see (a) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupali, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'brate, A. *J. Am. Chem. Soc.* **2003**, 125, 15443. (b) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, 125, 46. (c) Lin, S.-Y.; Chen, C.-L.; Lee, Y.-J.; *J. Org. Chem.* **2003**, *68*, 2968. (d) Boger, D. L.; Ichikawa, S.; Jing, H. *J. Am. Chem. Soc.* **2000**, 122, 12169. (e) Jensen, M. S.; Yang, C.; Hsiao, Y.; Rivera, N.; Wells, K. M.; Chung, J. Y. L.; Yasuda, N.; Hughes, D. L.; Reider, P. J.; *Org. Lett.* **2000**, *2*, 1081.

(4) Kuribayashi, T.; Gohya, S.; Mizuno, Y.; Satoh, S. *J. Carbohyd. Chem.* **1999**, *18*, 383.

(5) Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665.

(6) For leading references to Suzuki couplings of aryl chlorides, see (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722; (b) Littke, A. F.; Fu, G. C. *Angew*

Chem., Int. Ed. Engl. **1998**, *37*, 3387. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (d) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540. (e) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (f) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (g) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (h) Urgaonkar, S. Nagarajan, M. Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

(7) For leading references to Heck reactions of aryl chlorides, see (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031. (c) Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. *Adv. Synth. Catal.* **2002**, *344*, 495. (d) Proeckl, S. S.; Kleist, W.; Gruber, M. A.; Koehler, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1881.

(8) For leading references to Buchwald-Hartwig amination reactions of aryl chlorides, see (a) Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (c) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (d) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (e) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics* **1999**, *18*, 1840. (f) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (g) Reddy, N. P.; Tanaka, M.; *Tetrahedron Lett.* **1997**, *38*, 4807. (h) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

(9) For Pd-catalyzed Stille reactions of activated aryl chlorides, see, Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301.

(10) (a) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed. Engl.* **1999**, *38*, 2411. (b) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(11) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(12) Available from Strem Chemicals.

(13) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

(14) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127.

(15) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551.

(16) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.

(17) For recent reviews, see (a) Verkade, J. G. *Top. Curr. Chem.* **2002**, *233*, 1. (b) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 7819. (c) Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3.

(18) (a) Urgaonkar, S. Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452. (b) Urgaonkar, S.; Verkade, J. G. *Adv. Synth. Catal.* **2004**, *346*, 611. (c) Urgaonkar, S.; Verkade, J. G. *Tetrahedron* **2004**, in press. Also see ref 8h. (c) Urgaonkar, S.; Verkade, J. G. *Tetrahedron* **2004**, in press.

(19) (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (b) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.

(20) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421.

(21) From the screening of various additives to activate the tin reagent, we found that CsF can be replaced by Me_4NF. Other fluoride sources such as KF and ZnF_2 were much less effective. Amines such as Cy_2NMe (an additive successfully used by Wolf[15]) gave only a moderate yield.

(22) Nakatsu, K.; Kinoshita, K.; Kanda, H.; Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Chem. Lett.* **1980**, 913. See also: ref 7a.

(23) (a) Navarro, O.; Kelly, R. A.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194. (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. (c) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (d) Walker, S. D.; Barder, T. E.; Martineli, J. R.; Bulchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(24) For recent examples, see: Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823. See also: refs 13 and 15.

(25) Stille couplings of activated vinyl chlorides are known. See: (a) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1607. (b) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048. (c) May, P. D.; Larsen, S. D. *Synlett* **1997**, 895.

(26) For an excellent review of the mechanisms of the Stille reaction, see: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.

(27) Pd-arene interactions in palladium complexes have been proposed to contribute to their catalytic activity. See (a) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7856. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336. See also: refs 8a, 22c, and 22d.

CHAPTER 10. LIGAND-, COPPER-, AND AMINE-FREE SONOGASHIRA REACTION OF ARYL IODIDES AND BROMIDES WITH TERMINAL ALKYNES

A paper published in *The Journal of Organic Chemistry*

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Abstract

Conditions for an efficient ligand-, copper-, and amine-free palladium-catalyzed Sonogashira reaction of aryl iodides and bromides with terminal alkynes have been developed. Critical to the success of this new protocol is the use of tetrabutylammonium acetate as the base. Noteworthy features of this method are room temperature conditions and the tolerance of a broad range of functional groups in both reaction partners.

Published Manuscript

The palladium-catalyzed reaction of aryl halides with terminal alkynes, known as the Sonogashira reaction, constitutes an important facet of alkyne as well as of organopalladium chemistry.[1,2] This reaction is generally cocatalyzed by Cu(I), and an amine as a base and a phosphine as a ligand for palladium are also typically included.[3] An important side reaction encountered with the presence of a Cu(I) cocatalyst is the Glaser-type oxidative dimerization of the alkyne.[4] To address this issue, several reports have described copper-free Sonogashira reactions, but none of them are free of an amine and a ligand simultaneously, while also operating at room temperature.[5] For example, in 1986, Cacchi et al. reported the coupling of enol triflates with terminal alkynes under copper-free conditions, but a phosphine-ligated palladium precursor and a temperature of 60 °C was employed.[6] In 1993, Linstrumelle published a paper on the Pd-catalyzed coupling of aryl or vinyl halides (I, Br, OTf) with terminal alkynes.[7] In this report, only one example of a phosphine- and copper-free (but not amine-free) Sonogashira coupling of a vinyl iodide with a terminal alkyne was described, and the coupling proceeded in only moderate yield (57%). For an aryl iodide (only iodobenzene was used), a phosphine-ligated palladium source was included under copper-free conditions.

In both cases, 5 mol % palladium catalyst was employed. Herrmann reported a procedure for the Sonogashira reaction of aryl bromides, but it was necessary to use air-sensitive and pyrophoric P(*t*-Bu)$_3$ as a ligand, although the coupling did proceed with only 0.5 mol % of palladium and ligand.[8] It is worthy of note that P(*t*-Bu)$_3$ can be replaced with the air-stable [(*t*-Bu)$_3$PH]BF$_4$ in Sonogashira couplings.[9] Ryu described a Sonogashira method for coupling aryl iodides in ionic liquids, but it required an elevated temperature (60 °C) as well as the use of a phosphine ligand.[10] Recently, Nájera has disclosed a palladacycle catalyst for the cross-coupling of aryl iodides and terminal alkynes.[11] However, this methodology requires relatively harsh conditions (110 °C) and a multi-step synthesis of the catalyst. TBAF, TBAOH, and Ag_2O were used by Mori as activators for the Sonogashira coupling of aryl iodides, but an elevated temperature (60 °C) and a phosphine-based palladium-catalyst were needed in all three cases.[12] Moreover, use of a silver catalyst not only would add cost to the catalyst but also to expense of metal waste disposal/recovery. Astruc described the use of a preformed Pd(II)-phosphine catalyst for a Sonogashira coupling of aryl halides in neat Et_3N.[13] Leadbeater has reported a copper-free Sonogashira methodology for aryl iodides and activated aryl bromides with the traditional palladium catalyst Pd(PPh$_3$)$_2$Cl$_2$ (4 mol %) at 70 °C in neat piperidine.[14] Interestingly, however, the observation was made that under phosphine- and copper-free conditions, neither palladium acetate nor palladium on charcoal catalyzed the aforementioned reaction. More recently, a report by Buchwald has appeared describing the coupling of aryl chlorides and aryl tosylates with terminal alkynes, utilizing a bulky biphenylphosphine ligand under copper- and amine-free conditions.[15]

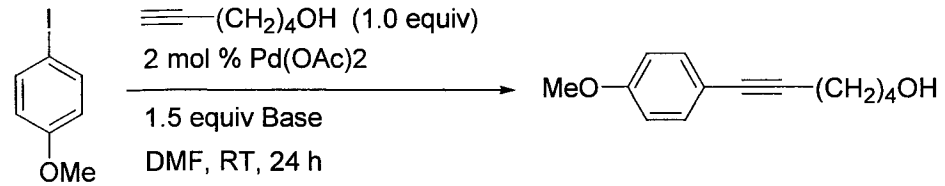
From an industrial as well as an economic standpoint, a ligandless and copper-free process would provide much needed impetus to the development of improved catalyst systems for Sonogashira couplings. Further, such a process would be advantageous for synthetic chemists who would generally prefer not to use expensive and sensitive ligands. In addition, the elimination of amines (generally used in large excess) would be welcome because industrial wastes containing them would require treatment for environmental purposes.

Our continuing interest in palladium-catalyzed organic transformations[16-18] prompted us to extend our attention to the Sonogashira reaction. Herein we report for the first time a room temperature, general, and efficient procedure for a ligand-, copper-, and amine-free

Sonogashira reaction of aryl iodides and bromides with terminal alkynes using $Pd(OAc)_2$ or $Pd_2(dba)_3$ as the catalyst and tetrabutylammonium acetate as the base.

For preliminary optimization of the reaction conditions, we studied the reaction of electron-rich 4-iodoanisole and 5-hexyn-1-ol in the presence of 2 mol % of $Pd(OAc)_2$ in DMF at room temperature (Table 1). An important initial goal was to find a suitable base that would effect the desired reaction. Surprisingly, commonly used secondary and tertiary amine bases such as triethylamine, DBU (diazabicyclo[5.4.0]undec-7-ene), *N*-ethyldiisopropylamine (*i*-Pr_2NEt), piperidine, and diisopropylamine (*i*-Pr_2NH) as well as

TABLE 1. Screening of Bases for Sonogashira Coupling of 4-iodoanisole and 5-hexyn-1-ol



entry	base	yield[a] (%)
1	Bu_4NOAc	93[b]
2	Cs_2CO_3	69
3	Et_3N	5
4	DBU	8
5	*i*-Pr_2NEt	5
6	piperidine	5
7	*i*-Pr_2NH	10
8	Na_2CO_3	30
9	NaO-*t*-Bu	0
10	NaOAc	25

[a] Isolated yields (average of two runs). [b] Reaction time was 6 h.

Na_2CO_3, NaO-*t*-Bu, and NaOAc gave inferior results. Gratifyingly, however, both Cs_2CO_3 and Bu_4NOAc were effective as bases, with Bu_4NOAc being the more reactive, allowing the reaction to be completed in 6 h. Among the solvents screened (THF, toluene, dioxane, CH_3CN, and DMF), DMF proved to be the most efficient. Other palladium sources such as $PdCl_2$, $Pd_2(dba)_3$, and $[(\pi\text{-allyl})PdCl]_2$ were also effective catalysts for the aforementioned reaction.

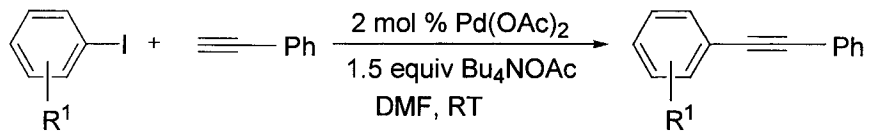
Using equimolar reagent concentrations, 2 mol % $Pd(OAc)_2$, 1.5 equiv Bu_4NOAc, and DMF as the solvent at room temperature, reactions of a series of substituted aryl iodides were carried out via the palladium-catalyzed Sonogashira reaction with phenylacetylene (Table 2). Good to excellent yields were generally obtained under these *ligandless, copper-, and amine-free* conditions. Functional groups such as carboxyethyl, keto, and nitro were well tolerated (Table 2, entries 1-3). Aryl iodides with electron-withdrawing groups gave higher yields than those with electron-neutral or electron-rich groups, and the coupling proceeded with substantially lower palladium catalyst loading. The cross-coupling of sterically hindered aryl iodides (2-iodotoluene and 2-iododanisole) also proceeded quite well (Table 2, entries 4 and 6). As expected, no homo-coupling product was detected by GC under these conditions. It may be noted that while the reactions of aryl iodides possessing electron-withdrawing groups were completed in 3 h the electron-neutral and electron-rich aryl iodides reacted in 6 h.

In an effort to further expand the scope of our ligand-, copper-, and amine-free Sonogashira reaction, we next investigated the reaction of substituted aryl iodides with a series of aliphatic terminal alkynes as summarized in Table 3. The yields were generally higher than those obtained when phenylacetylene was used as the reaction partner. Unfunctionalized alkynes, for example, 1-octyne in Table 3 (entries 2, 3, 6, and 13) as well as functionalized alkynes bearing a hydroxy group (entries 4, 8, 10, 12, and 15), a chloride group (entry 14), a cyano group (entry 18), or a TIPS group (entry 17) reacted efficiently with various aryl iodides to afford the corresponding aryl alkynes in excellent yields. Even a terminal alkyne with an alkene functionality underwent Sonogashira coupling in good yields (entries 1, 5, 7, 9, 11, and 16).

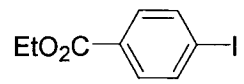
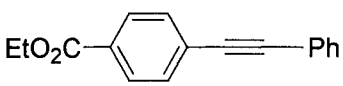
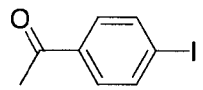
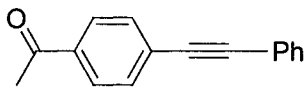
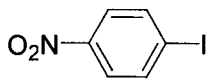
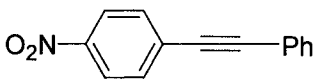
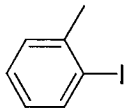
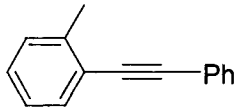
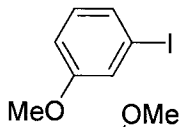
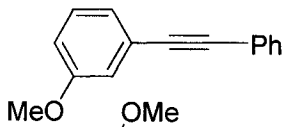
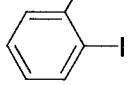
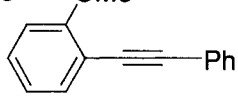
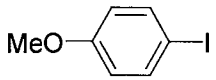
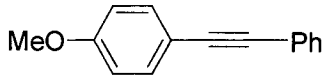
The efficiency of aryl bromides as a coupling partner under ligandless, copper-, and amine-free conditions was also studied (Table 4). Although $Pd_2(dba)_3$ was employed as the catalyst

in these reactions, $Pd(OAc)_2$ was also found to be a suitable palladium precursor. However, this method was effective only for electron-deficient aryl bromides

TABLE 2. Ligand, Copper, and Amine-Free Sonogashira Couplings of Aryl Iodides with Phenylacetylene



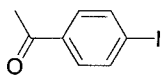
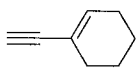
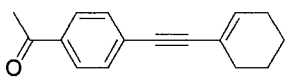
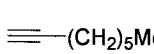
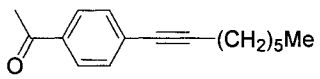
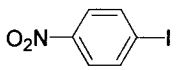
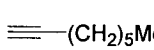
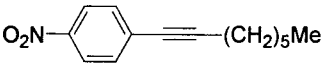
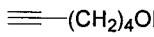
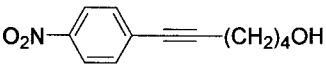
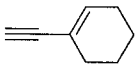
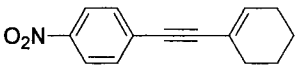
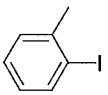
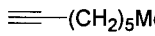
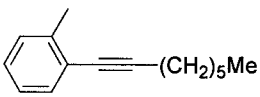
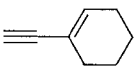
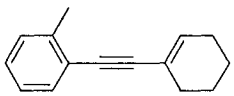
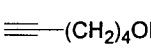
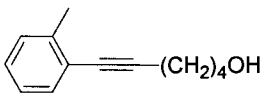
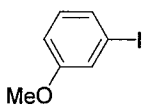
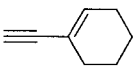
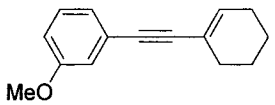
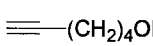
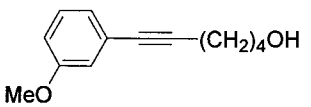
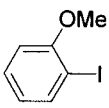
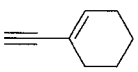
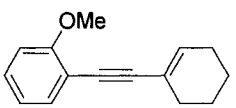
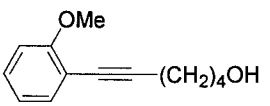
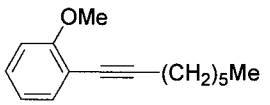
1.0 equiv 1.0 equiv

entry	aryl iodide	product	time (h)	yield (%)[a]
1			3	96[b]
2			3	97[b]
3			3	97[b]
4			6	68
5			6	73 (80)[c]
6			6	74 (79)[c]
7			6	77 (86)[c]

[a] Isolated yields (average of two runs). [b] 1 mol % $Pd(OAc)_2$ was employed. [c] Parenthesized yields were obtained with 3 mol % of $Pd(OAc)_2$

and it required a slightly higher catalyst loading (4 mol % Pd) to provide good to excellent yields of the desired product. Thus, aryl bromides with nitro (entries 1-3), keto (entry 4), and cyano (entries 5-7) functional groups were smoothly coupled with a variety of terminal alkynes. Unfortunately, the Sonogashira couplings of electron-rich aryl bromides were sluggish under these conditions.

TABLE 3. Ligand, Copper, and Amine-Free Sonogashira Couplings of Aryl Iodides with Aliphatic Terminal Alkynes[a]

entry	aryl iodide	alkyne	product	time (h)	yield (%)[b]
1				3	90[c]
2				3	94[c]
3				3	96[c]
4				3	98[c]
5				3	97[c]
6				6	95
7				6	96
8				6	89
9				6	70 (81)[d]
10				6	85
11				6	75 (86)[d]
12				6	77 (86)[d]
13				6	93

[a] For reaction conditions, see Table 1. [b] Isolated yields (average of two runs). [c] 1 mol % $Pd(OAc)_2$ was employed. [d] Parenthesized yield were obtained with 3 mol % of $Pd(OAc)_2$. [e] $Pd_2(dba)_3$ was used in place of $Pd(OAc)_2$.

TABLE 3. Continued

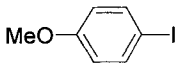
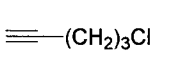
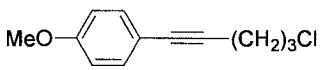
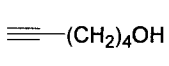
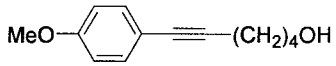
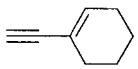
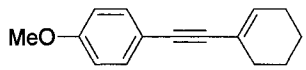
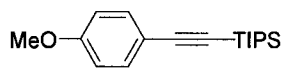
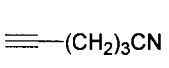
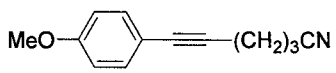
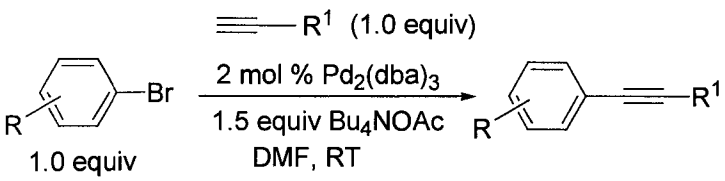
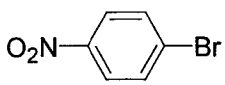
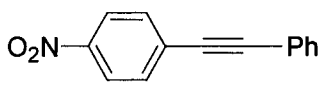
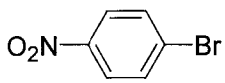
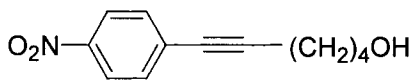
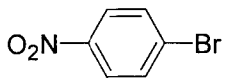
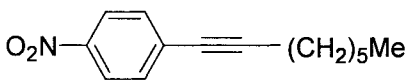
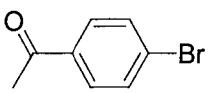
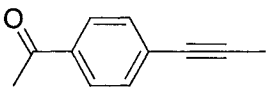
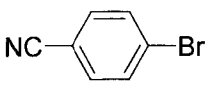
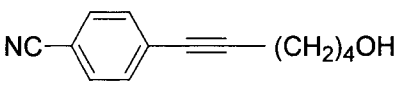
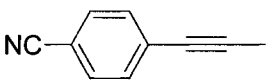
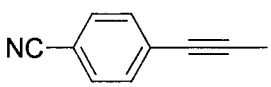
entry	aryl iodide	alkyne	product	time (h)	yield (%)[b]
14				6	80[e]
15				6	93
16				6	76 (84)[d]
17				6	97
18				6	87[e]

TABLE 4. Ligand-, Copper-, and Amine-Free Sonogashira Couplings of Aryl Bromides with Terminal Alkynes



entry	aryl bromide	product	time (h)	yield (%)[a]
1			5	86
2			5	92
3			5	91
4			5	90
5			8	94
6			12	89
7			24	70

[a] Isolated yields (average of two runs).

Presently, the beneficial effect of Bu_4NOAc in these reactions is not clear. Undoubtedly, Bu_4NOAc acts as a mild base to deprotonate the most acidic hydrogen in the alkyne. In addition, it may facilitate the reduction of $Pd(OAc)_2$ to a catalytically active Pd(0) species. The latter phenomenon has been observed previously by Caló[19] and by Reetz[20] and co-workers, who observed Pd nanoparticle formation, albeit at elevated temperatures. However, we have found that the reaction in Scheme 1 proceeds in the presence of mercury, thus supporting a homogeneous catalytic pathway.[21] A particular role for the tetrabutylammonium cation seems to be precluded because we found that Me_4NOAc can be substituted for Bu_4NOAc. On the other hand as expected, the coupling of 4-iodoanisole and 5-hexyn-1-ol did not proceed in the presence of Bu_4NBr (TBAB). These results indicate that the acetate anion in combination with a bulky cation plays a very essential role in promoting such coupling reactions, perhaps by providing a naked more reactive acetate anion. Another possibility is that in the catalytic cycle, the oxidative addition adduct ArPd(II)X, a 12 e^- unstable complex, could be stabilized by tetrabutylammonium acetate to afford a 16 e^- complex $[ArPd(II)X_3]^{2-}\ 2Bu_4N^+$ (X = OAc, and/or I or Br) in which the metal center could be expected to be more stable and more electrophilic thus facilitating its complexation with an alkyne. Deprotonation (by Bu_4NOAc), isomerization, and product-forming reductive elimination would constitute the remaining steps of the catalytic cycle.

In summary, we have established that $Pd(OAc)_2$ or $Pd_2(dba)_3$ catalyzes the Sonogashira reaction of aryl iodides and bromides at room temperature in the absence of ligand, amine, and Cu(I). The choice of tetrabutylammonium acetate as the base is important for obtaining high yields of arylalkynes. The methodology encompasses a wide variety of functional groups, and it is worthwhile noting that our protocol employs a relatively low palladium catalyst loading. To the best of our knowledge, this is the first ligand-, copper-, and amine-free method for the cross-coupling of aryl iodides and bromides with terminal alkynes. These conditions render our protocol potentially attractive for industrial as well academic applications of Sonogashira couplings.

Experimental Section

General procedure for the Sonogashira reaction: An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with Bu_4NOAc (1.5 mmol) and $Pd(OAc)_2$ (1-3 mol %) or $Pd_2(dba)_3$ (2 mol % for aryl bromides) inside a nitrogen-filled glove box. The flask was capped with a rubber septum and then it was removed from the glove box. An aryl iodide or bromide (1.0 mmol) and then DMF (3 mL) were then added and after 5 min of stirring, the alkyne (1.0 mmol) was added. Stirring was continued at room temperature under argon for the corresponding reaction times indicated in the Tables, after which the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (4 x 10 mL). The combined ether layers were dried over Na_2SO_4, filtered, concentrated, and purified by alumina gel flash chromatography using hexanes or hexanes/ether to elute the desired coupling product.

Acknowledgment

The National Science Foundation is gratefully acknowledged for financial support of this work in the form of a grant.

Supporting Information Available

Experimental details and complete characterization of compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org. This is also available in the appendix I in this thesis.

References

(1) Stang, P. J. In *Modern Acetylene Chemistry*; Diederich, F., Ed.; VCH: Weinheim, Germany, 1995.

(2) Sonogashira, K. In *Metal-Catalyzed Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: NewYork, 1998.

(3) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Ind.* **1995**, 129. (d) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566.

(4) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

(5) It should be noted that the examples for copper-free procedures listed in this paper are representative and not comprehensive.

(6) Cacchi, S.; Morera, E.; Ortar, G. *Synthesis* **1986**, 320.

(7) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

(8) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679.

(9) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(10) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.

(11) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365.

(12) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.

(13) Méry, D.; Heuzé, K.; Astruc, D. *Chem. Commun.* **2003**, 1934.

(14) Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653.

(15) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.

(16) (a) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452. (b) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815. (c) Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

(17) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

(18) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051.

(19) Caló, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, *68*, 2929.

(20) Reetz, M. T.; Maase, M. *Adv. Mater.* **1999**, *11*, 773.

(21) Widegren, J. A.; Bennett, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10301.

CHAPTER 11. Pd/P(*i*-BuNCH$_2$CH$_2$)$_3$N: AN EFFICIENT CATALYST FOR SUZUKI CROSS-COUPLING OF ARYL BROMIDES AND CHLORIDES WITH ARYLBORONIC ACIDS

A paper published in the *Tetrahedron Letters*

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Abstract

$Pd(OAc)_2$ in combination with the commercially available ligand P(*i*-BuNCH$_2$CH$_2$)$_3$N catalyzes the Suzuki cross-coupling reaction of a wide variety of aryl bromides and chlorides with arylboronic acids, affording the desired biaryls in excellent yields. It has also been shown that $P(NMe_2)_3$ can be employed as a ligand, though with significantly more limited success.

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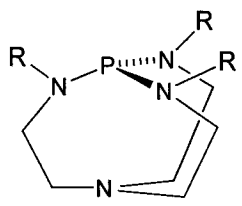
The reaction of halides (or halide equivalents) with arylboronic acids to generate C-C bonds is an important transformation in organic synthesis.[1] Ever since the first report in 1981 by Suzuki and co-workers on their preparation of biaryls,[2] a variety of improvements in catalyst precursors have been described. These studies revealed the crucial role played by the ancillary ligands in the efficiency of this reaction. Sterically hindered, electron-rich alkyl phosphines[3] and carbene[4] ligands have received increasing interest in recent years. However, the development of new ligands or the application of existing ligands in this reaction, particularly those involving aryl chlorides as substrates, is still of considerable importance.

Although acyclic triaminophosphine ligands are well known in transition metal chemistry, they have not been used in metal-catalyzed cross-coupling reactions probably because of their diminished electron-donating capability as rationalized by Woollins[5] recently on the basis of differences in geometries at the nitrogens. Structures of free triaminophosphines and of their transition metal complexes[6] determined by diffraction techniques reveal that each phosphine ligand bears two nearly planar nitrogens and one pyramidal nitrogen. While the

two planar nitrogens are capable of donating electron density to phosphorus, the pyramidal nitrogen is oriented such that its lone pair is *anti* to the phosphorus lone pair, thus allowing that nitrogen to act simply as an electron withdrawing substituent on the phosphorus.

We reasoned that by making the backbone of the triaminophosphine fairly rigid but strain-free in a bicyclic framework in which all three nitrogens would be planar as in pro-azaphosphatranes **1-6**, we could potentially avoid the reduced electron donating character associated with acyclic triaminophosphines. Thus, in contrast to acyclic analogues of **1-6**, all three nitrogens in the cage structure would augment the electron-density on the phosphorus atom. As is seen in **1-6**, the electronic and steric nature of the phosphorus can be fine tuned by the substituents on each PN_3 nitrogen.[7]



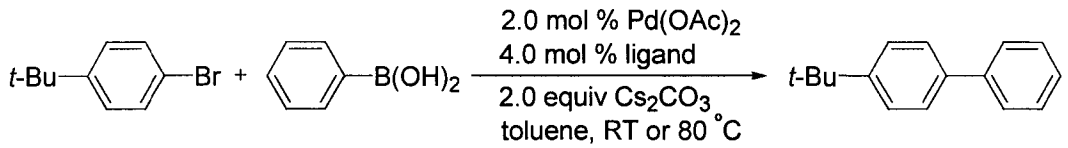
1 R = Methyl
2 R = Ethyl
3 R = *i*-Propyl
4 R = *i*-Butyl
5 R = *neo*-Pentyl
6 R = 4-Pyridyl

Herein we report that bicyclic triaminophosphine **4** (commercially available from Aldrich) is an excellent ligand (and the best of the bicyclic series shown above) in palladium-catalyzed Suzuki cross-coupling reaction of aryl halides, including the less reactive aryl chlorides.[8] We also demonstrate that the commercially available acyclic triaminophosphine $P(NMe_2)_3$ can also be used in the reactions involving aryl bromides and chlorides, although with much less efficiency than **4**.

For optimization studies, we initially screened bicyclic **1-6** and the three acyclic triaminophosphine ligands shown in Table 1 for cross-coupling of 1-bromo-4-*tert*-butylbenzene and phenylboronic acid in the presence of 2.0 equiv. of Cs_2CO_3, 2.0 mol % of $Pd(OAc)_2$ and 4.0 mol % of ligand in toluene. From the results summarized in Table 1, it is evident that bicyclic triaminophosphine **4** is the most effective of the triaminophosphine ligands examined, by a substantial margin, affording a 96% yield of 4-*tert*-butylbiphenyl in 6 h at 80 °C (Table 1, entry 6) and a 90% yield of the same product at room temperature in 28 h (Table 1, entry 7). The other bicyclic ligands were considerably less catalytically active than **4** (Table 1, entries 1–5, 9 and 10) for reasons that are not clear at this time. It is likely

that the *iso*-butyl groups on the PN_3 nitrogens provide a particularly effective steric and electronic environment at the phosphorus for stabilization of the catalytically active species. Interestingly, the acyclic triaminophosphines $P(NMe_2)_3$ and $P(N\text{-}i\text{-}Bu_2)_3$ also furnished the desired product in good yields (Table 1, 87% yield, entry 11 and 84% yield, entry 14, respectively) at 80 °C. Although coupling for ligands **1**, **2**, **4** and $P(NMe_2)_3$ proceeded slowly at room temperature, the reaction proceeds significantly faster at 80 °C.

Table 1. Effect of various triaminophosphine ligands in the Pd-catalyzed cross-coupling of 1-bromo-4-*tert*-butylbenzene with phenylboronic acid[a]



Entry	Ligand	Temp (°C)	Time (h)	Yield (%)
1	**1**	rt	48	52
2	**1**	80	18	69
3	**2**	rt	30	16
4	**2**	80	26	72
5	**2**	80	18	46
6	**4**	80	9	96
7	**4**	rt	28	90
8	**None**	80	20	45
9	**5**	80	24	68
10	**6**	80	24	14
11	**$P(NMe_2)_3$**	80	18	87
12	**$P(NMe_2)_3$**	rt	40	85
13	**$P(NEt_2)_3$**	80	33	31
14	**$P(N\text{-}i\text{-}Bu_2)_3$**	80	24	84

[a] Isolated yields (average of two runs).

We next investigated a variety of solvents and bases for the aforementioned coupling reaction catalyzed by the $Pd(OAc)_2$/**4** system (Table 2). Toluene was found to be the most efficacious solvent. Although dioxane and DMF gave comparable yields, the reaction times were somewhat longer (Table 2, entries 1 and 2). Employing THF as the solvent significantly decreased the yield of the desired product (Table 2, entry 3). Among the bases explored, Cs_2CO_3 gave the fastest reaction rates although CsF was also a suitable base (Table 2, entry 4). However, reactions involving KF, K_3PO_4 or K_2CO_3 as a base failed to provide complete conversion even after 20 h (Table 2, entries 5, 6 and 7).

Table 2. Effect of bases and solvents on the $Pd(OAc)_2$/**4**-catalyzed cross-coupling of 1-bromo-4-*tert*-butylbenzene with phenylboronic acid using the conditions given in Table 1

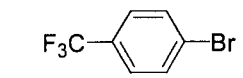
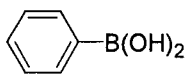
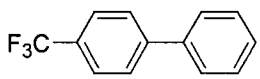
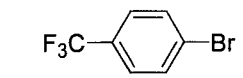
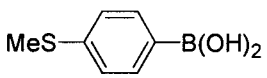
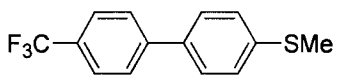
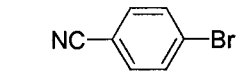
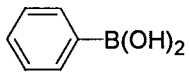
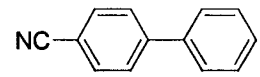
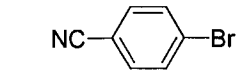
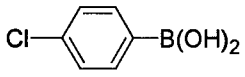
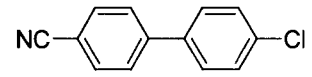
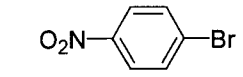
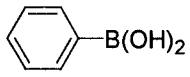
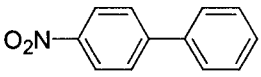
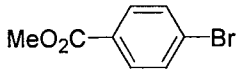
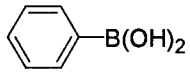
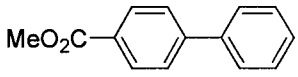
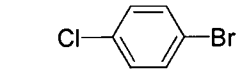
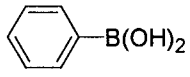
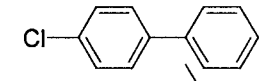
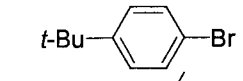
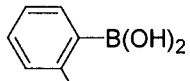
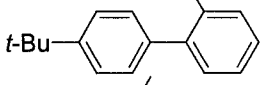
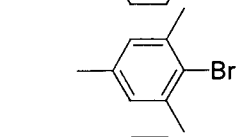
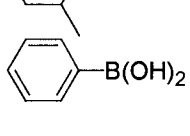
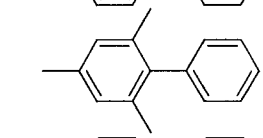
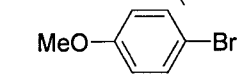
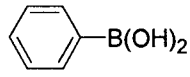
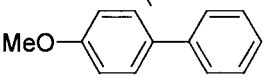
Entry	Base	Solvent	Time (h)	Yield (%)[a]
1	Cs_2CO_3	Dioxane	13	95
2	Cs_2CO_3	DMF	16	91
3	Cs_2CO_3	THF	20	72
4	CsF	Toluene	10	90
5	KF	Toluene	20	78[b] (34)[c]
6	K_3PO_4	Toluene	20	82[b] (19)[c]
7	K_2CO_3	Toluene	13	63

[a] Isolated yields (average of two runs). [b] 90% conversion based on the recovered starting material. [c] The reaction was performed at room temperature and the reaction time was 40 h.

With optimized conditions in hand, we evaluated the scope of the coupling of aryl bromides with various arylboronic acids. It is clear from Table 3 that aryl bromides containing electron-withdrawing groups such as trifluoromethyl, cyano, nitro and ester groups are coupled in excellent yields (Table 3, entries 1–5 and 6). Not surprisingly, the $Pd(OAc)_2$/**4** catalyst system also efficiently and highly selectively catalyzes the reaction of an aryl bromide possessing a chloride functionality (Table 3, entry 7). The use of acyclic $P(NMe_2)_3$ as a ligand also gave satisfactory yields with electron-deficient aryl bromides (Table 3, see yields in parenthesis for entries 1, 3 and 6). The $Pd(OAc)_2$/**4** catalytic system also proved to be highly efficient for electron-neutral and electron-rich aryl bromides. For example,

combining 1-bromo-4-*tert*-butylbenzene with sterically hindered *o*-tolylboronic acid provided the corresponding biaryl in 96% isolated yield (Table 3, entry 8). Sterically demanding di-*ortho*-substituted-2-bromomesitylene also reacted in high yield (Table 3, entry 9). Electron-rich 4-bromoanisole was also a suitable coupling partner (Table 3, entry 10). In contrast, the Suzuki cross-coupling reactions of unactivated (electron-neutral) and deactivated (electron-rich) aryl bromides employing the acyclic triaminophosphine $P(NMe_2)_3$ as the ligand proceeded only in moderate to poor yields.

Table 3. Suzuki cross-coupling of aryl bromides with arylboronic acids[a]

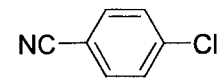
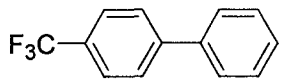
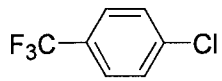
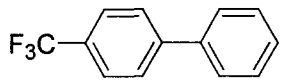
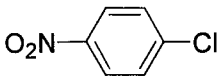
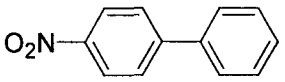
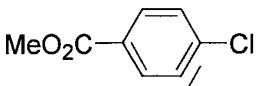
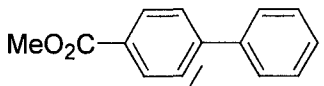
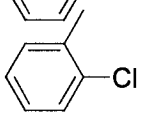
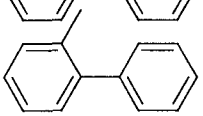
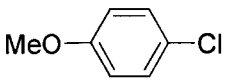
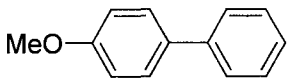
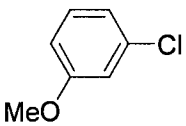
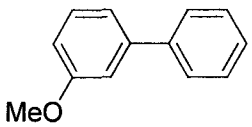
Entry	Aryl Bromide	Arylboronic Acid	Product	Yield (%)[b]
1				99 (57)[c]
2				98
3				99 (90)[c]
4				95
5				96
6				90 (85)[c]
7				90
8				96
9				99 (76)[c]
10				93 (82)[c]

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.5 mmol of arylboronic acid, 2.0 mmol of Cs_2CO_3, 2.0 mol % $Pd(OAc)_2$, 4.0 mol % ligand **4**, 5 mL of toluene, 80 °C, 4-12 h, reaction times have not been minimized. [b] Isolated yields (average of two runs). [c] Yields in parenthesis refer to reactions in which $P(NMe_2)_3$ was employed as a ligand.

Although we were successful in synthesizing biaryls containing two *ortho* substituents, our attempts to synthesize *tri-* or *tetra*-ortho substituted biaryls were unsuccessful even with increased catalyst loading and/or longer reaction times.[9]

We next examined Suzuki reactions of usually unreactive aryl chlorides using $Pd(OAc)_2$/**4** as a catalyst system (Table 4). The low reactivity of such substrates has been attributed to their aversion to add oxidatively to a Pd(0) complex because of a large C-Cl bond dissociation energy (402 kJ mol^{-1}; 298 K).[10] A slightly higher catalyst loading (4 mol % Pd) was required for these reactions to proceed to completion. The reaction of

Table 4. Suzuki cross-coupling of aryl chlorides with phenylboronic acid[a]

Entry	Aryl Chloride	Product	Yield (%)[b]
1			95 (84)[c]
2			90 (80)[c]
3			99
4			98
5			92
6			90
7			88

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.5 mmol of arylboronic acid, 2.0 mmol of Cs_2CO_3, 4.0 mol % $Pd(OAc)_2$, 8.0 mol % ligand **4**, 5 mL of toluene, 80 °C, 18 h, reaction times have not been minimized. [b] Isolated yields (average of two runs). [c] Yields in parenthesis refer to reactions in which 10 mol % $Pd(OAc)_2$ and 20 mol % $P(NMe_2)_3$ were employed.

electron-poor (Table 4, entries 1, 2, 3 and 4) and electron-rich (Table 4, entries 6 and 7) aryl chlorides with phenylboronic acid provided very good yields of the biaryl product. Sterically hindered 2-chlorotoluene was equally reactive and the desired product was isolated in 92%

yield (Table 4, entry 5). In contrast, cross-coupling of aryl chlorides with phenylboronic acid in the presence of $P(NMe_2)_3$ resulted in no detectable product formation even over 36 h when 4 mol % $Pd(OAc)_2$ was employed. However, the use of 10 mol% $Pd(OAc)_2$ and 20 mol % $P(NMe_2)_3$ did allow cross-coupling of electron-poor aryl chlorides with phenylboronic acid and the desired biaryls were obtained in acceptable yields (Table 4, parenthesized yields for entries 2 and 4). The lower yields obtained with the $Pd(OAc)_2/P(NMe_2)_3$ catalyst system were due largely to the formation of hydrodehalogenation products. Since triaminophosphines are apparently less electron-rich than trialkylphosphines, their effectiveness in the activation of C-Cl bond under our conditions is quite remarkable.

In summary, we have shown that the new, cheap and readily accessible catalyst system $Pd(OAc)_2$/**4** is effective for the convenient and efficient synthesis of unsymmetrical biaryls from aryl bromides or chlorides. While the catalyst system $Pd(OAc)_2/P(NMe_2)_3$ is also effective for aryl bromides, it is not very efficient with aryl chlorides.

Acknowledgement

Research support in the form of a grant from the National Science Foundation is gratefully acknowledged.

References

1. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2458; Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263; (c) Suzuki, A. In *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

2. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

3. (a) Little, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020; (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550; (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413; (d) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797

4. (a) Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Bossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848; (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org.*

Chem. **1999**, *64*, 3804; (c) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T. Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186; (d) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866.

5. (a) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065. (b) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721.

6. (a) Crowley, A. H.; Lattman, M.; Stricklen, P. M.; Verkade, J. G. *Inorg. Chem.* **1982**, *21*, 543; (b) Molloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696; (c) Xi, S. K.; Schmidt, H.; Lensink, C.; Kim, S.; Wintergrass, D.; Daniels, L. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1990**, *29*, 2214; (d) Socol, S. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 88.

7. For a recent review of the chemistry of pro-azaphosphatranes, see: Verkade, J. G. *Top. Curr. Chem.*, in press.

8. **General procedure**: An oven-dried Schlenk flask, equipped with a magnetic stir bar, septum, and a condenser with an argon inlet–outlet was charged with aryl halide (1.0 mmol), arylboronic acid (1.5 mmol), base (1.5 mmol), $Pd(OAc)_2$ (2 mol % for aryl bromide and 4 mol % for aryl chloride), ligand (4 mol % for aryl bromide and 8 mol % for aryl chloride) and 5 mL of solvent. The flask was immersed in an oil bath at the temperature indicated in the tables. Upon complete consumption of starting material as determined by TLC analysis, the reaction mixture was adsorbed onto silica and the biaryl product was isolated by column chromatography (hexanes/EtOAc). All the biphenyl products are known compounds.

9. For Suzuki cross-coupling of hindered substrates, see: Yin, J.; Rainka, M. P.; Zhang, X. – X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

10. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

Supporting Materials

The ^1H NMR spectra for the reaction products are available in the appendix J in this thesis.

CHAPTER 12. GENERAL CONCLUSIONS

Conclusions

In conclusion, this thesis describes our efforts to introduce for the first time a new class of triaminophosphine ligand, namely, proazaphosphatranes, in a variety of palladium-catalyzed reactions such as Buchwald-Hartwig amination, Stille, and Suzuki reactions. From the data presented and the discussions, the following conclusions can be reached:

1. Proazaphosphatranes can serve as a highly efficient ligand for the aforementioned reactions provided a fine balance of steric and electronic requirement is met. In this regard, we have shown that the proazaphosphatrane P(*i*-BuNCH$_2$CH$_2$)$_3$N is the ligand of choice for the Buchwald-Hartwig amination reaction of aryl halides with amines. While aryl bromides and iodides readily participated in these reactions it was found that even notoriously less reactive but industrially important aryl chlorides were also suitable coupling partners, which constitutes an important contribution in this area. This ligand was found to work in the presence of strong base such as NaO-*t*-Bu. Later, we found that even NaOH could be employed as a base that tolerates nitro and ketone functional groups. We extended this methodology based on P(*i*-BuNCH$_2$CH$_2$)$_3$N as a ligand for the amination of aryl bromides and chlorides possessing functional groups such as amide, alcohol, phenolic –OH, -NHC(O)CH$_3$, and keto by using LiN(SiMe$_3$)$_2$ as the base. We also utilized this ligand in the synthesis of *N*-aryl-aza-crown ethers.

2. Another bicyclic triaminophosphine, P(*i*-BuNCH$_2$)$_3$CMe, was also found to be effective in the Buchwald-Hartwig amination reaction of aryl bromides, iodides, and chlorides with a variety of amines. With the use of this ligand, a weak base such as Cs_2CO_3 was able to function as the base, thus allowing base-sensitive functional groups to be present in the substrates. We also used this ligand in the synthesis of *N*-aryl-aza-crown ethers by aminating base-sensitive substrates with the aza-crown ether.

3. We have provided the second general method for the Stille reactions of aryl chlorides with organotin compounds. Not surprisingly however, P(*i*-BuNCH$_2$CH$_2$)$_3$N was again found to be an efficient ligand. We also discovered that by further fine tuning of the ligand, we were able to generate a more active catalyst for these reactions. Thus, P(PhCH$_2$NCH$_2$CH$_2$)$_3$N was a

more general ligand for the aforementioned transformation. Using this ligand, we were able to couple aryl and vinyl chlorides and aryl triflates at 100 °C and aryl bromides at room-temperature. We were also successful in synthesizing sterically hindered (tri- and tetra-*ortho*-substituted) biaryls in excellent yields using this ligand.

4. The ligand $P(i\text{-}BuNCH_2CH_2)_3N$ also proved effective in the Suzuki reaction of aryl bromides and chlorides with arylboronic acids. We found in addition that the acyclic triaminophosphine $P(NMe_2)_3$ could also serve as the ligand in this reaction, although with limited success.

5. Finally, we developed the first ligand-, copper-, and amine-free Sonogashira reaction of aryl iodides and activated aryl bromides with terminal alkynes. The use of tetrabutylammonium acetate as the base was found to be critical to the success of this reaction.

Future Prospects

In the near future there are numerous possibilities paralleling the lines of research developed in this thesis. There are several immediate tasks:

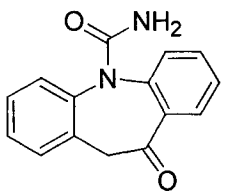
1. The Buchwald-Hartwig amination using $P(i\text{-}BuNCH_2CH_2)_3N$ as the ligand should be extended to include aryl triflates as the reaction partner. Since aryl triflates can be readily synthesized from phenols, there is a strong interest in their applicability in the aforementioned reaction.[1] However, a problem that one could face is the hydrolysis of triflates under the strongly basic conditions used in this reaction (NaO-*t*-Bu). This could be solved by using aryl nonaflates ($ArONf = ArOSO_2(CF_2)_3CF_3$) as the coupling partner instead which are known to be more stable to hydrolysis and which can also be readily synthesized using commercially available starting materials.[2,3] Another possibility is to employ $P(i\text{-}BuNCH_2)_3CMe$ as the ligand with which a weak base may be effective. Finally, it would be worth screening various proazaphosphatranes, as it is highly likely that less bulkier proazaphosphatranes such as $P(MeNCH_2CH_2)_3N$ or $P(i\text{-}PrNCH_2CH_2)_3N$ could be effective owing to the larger size of triflates or nonaflates.

2. The Sonogashira project is in its early stages. It should be extended to cover unactivated and deactivated aryl bromides and chlorides. Various reaction parameters (i.e., ligand, base,

solvent, temperature, addition of reagents) should be thoroughly screened to determine the optimal conditions.

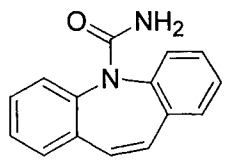
3. The palladium-catalyzed Hiyama-type cross-coupling of organosilicon reagents with aryl chlorides using $P(i\text{-}BuNCH_2CH_2)_3N$ as the ligand needs to be examined. Organosilicon compounds are readily available, less toxic, and show high functional-group tolerance compared with other organometallic reaction partners, and thus hold considerable promise in cross-coupling chemistry.[4,5] However, there are relatively few reports on the cross-coupling of arylsilanes (e.g., phenyltrimethoxysilane which is commonly used) with aryl chlorides, probably due to slow transmetalation of silicon to palladium.[6] In this context, fluoride additives are commonly employed to activate silicon presumably via formation of a more reactive hyper-coordinate penta-valent silicon intermediate. Thus a systematic screening of various fluoride additives is needed. It might also be useful to employ trifluoroarylsilanes instead of trimethoxarylysilanes. Very recently, Fu has reported the nickel-catalyzed cross-coupling of trifluoroarylsilanes with secondary alkyl bromides.[7] He observed that trifluoroarylsilanes were uniquely effective whereas phenyltrimethoxysilane provided only a trace of the cross-coupled product. Trifluoroarylsilanes are easily prepared from trichloroarylsilanes and Na_2SiF_6.[8]

4. A new approach to a precursor to the skeleton of oxcarbazepine[9] **1**, namely **3**, can be envisioned based on the palladium-catalyzed Buchwald-Hartwig amination and the palladium-catalyzed intramolecular α–arylation of ketones as shown in Scheme 1. Oxcarbazepine is considered as a safe alternative to Carbamazepine **2**, a widely prescribed antiepileptic drug.[10]



1

Oxcarbazepine



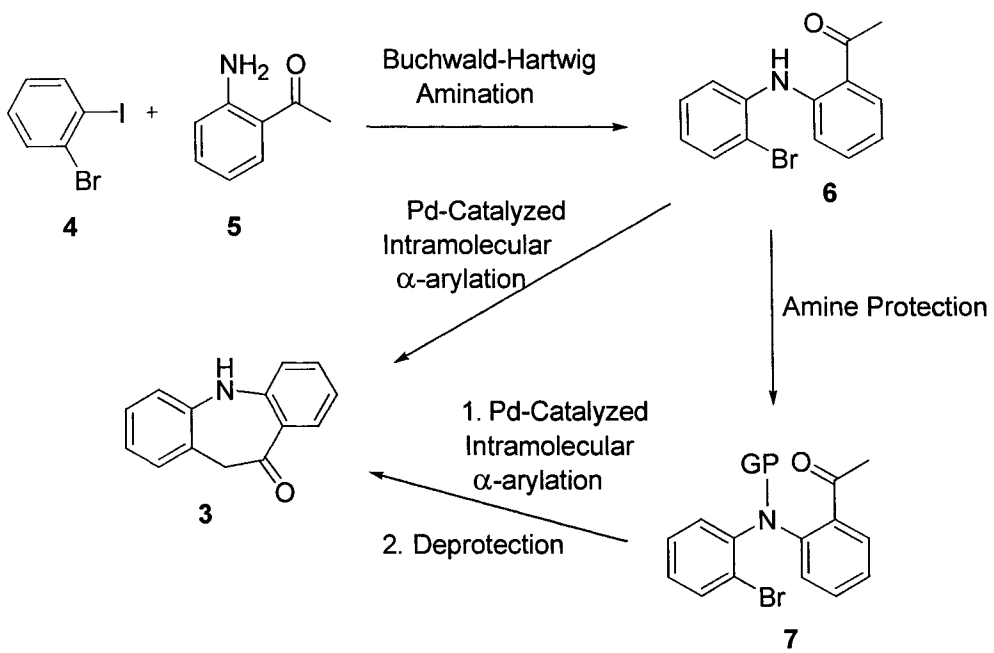
2

Carbamazepine

Thus, the chemoselective palladium-catalyzed reaction of 2-bromoiodobenzene (**4**) with 2'-aminoacetophenone (**5**) would give the aryl bromide (**6**). This could be achieved by using

methodology developed by us with P(*i*-BuNCH$_2$CH$_2$)$_3$N as the ligand in the presence of NaOH as the base.[11] Alternatively, catalyst systems developed by Buchwald and Hartwig could also be tested.[12] Synthesis of **6** sets the stage for a palladium-catalyzed intramolecular α-arylation of the ketone functionality.[13] This key reaction could also be performed after introducing a suitable protecting-group (PG) for the amine. Carbamoylation of **3** to give **1** could be performed using the literature procedure.[9b,14]

Scheme 1. An approach to the core skeleton of oxcarbazepine



References

1. For palladium-catalyzed aminations of aryl triflates, see: (a) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 1095. (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (d) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. *J. Org. Chem.* **1997**, *62*, 1268.

2. For palladium-catalyzed aminations of aryl nonaflates, see: Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563.

3. Zhang, X.; Sui, Z. *Tetrahedron Lett.* **2003**, *44*, 3071.

4. For a review of the Hiyama reaction, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61.

5. (a) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876. (b) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137.

6. (a) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (b) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137.

7. Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.

8. Damrauer, R.; Simon, R. A.; Kanner, B. *Organometallics* **1988**, *7*, 1161 and refernces therein.

9. (a) Kaufmann, D.; Fünfschilling, P.; Beutler, U.; Hoehn, P.; Lohse, O.; Zaugg, W. *Tetrahedron Lett.* **2004**, *45*, 5275. (b) Lohse, O.; Beutler, U.; Fünfschilling, P.; Furet, P.; France, J.; Kaufmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385.

10. *Intractable Epilepsy*; Johannessen, S. I.; Gram, L.; Sillanpää, M.; Tomson, T., Ed.; Wrighston Biomedical Publishing: Petersfield, 1995.

11. See chapter 4 of this thesis.

12. (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (b) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (d) Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479. (e) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553 and references therein.

13. (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581. (c) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577.

14. Milanese, A. WO Patent Application 96/21649, 1996; *Chem. Abstr.* **1996**, *125*, 195448.

APPENDIX A

CHAPTER 2

References for known compounds

^{1}H NMR spectra for reaction products

^{13}C NMR spectra for previously unknown reaction products

References for known compounds

***N*-(*p*-Cyanophenyl)morpholine** (Table 2, entry 1). Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(*p*-Cyanophenyl)pyrrolidine** (Table 2, entry 2). Kaugars, G.; Watt, W. J. Heterocycl. Chem. 1993, 30, 497.

***N*-(*p*-Cyanophenyl)aniline** (Table 2, entry 3). Hartwig, J. F.; Driver, M. S.; Louie, J.; Hamann, B. U. S. Patent 5817877, 1998; Chem. Abstr. 1998, 129, 275692.

***N*-*sec*-Butyl-4-cyanoaniline** (Table 2, entry 5). Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett.* **1990**, 537.

***N*-(4-Chlorophenyl)cyclohexylamine** (Table 2, entry 6). Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A. Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

***N*-(4-*tert*-Butylphenyl)aniline** (Table 2, entry 7). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

***N*-Methyl-*N*-(4-*tert*-butylphenyl)aniline** (Table 2, entry 8). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

***N*-(4-*tert*-Butylphenyl)piperidine** (Table 2, entry 9). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.

***N, N*-Diethyl-4-*tert*-butylaniline** (Table 2, entry 11). Kamikawa, K.; Sugimoto, S.; Uemura, M. *J. Org. Chem.* **1998**, *63*, 8407.

***N*-(2,4,6-Trimethylphenyl)-*o*-anisidine** (Table 2, entry 14). Sundberg, R. J.; Sloan, K. B. *J. Org. Chem.* **1973**, *38*, 2052.

***N*-(2',4',6'-Trimethylphenyl)-2,6-dimethylaniline** (Table 2, entry 15). Freeman, H. S.; Butler, J. R.; Freedman, L. D. *J. Org. Chem.* **1978**, *43*, 4975.

***N*-(2-Methylphenyl)cyclohexylamine** (Table 2, entry 16). Micovic, I. V.; Ivanovic, M. D.; Piatak, D. M.; Bojic, V. D. *Synthesis* **1991**, 1043.

***N*-(2,6-Dimethylphenyl)-*p*-anisidine** (Table 2, entry 17). Kawai, H.; Nieda, S.; Nakai, T.; Tamiguchi, M.; Tsunemitsu, K. Ger. Offen. 3838374, 1989; *Chem. Abstr.* **1989**, 111, 222206.

***N*-Methyl-*N*-(4-methoxyphenyl)aniline** (Table 2, entry 18). Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

***N*-(4-Methoxyphenyl)piperidine** (Table 2, entry 19). Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829.

***N*-(4-Methoxyphenyl)morpholine** (Table 2, entry 20). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

2-Methoxy-2'-phenyldiphenylamine (Table 2, entry 21). Spagnolo, P.; Zanirato, P. *J. Chem. Soc., Perkin Trans. 1.* **1988**, 2615.

***N*-(3-Methoxyphenyl)aniline** (Table 2, entry 22). Yang, M.; Wang, X.; Li, H.; Livant, P. *J. Org. Chem.* **2001**, *66*, 6729.

***N*-(2-Ethylphenyl)-4'-methoxy-2'-methylaniline** (Table 2, entry 23). Yonese, N.; Omatsu, M.; Kondo, M. Eur. Pat. Appl. 155593, 1985; *Chem. Abstr.* **1985**, 104, 216597.

***N*-(4-Methoxy-2-methylphenyl)-2',6'-dimethylaniline** (Table 2, entry 24). Dwyer-Hallquist, P.; Becker, W. J.; Miller, R. E.; Glanz, K. D. Eur. Pat. Appl. 276980, 1988; *Chem. Abstr.* **1988**, 110, 66974.

***N*-(3-Pyridinyl)morpholine** (Table 2, entry 25). Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

***N*-(4-Chlorophenyl)-2',6'-dimethylaniline** (Table 2, entry 26). Geigy, J. R.; A. –G. Neth. Appl. 6604752, 1966; *Chem. Abstr.* **1966**, 67, 81925.

***N*-(2,6-Dimethylphenyl)aniline** (Table 3, entry 1). Freeman, H. S.; Butler, J. R.; Freedman, L. D. *J. Org. Chem.* **1978**, *43*, 4975.

***N*-(2-Ethylphenyl)morpholine** (Table 3, entry 2). Himmelreich, R. G.; Spiess, W. Eur. Pat. Appl. 29617, 1981; *Chem. Abstr.* **1981**, 95, 132649.

***N*-(4-Chlorophenyl)morpholine** (Table 3, entry 4). Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561.

***N*-(4-Methylphenyl)-*p*-anisidine** (Table 3, entry 5). Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

***N*-(4-Methylphenyl)piperidine** (Table 3, entry 6). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

***N*-(2-Methylphenyl)-*p*-anisidine** (Table 3, entry 7). Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

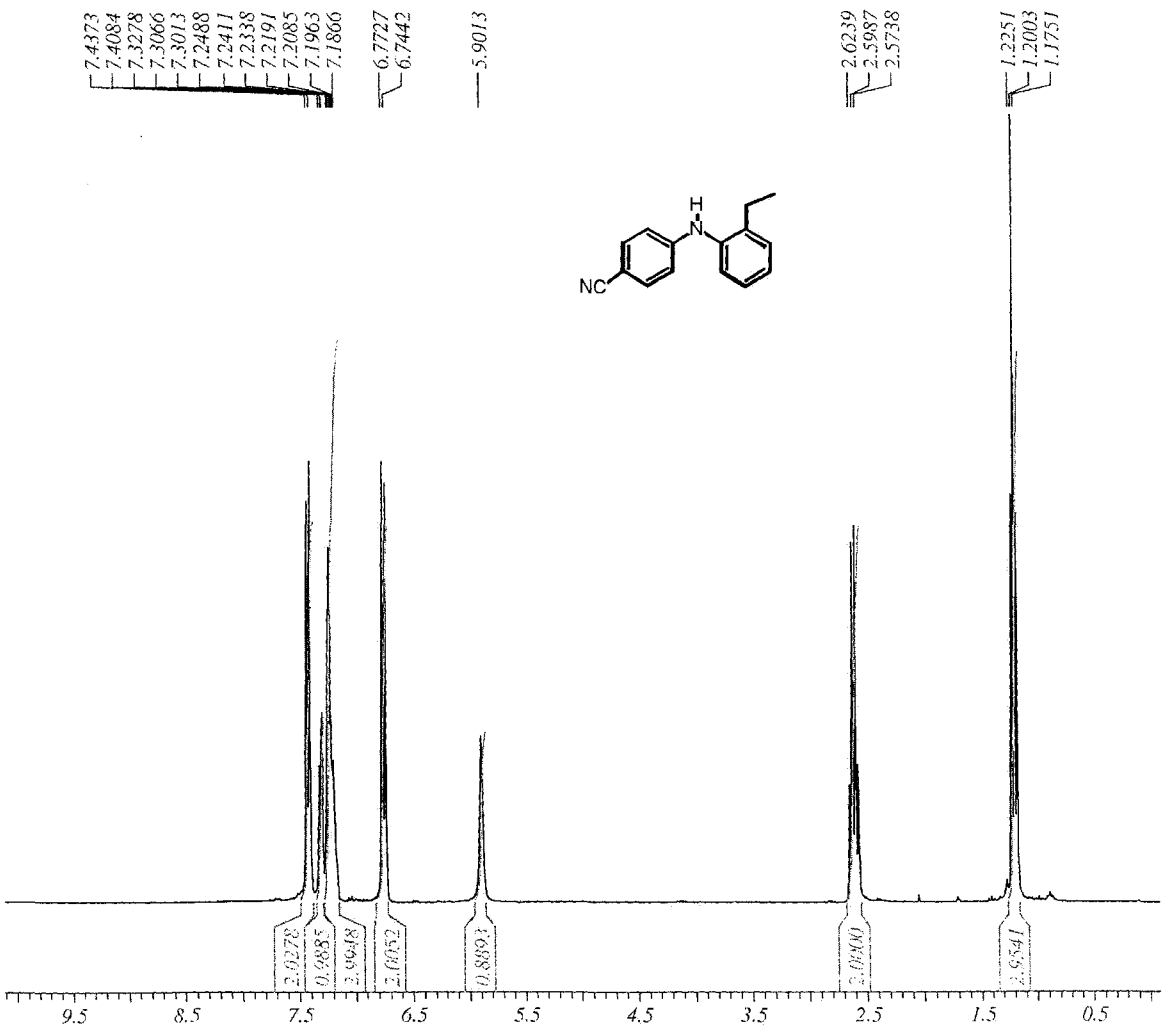
4-Methoxy-2'-phenyldiphenylamine (Table 3, entry 11). Spagnolo, P.; Zanirato, P. *J. Chem. Soc., Perkin Trans. 1.* **1988**, 2615.

***N*-(4-Methylphenyl)cyclohexylamine** (Table 3, entry 14). Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

***N*-(4-Methoxyphenyl)-*N*,*N*-diphenylamine** (Table 4, entry 2). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(4-*tert*-Butylphenyl)-*N*,*N*-diphenylamine** (Table 4, entry 5). Creason, S. C.; Wheeler, J.; Nelson, R. F. *J. Org. Chem.* **1972**, *37*, 4440.

***N*-(4-*tert*-Butylphenyl)morpholine** (Table 4, entry 8). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.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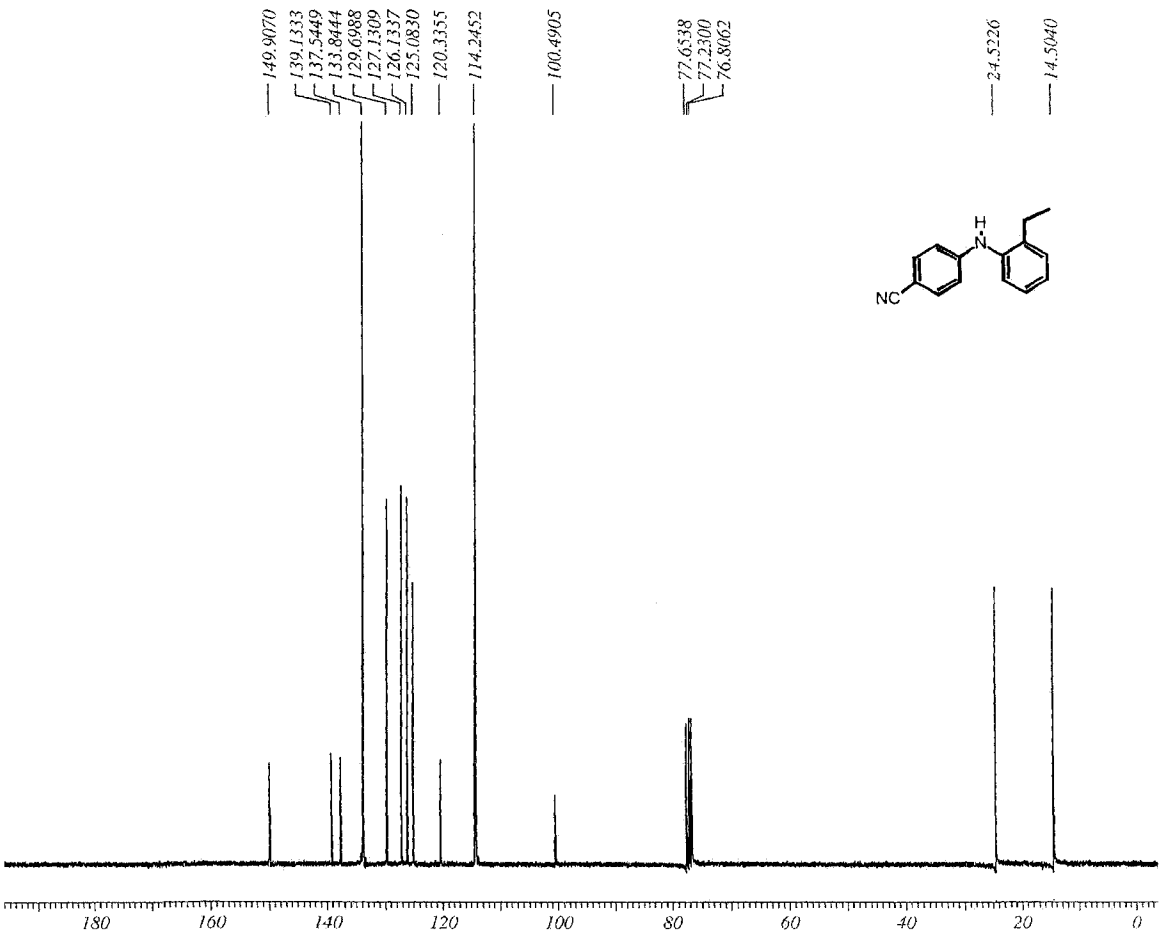
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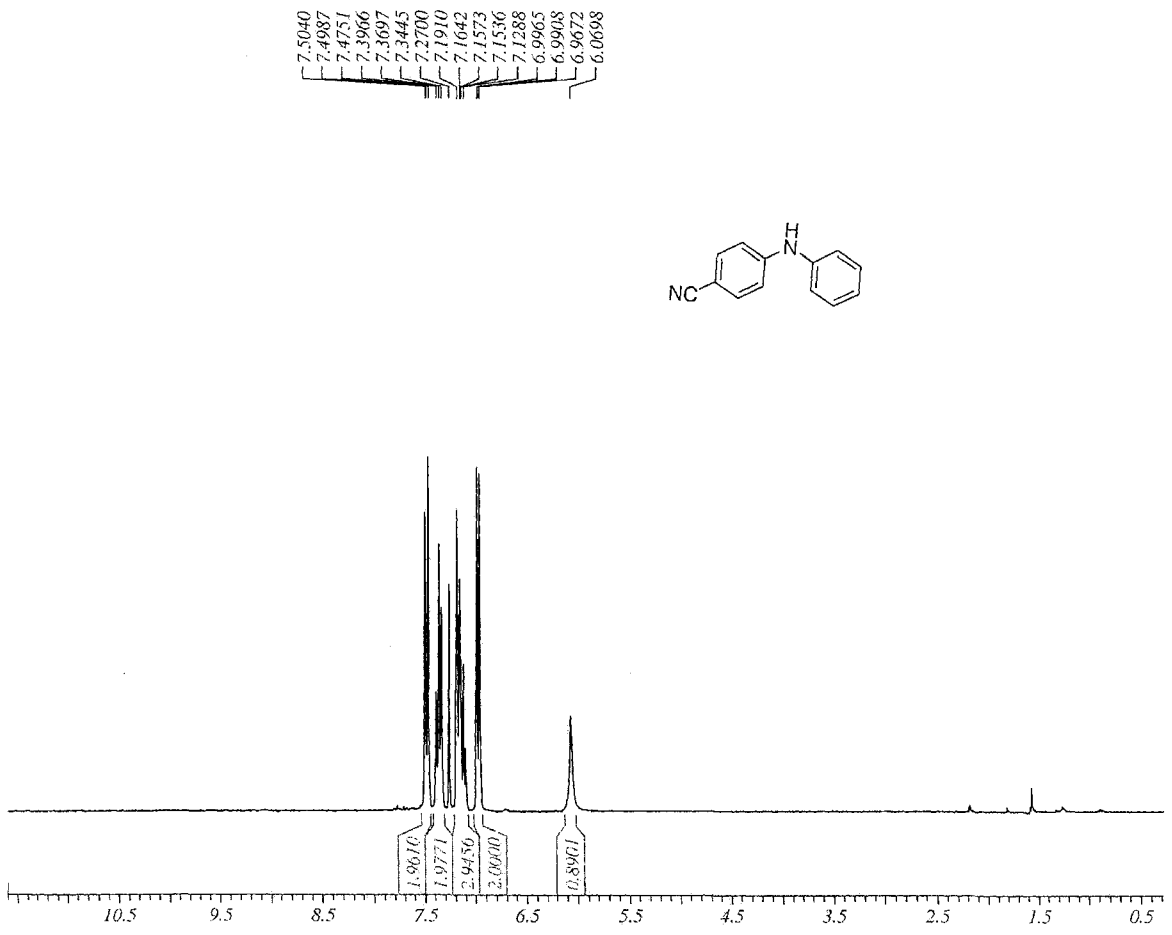
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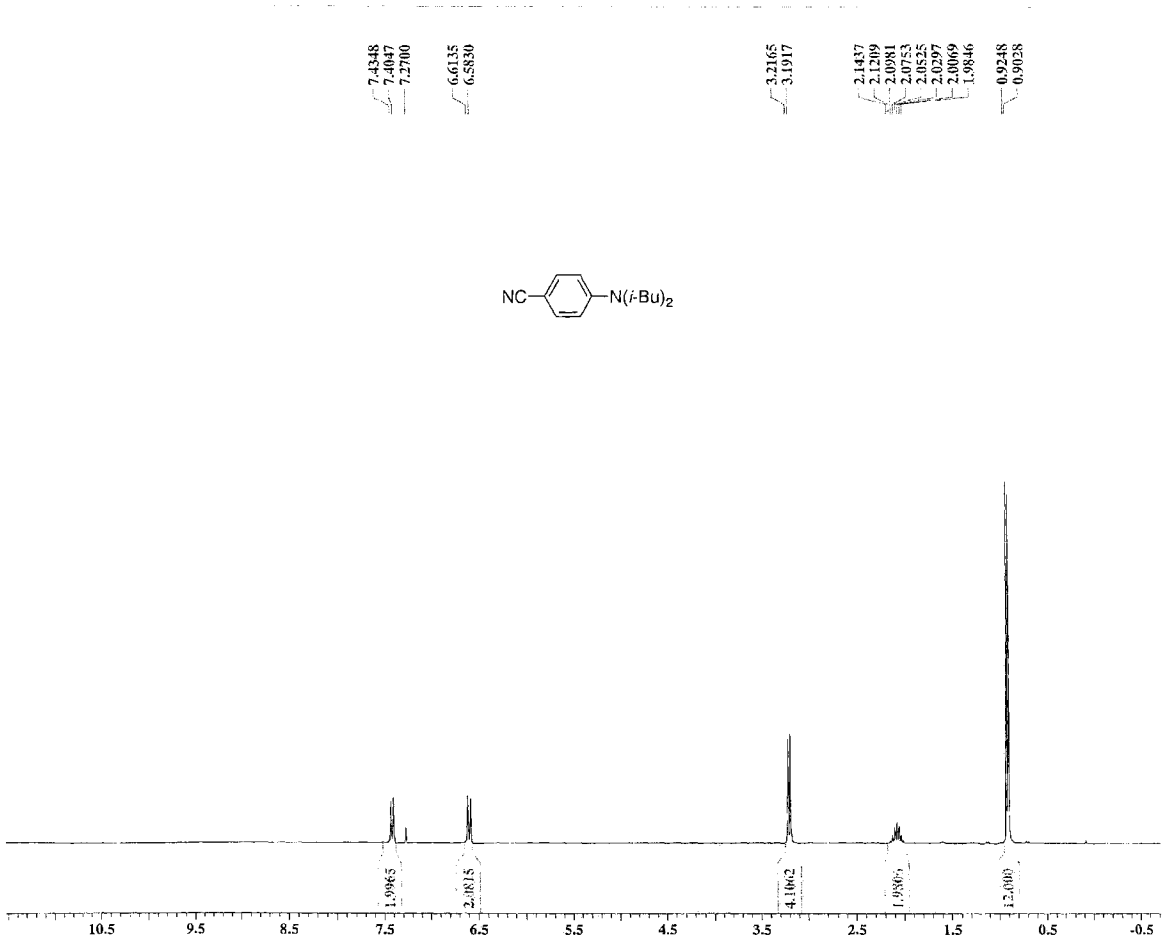
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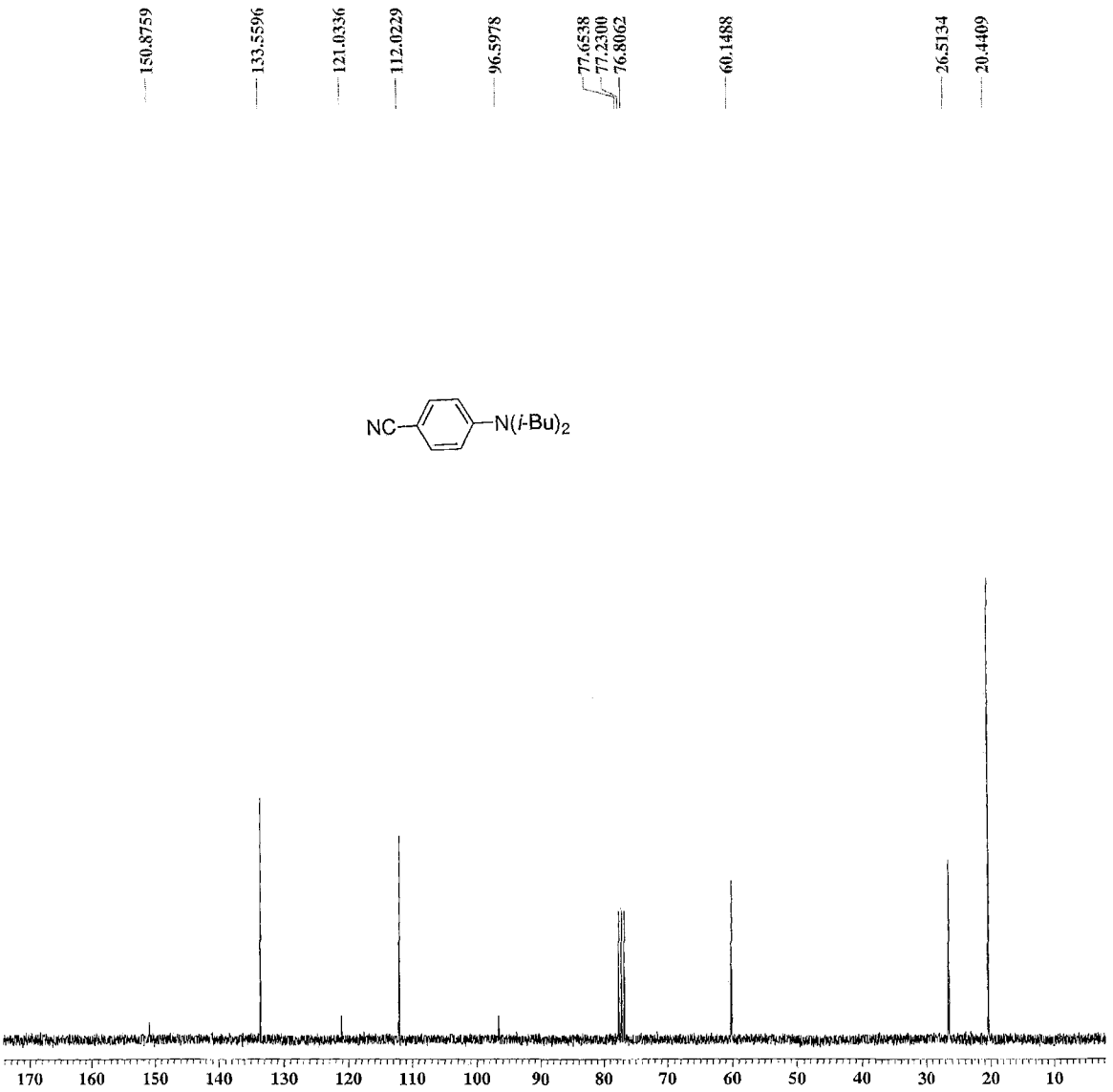
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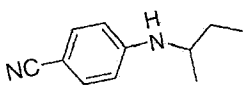

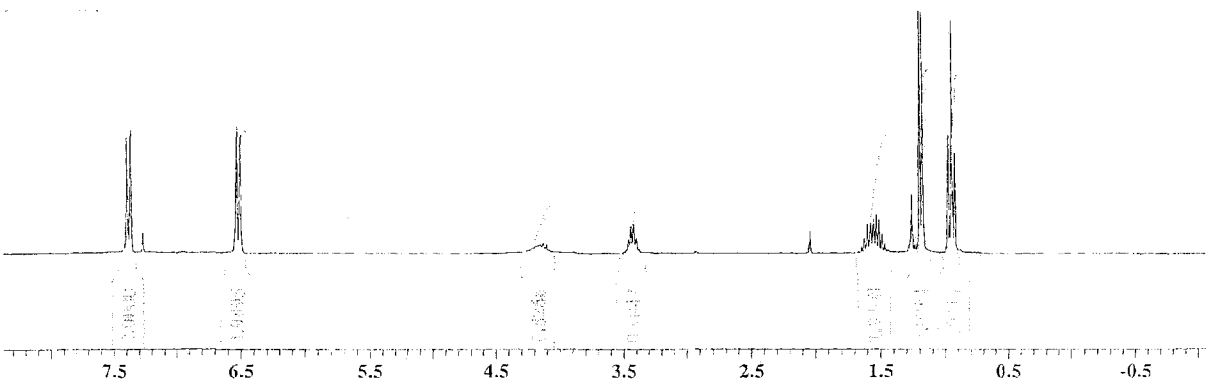

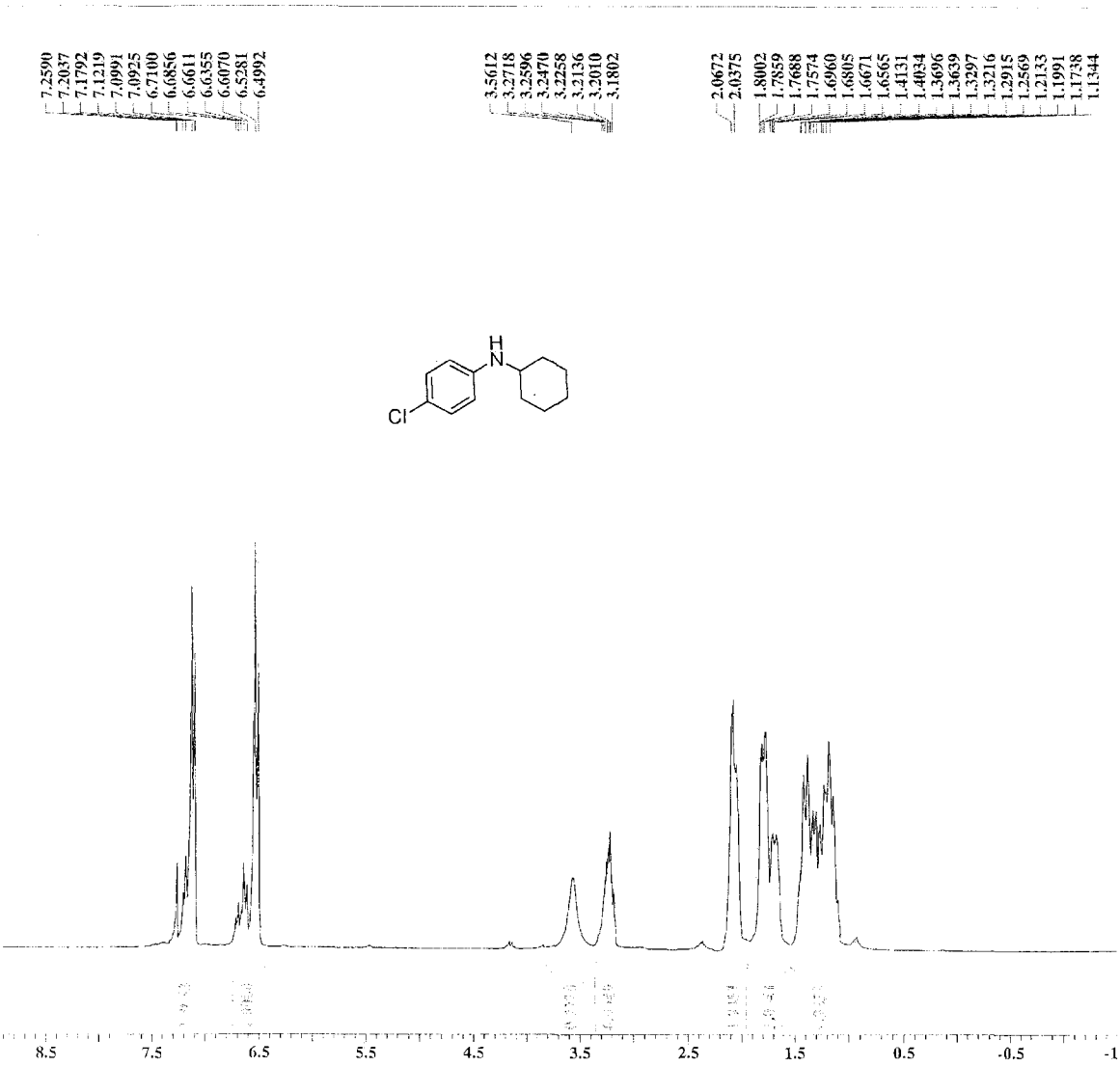
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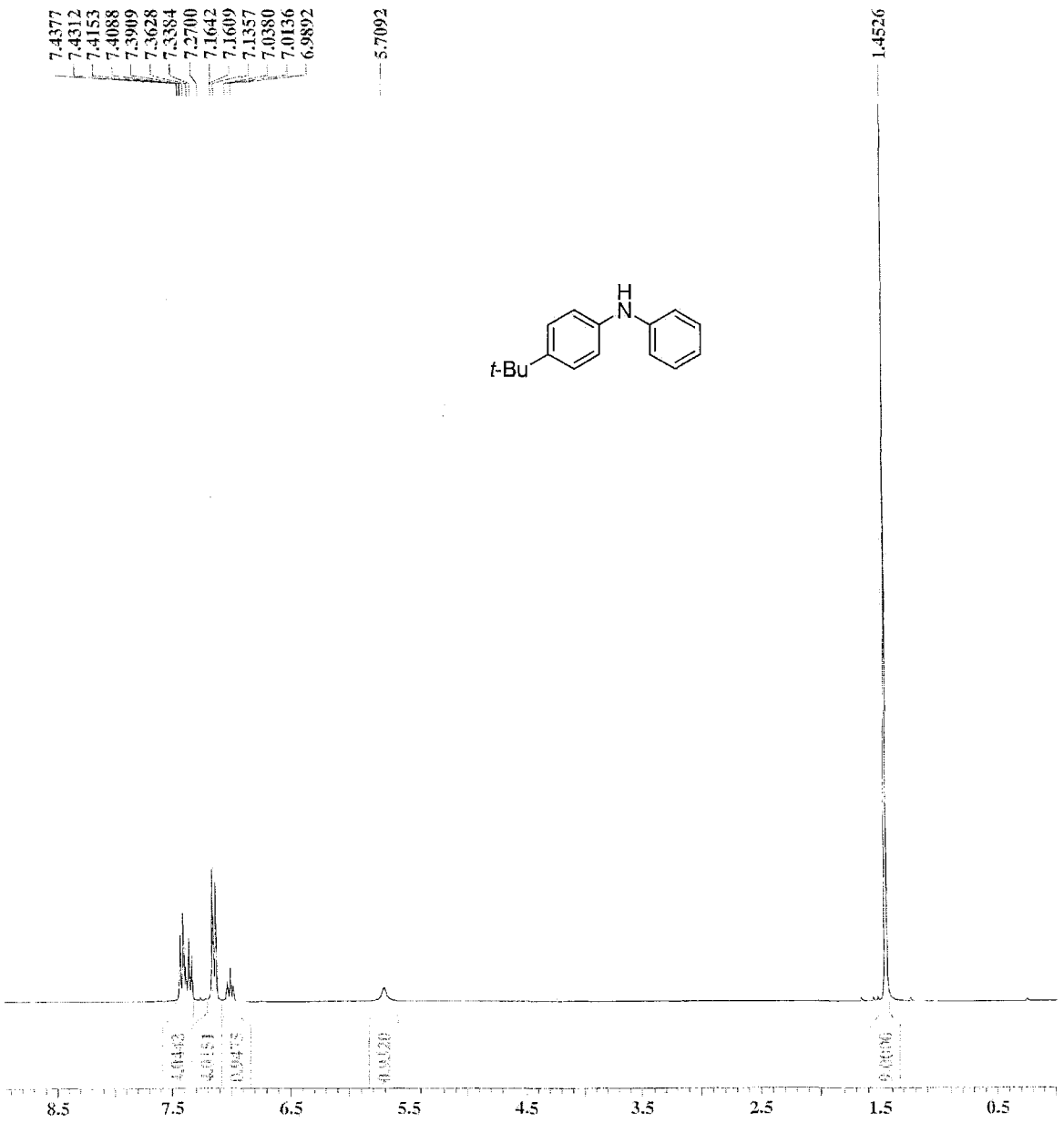
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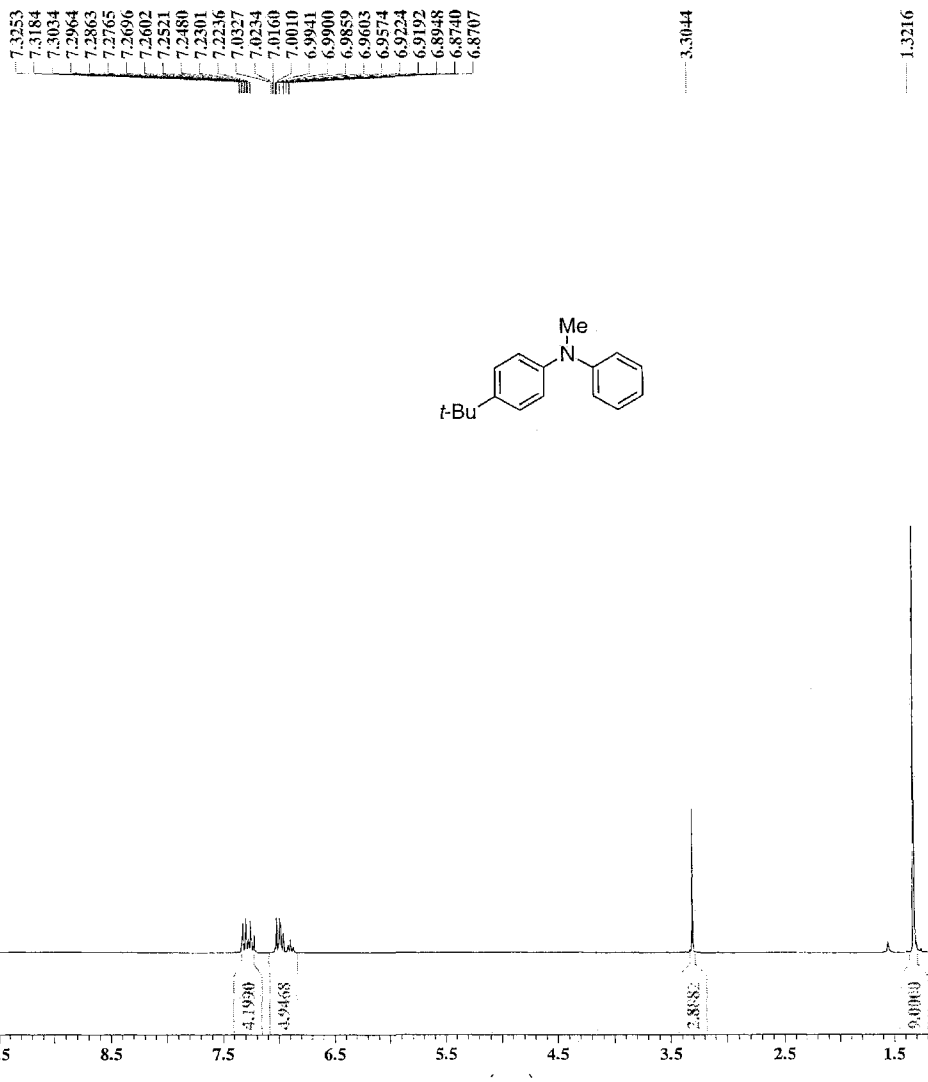
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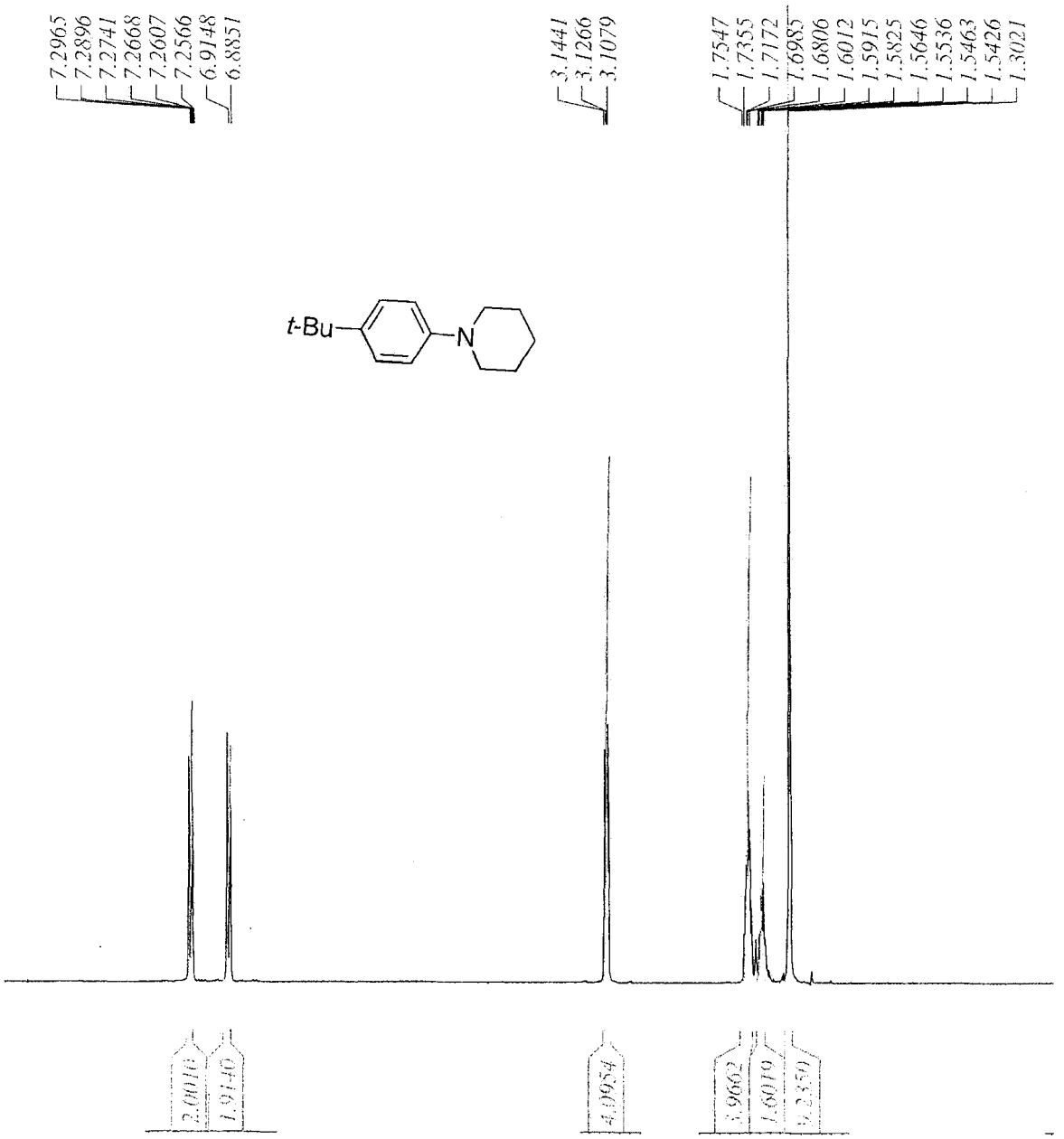
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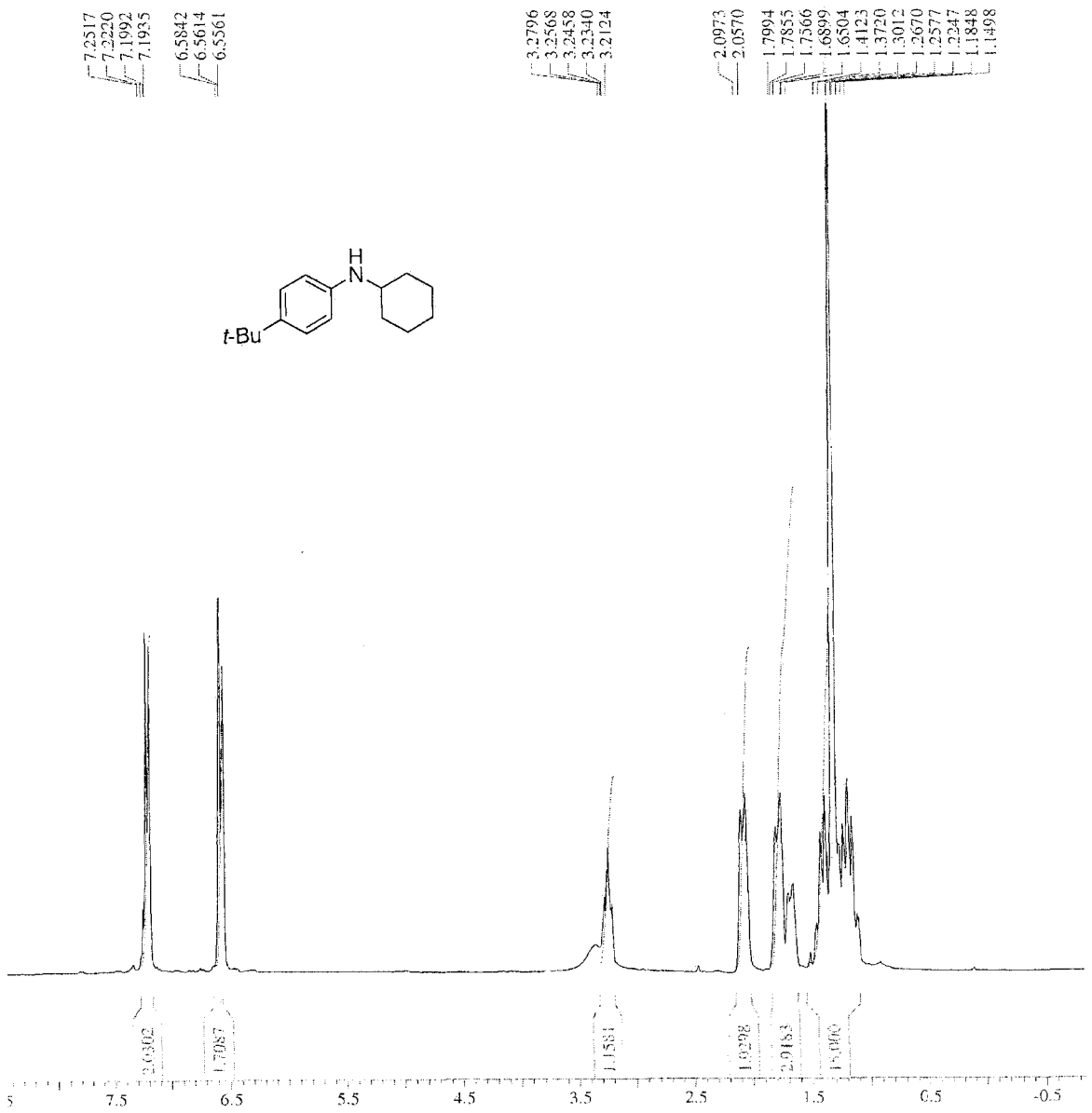
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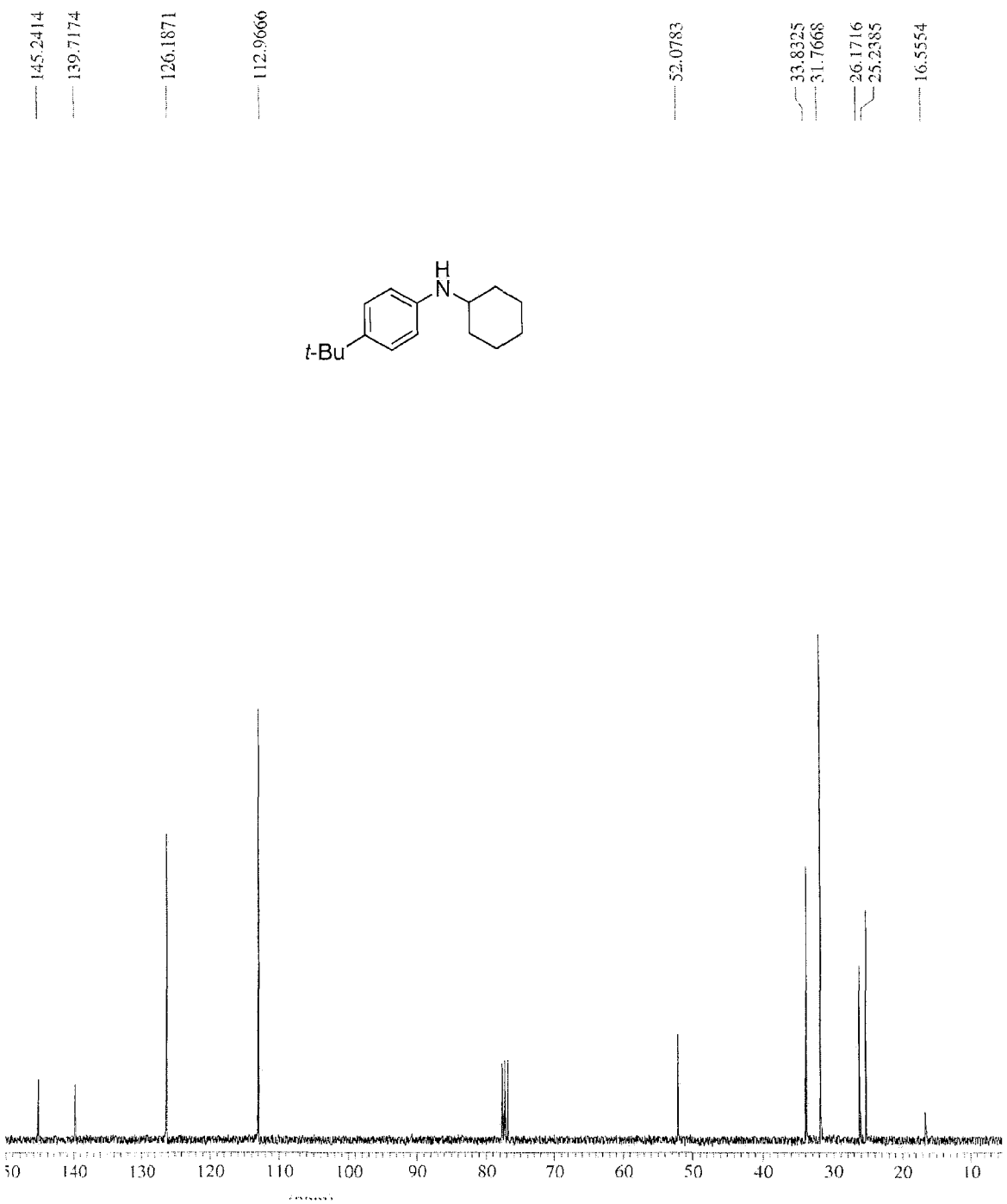
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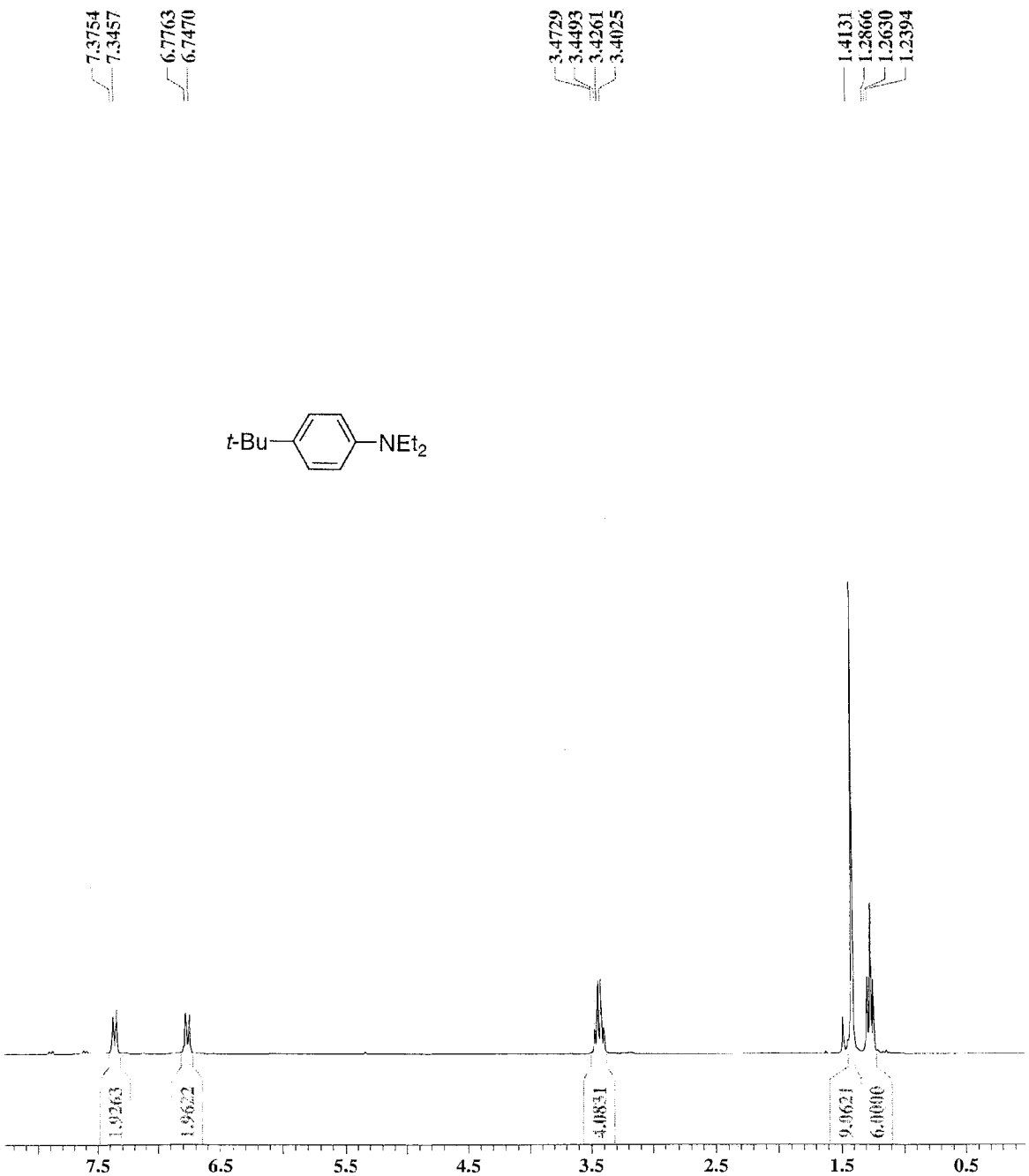
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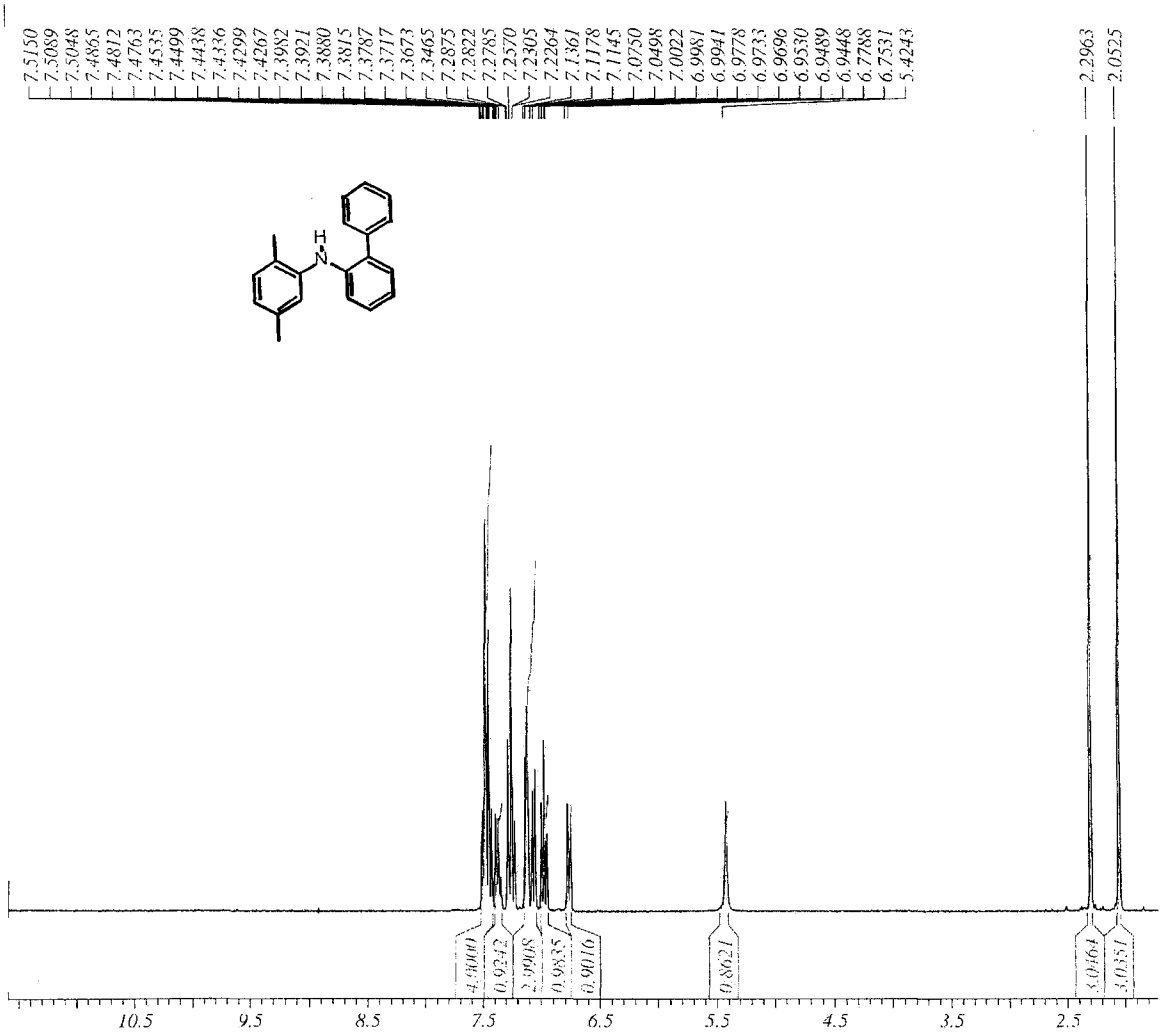
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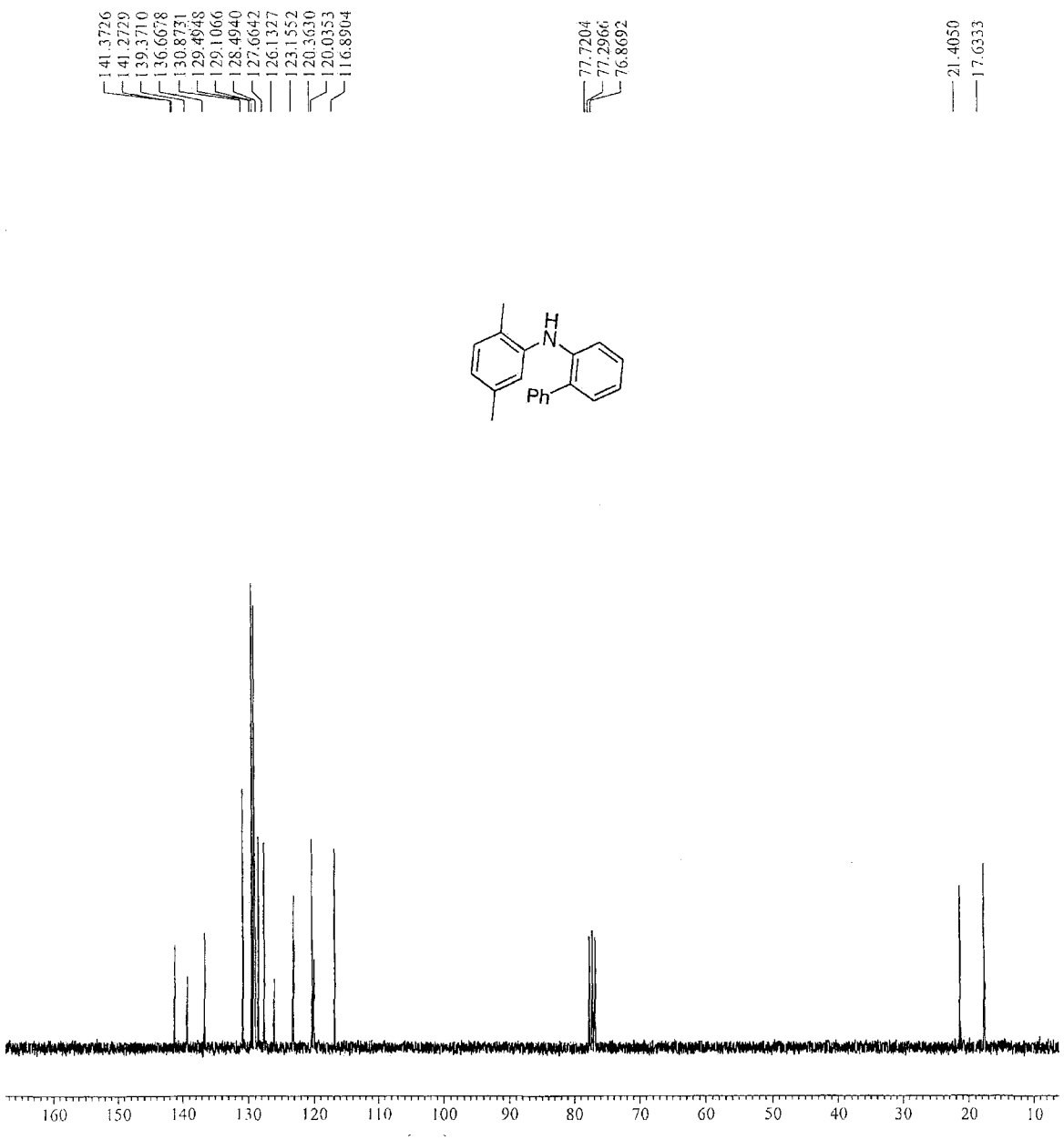
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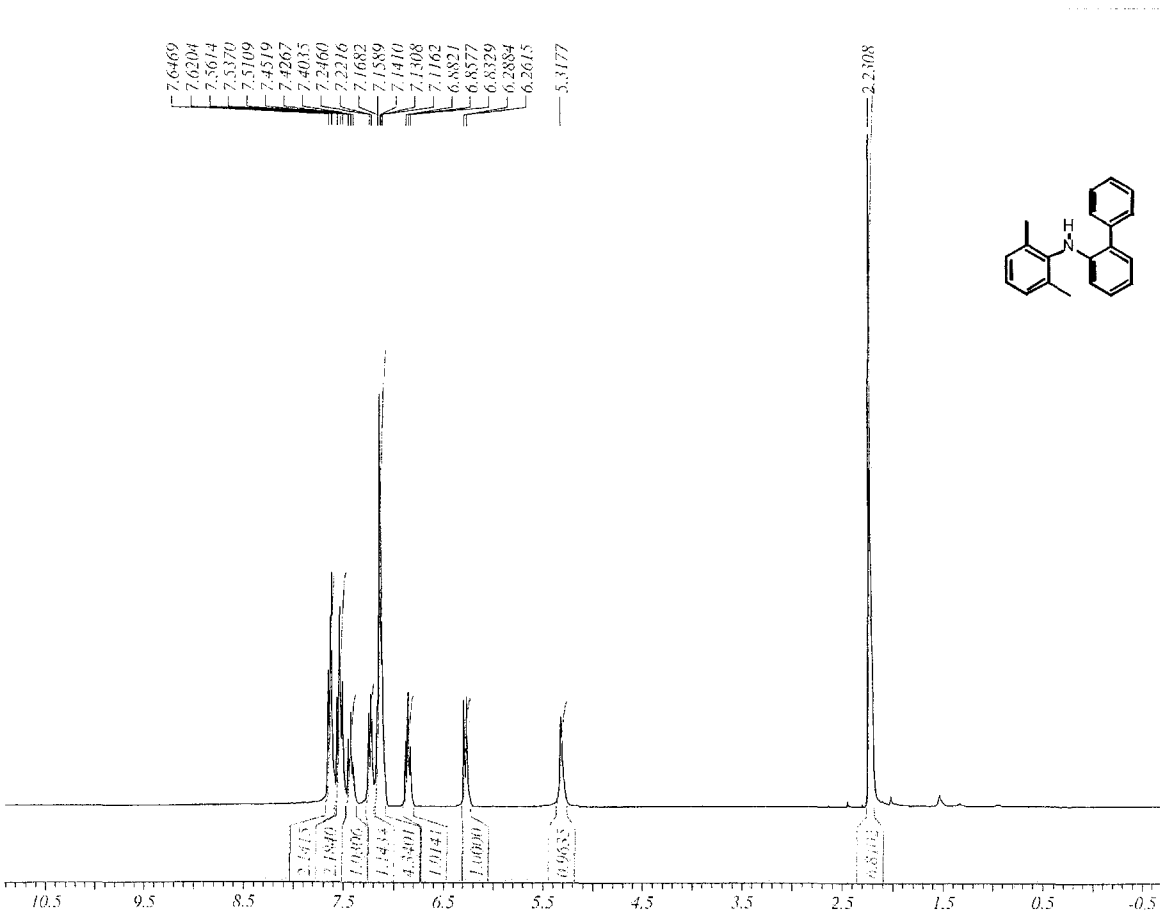
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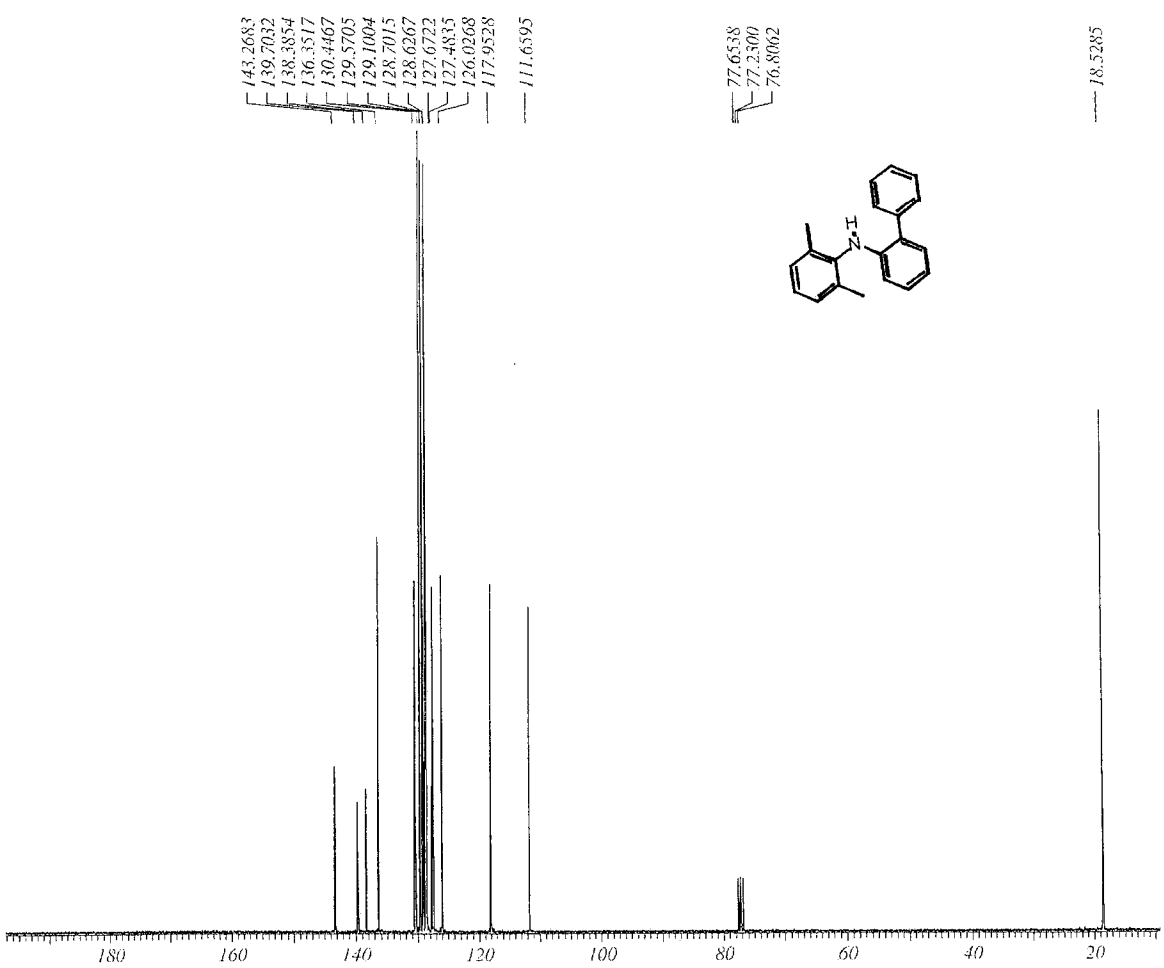
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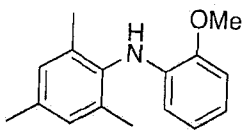
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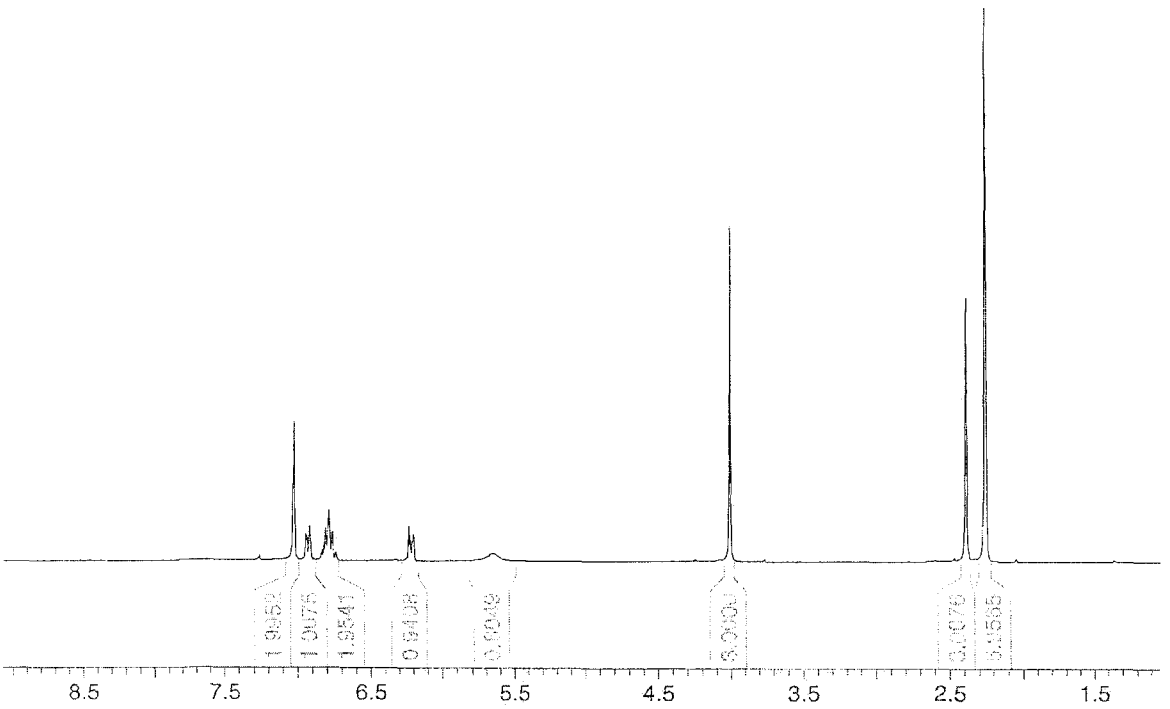
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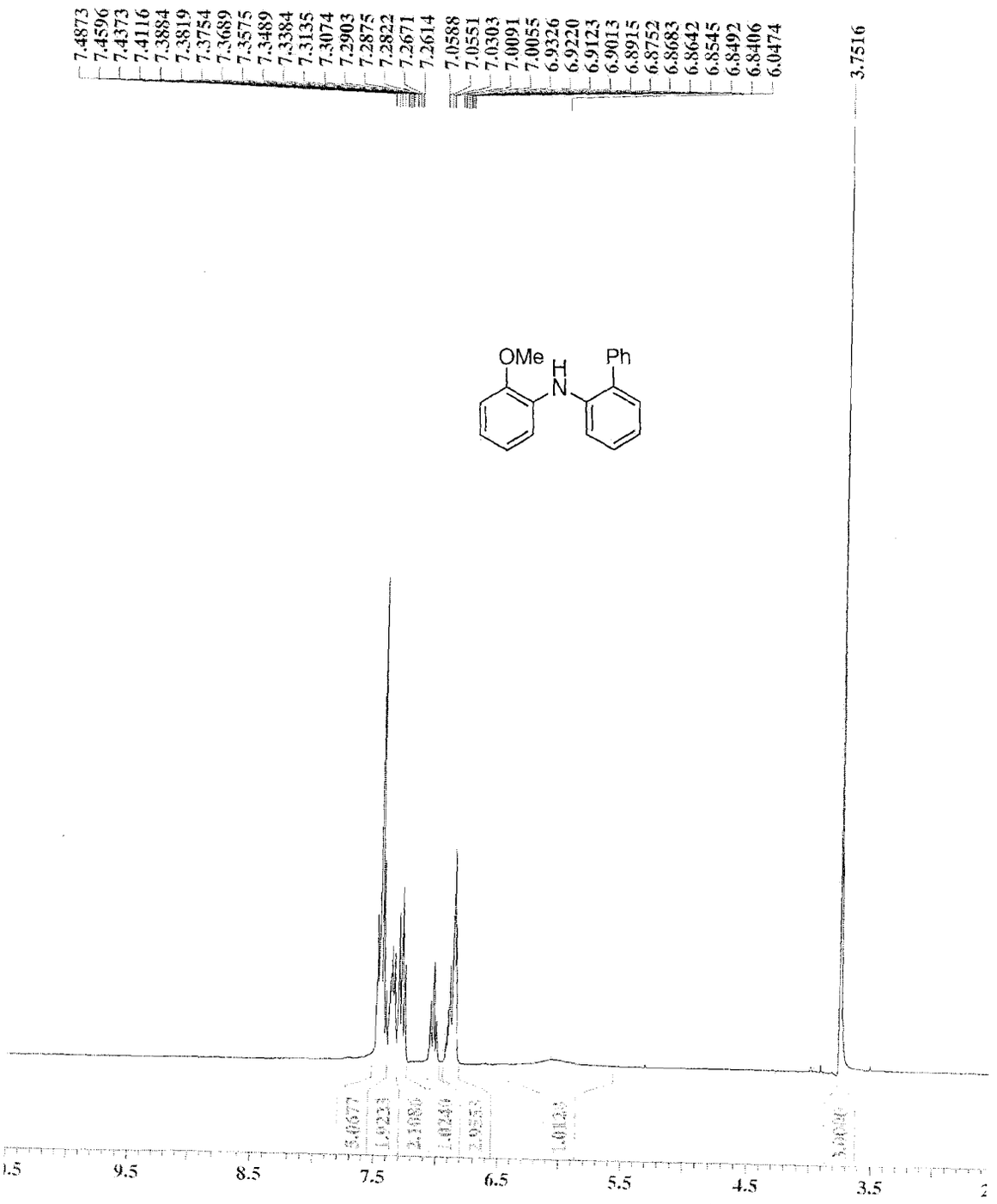
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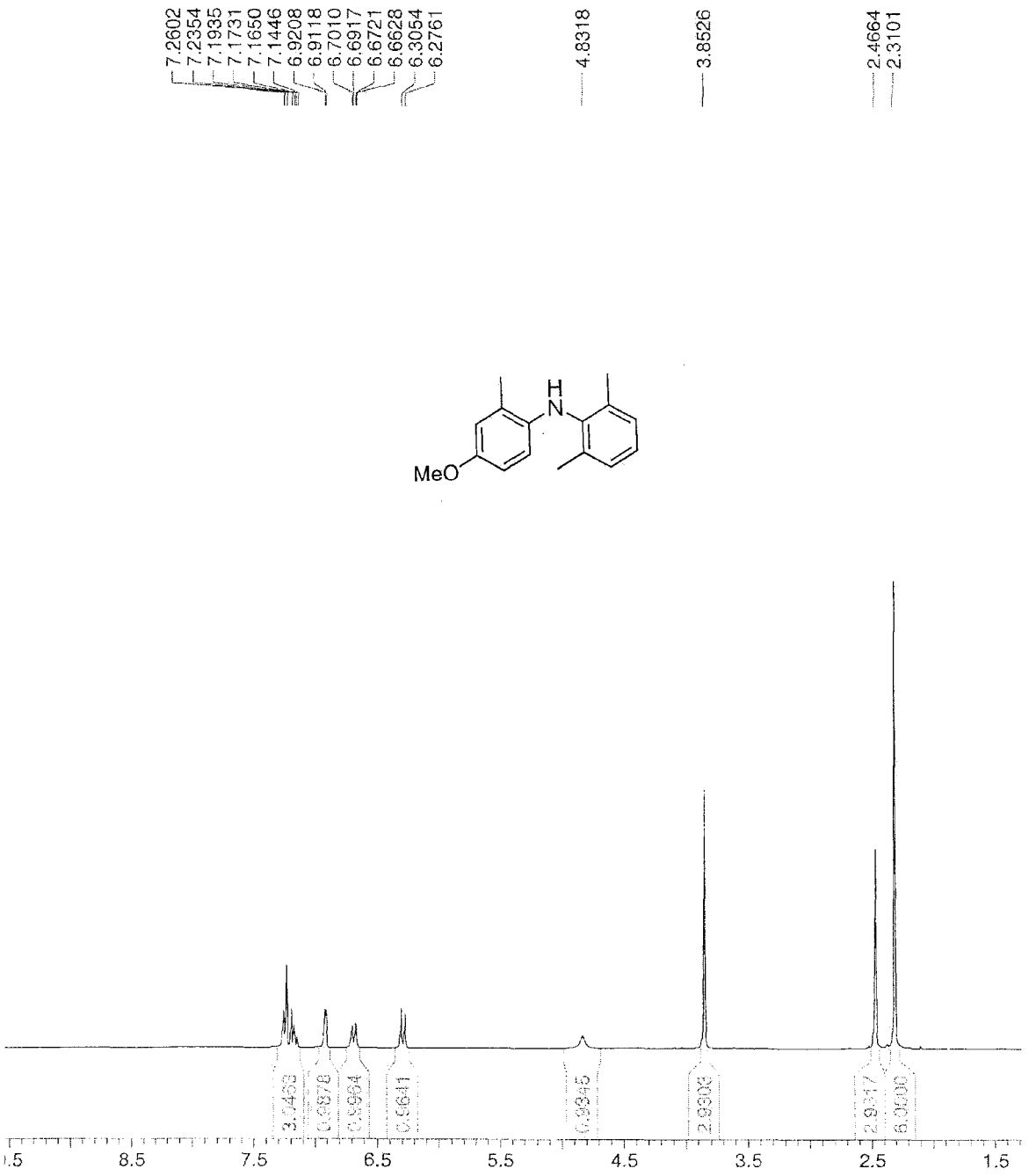
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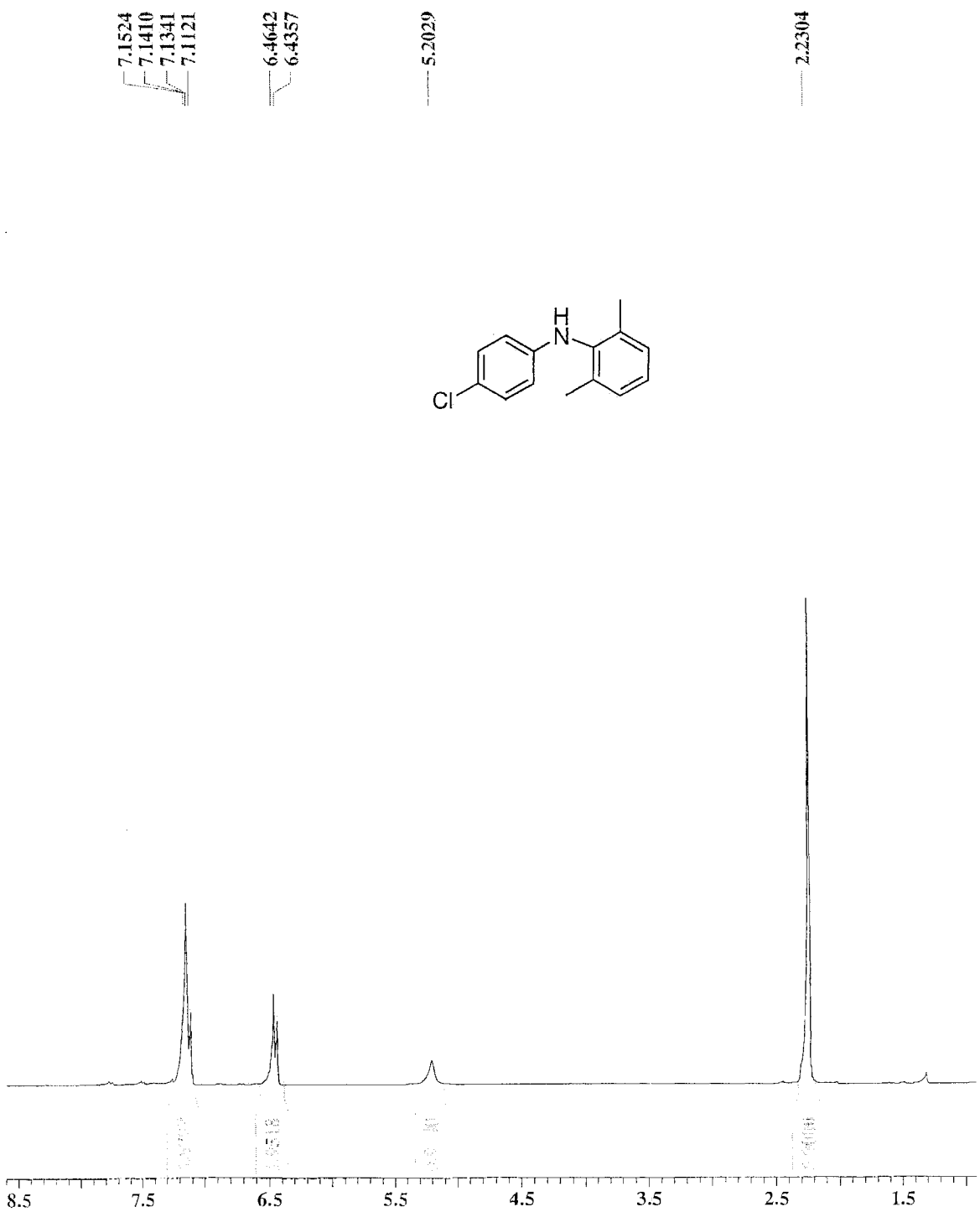
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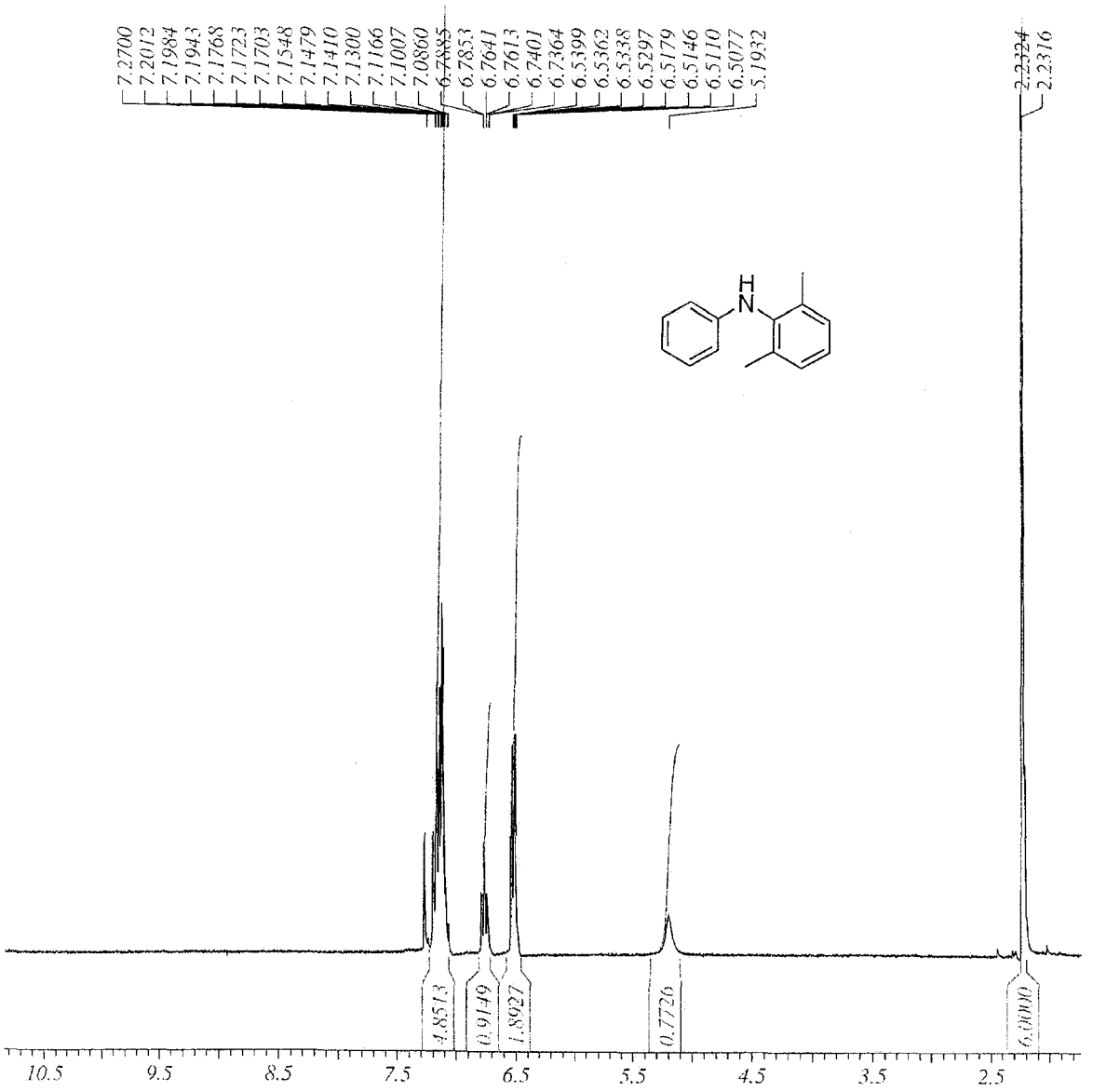
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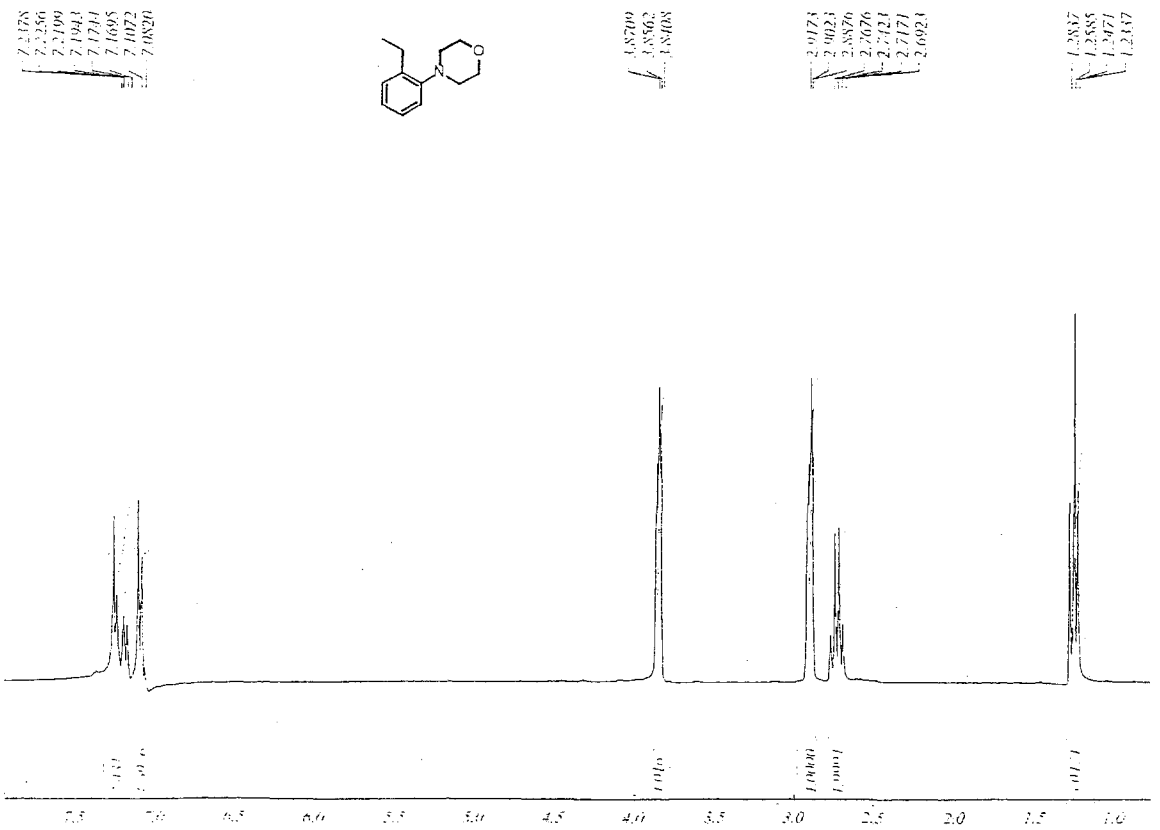

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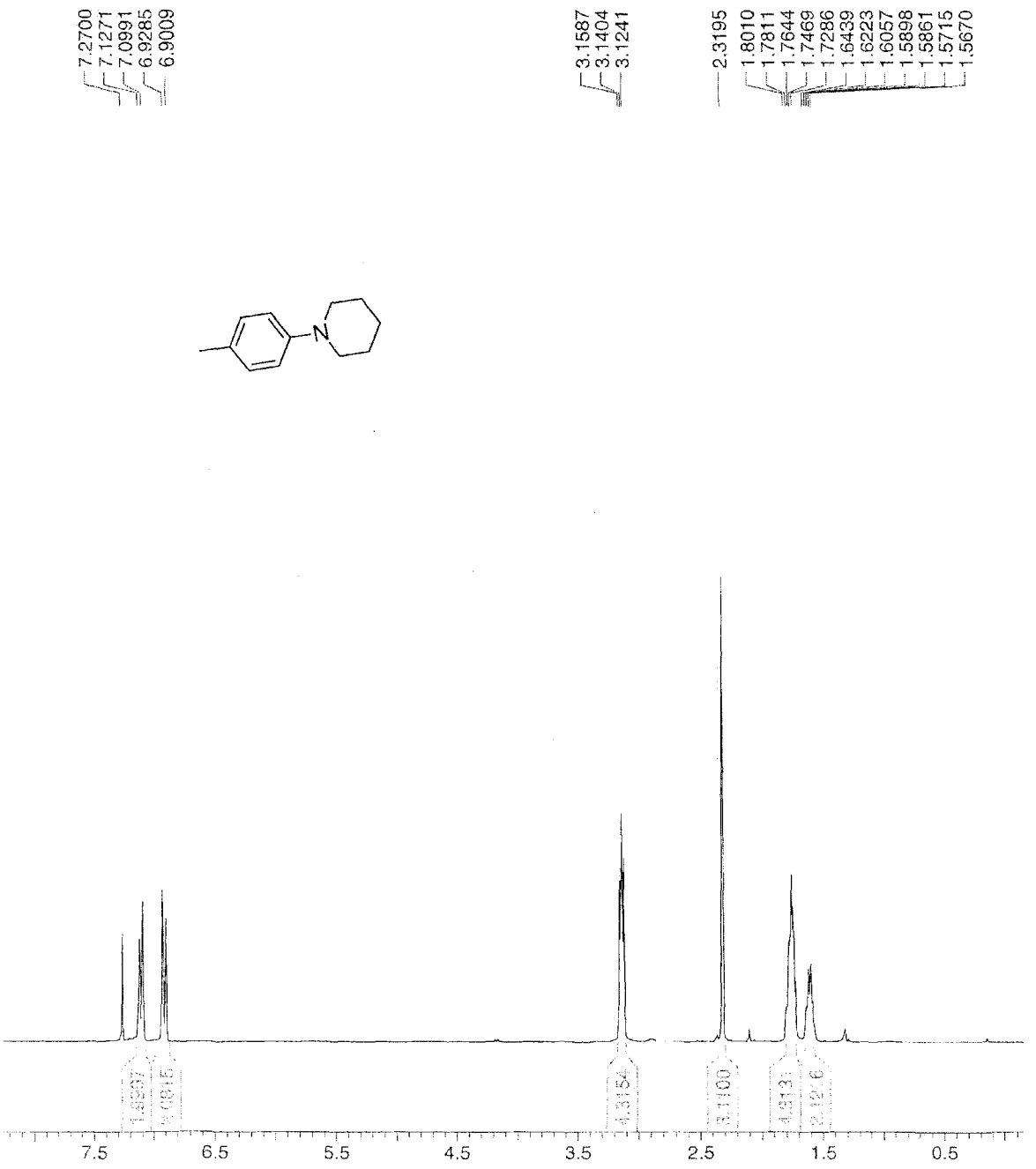
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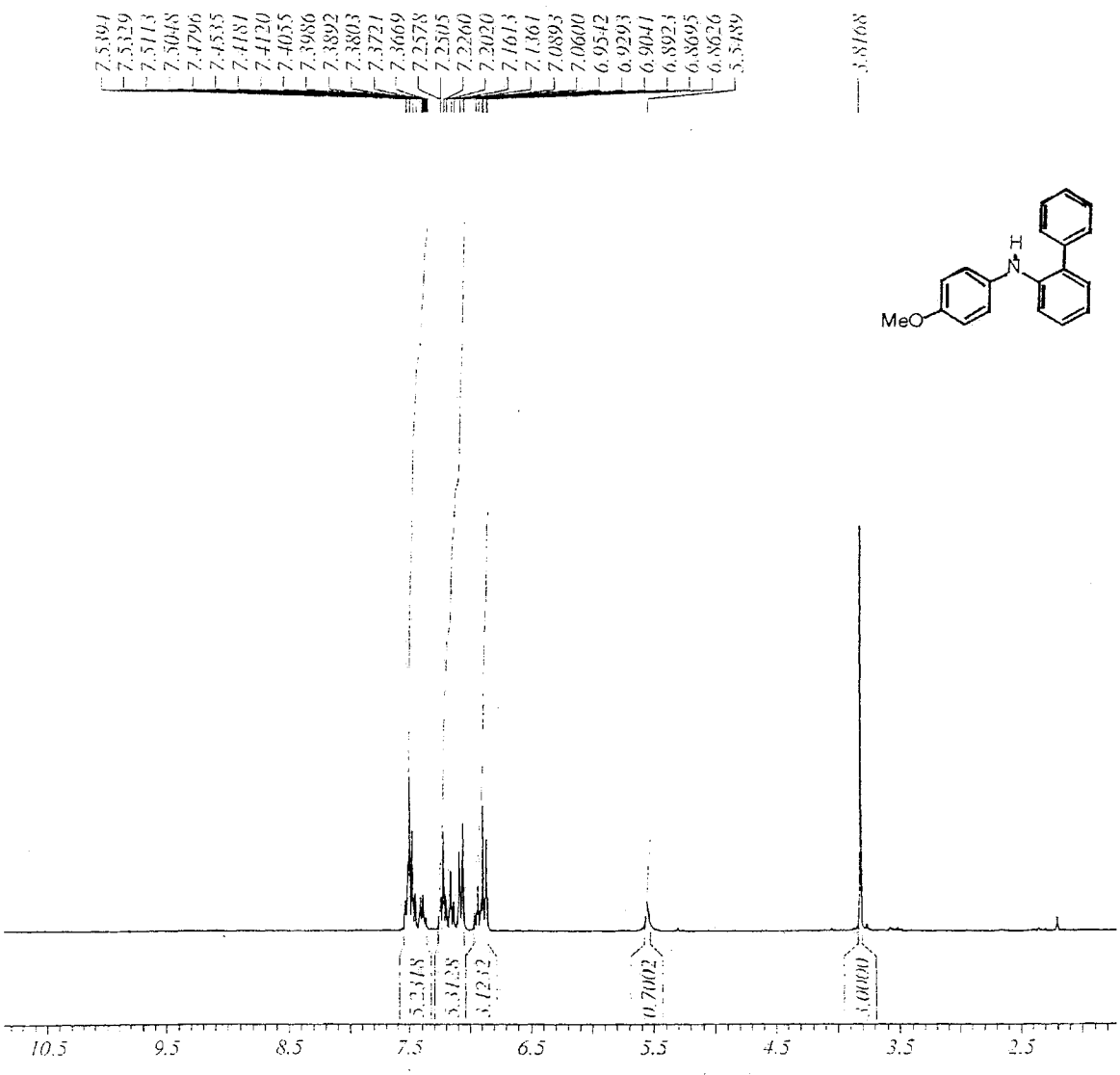
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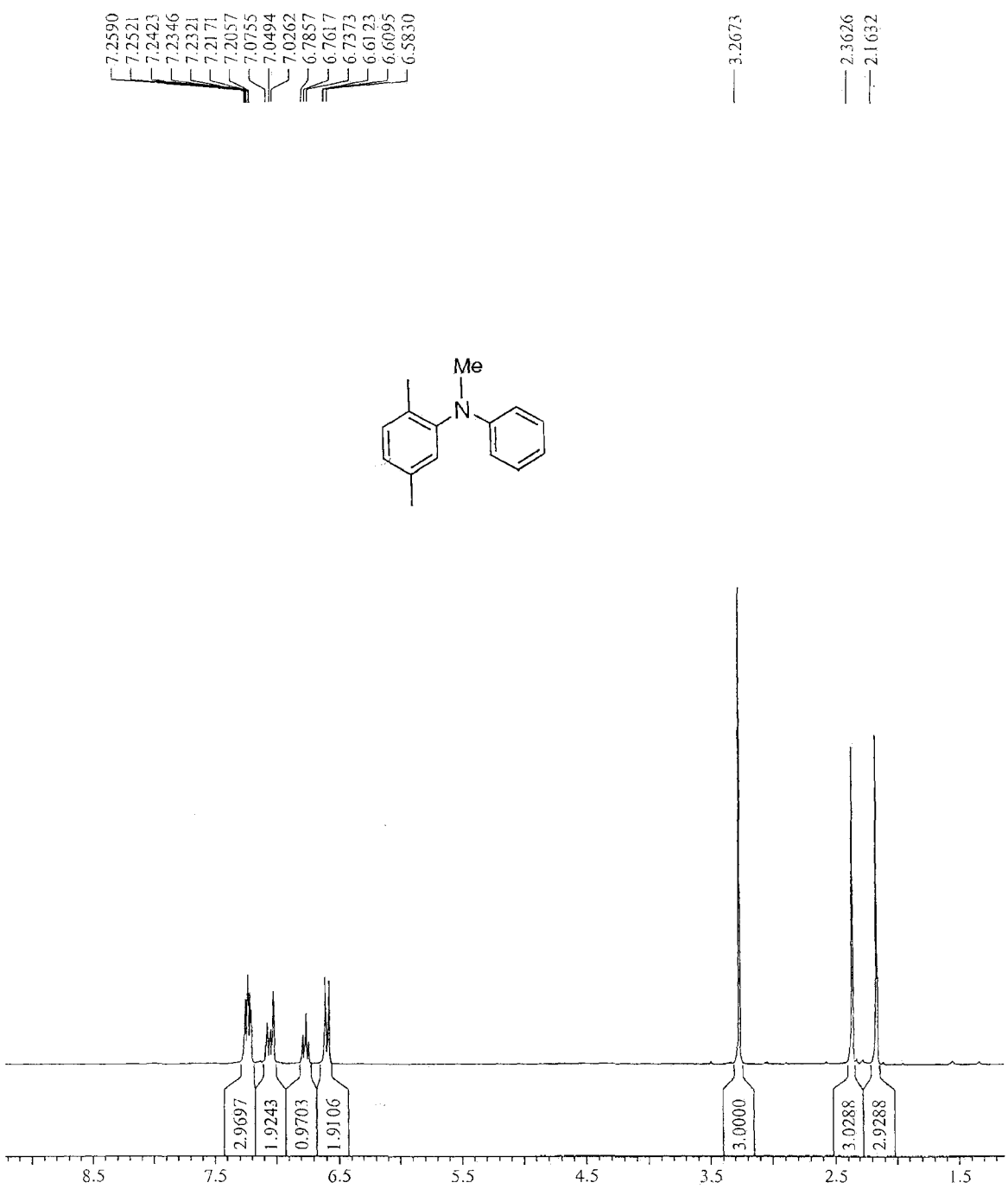
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APPENDIX B

CHAPTER 3

Experimental Section

References for known compounds

Experimental Section

General. All reactions were performed under an atmosphere of argon in oven-dried glassware. Toluene was collected from a Grubbs type solvent purification system (Innovative Technologies) and stored over 4 Å molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates and visualized with short wavelength UV light (254 nm). Silica gel 60 (9385, 230-400 mesh) was used for column chromatography. Melting points were determined in unsealed capillary tubes and are uncorrected. The yields reported are isolated yields and are the average of two runs. All commercially available reagents were used as received. Although Ligand **1** is commercially available from Aldrich, we prepared it according to our previously reported procedure (Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467). All compounds in Tables 1 - 4 gave satisfactory NMR (^{1}H and ^{13}C) and HRMS data.

$Pd_2(dba)_3$/1-catalyzed amination of aryl chlorides and chloropyridines with anilines and cyclic secondary amines (Tables 1 - 3). *General Procedure:* An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (2 mol %; 4 mol % for diphenylamine) and NaO-*t*-Bu (1.5 mmol) inside a nitrogen-filled glovebox. The flask was capped with a rubber septum and removed from the glovebox. Ligand **1** (8 mol %; 16 mol % for diphenylamine) was then added by microliter syringe. Aryl halide (1.0 mmol), amine (1.2 mmol) and toluene (5 mL) were then successively added by syringe. The flask was placed in an 80 °C oil bath and the reaction mixture was stirred until the starting material had been completely consumed as judged by TLC. The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography using hexanes/EtOAc as the eluent.

$Pd(OAc)_2$/1-catalyzed amination of aryl chlorides with primary amines and an acyclic secondary amine (Table 4). *General Procedure:* An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (5 mol %) and NaO-*t*-Bu (1.5 mmol) inside a nitrogen-filled glovebox. The flask was capped with a rubber septum and removed from the glovebox. After ligand **1** (10 mol %) was added by microliter syringe, aryl halide (1.0 mmol), amine (1.5 mmol) and toluene (5 mL) were then added successively by syringe.

The flask was placed in an 80 °C oil bath and the reaction mixture was stirred until the starting material had been completely consumed as judged by TLC. The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography using hexanes/EtOAc as the eluent.

References for known compounds

***N*-Methyl-*N*-(4-cyanophenyl)aniline** (Table 1, entry 1). Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

***N*-(4-Cyanophenyl)aniline** (Table 1, entry 2). Hartwig, J. F.; Driver, M. S.; Louie, J.; Hamann, B. U.S. Patent 5817877, 1998; *Chem Abstr.* **1998**, 129, 275692.

***N*-(4-Cyanophenyl)piperidine** (Table 1, entry 3). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

***N*-(4-Cyanophenyl)morpholine** (Table 1, entry 4). Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

***N*-(4-Methylphenyl)-2',6'-dimethylaniline** (Table 1, entry 5). Sallmann, A.; Pfitser, R. Ger. Offen. 1815802, 1969; *Chem Abstr.* **1969**, 72, 12385.

***N*-(4-Methylphenyl)-*p*-anisidine** (Table 1, entry 6). Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

***N*-(4-Methylphenyl)piperidine** (Table 1, entry 7). Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

***N*-(4-Methylphenyl)morpholine** (Table 1, entry 8). Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 5689.

***N*-(2-Methylphenyl)-*p*-anisidine** (Table 1, entry 9). Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

***N*-(3-Methoxyphenyl)aniline** (Table 1, entry 10). Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

***N*-Methyl-*N*-(3-methoxyphenyl)aniline** (Table 1, entry 11). Wolfe, J. P.; Wagaw, S. Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

***N*-(4-Methoxyphenyl)morpholine** (Table 1, entry 12). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-(4-Methoxyphenyl)piperidine** (Table 1, entry 13). Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron.* **1999**, *55*, 12829.

***N*-(3-Pyridyl)aniline** (Table 1, entry 14). Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.

***N*-Methyl-*N*-(3-pyridyl)aniline** (Table 1, entry 15). Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

***N*-(3-Pyridyl)piperidine** (Table 1, entry 16). Jamart-Gregoire, B.; Leger, C.; Caubere, P. *Tetrahedron Lett.* **1990**, *31*, 7599.

***N*-(3-Pyridyl)morpholine** (Table 1, entry 17). Jamart-Gregoire, B.; Leger, C.; Caubere, P. *Tetrahedron Lett.* **1990**, *31*, 7599.

***N*-(2-Pyridyl)piperidine** (Table 1, entry 18). Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2875.

***N*-(2-Pyridyl)morpholine** (Table 1, entry 19). Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

***N*-(4-Cyanophenyl)diphenylamine** (Table 1, entry 20). Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

***N*-(4-Methylphenyl)diphenylamine** (Table 1, entry 21). Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-Methoxyphenyl)diphenylamine** (Table 1, entry 22). Sukata, K.; Akagawa, T. *J. Org. Chem.* **1989**, *54*, 1476.

***N*-(4-Cyanophenyl)cyclohexylamine** (Table 2, entry 1). Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

***N*-(2-Methylphenyl)cyclohexylamine** (Table 2, entry 2). Micovic, I. V.; Ivanovic, M. D.; Piatak, D. M.; Bojic, V. D. *Synthesis.* **1991**, 1043.

***N*-(3-Methoxyphenyl)cyclohexylamine** (Table 2, entry 3). Yamada, K.; Hukota, M.; Shikano, T.; Nagasaki, M. PCT Int. Appl. 9514668, 1995; *Chem Abstr.* **1995**, 123, 285772.

***N*-(4-Cyanophenyl)hexylamine** (Table 2, entry 4). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

***N*-(3-Methoxyphenyl)hexylamine** (Table 2, entry 5). Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820.

***N*,*N*-Diethyl-4-cyanoaniline** (Table 2, entry 6). Coraor, G. R.; Riem, R. H.; MacLachlan, A.; Urban, E. J. *J. Org. Chem.* **1971**, *36*, 2272.

APPENDIX C

CHAPTER 4

References for known compounds

^{1}H NMR spectra for reaction products

References for known compounds

***N*-(4-Methoxyphenyl)morpholine** (product in Table 1 and eq 1, and Table 3, entry 1). Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

***N*-(4-*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)piperazine** (Table 2, entries 1 and 2). Perez, M.; Potier, P.; Halazy, S. *Tetrahedron Lett.* **1996**, *37*, 8487.

***N*-(4-*tert*-Butoxycarbonyl)-*N*-(4-cyanophenyl)piperazine** (Table 2, entry 3). Tsubouchi, H.; Sasaki, H.; Kuroda, H.; Itotani, M.; Hasegawa, T.; Haraguchi, Y.; Kuroda, T.; Matsuzaki, T.; Tai, K.; Komatsu, M.; Matsumoto, M.; Hashizume, H.; Tomishige, T.; Seike, Y.; Kawasaki, M.; Sumida, T.; Miyamura, S. *PCT Int. Appl.* 2004033463, 2004; *Chem Abstr.* **2003**, *140*, 357387.

***N*-(4-*tert*-Butoxycarbonyl)-*N*-(3-methoxyphenyl)piperazine** (Table 2, entry 4). Lippard, S. J.; Hilderbrand, S. *U.S. Patent* 2003068275, 2003; *Chem. Abstr.* **2003**, *138*, 300171.

***N*-(4-*tert*-Butoxycarbonyl)-*N*-(4-methylphenyl)piperazine** (Table 2, entries 5 and 6). Tsubouchi, H.; Sasaki, H.; Kuroda, H.; Itotani, M.; Hasegawa, T.; Haraguchi, Y.; Kuroda, T.; Matsuzaki, T.; Tai, K.; Komatsu, M.; Matsumoto, M.; Hashizume, H.; Tomishige, T.; Seike, Y.; Kawasaki, M.; Sumida, T.; Miyamura, S. *PCT Int. Appl.* 2004033463, 2004; *Chem Abstr.* **2004**, *140*, 357387.

***N*-(4-*tert*-Butoxycarbonyl)-*N*-(2-pyridyl)piperazine** (Table 2, entry 7). Ohnmacht, C. J.; Malick, J. B. *U.S. Patent* 4247549, 1981; *Chem. Abstr.* **1981**, *94*, 197553.

***N*-(4-Cyanophenyl)morpholine** (Table 3, entry 2). Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

***N*-(3-Methoxyphenyl)morpholine** (Table 3, entry 3). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(4-Methylphenyl)morpholine** (Table 3, entry 4 and eq 2). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-(2-Pyridyl)morpholine** (Table 3, entry 5). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(3-Pyridyl)morpholine** (Table 3, entry 6). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-Methyl-*N*-(4-methoxyphenyl)aniline** (Table 4, entry 1 and Table 9, entry 8). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

.***N*-Methyl-*N*-(4-cyanophenyl)aniline** (Table 4, entry 2). Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

***N*-Methyl-*N*-(3-methoxyphenyl)aniline** (Table 4, entry 3). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-Methyl-*N*-(4-methylphenyl)aniline** (Table 4, entry 4). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-Methyl-*N*-(2-pyridyl)aniline** (Table 4, entry 5). Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.

***N*-Methyl-*N*-(3-pyridyl)aniline** (Table 4, entry 6). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-(4-Methoxyphenyl)diphenylamine** (Table 5, entries 1 and 2). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(4-Cyanophenyl)diphenylamine** (Table 5, entry 3). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-(3-Methoxyphenyl)diphenylamine** (Table 5, entries 4 and 5). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-(4-Methylphenyl)diphenylamine** (Table 5, entries 6 and 7). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(2-Pyridyl)diphenylamine** (Table 5, entries 8 and 9). Kanemaru, T.; Nagahara, S.; Senoo, A. Eur. Pat. Appl. 449742, 1991; *Chem. Abstr.* **1991**, *116*, 204473.

***N*-(4-Trifluoromethylphenyl)diphenylamine** (Table 5, entry 10). Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.

***N*-(2-Methylphenyl)diphenylamine** (Table 5, entries 11 and 12). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(4-Methoxyphenyl)-*p*-anisidine** (Table 6, entries 1 and 2). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-Methoxyphenyl)-*p*-toluidine** (Table 6, entries 3 and 10). Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

***N*-(4-Methoxyphenyl)aniline** (Table 6, entry 4 and Table 9, entry 9). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(3-Methoxyphenyl)-*p*-anisidine** (Table 6, entries 5 and 6). Barton, D. H. R.; Donnelly, D. M. X.; Finet, J. P.; Guiry, P. J. *J. Chem. Soc., Perkin Transactions 1* **1991**, *9*, 2095.

***N*-(3-Methoxyphenyl)-*p*-toluidine** (Table 6, entries 7 and 8). Beard, R. L.; Teng, M.; Colon, D. F.; Duong, T. T.; Chandraratna, R. A. U.S. Patent 5739338, 1998; *Chem. Abstr.* **1998**, 128, 282789.

***N*-(3-Methoxyphenyl)aniline** (Table 6, entry 9). Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

***N*-(4-Methylphenyl)aniline** (Table 6, entry 11). Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

***N*-(2-Methylphenyl)-*p*-anisidine** (Table 6, entry 12). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

***N*-(4-Methoxyphenyl)-2',6'-dimethylaniline** (Table 7, entry 1). Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

***N*-(4-Methylphenyl)-2',6'-dimethylaniline** (Table 7, entry 2). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-(2-Methylphenyl)-2',6'-dimethylaniline** (Table 7, entry 3). Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

***N*-(2-Methoxyphenyl)-2',6'-dimethylaniline** (Table 7, entry 4). Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chemical* **2002**, *182-183*, 515.

***N*-(2,6-Dimethylphenyl)-2',6'-dimethylaniline** (Table 7, entries 5, 6, and 7). Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chemical* **2002**, *182-183*, 515.

***N*-Cyclohexyl-4-cyanoaniline** (Table 8, entry 1). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-Cyclohexyl-4-methylaniline** (Table 8, entry 2). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

***N*-Cyclohexyl-2-methylaniline** (Table 8, entry 3). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-Cyclohexyl-3-methoxyaniline** (Table 8, entry 4). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

4-Cyano-*N*-hexylaniline (Table 8, entry 5). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

3-Methoxy-*N*-hexylaniline (Table 8, entry 6). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*,*N*-Dibutyl-4-cyanoaniline** (Table 8, entry 7). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*,*N*-Dibutyl-4-methylaniline** (Table 8, entry 8). Urgaonkar, S.; Xu, J-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

***N*-(4-Nitrophenyl)morpholine** (Table 9, entry 1). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

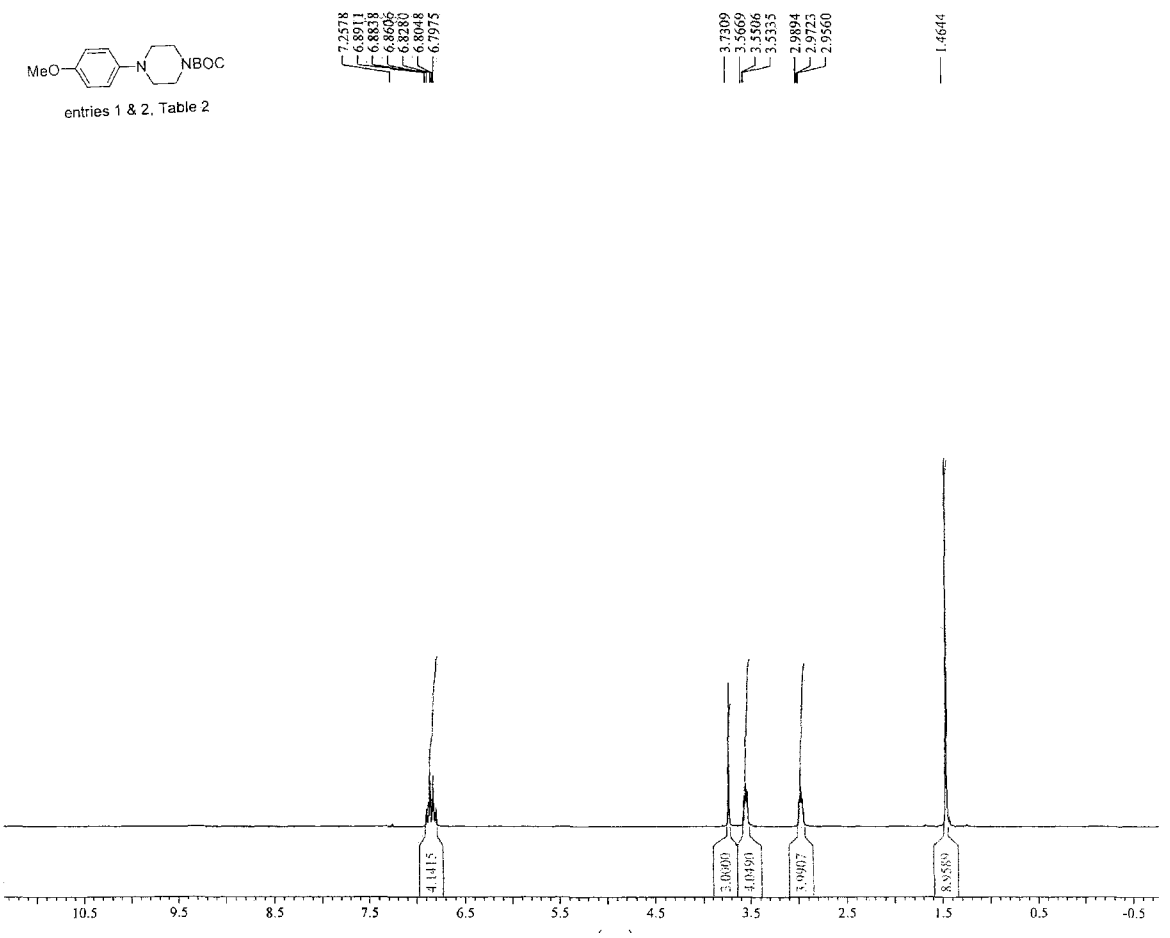
***N*-Methyl-*N*-(4-nitrophenyl)aniline** (Table 9, entry 2). Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.

***N*-(4-Nitrophenyl)diphenylamine** (Table 9, entries 3 and 4). Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791.

***N*-(4-Acetylphenyl)morpholine** (Table 9, entry 5). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(3-Methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane** (Table 9, entry 6). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-(4-Methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane** (Table 9, entry 7). Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397.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3.5669
3.5506
3.5335
2.9894
2.9723
2.9560
1.4644
4.1415
3.0699
4.0191
3.9907
8.9589
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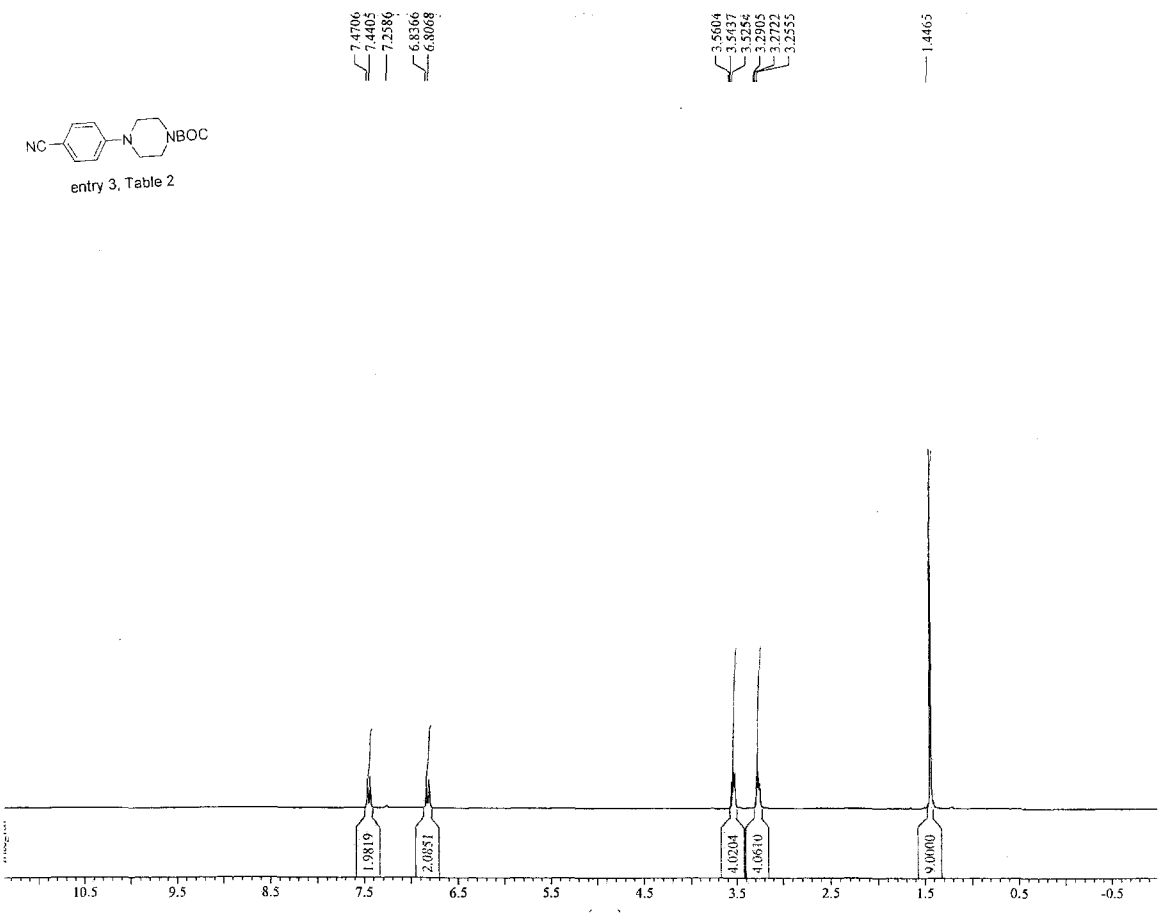
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3.2555
1.4465
NC
N
NBOC
entry 3, Table 2
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2.0051
4.0204
4.0610
9.0000
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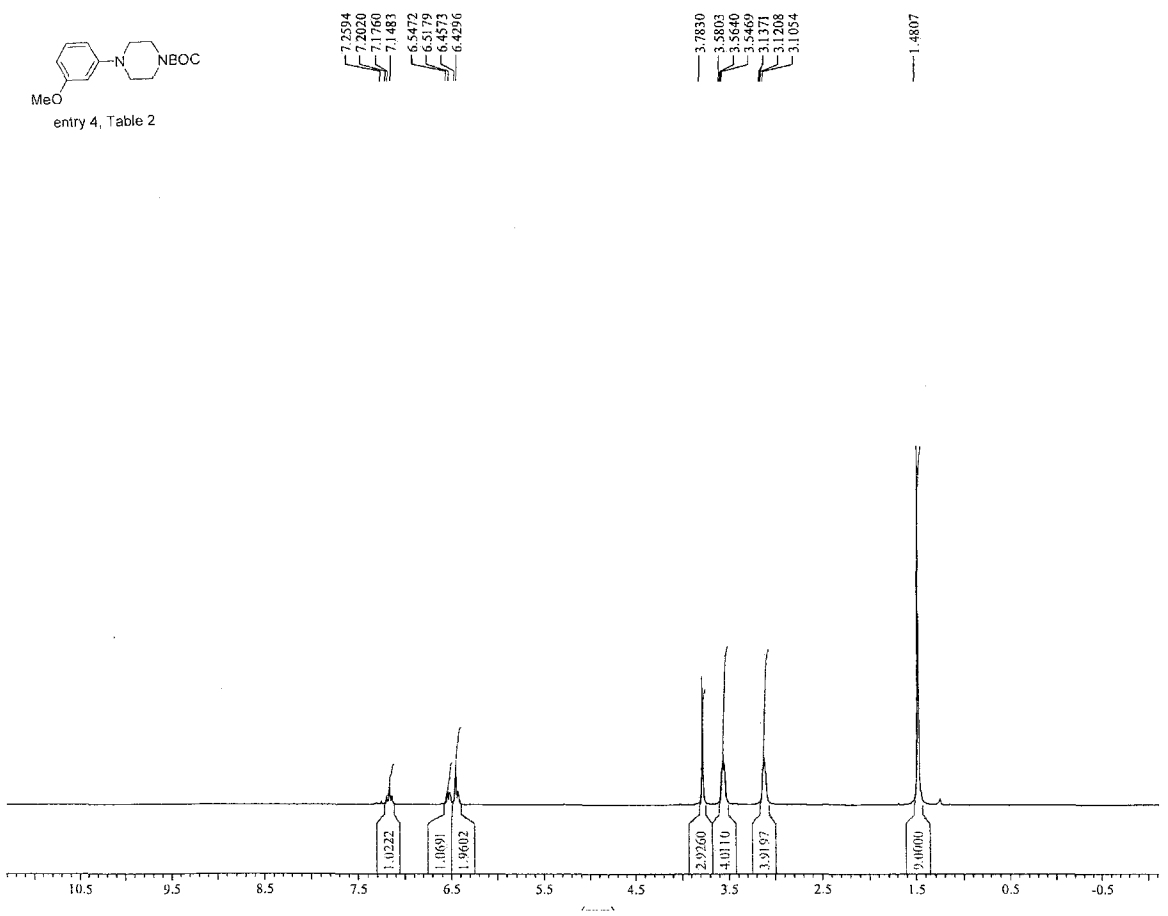
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3.5803
3.5640
3.5469
3.1371
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3.1054
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1.0222
1.0691
1.9602
2.9260
4.0110
3.9197
9.0000
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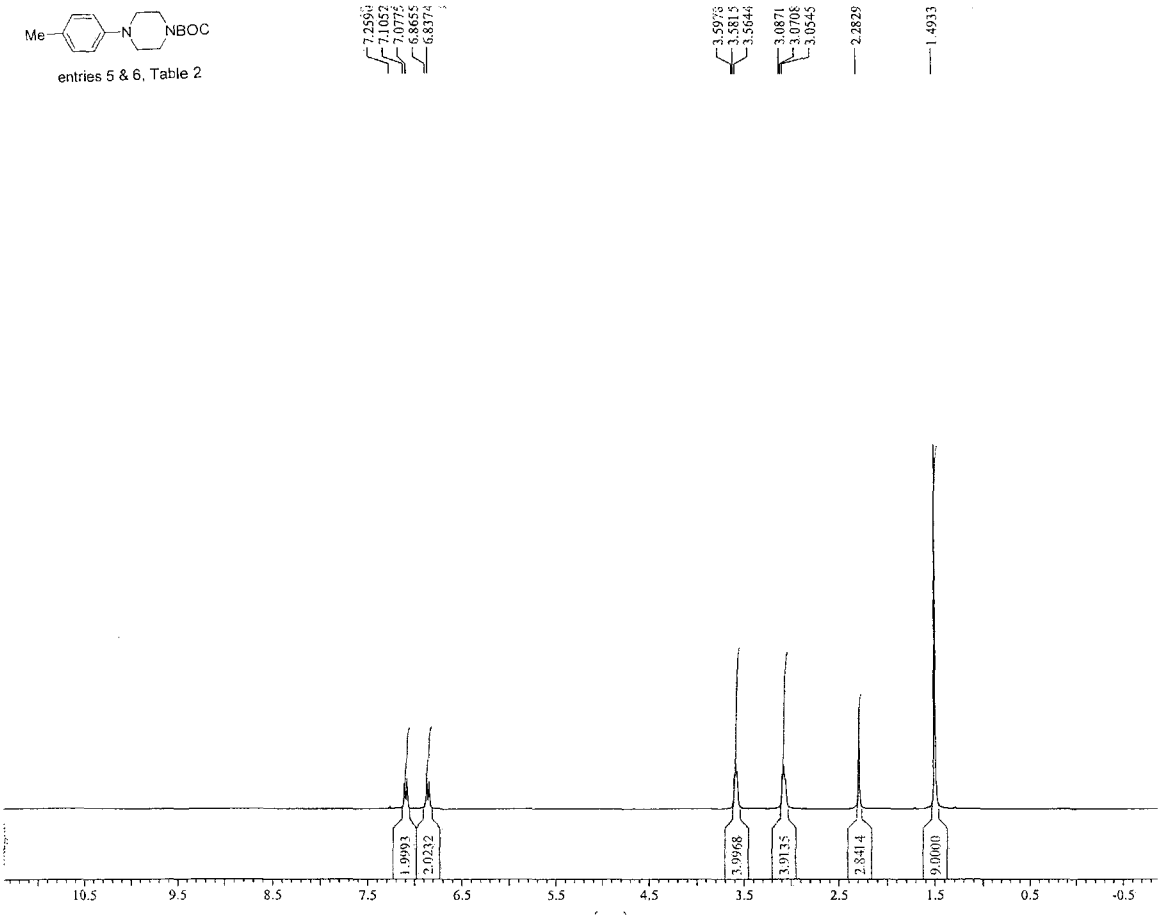
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3.5644
3.0871
3.0708
3.0545
2.2829
1.4933
1.9993
2.0232
3.9968
3.9135
2.8414
9.0000
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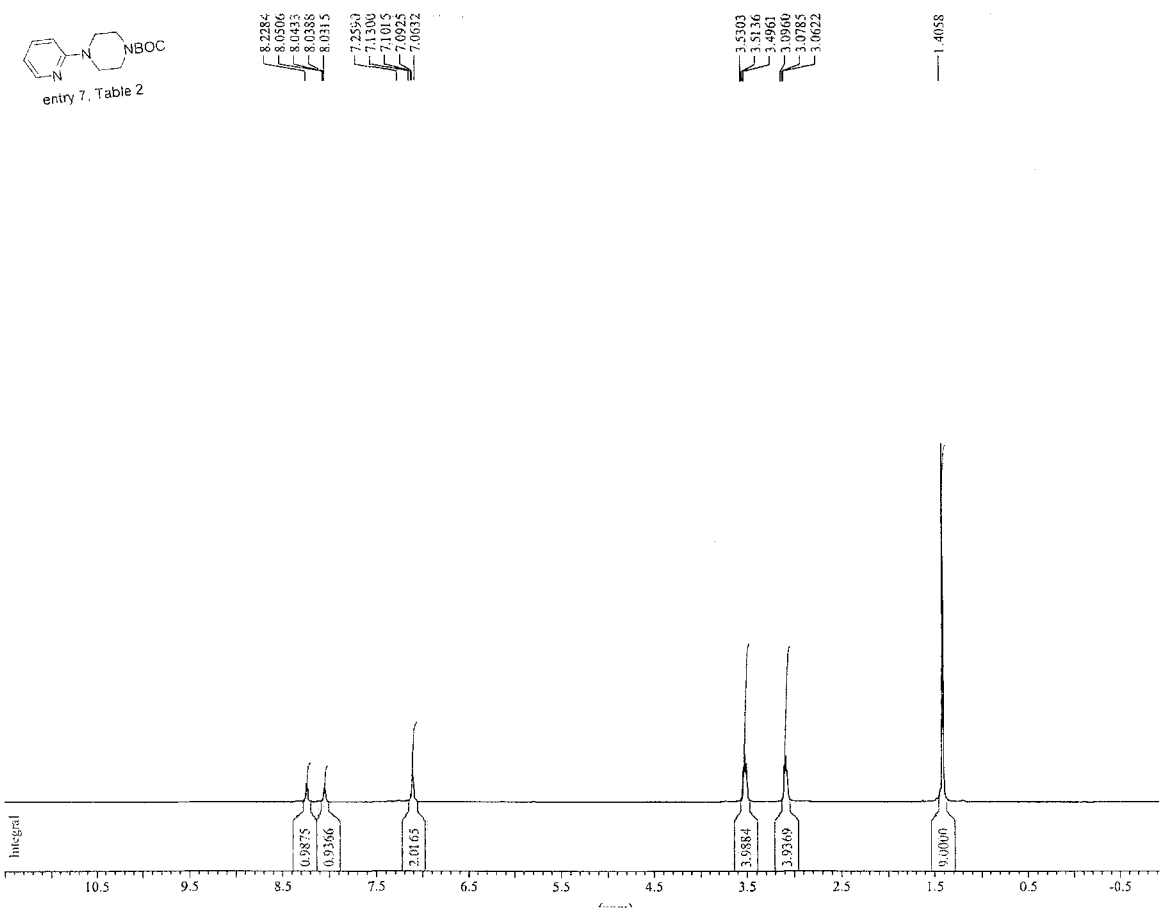
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7.0632
3.5303
3.5136
3.4961
3.0960
3.0785
3.0622
1.4058
Integral
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0.9366
2.0165
3.9884
3.9369
9.0000
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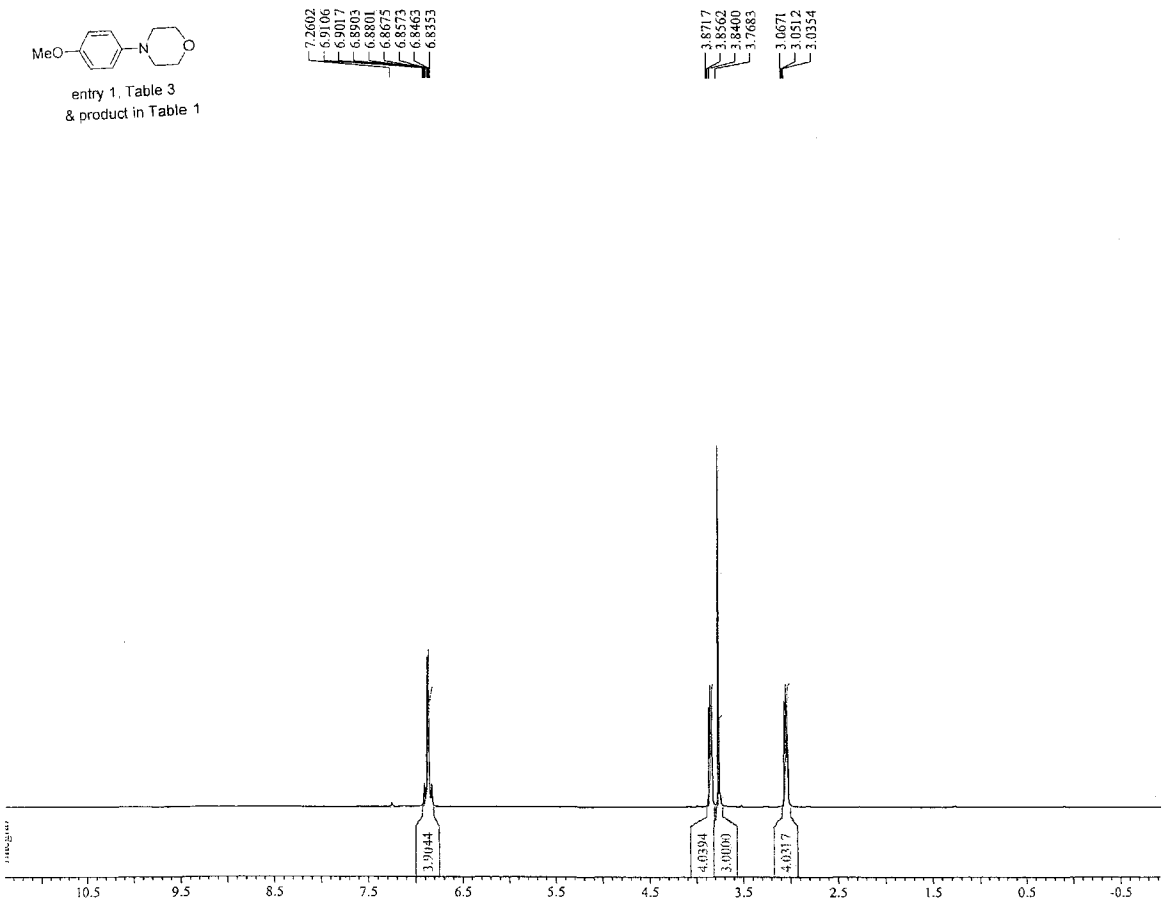
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entry 1, Table 3
& product in Table 1
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6.8573
6.8463
6.8353
3.8717
3.8562
3.8400
3.7683
3.0671
3.0512
3.0354
3.90044
4.03934
3.00000
4.03317
10.5
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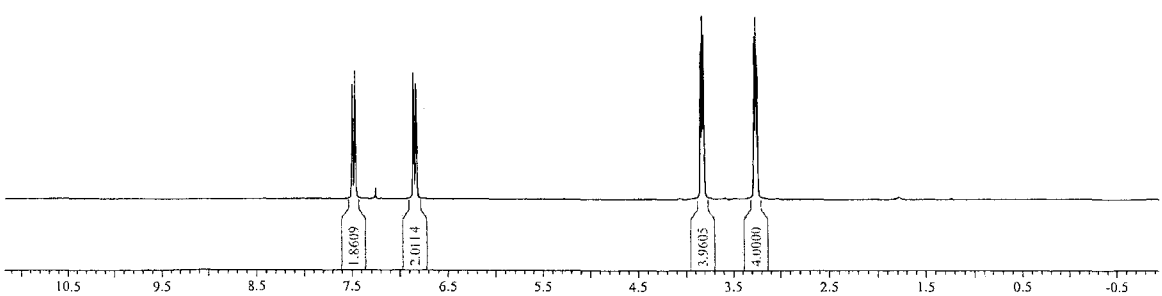
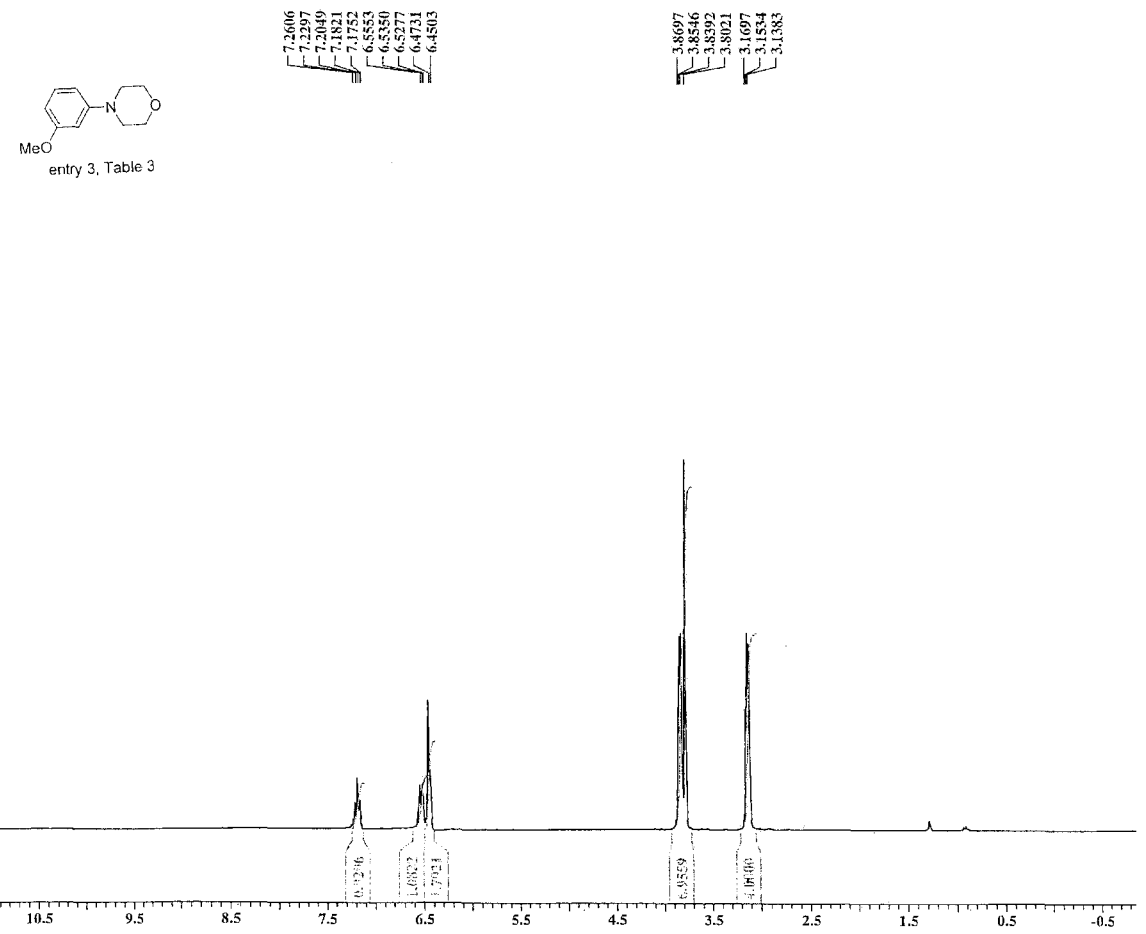
entry 2, Table 3





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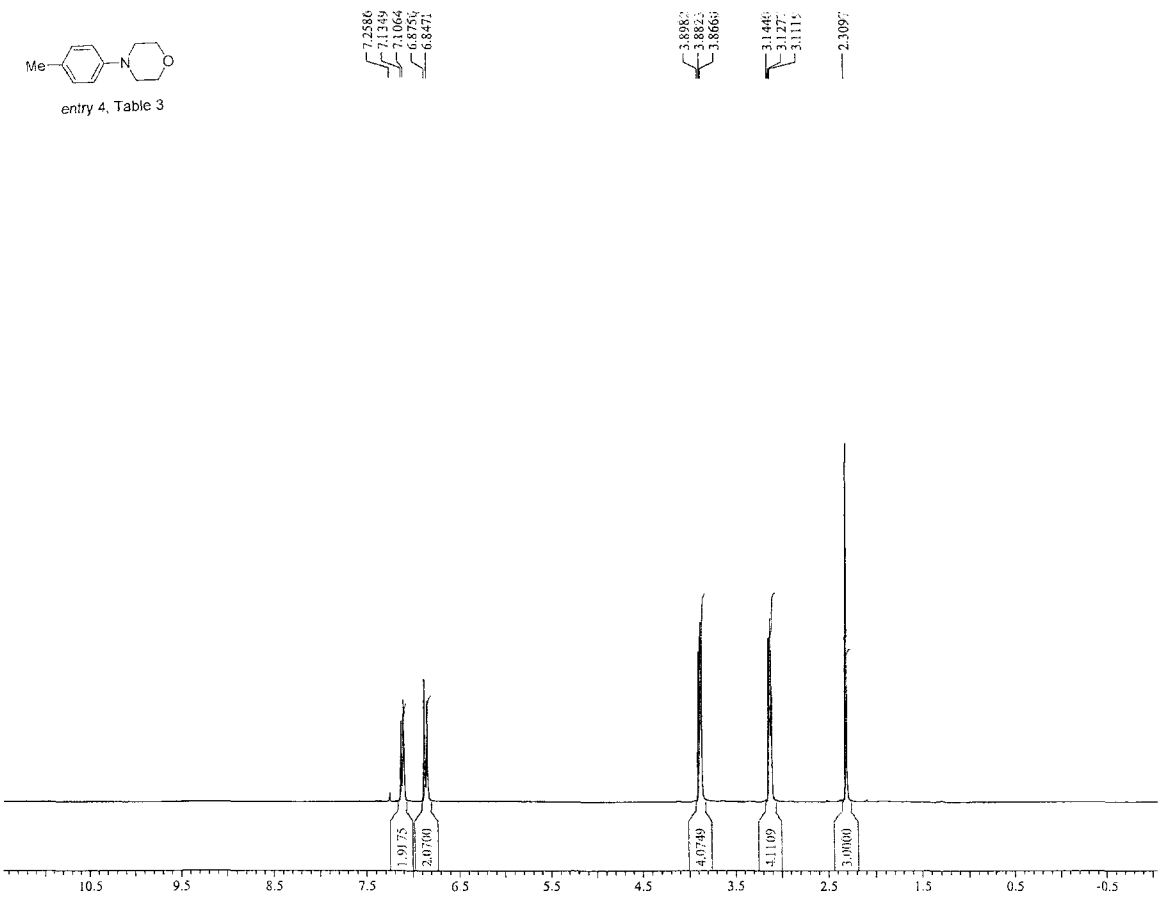

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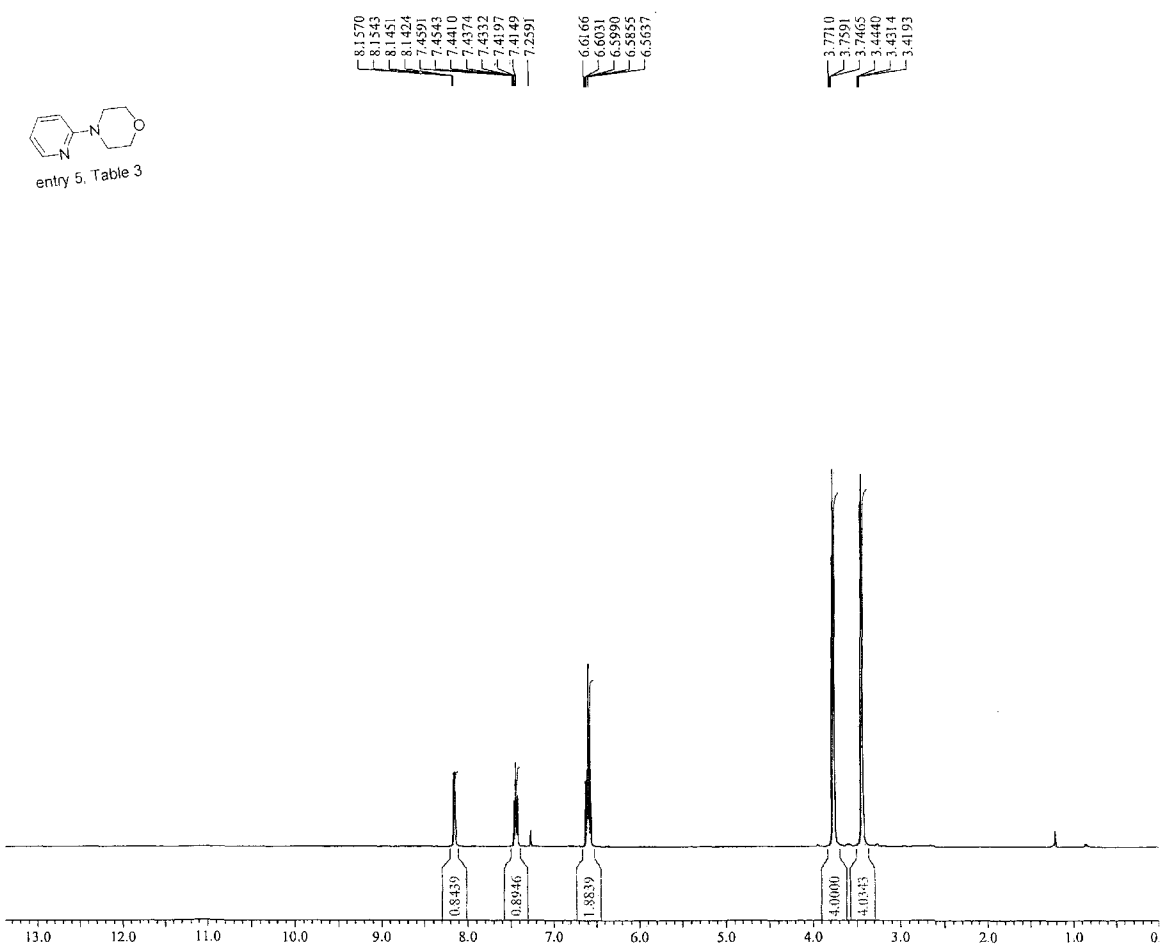
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7.4197
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7.2591
6.6166
6.6031
6.5990
6.5855
6.5657
3.7710
3.7591
3.7465
3.4440
3.4314
3.4193
entry 5, Table 3
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0.8946
1.9839
4.0000
4.0343
13.0
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1.0
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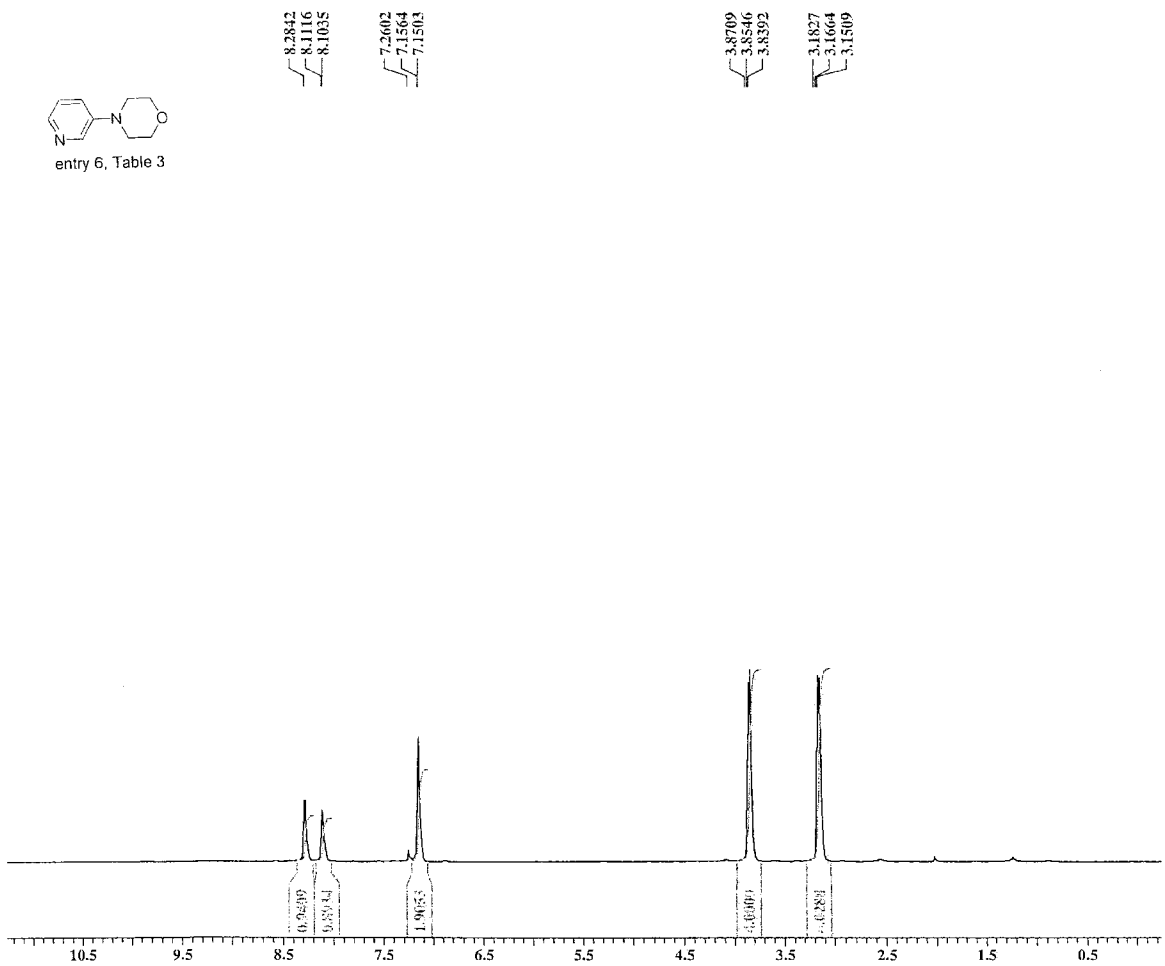

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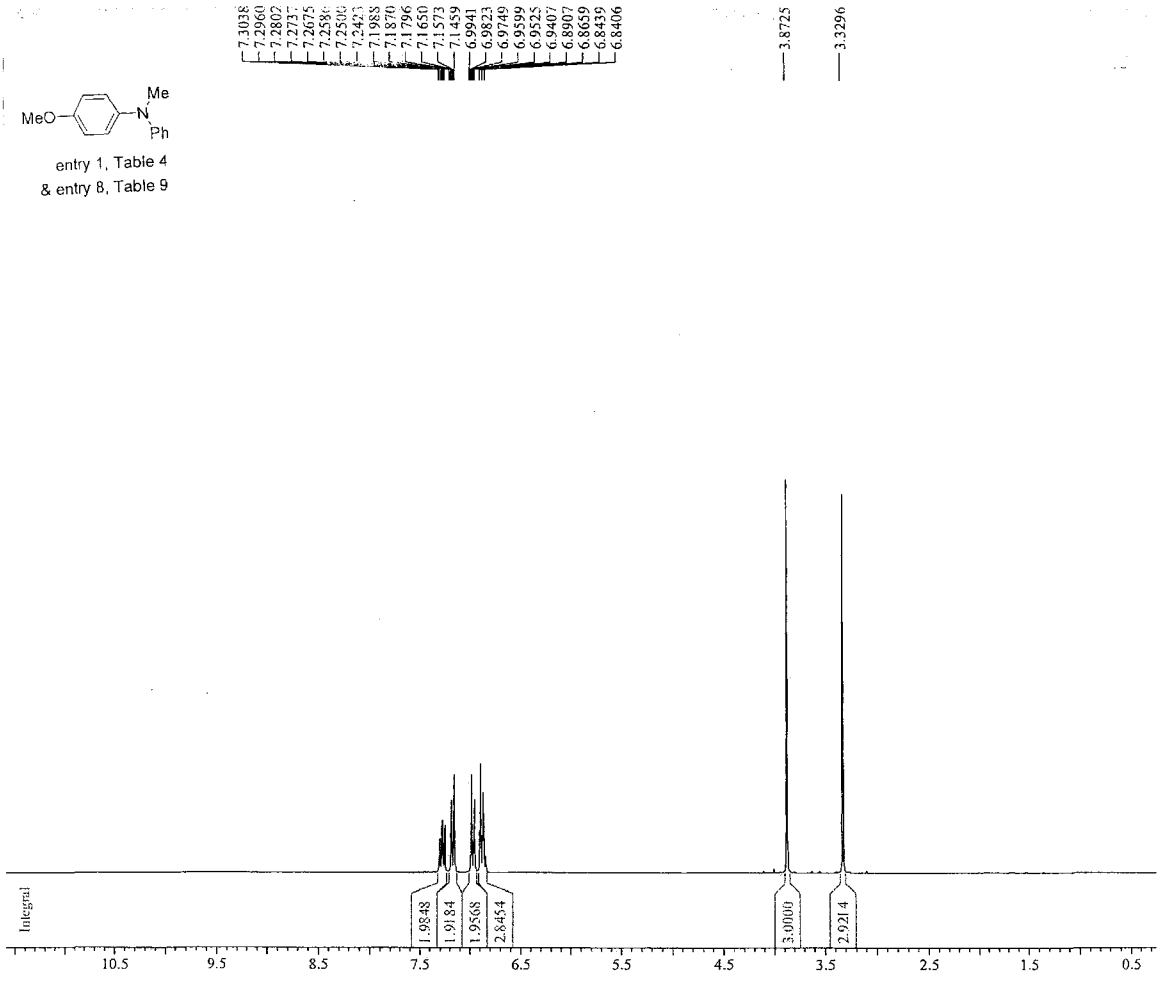
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6.8907
6.8659
6.8439
6.8406
3.8725
3.3296
Me
MeO
N
Ph
entry 1, Table 4
& entry 8, Table 9
Integral
1.9848
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1.9568
2.8454
3.0000
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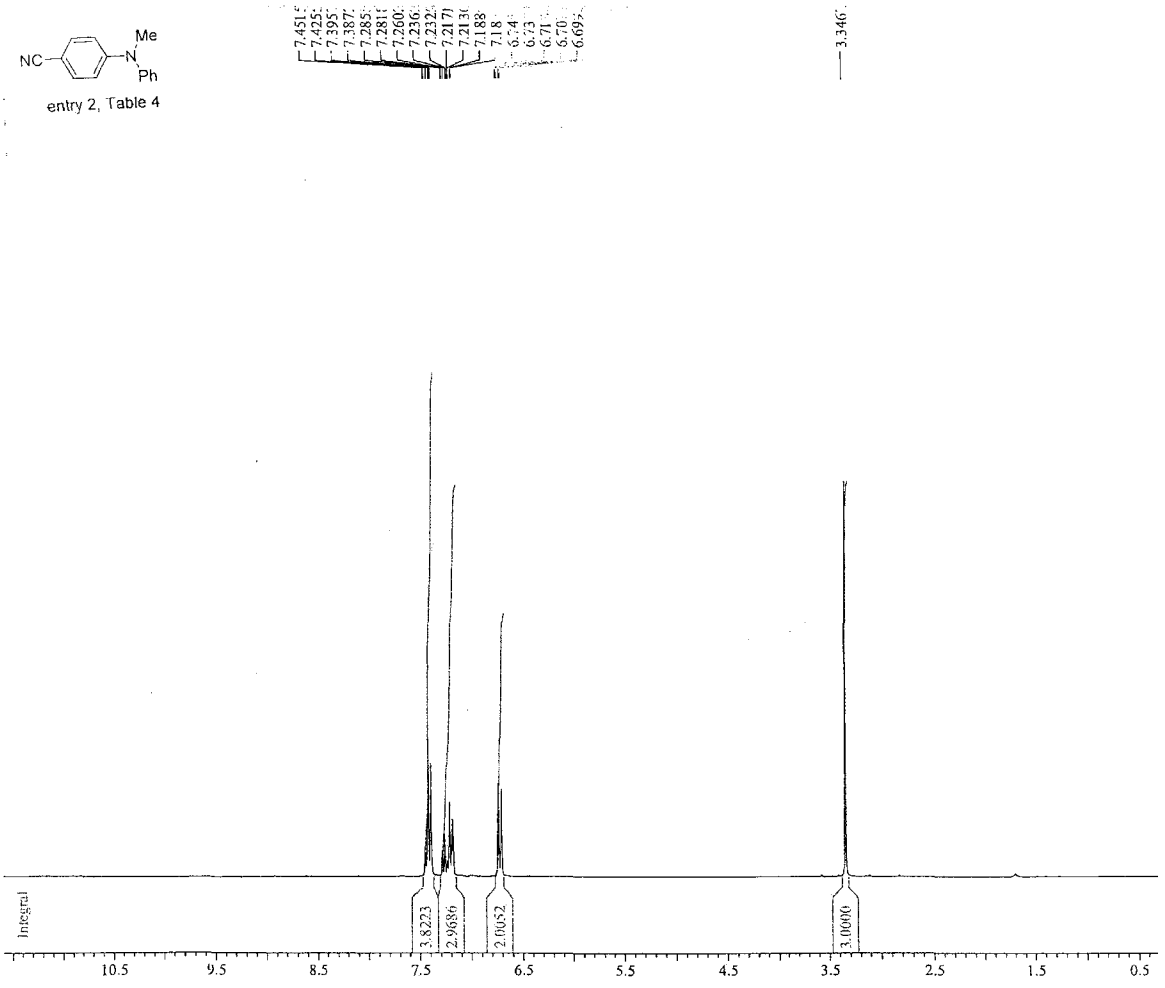
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Ph
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7.213
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7.18
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6.73
6.71
6.70
6.693
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Integral
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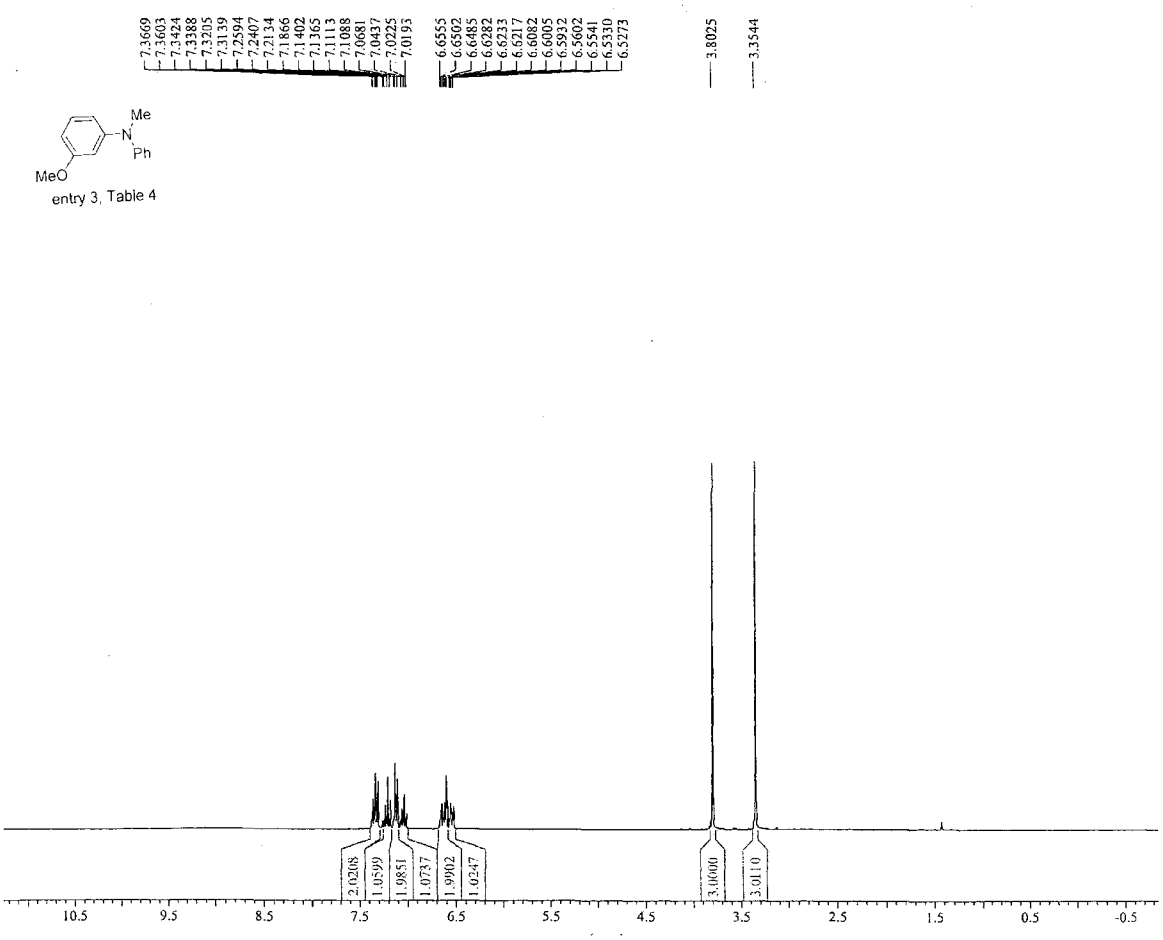
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6.6485
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6.6082
6.6005
6.5932
6.5602
6.5541
6.5330
6.5273
3.8025
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Me
N
Ph
MeO
entry 3, Table 4
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1.9902
1.0247
3.0000
3.0110
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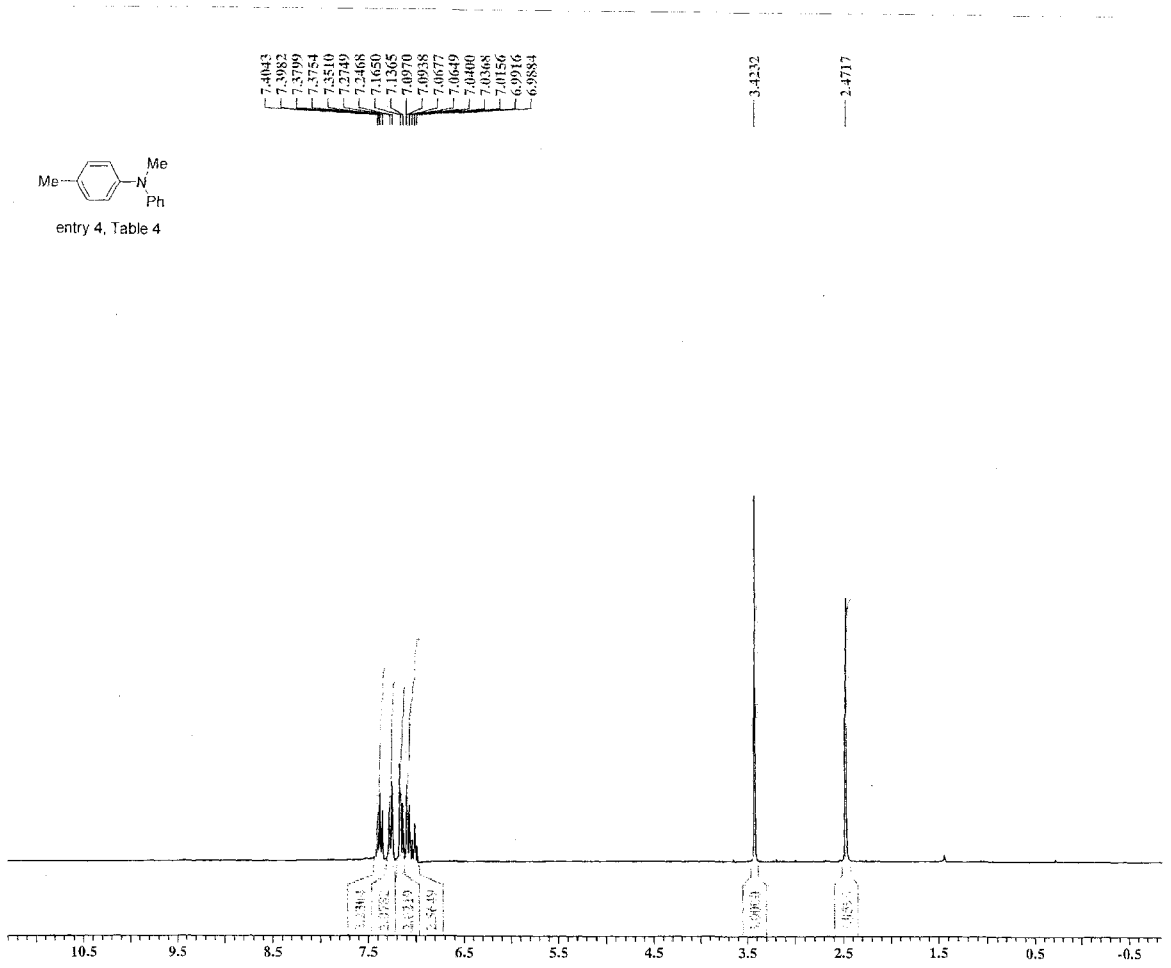

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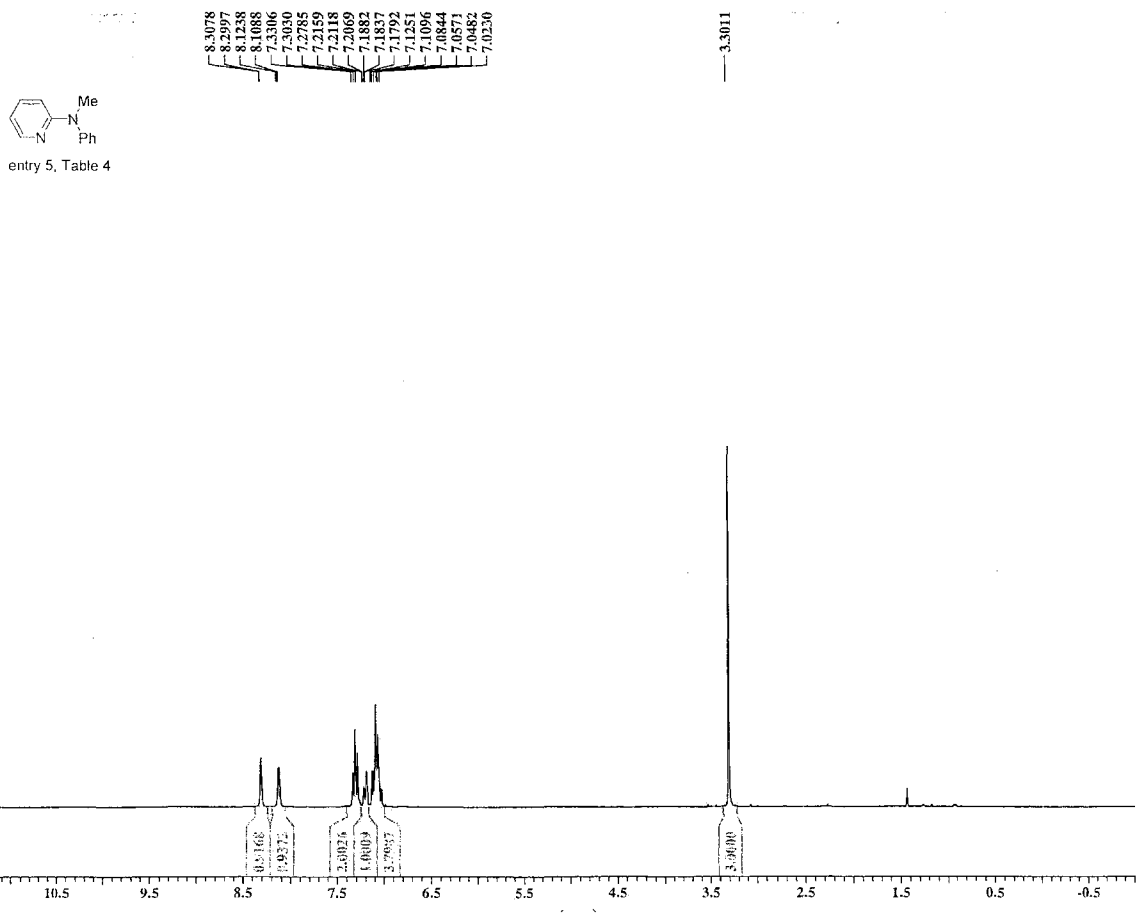

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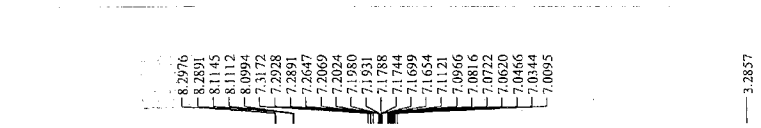

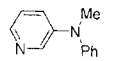

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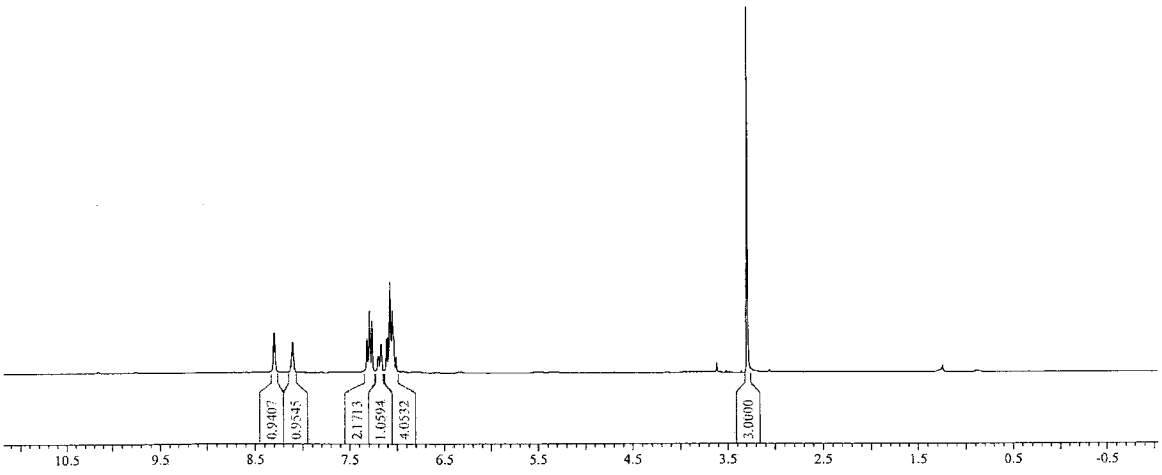

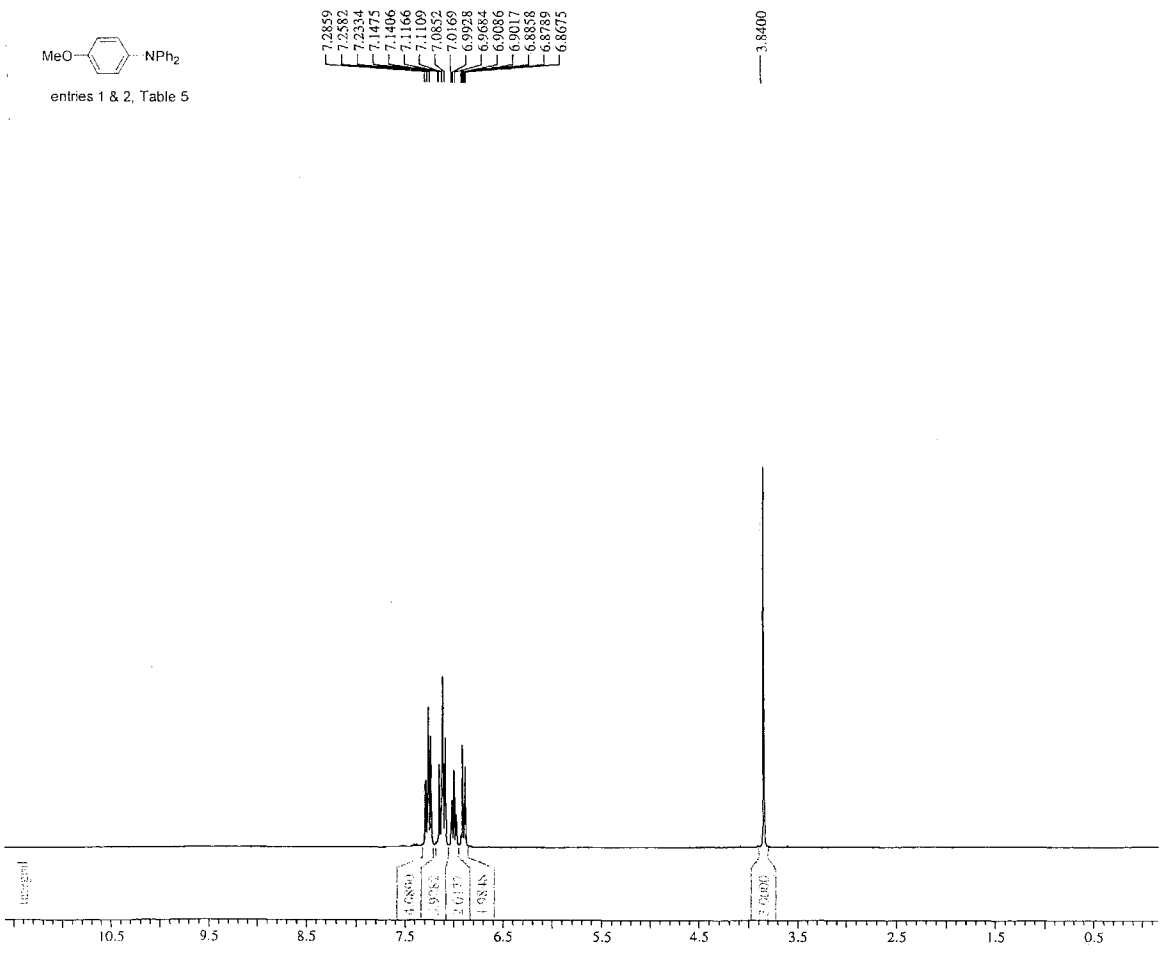
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6.8789
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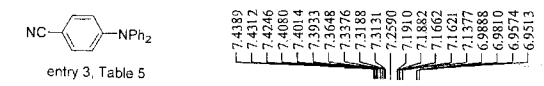
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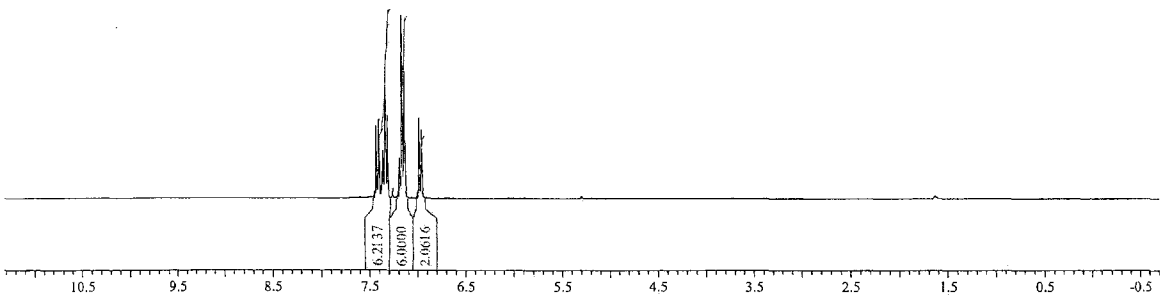
6.9513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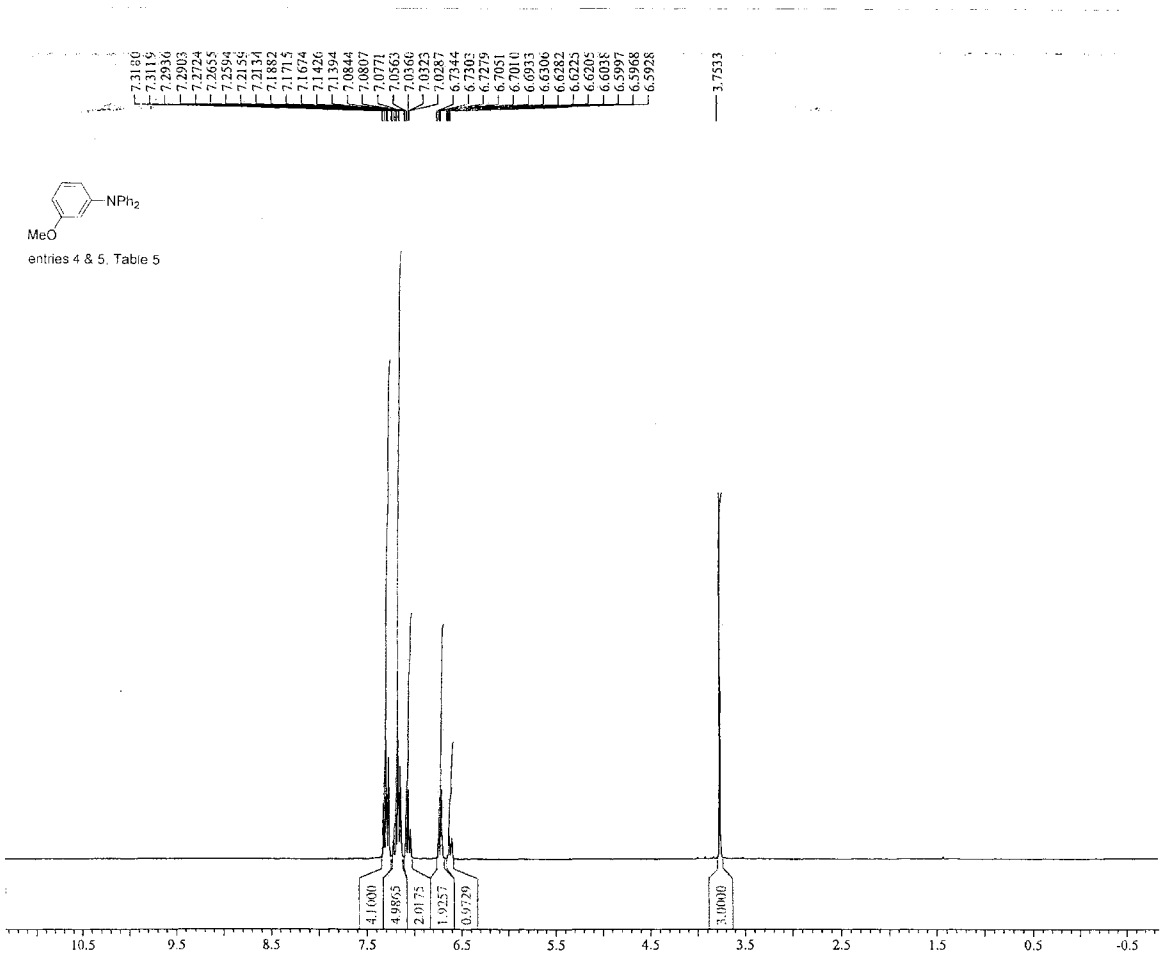
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6.6225
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6.6035
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NPh2
MeO
entries 4 & 5, Table 5
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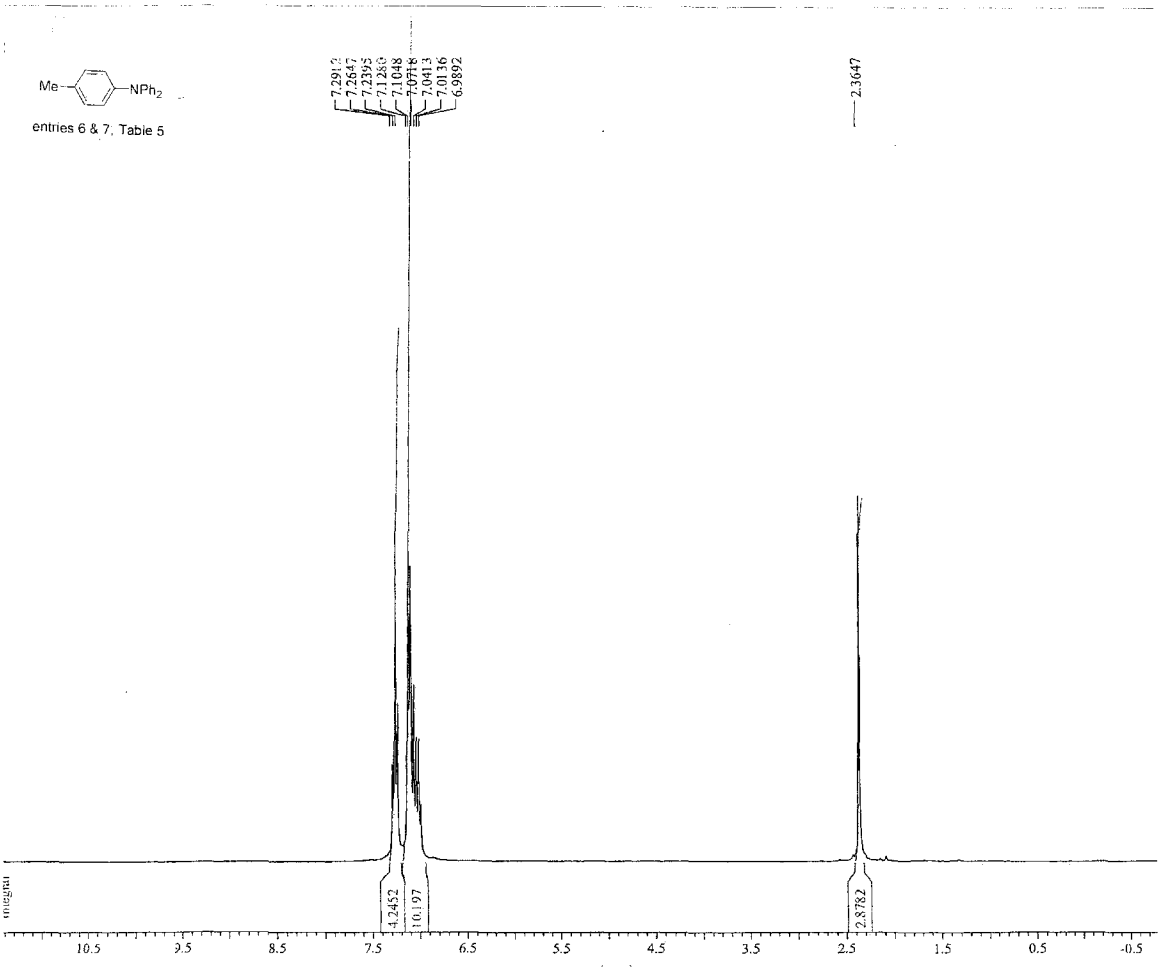
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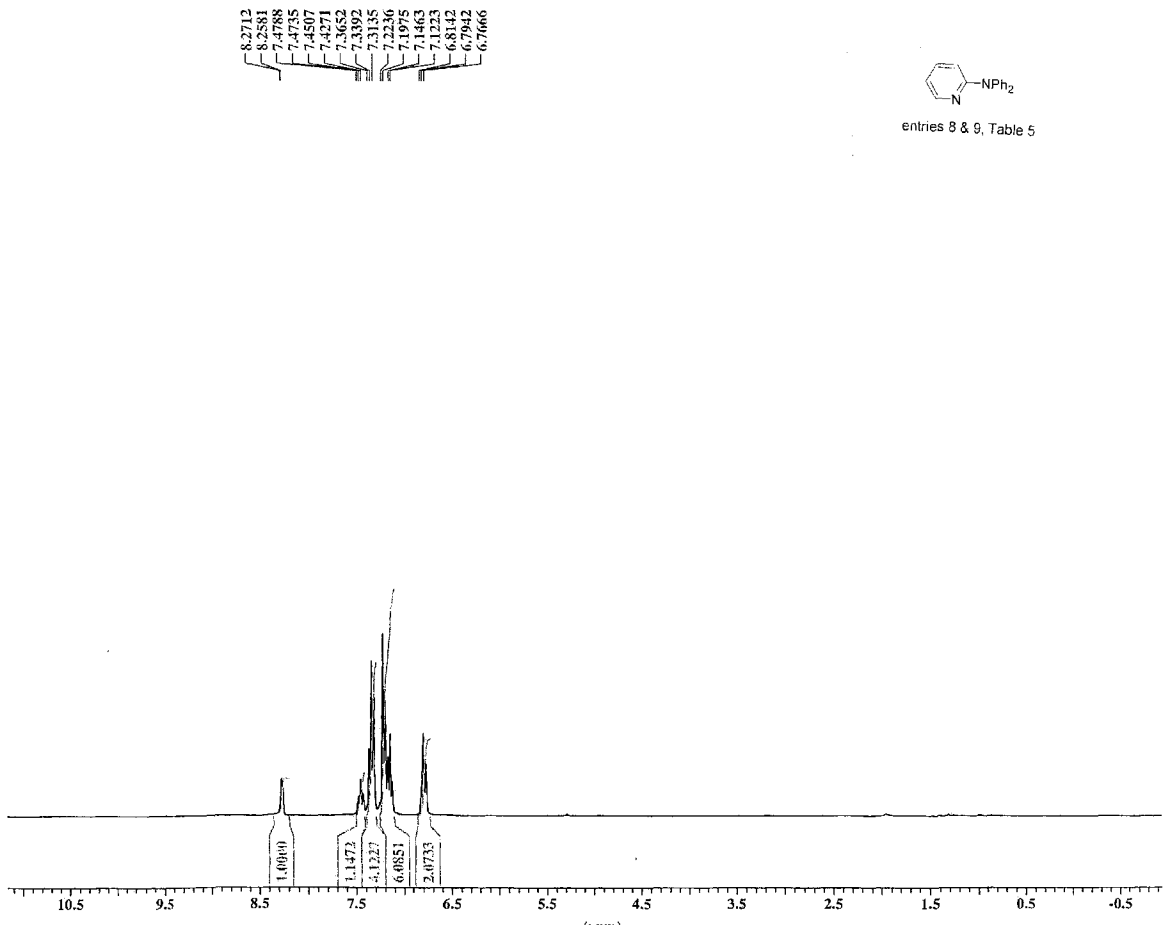
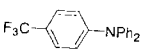
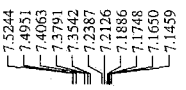
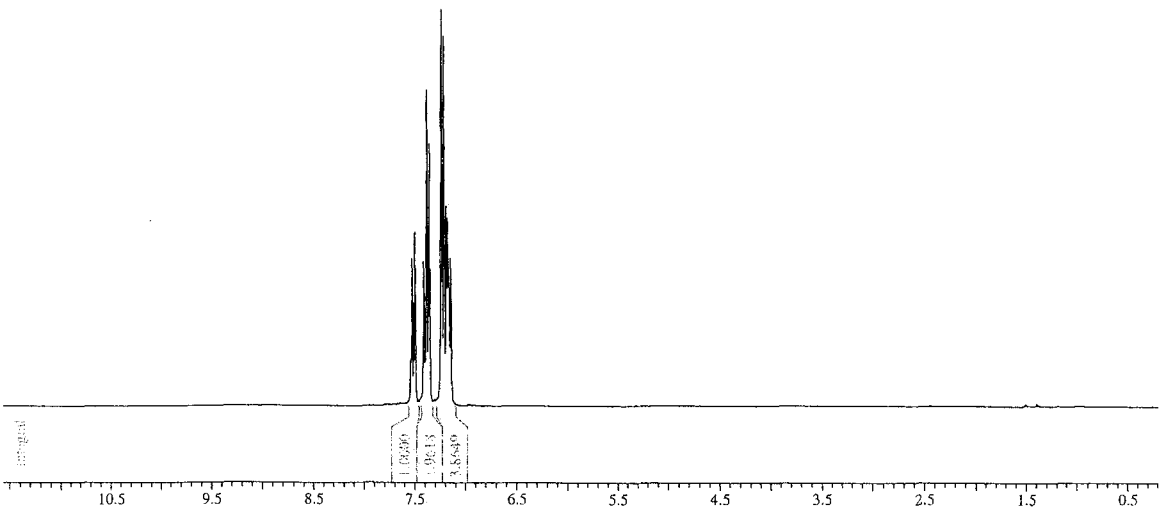
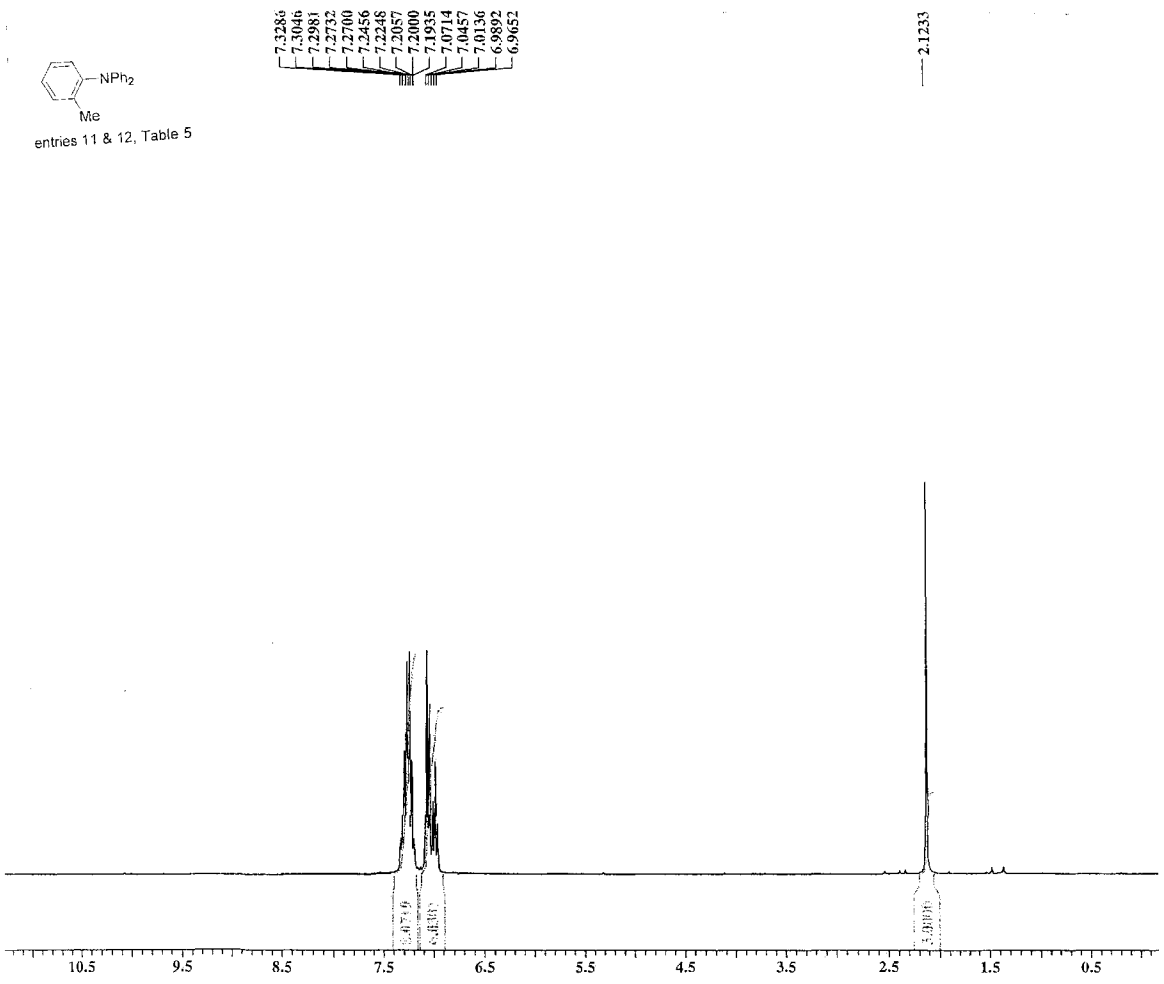

8.2712
8.2581
7.4788
7.4735
7.4507
7.4271
7.3652
7.3392
7.3135
7.2236
7.1975
7.1463
7.1223
6.8142
6.7942
6.7666
NPh2
N
entries 8 & 9, Table 5
1.0000
1.1472
4.1227
6.0851
2.0733
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5



entry 10, Table 5






NPh2
Me
entries 11 & 12, Table 5
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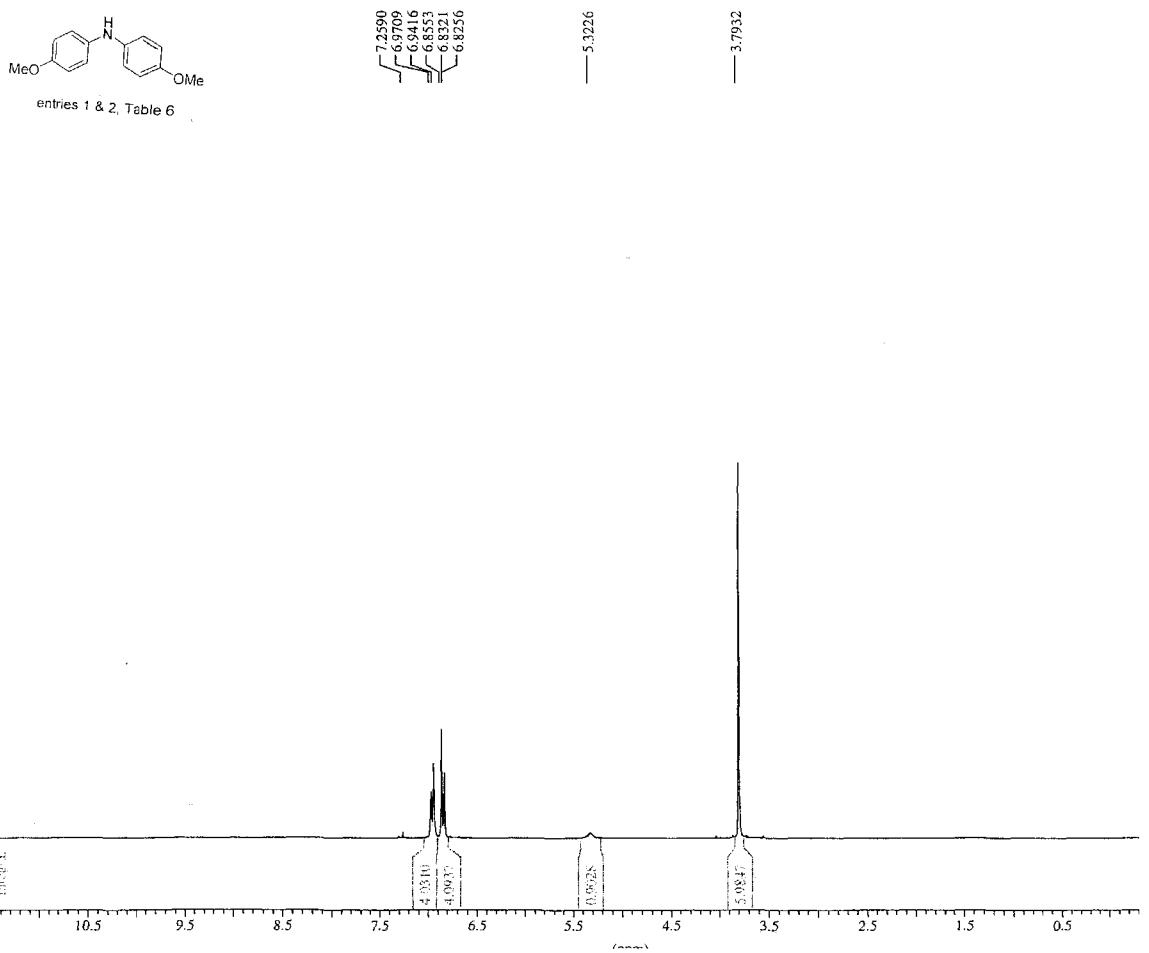
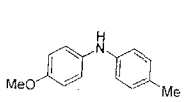
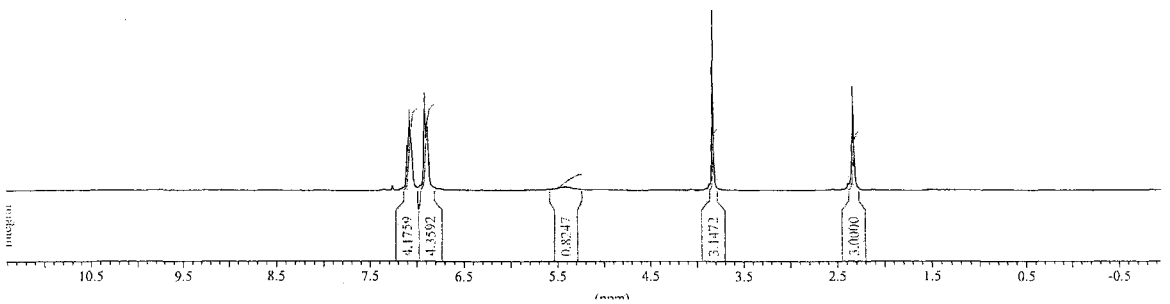
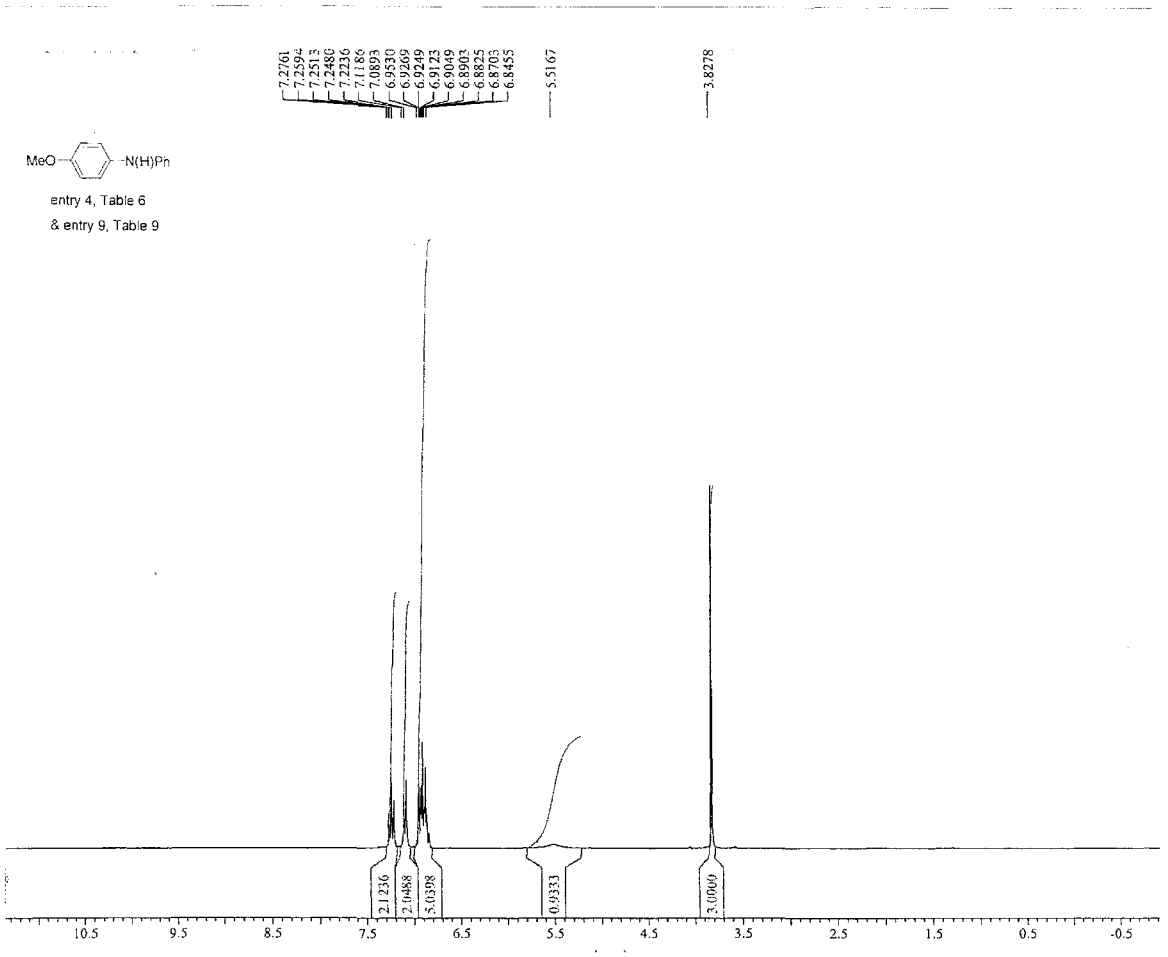
7.3046
7.2981
7.2732
7.2700
7.2456
7.2248
7.2057
7.2000
7.1935
7.0714
7.0457
7.0136
6.9892
6.9652
2.1233
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5

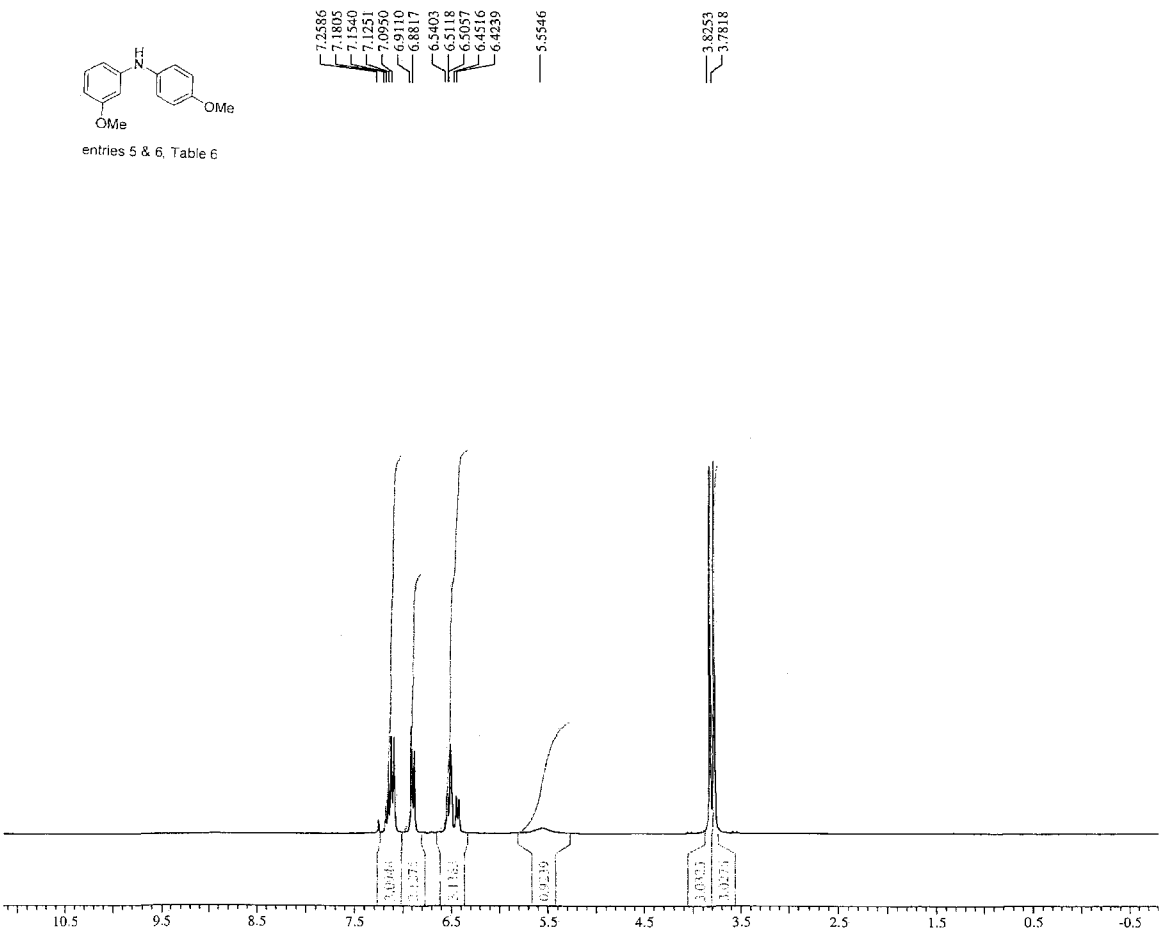

MeO
OMe
entries 1 & 2, Table 6
7.2590
6.9709
6.9416
6.8553
6.8321
6.8256
5.3226
3.7932
4.0310
4.0937
1.9628
5.0847
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5



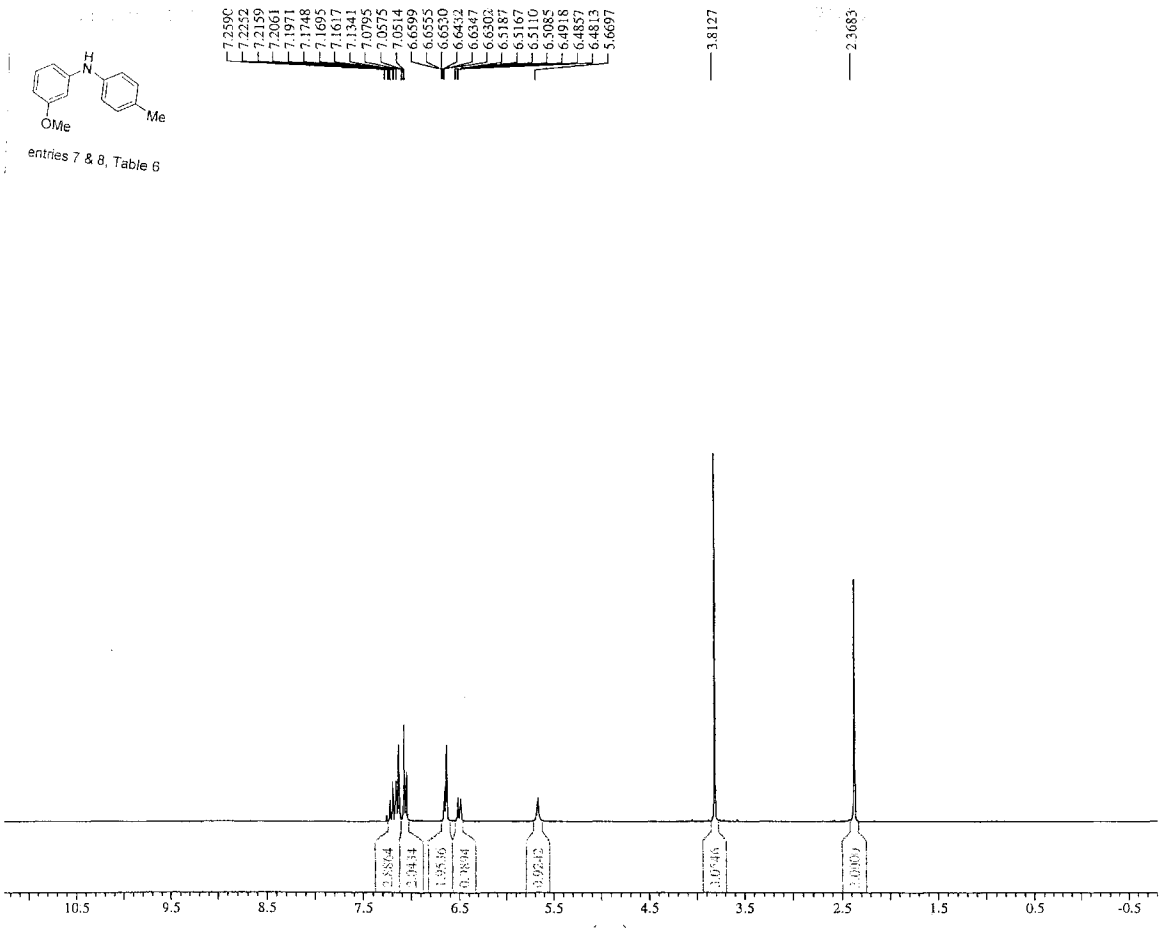
entries 3 & 10, Table 6

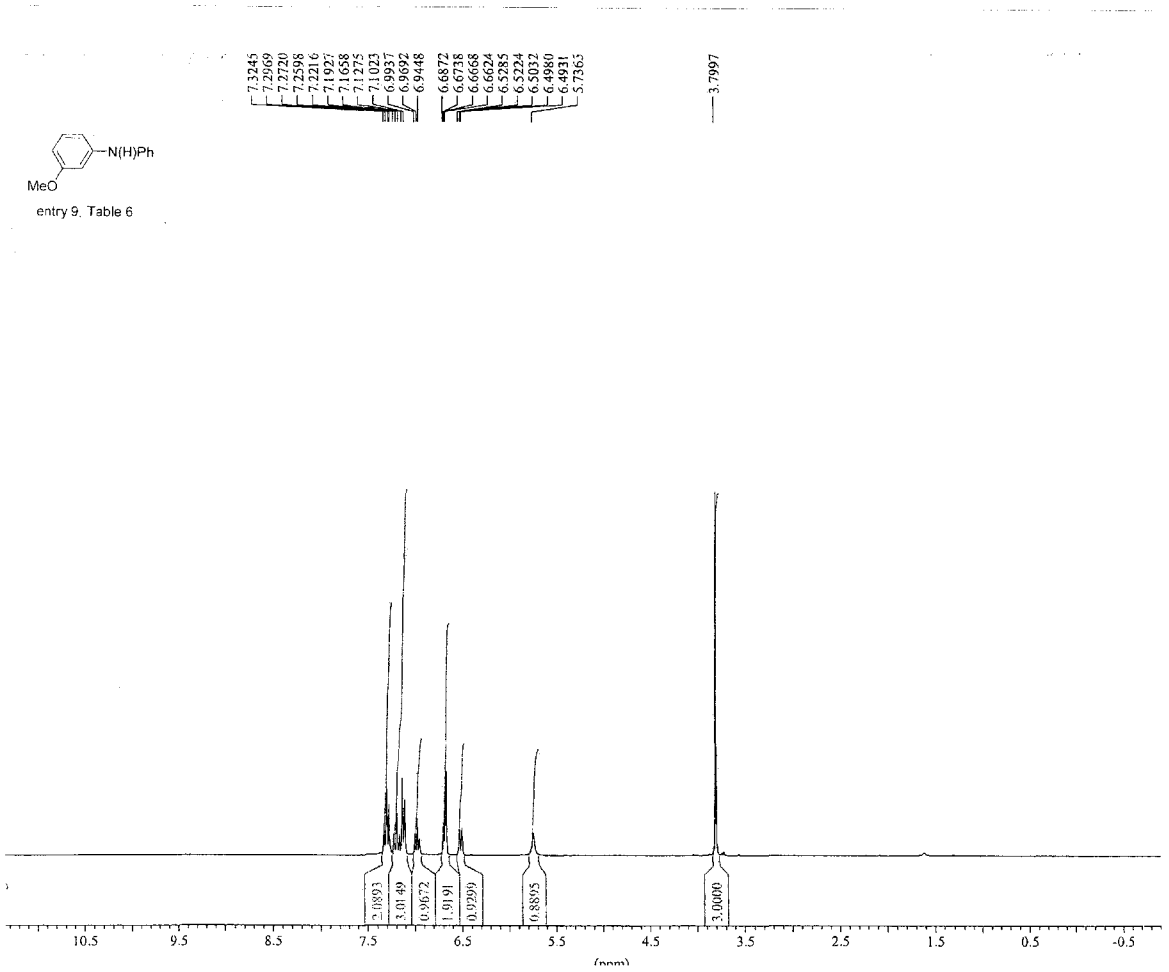


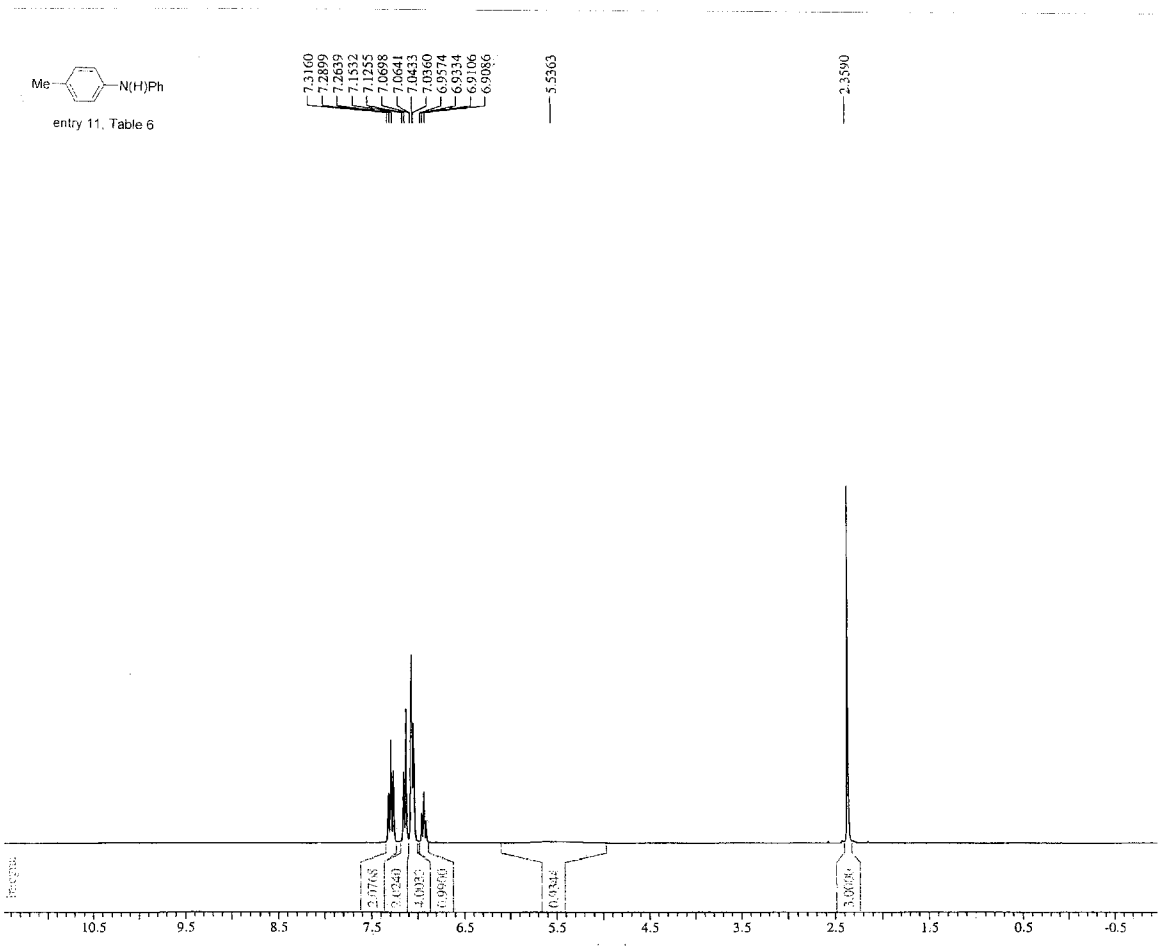

7.2761
7.2594
7.2515
7.2480
7.2236
7.1186
7.0893
6.9530
6.9269
6.9249
6.9123
6.9049
6.8903
6.8825
6.8705
6.8455
5.5167
3.8278
MeO
N(H)Ph
entry 4, Table 6
& entry 9, Table 9
2.1236
2.0488
5.0398
0.9333
3.0000
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5



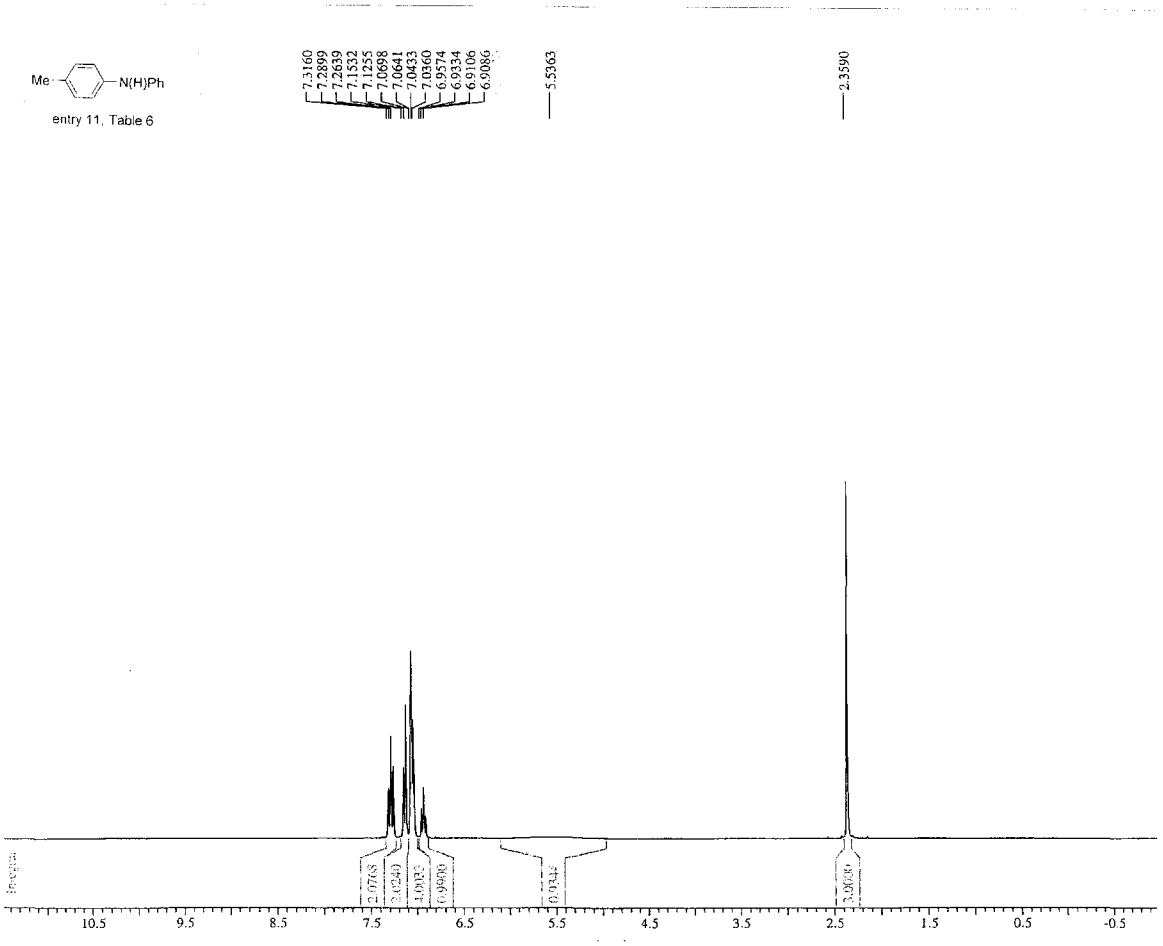
entries 5 & 6, Table 6

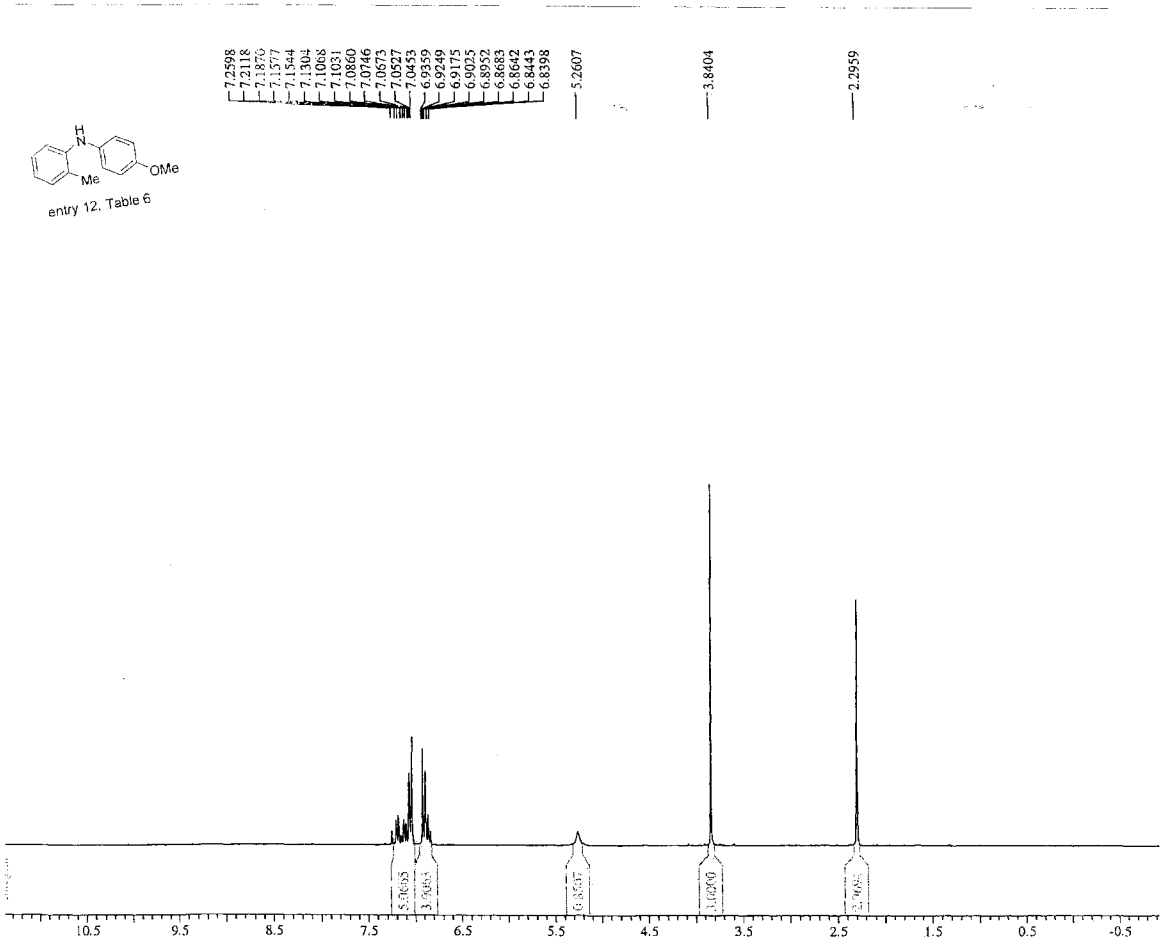

H
N
OMe
Me
entries 7 & 8, Table 6
7.2590
7.2252
7.2159
7.2061
7.1971
7.1748
7.1695
7.1617
7.1341
7.0795
7.0575
7.0514
6.6599
6.6555
6.6530
6.6432
6.6347
6.6302
6.5187
6.5167
6.5110
6.5085
6.4918
6.4857
6.4813
5.6697
3.8127
2.3683
2.8864
2.9434
1.9536
0.7894
3.9248
3.0546
3.0000
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5

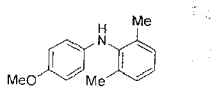

7.3245
7.2969
7.2720
7.2598
7.2216
7.1927
7.1658
7.1275
7.1023
6.9937
6.9692
6.9448
6.6872
6.6738
6.6668
6.6624
6.5285
6.5224
6.5032
6.4980
6.4931
5.7365
3.7997
N(H)Ph
MeO
entry 9, Table 6
2.0893
3.0149
0.9672
1.9191
0.9299
0.8895
3.0000
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
(ppm)


Me
N(H)Ph
entry 11, Table 6
7.3160
7.2899
7.2639
7.1532
7.1255
7.0698
7.0641
7.0433
7.0360
6.9574
6.9334
6.9106
6.9086
5.5363
2.3590
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5

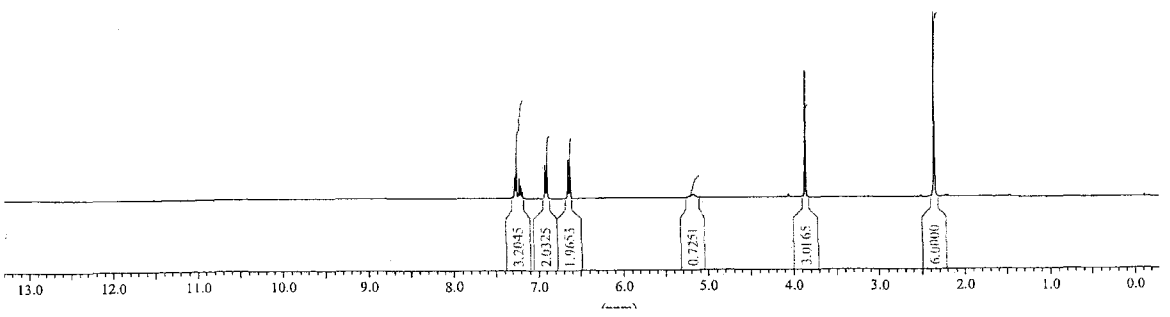
entry 12, Table 6
Me
OMe
7.2598
7.2118
7.1544
7.1304
7.1068
7.1031
7.0860
7.0746
7.0673
7.0527
7.0453
6.9359
6.9249
6.9175
6.9025
6.8952
6.8683
6.8642
6.8443
6.8398
5.2607
3.8404
2.2959
5.0665
3.6000

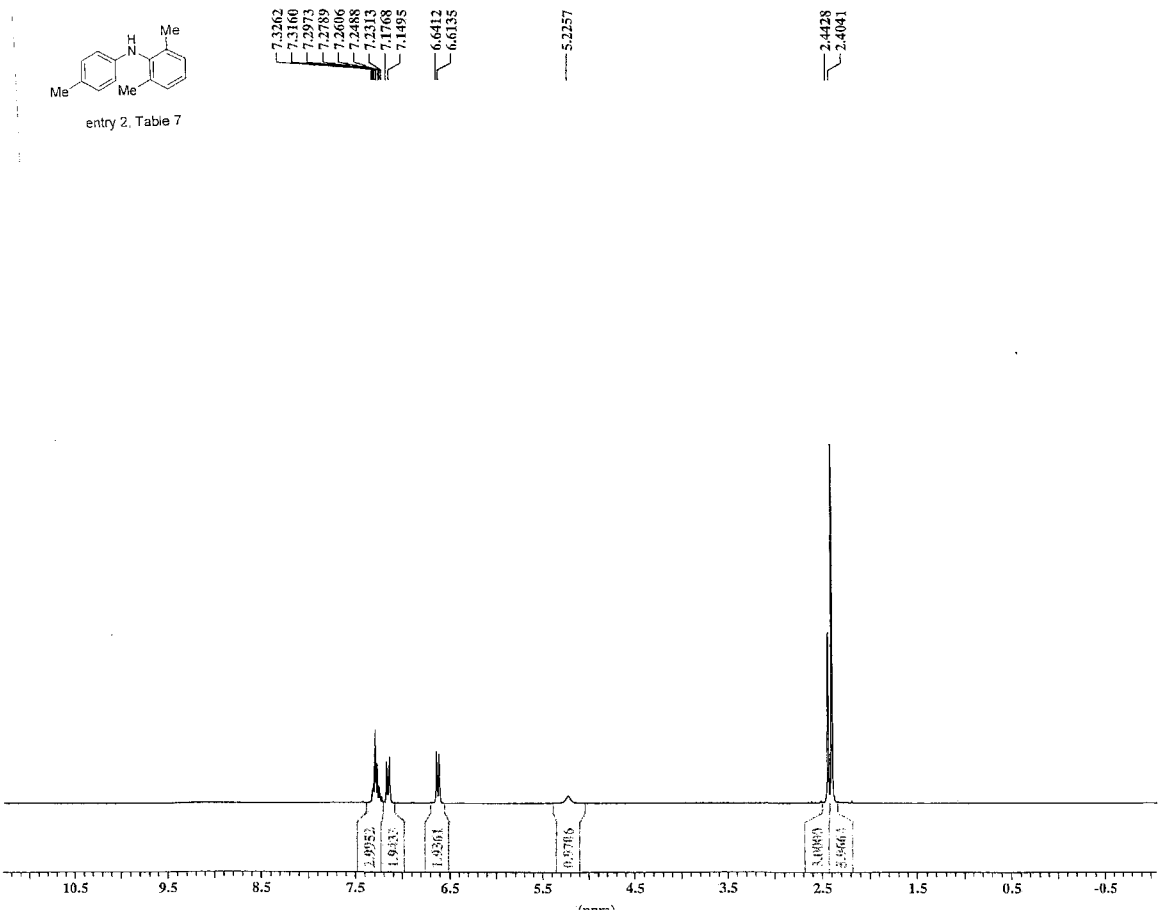

Me
N(H)Ph
entry 11, Table 6
7.3160
7.2899
7.2639
7.1532
7.1255
7.0698
7.0641
7.0433
7.0360
6.9574
6.9334
6.9106
6.9086
5.5363
2.3590
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5

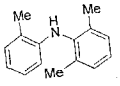

7.2598
7.2118
7.1577
7.1544
7.1304
7.1068
7.1031
7.0860
7.0746
7.0673
7.0527
7.0453
6.9359
6.9249
6.9175
6.9025
6.8952
6.8683
6.8642
6.8443
6.8398
5.2607
3.8404
2.2959
H
N
Me
OMe
entry 12, Table 6
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5



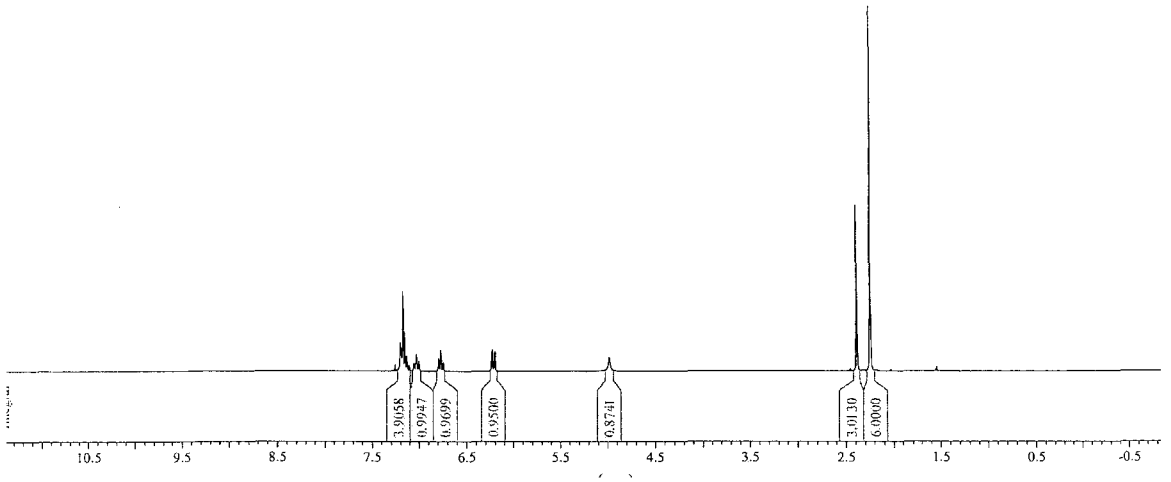
entry 1, Table 7

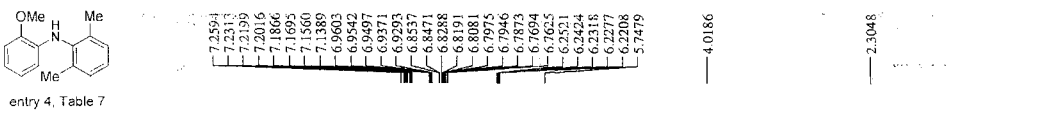



Me
H
N
Me
Me
entry 2, Table 7
7.3262
7.3160
7.2973
7.2789
7.2606
7.2488
7.2313
7.1768
7.1495
6.6412
6.6135
5.2257
2.4428
2.4041
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5

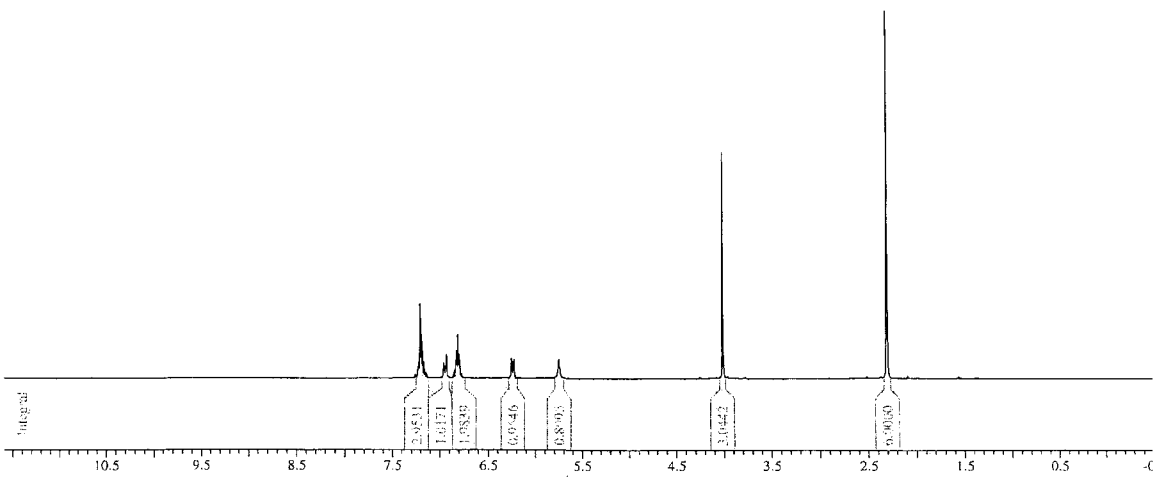


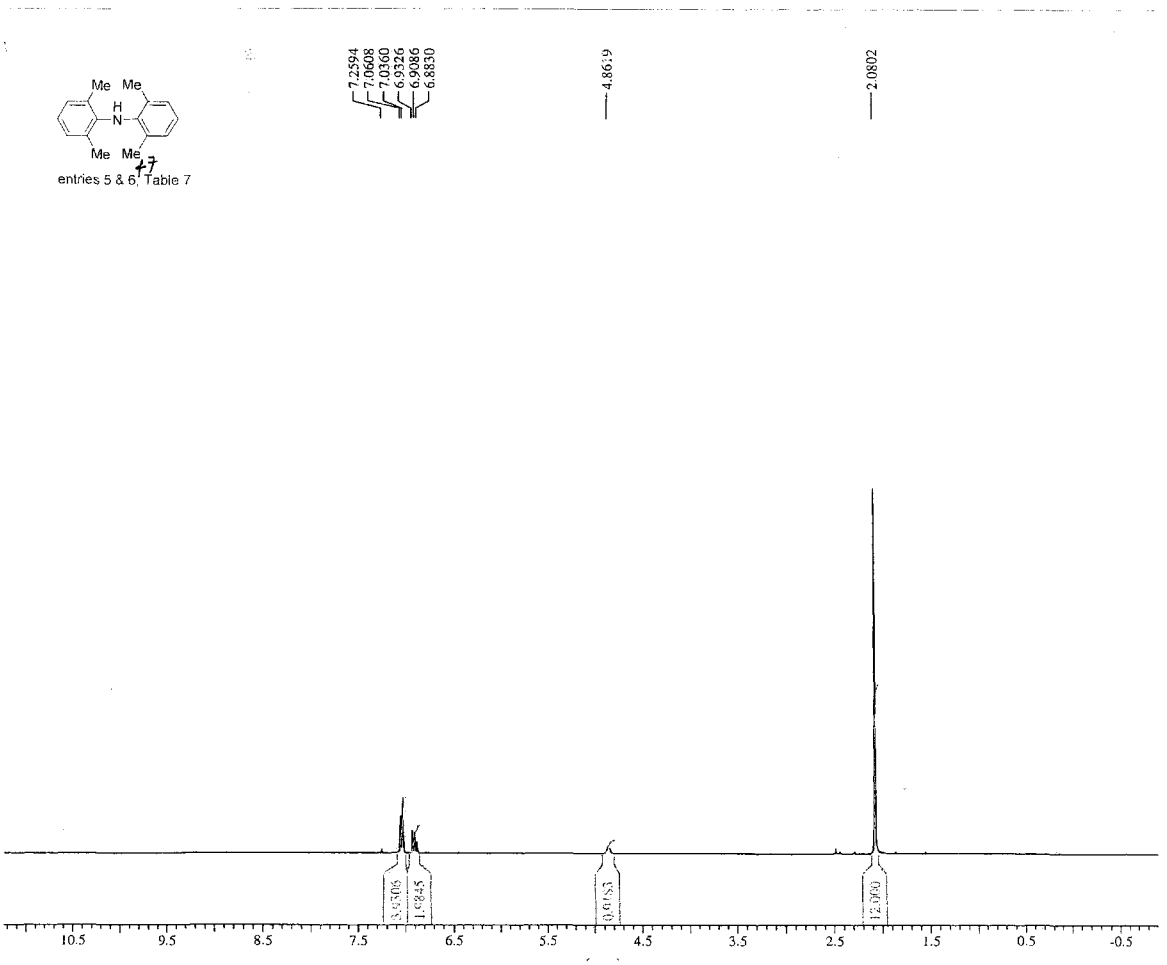
entry 3, Table 7





entry 4, Table 7




Me Me
H
N
Me Me
47
entries 5 & 6, Table 7
7.2594
7.0608
7.0360
6.9326
6.9086
6.8830
4.8619
2.0802
3.5305
1.9845
0.9183
12.0000
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5

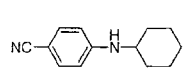
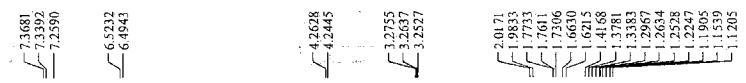
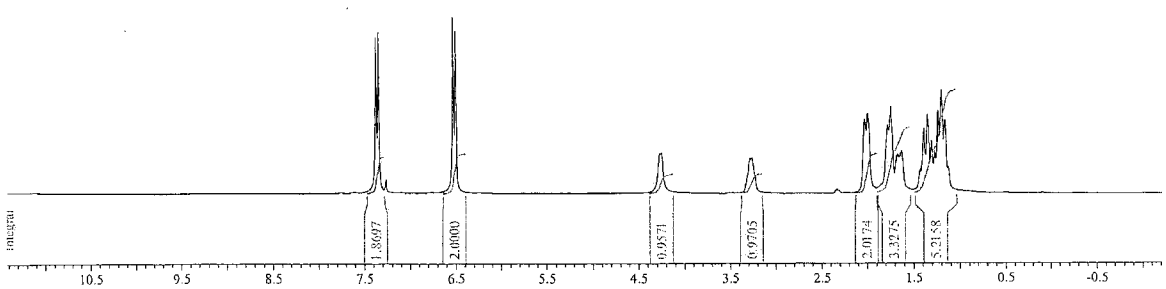
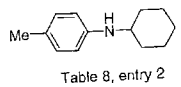


Table 8, entry 1







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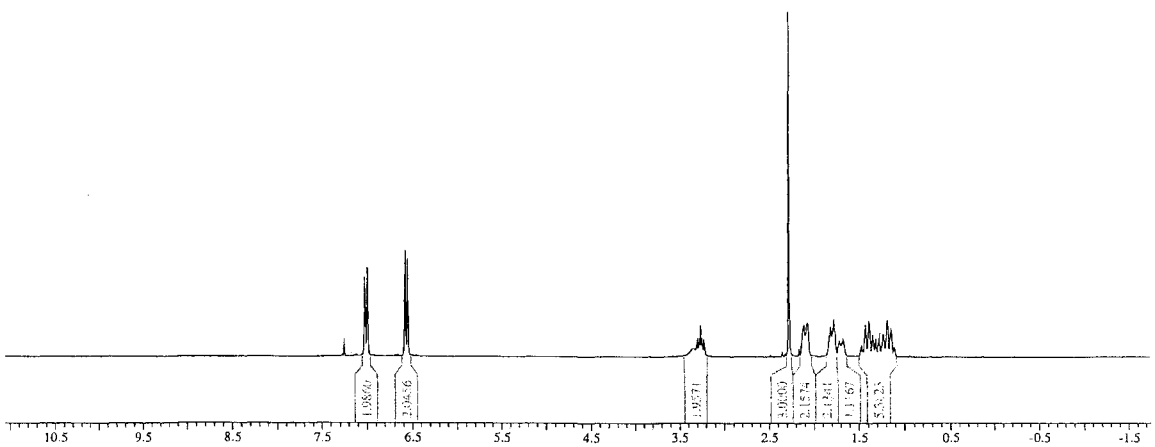


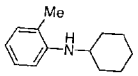


Table 8, entry 3

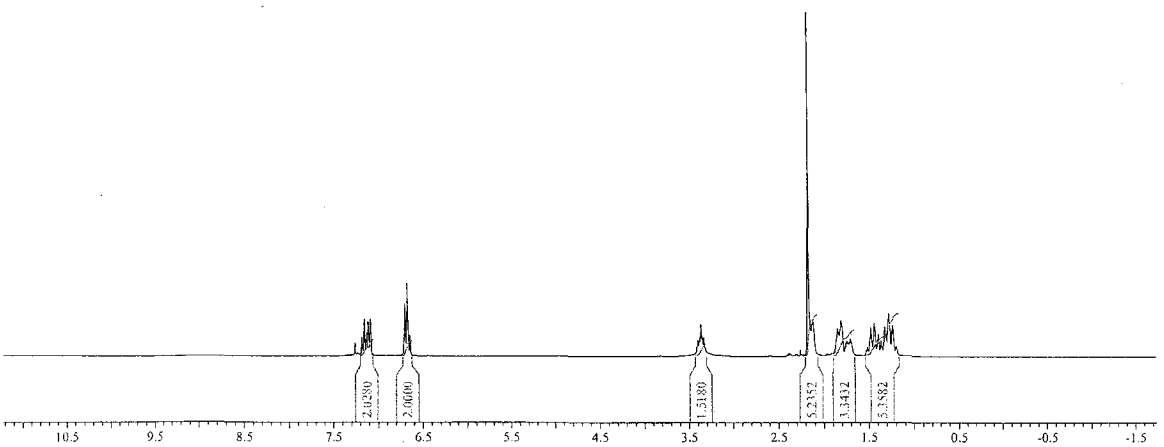
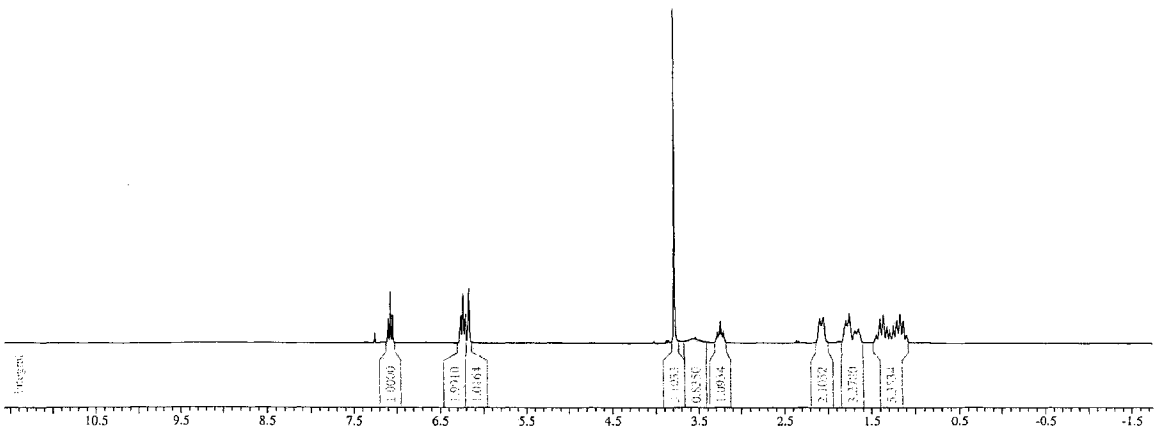
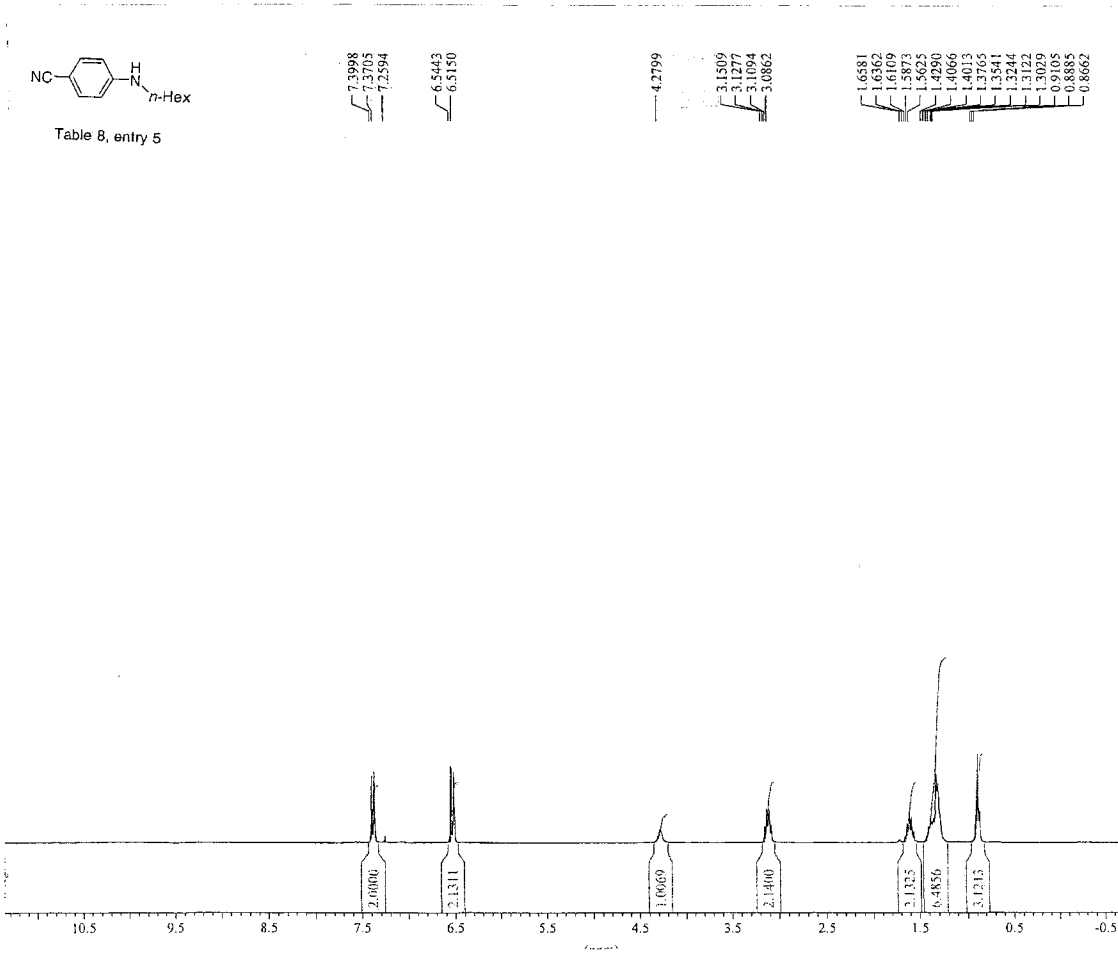


Table 8 entry 4




NC
H
N
n-Hex
Table 8, entry 5
7.3998
7.3705
7.2594
6.5443
6.5150
4.2799
3.1509
3.1277
3.1094
3.0862
1.6581
1.6362
1.6169
1.5873
1.5625
1.4290
1.4066
1.4013
1.3765
1.3541
1.3244
1.3122
1.3029
0.9105
0.8885
0.8662
2.0000
2.1311
1.0669
2.1400
3.1325
6.4856
3.0215
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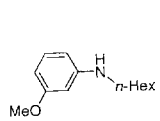
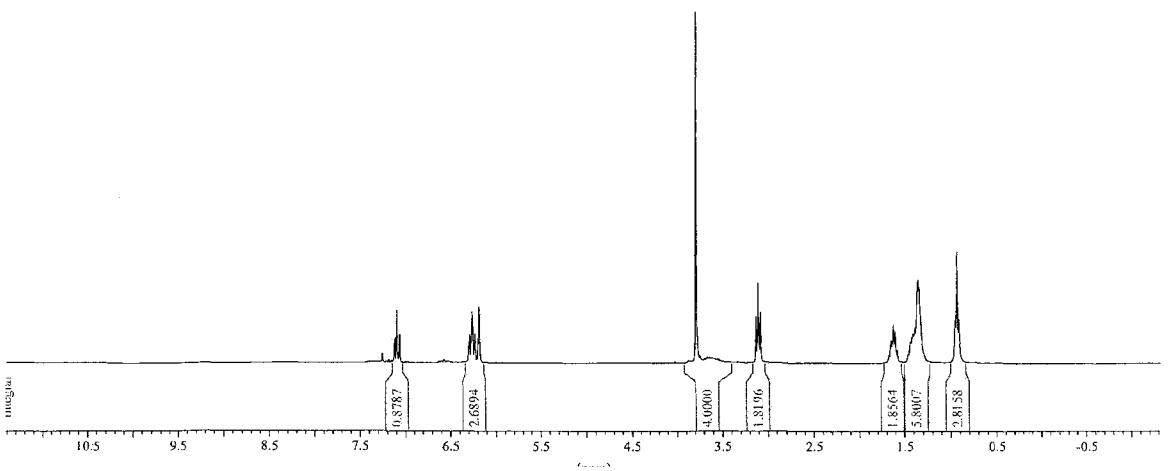


Table 8, entry 6



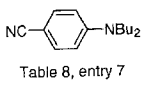
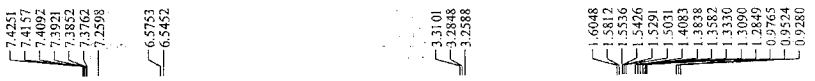
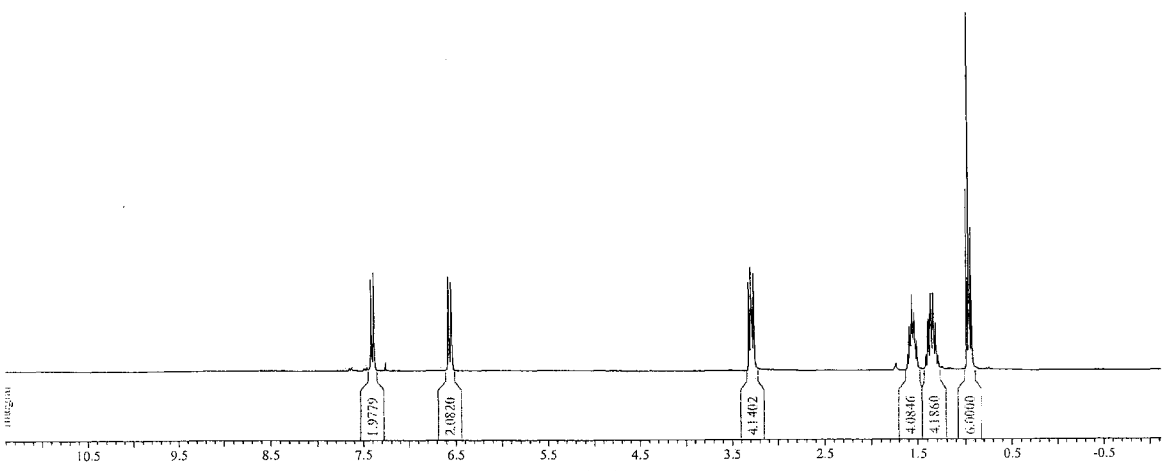
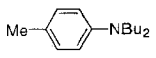


Table 8, entry 7







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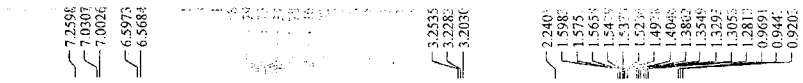

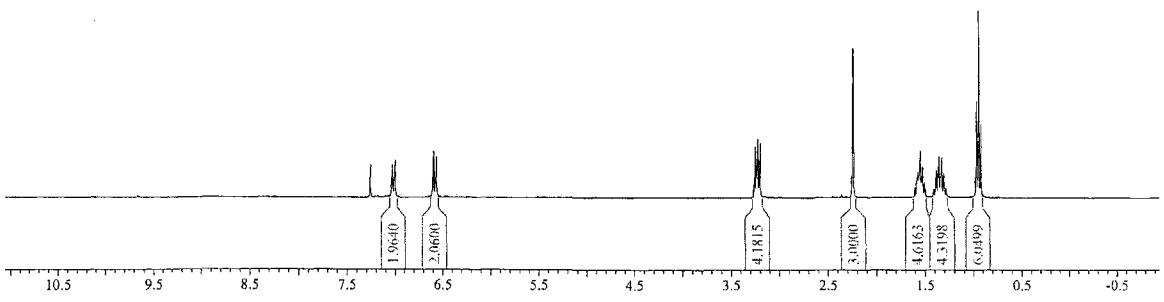

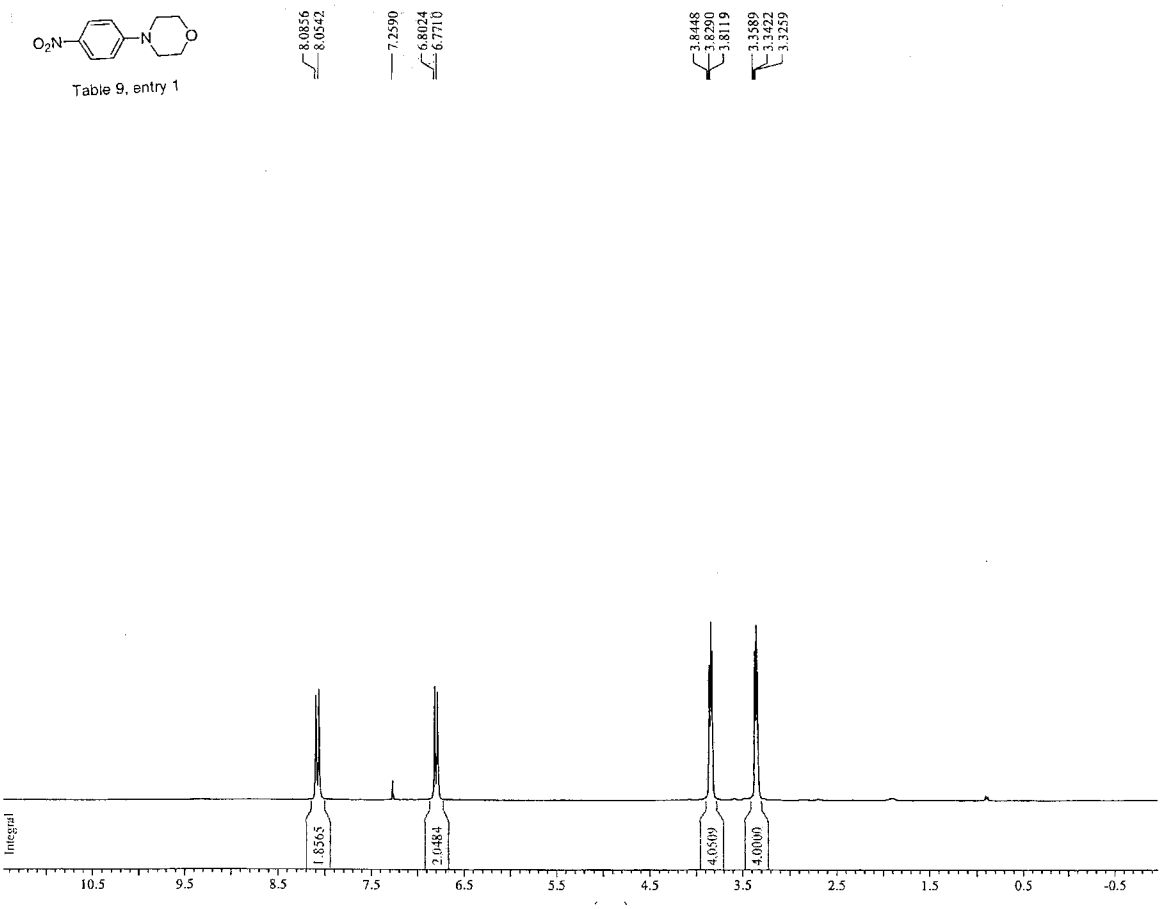
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3.3422
3.3259
Integral
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2.0484
4.0509
4.0000
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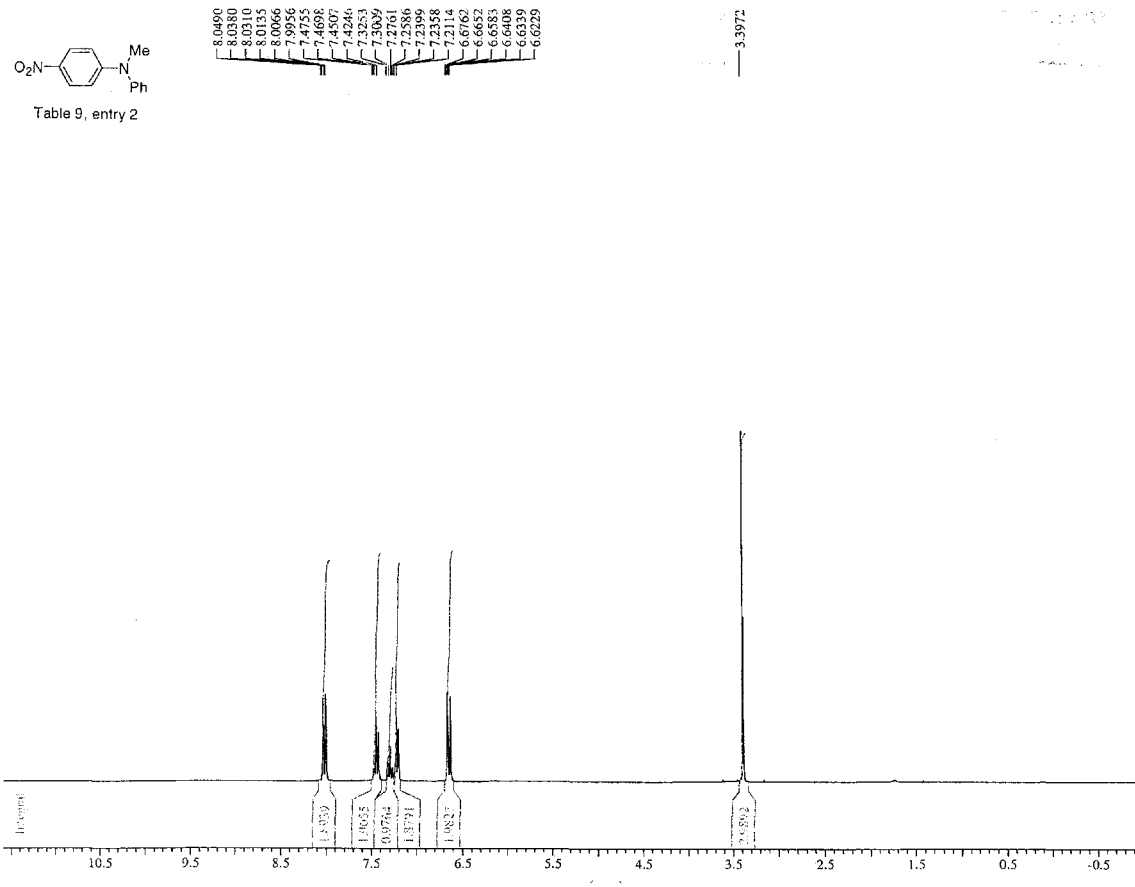
-0.5



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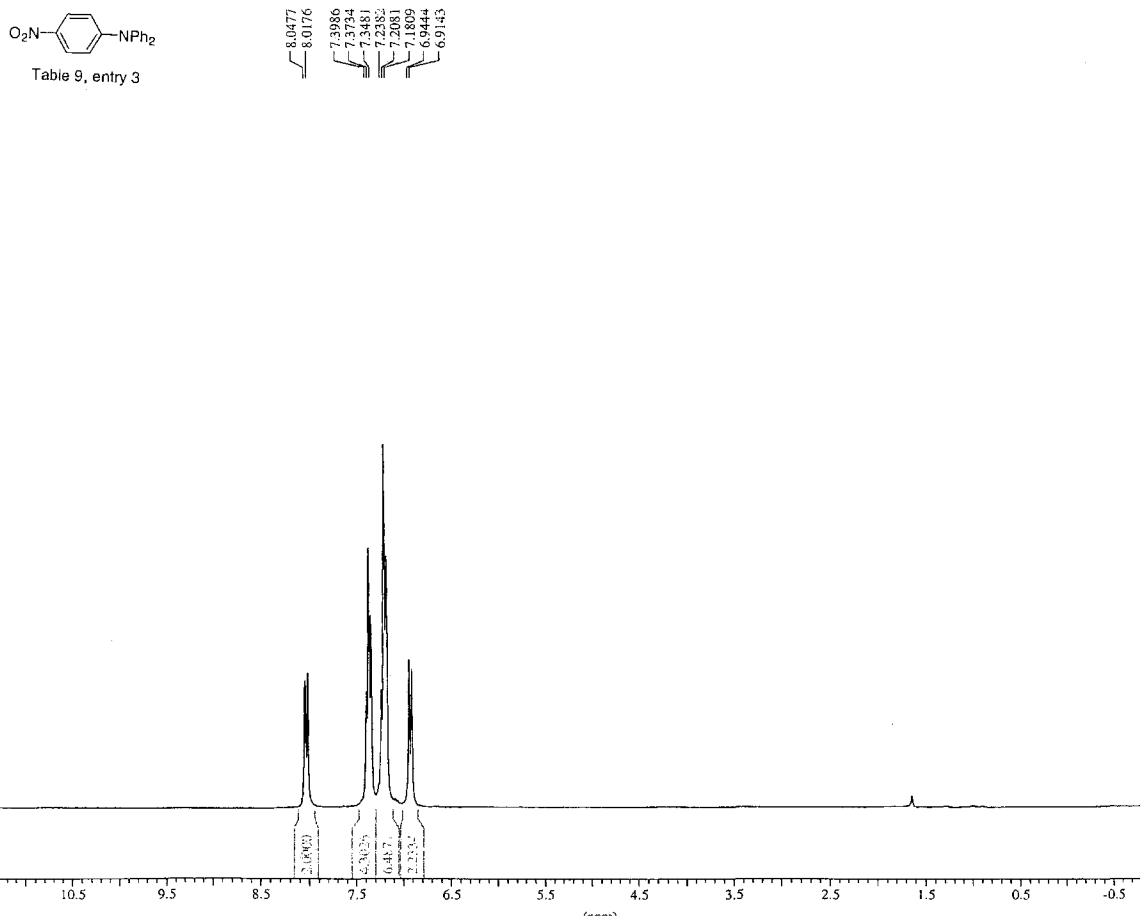

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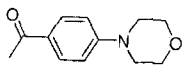

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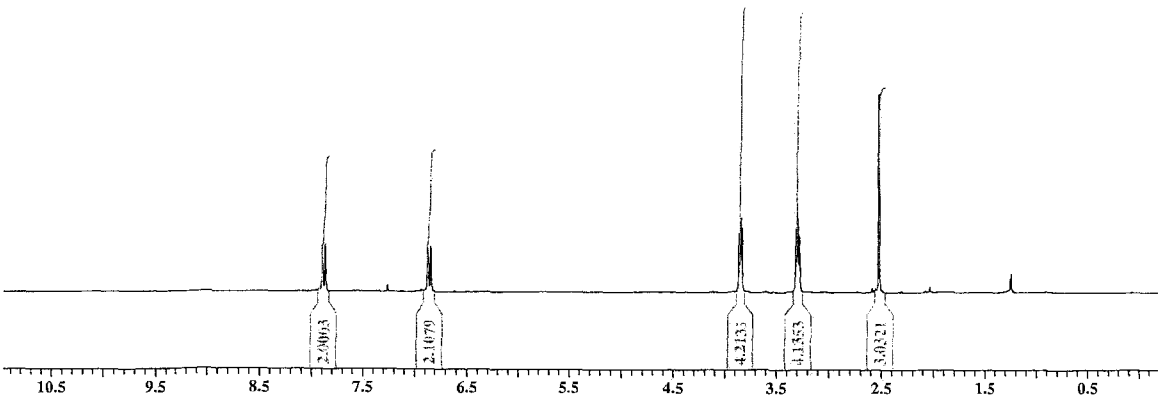

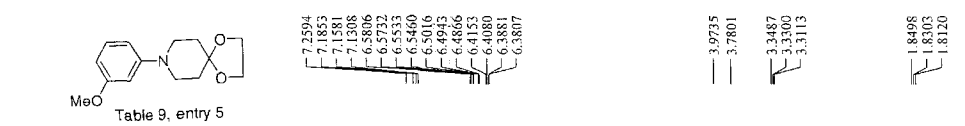

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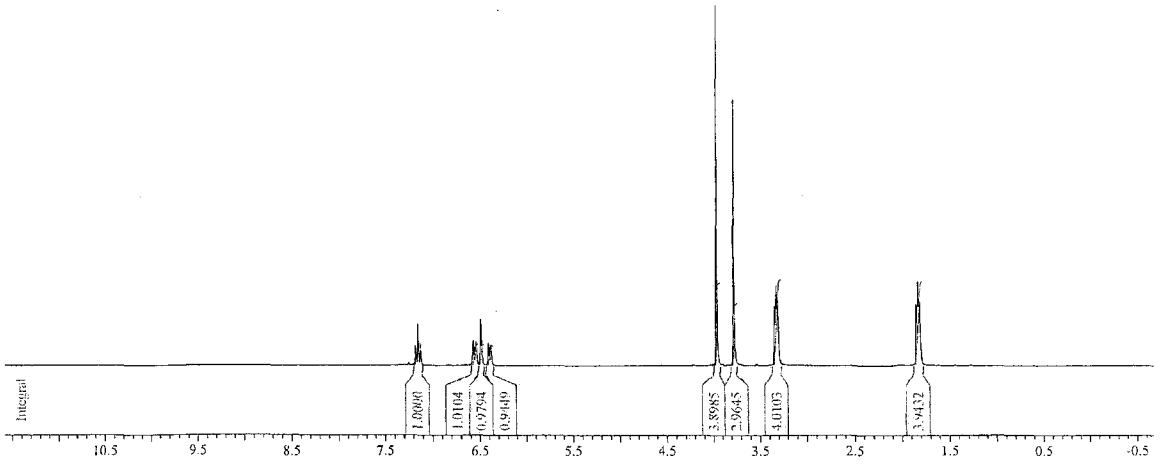

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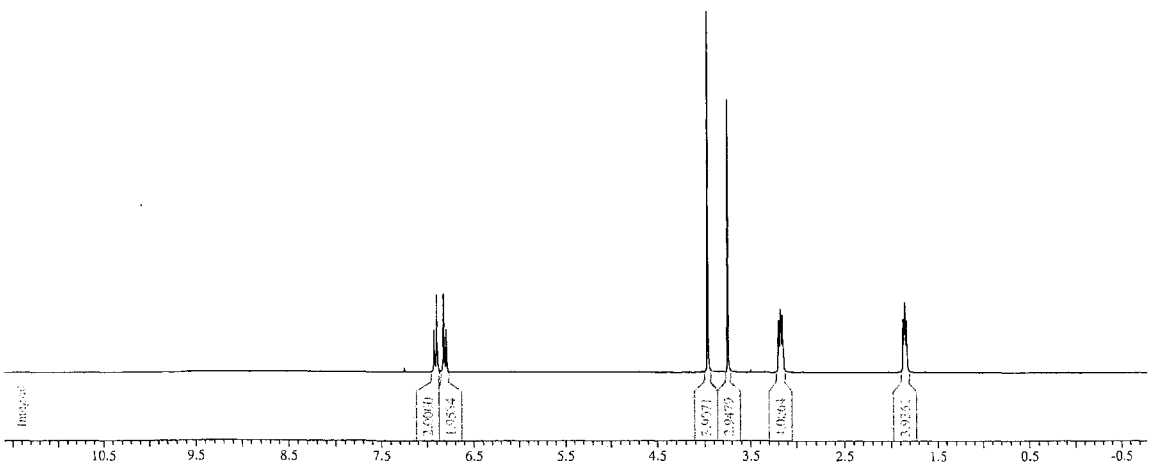
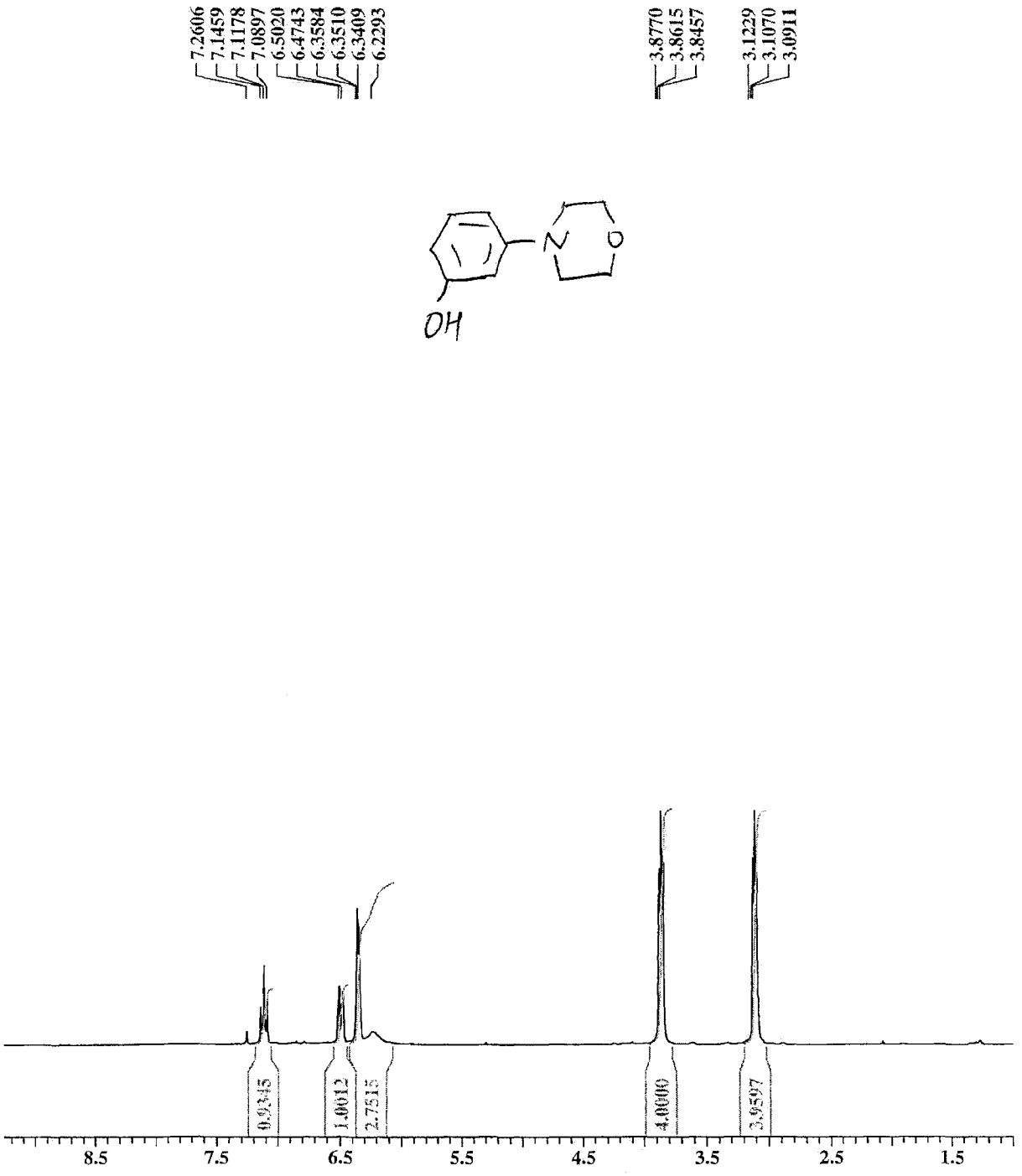


APPENDIX D

CHAPTER 5

^{1}H NMR spectra for reaction products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3.8615
3.8457
3.1229
3.1070
3.0911
OH
0.9345
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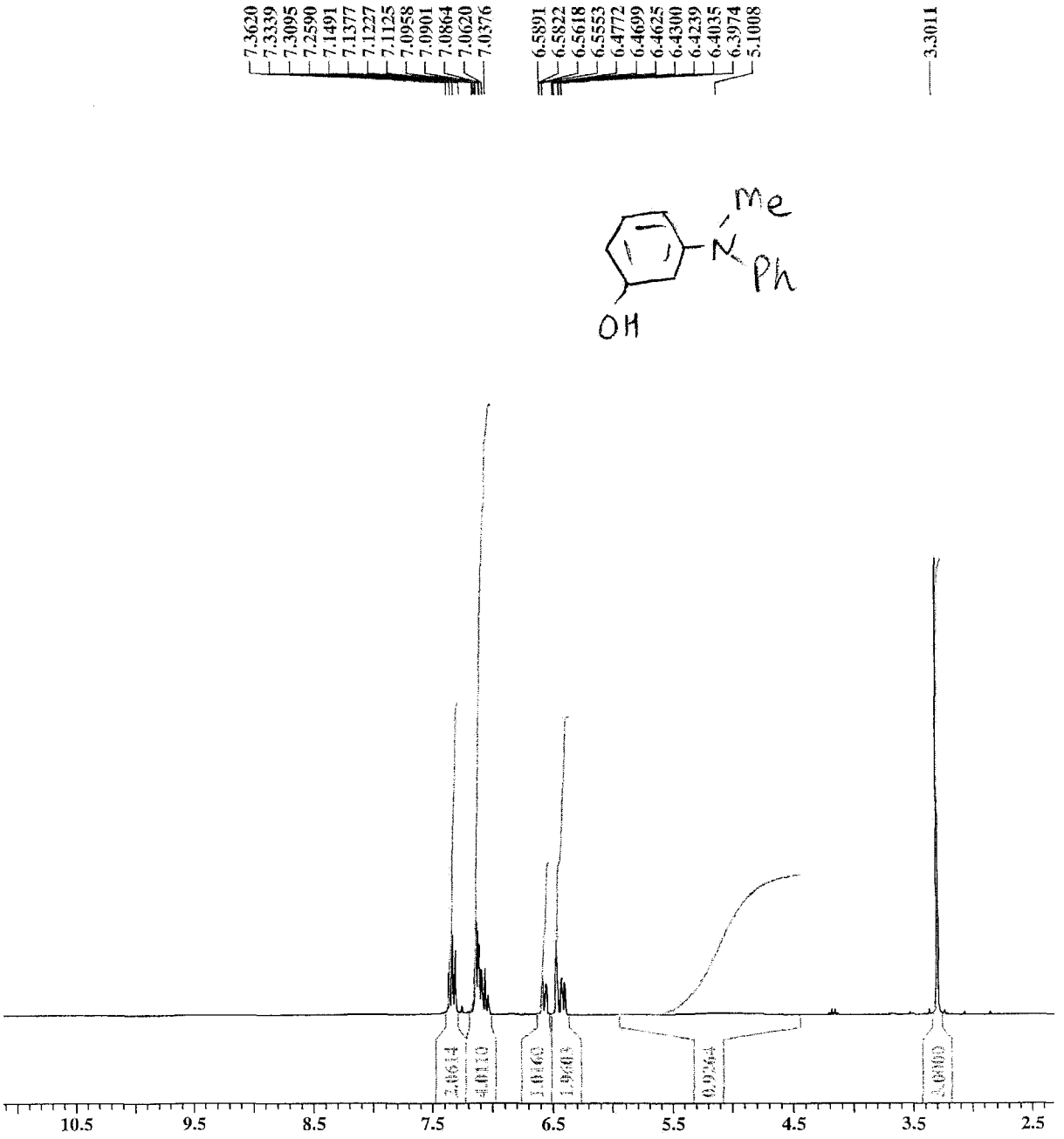
6.5
5.5
4.5
3.5
2.5
1.5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7.1227
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7.0958
7.0901
7.0864
7.0620
7.0376
6.5891
6.5822
6.5618
6.5553
6.4772
6.4699
6.4625
6.4300
6.4239
6.4035
6.3974
5.1008
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Ph
OH
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7.5
6.5
5.5
4.5
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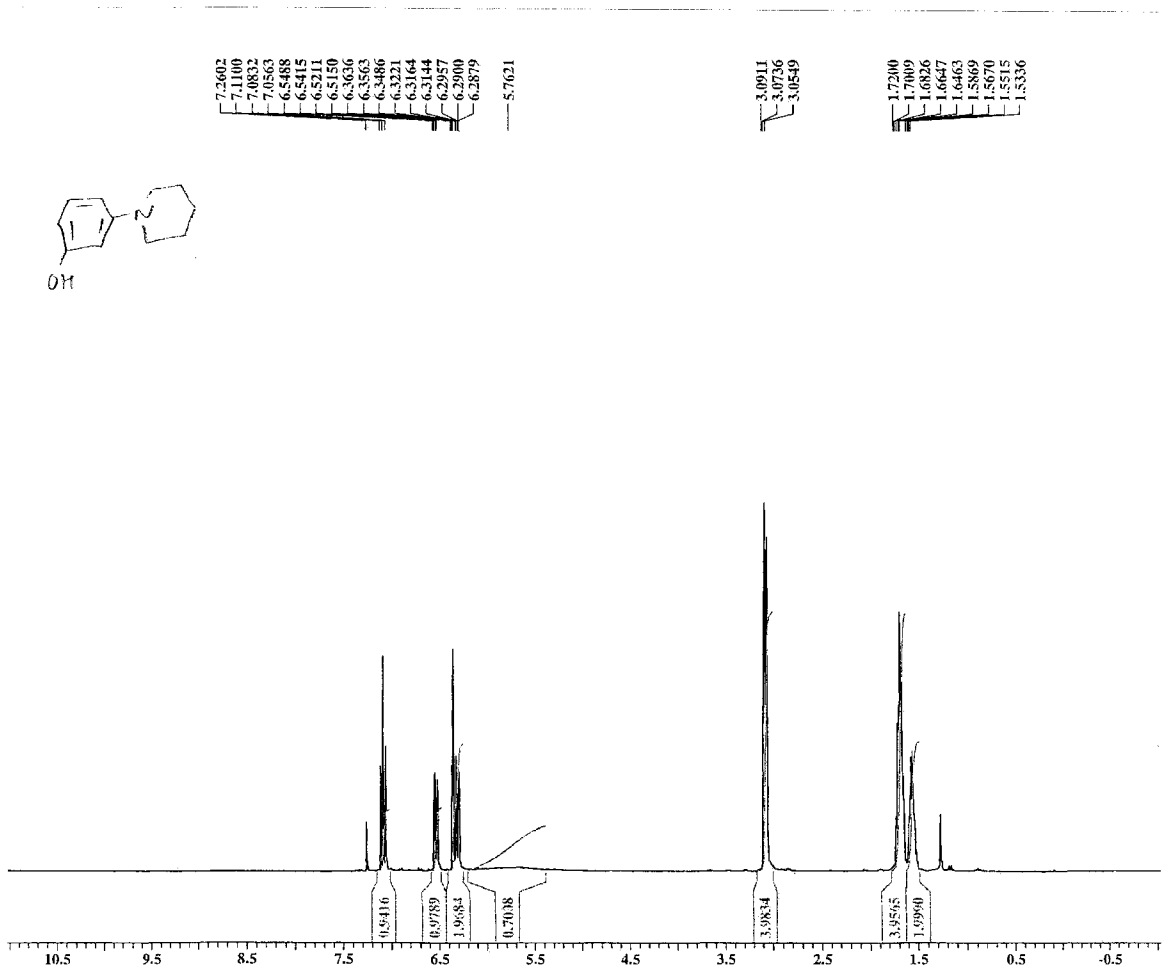
2.5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6.3221
6.3164
6.3144
6.2957
6.2900
6.2879
5.7621
3.0911
3.0736
3.0549
1.7200
1.7009
1.6826
1.6647
1.6463
1.5869
1.5670
1.5515
1.5336
OH
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0.97789
1.96984
0.70038
3.98834
3.95565
1.99990
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7.5
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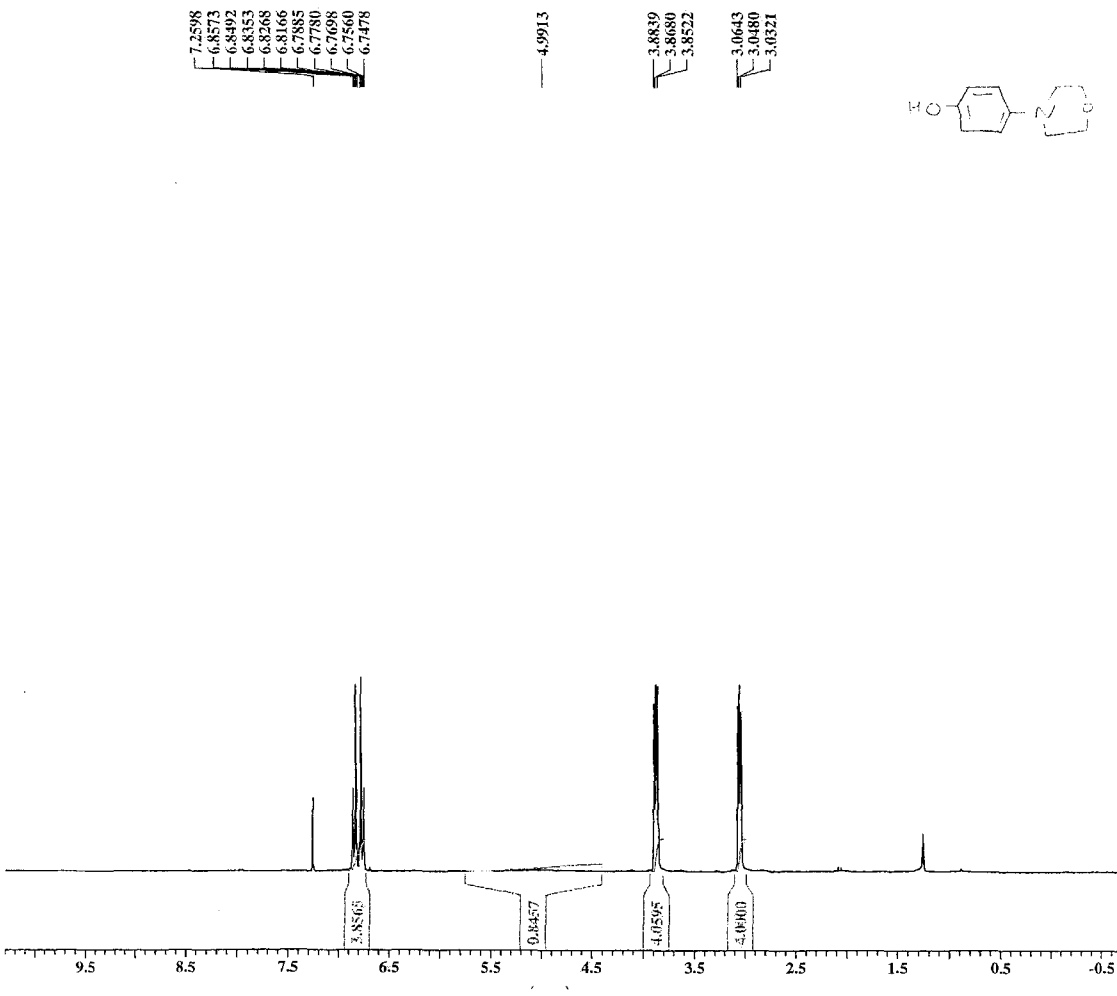
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6.7478
4.9913
3.8839
3.8680
3.8522
3.0643
3.0480
3.0321
HO
N
O
3.8565
0.8457
4.0595
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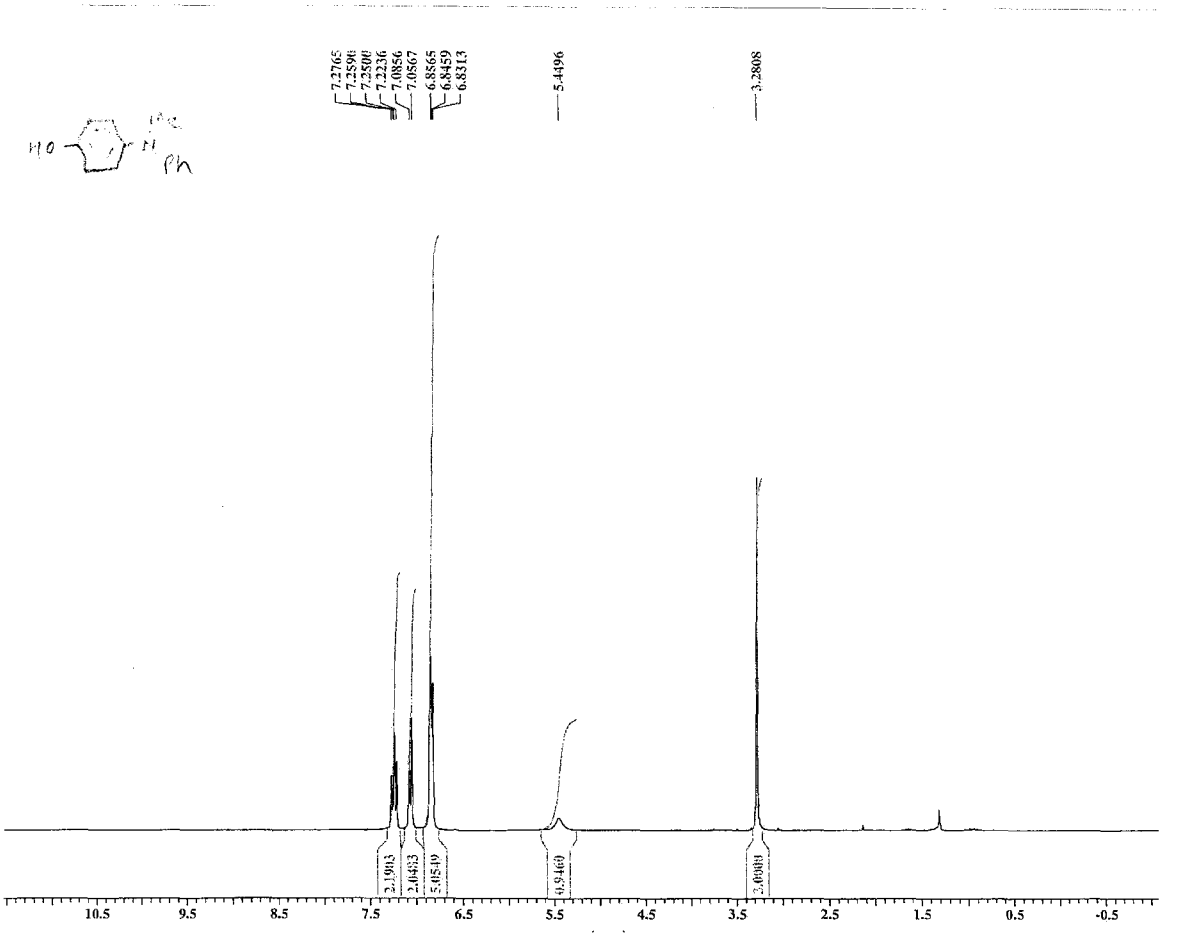
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HO
Ph
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2.0483
5.0549
4.9469
3.0989
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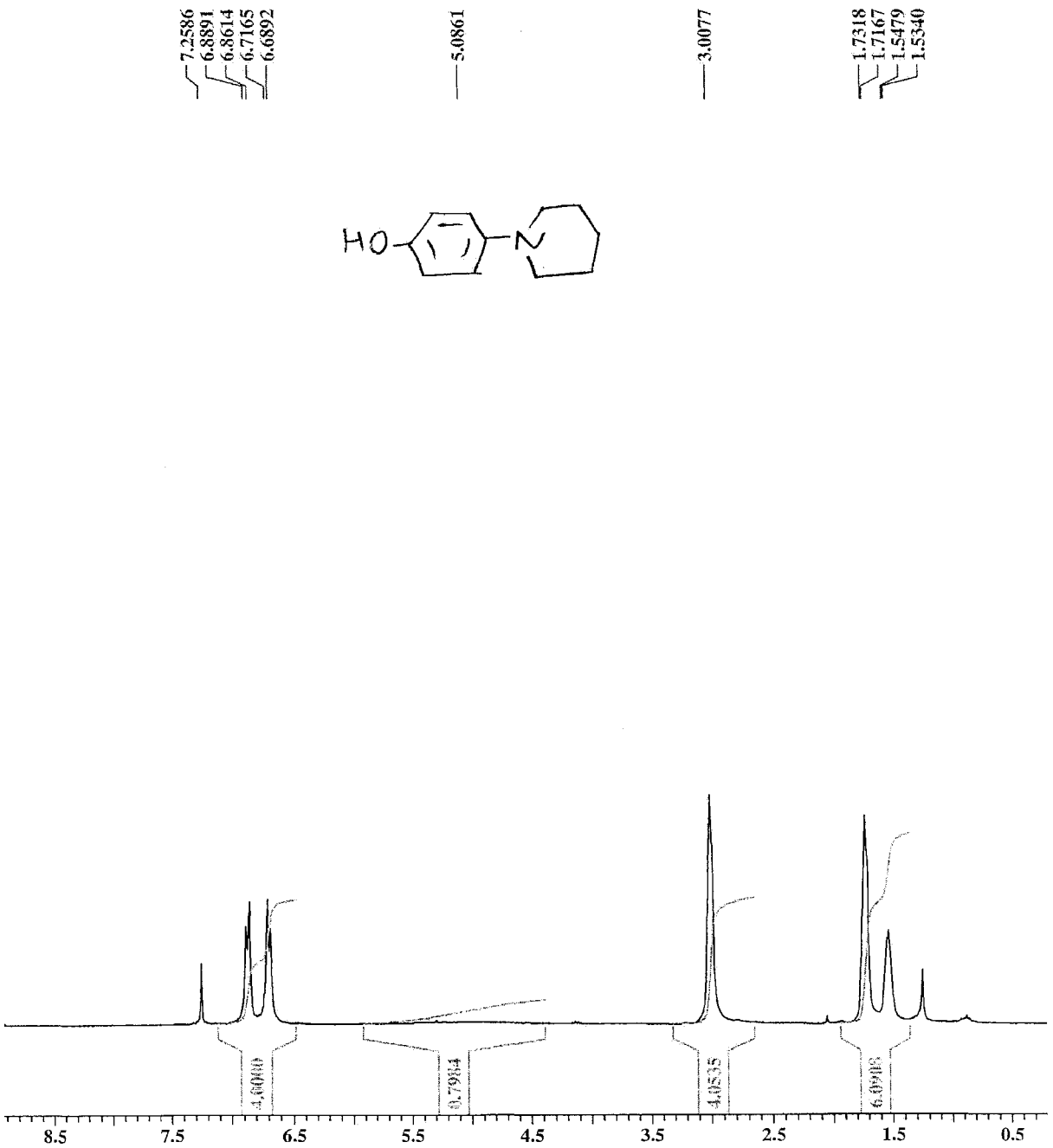
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HO
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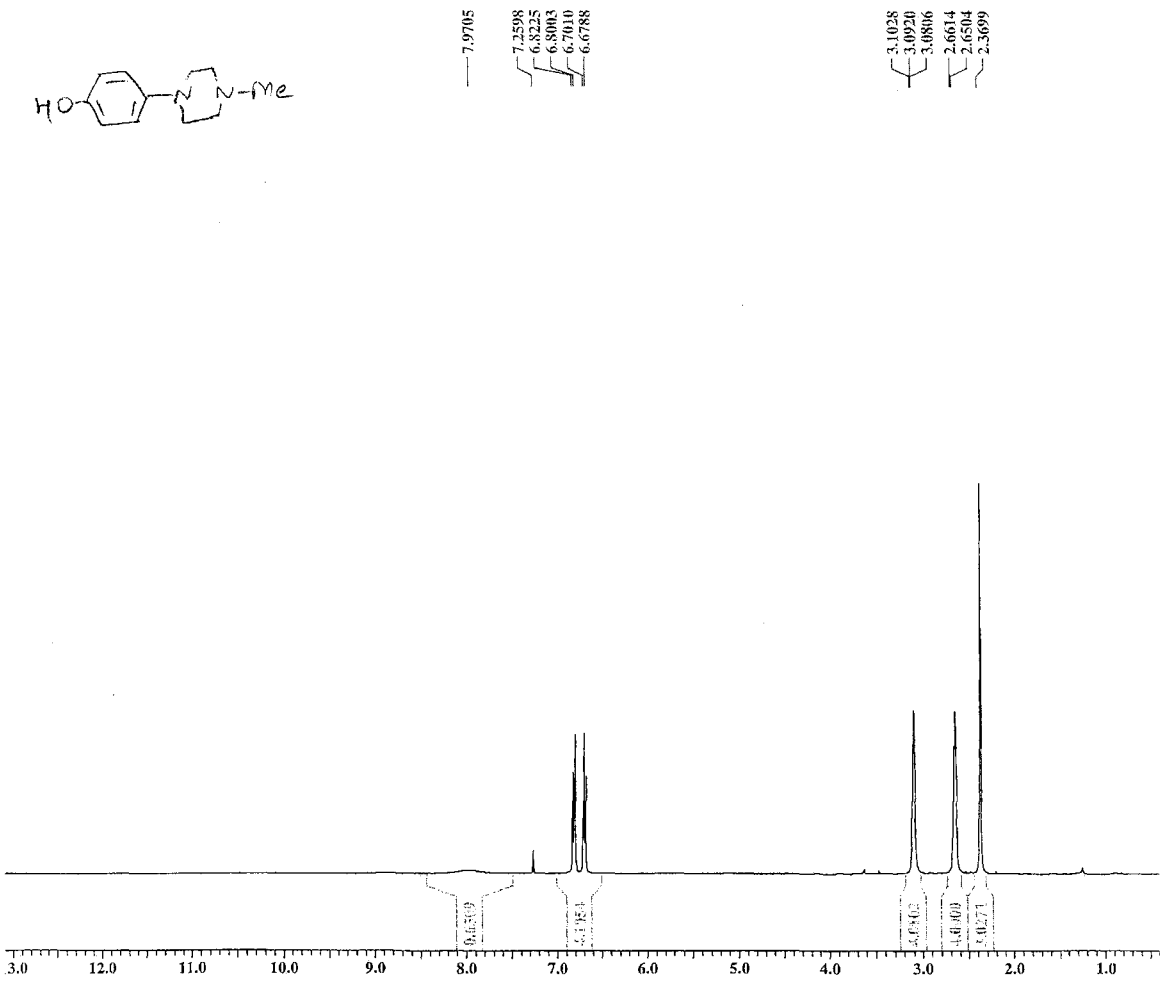
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2.6504
2.3699
3.0
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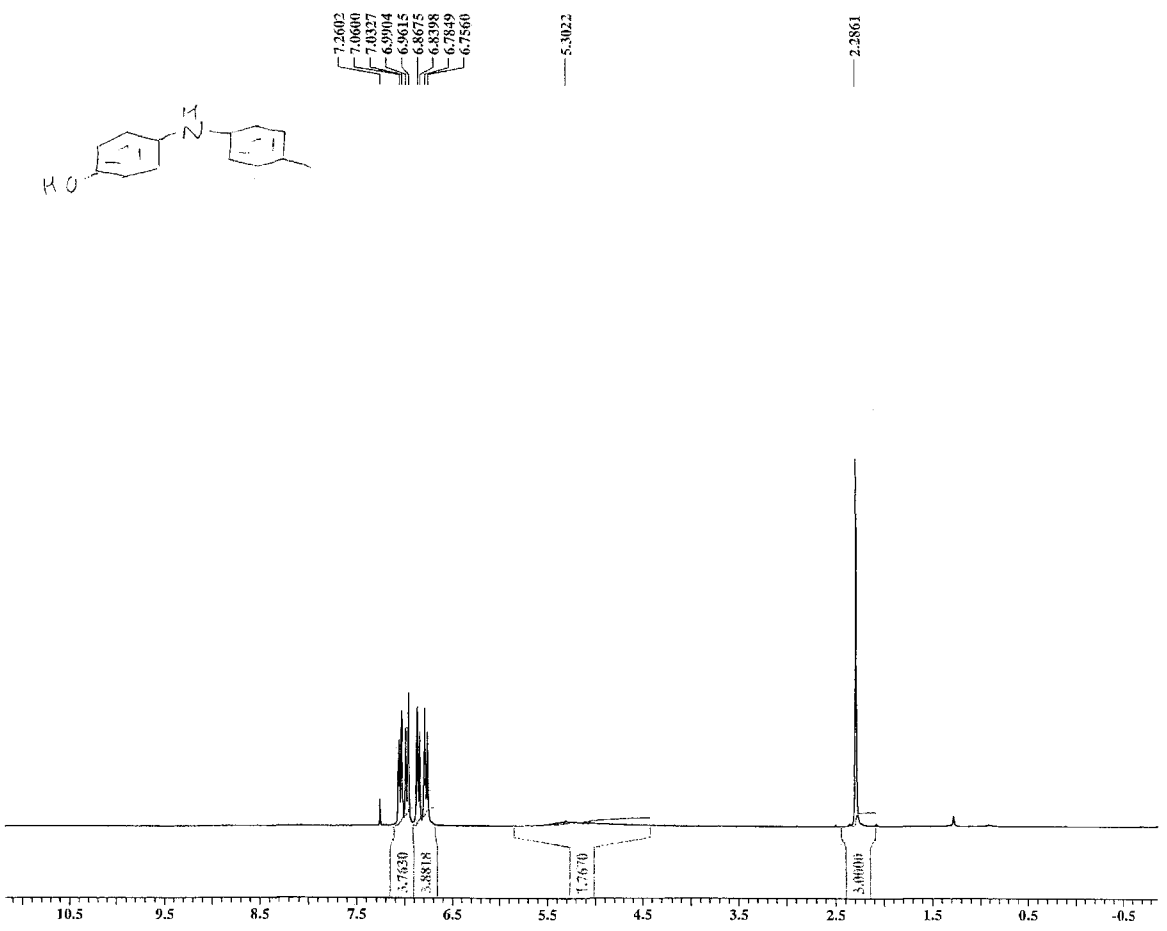
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2.2861
HO
H
N
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3.88818
1.76770
3.00000
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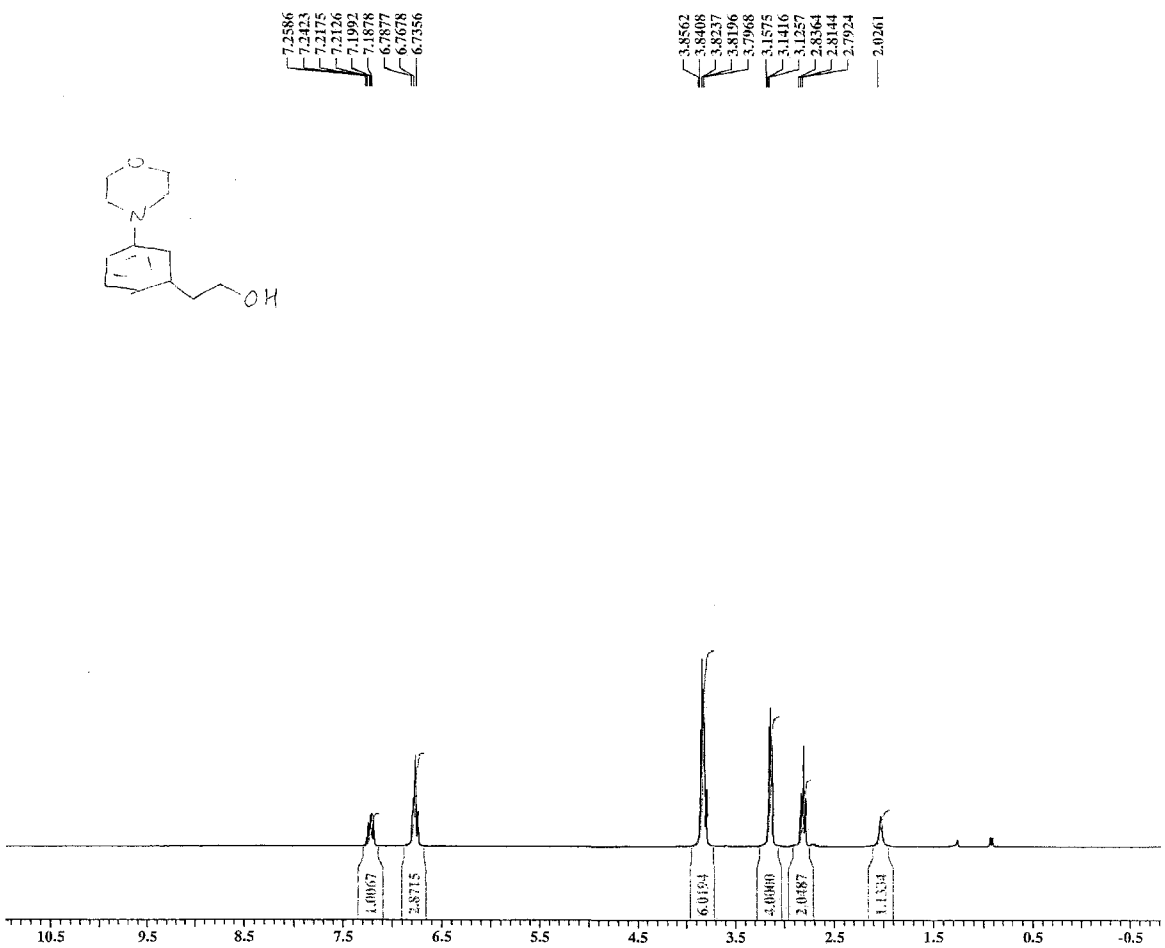
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3.8196
3.7968
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3.1416
3.1257
2.8364
2.8144
2.7924
2.0261
O
N
OH
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2.0000
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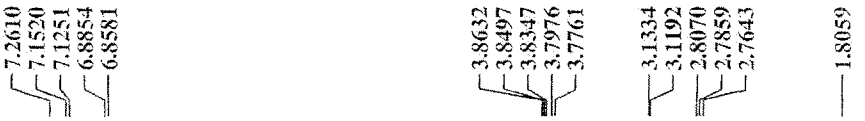
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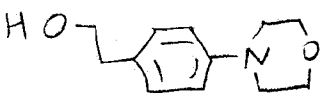
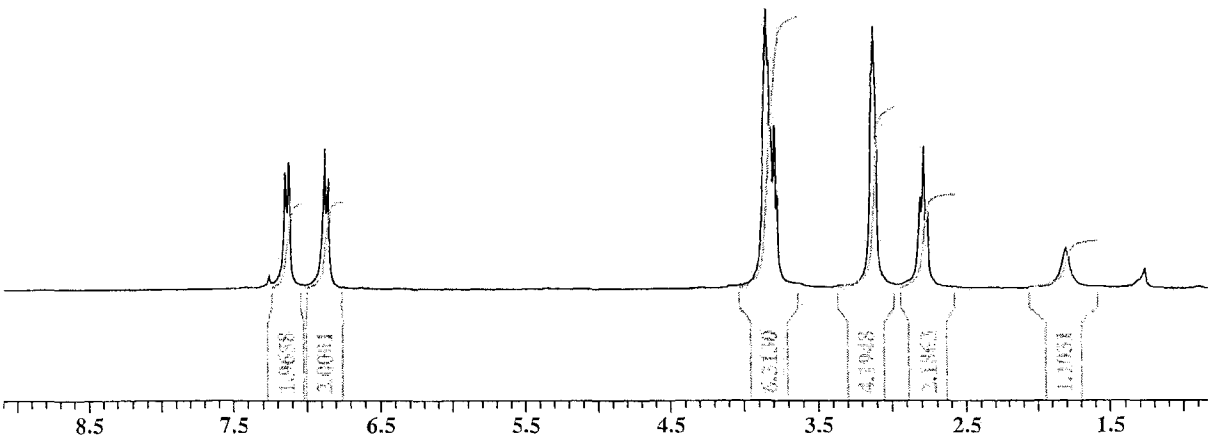

HO
N
O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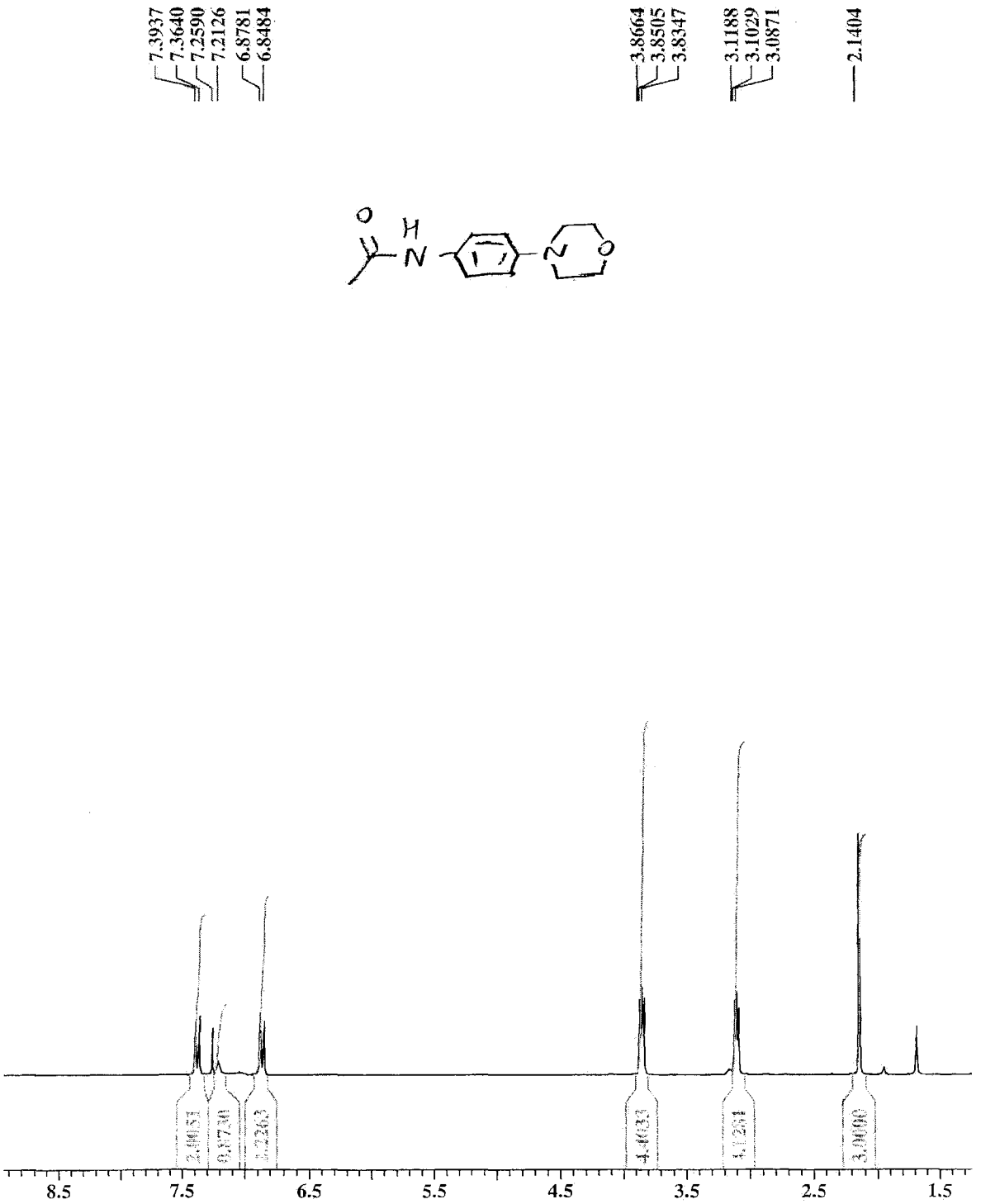
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N
O
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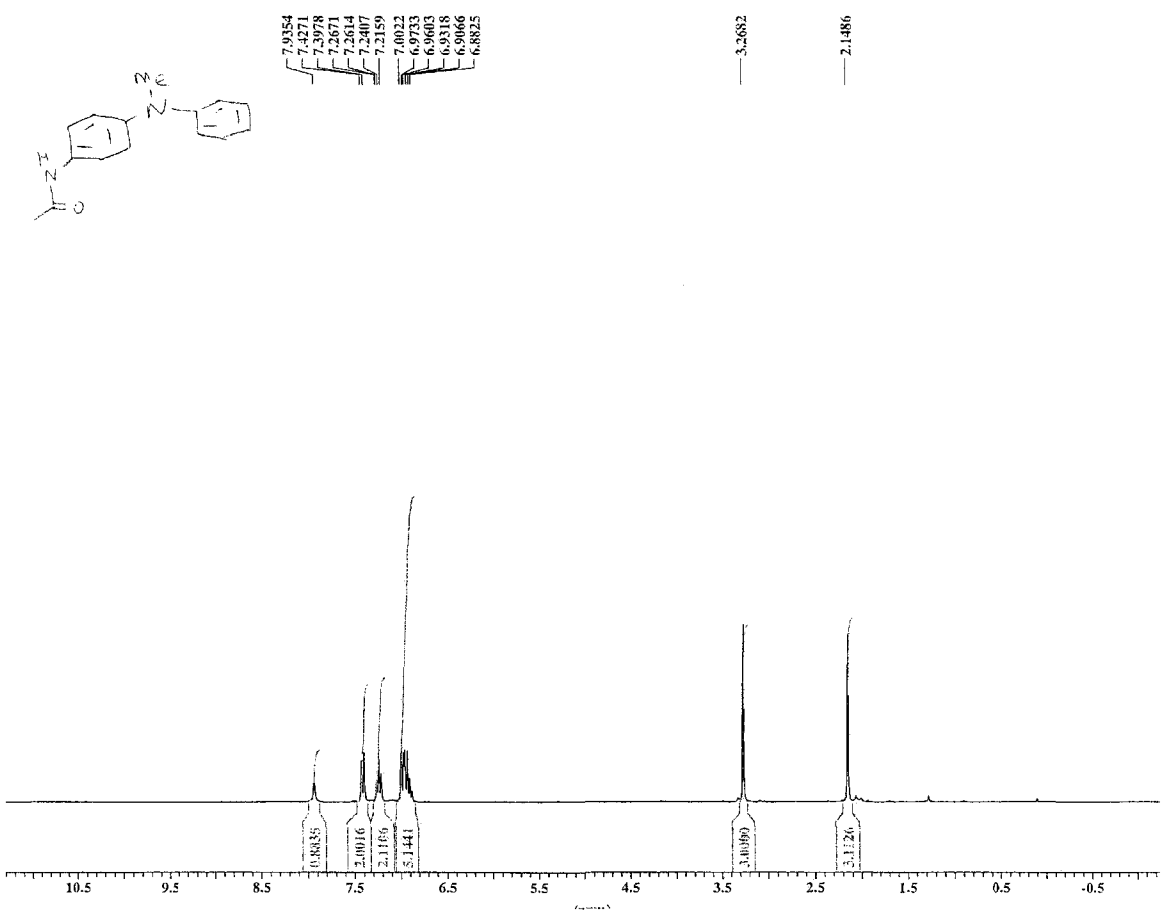
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1.8835
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5.1441
3.0499
3.1126
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
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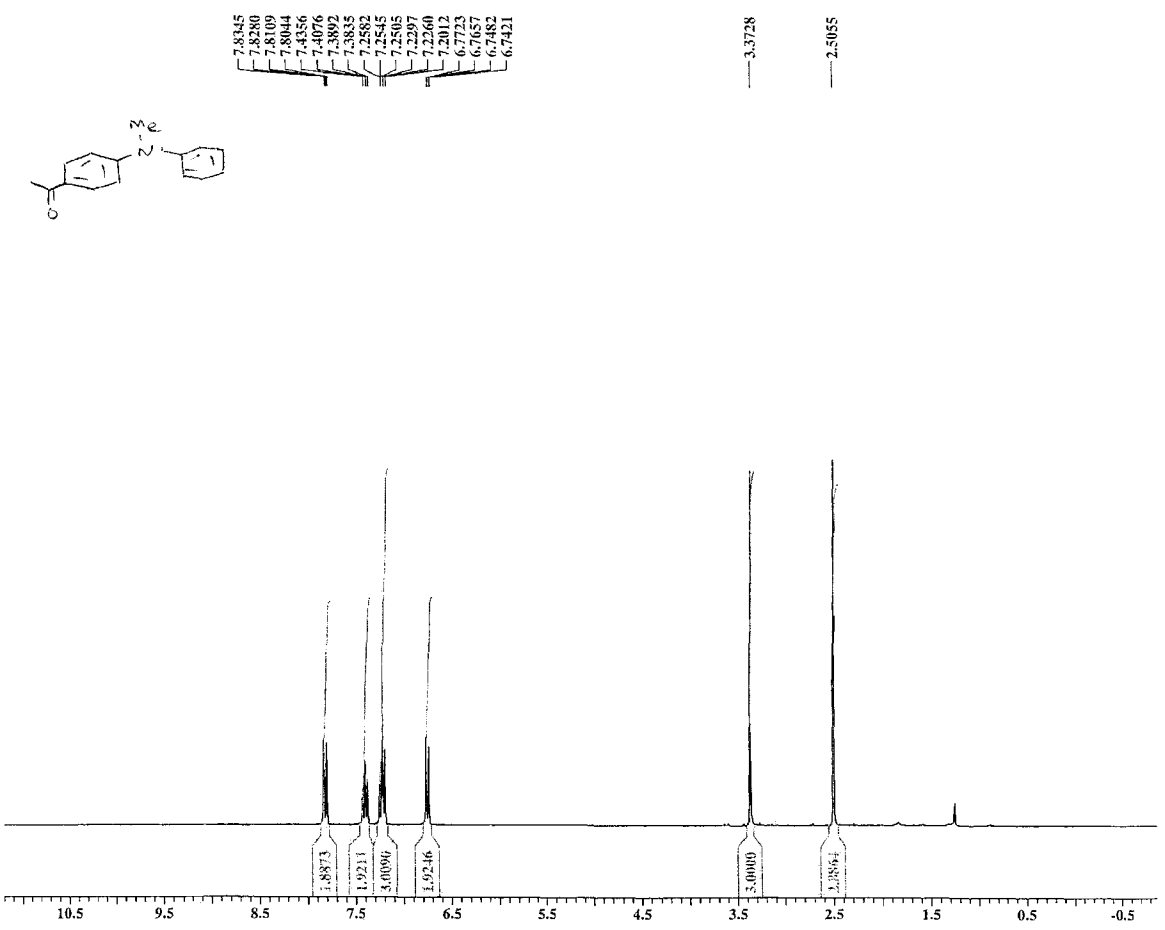
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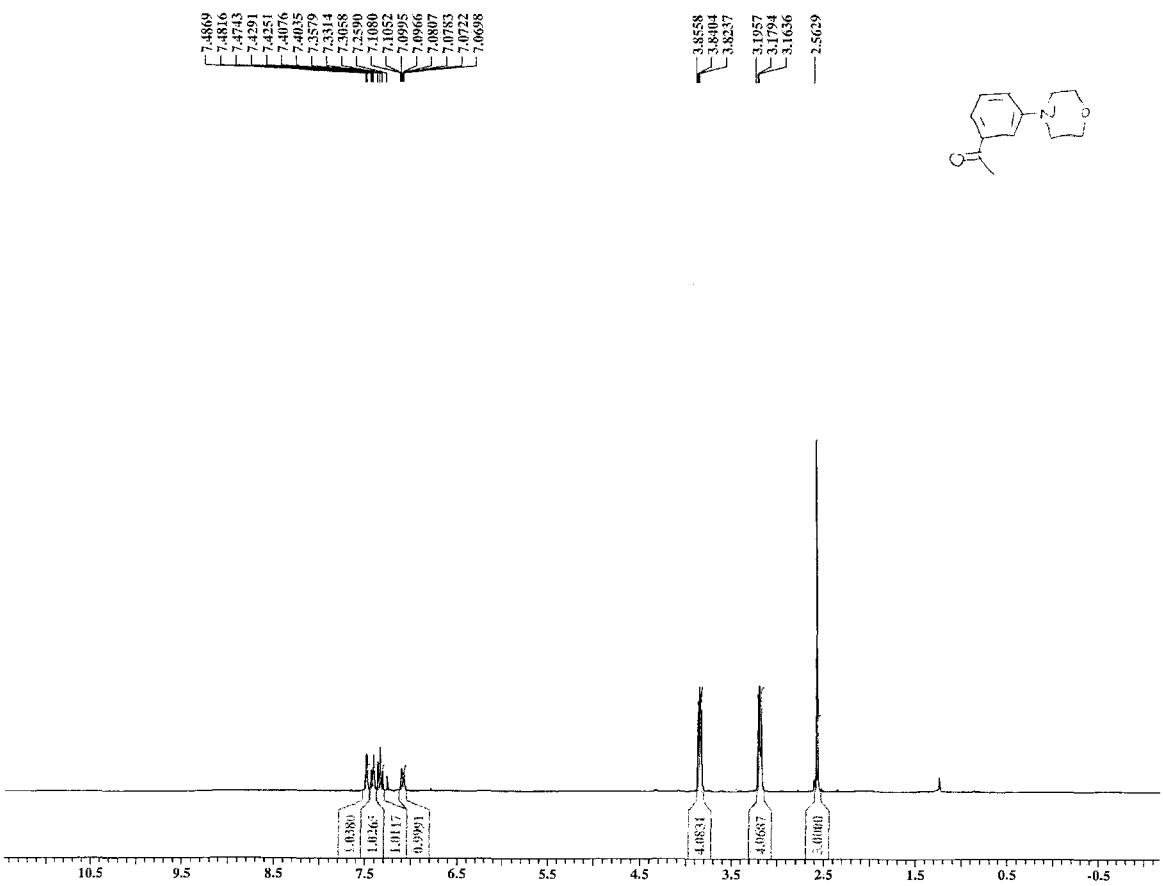
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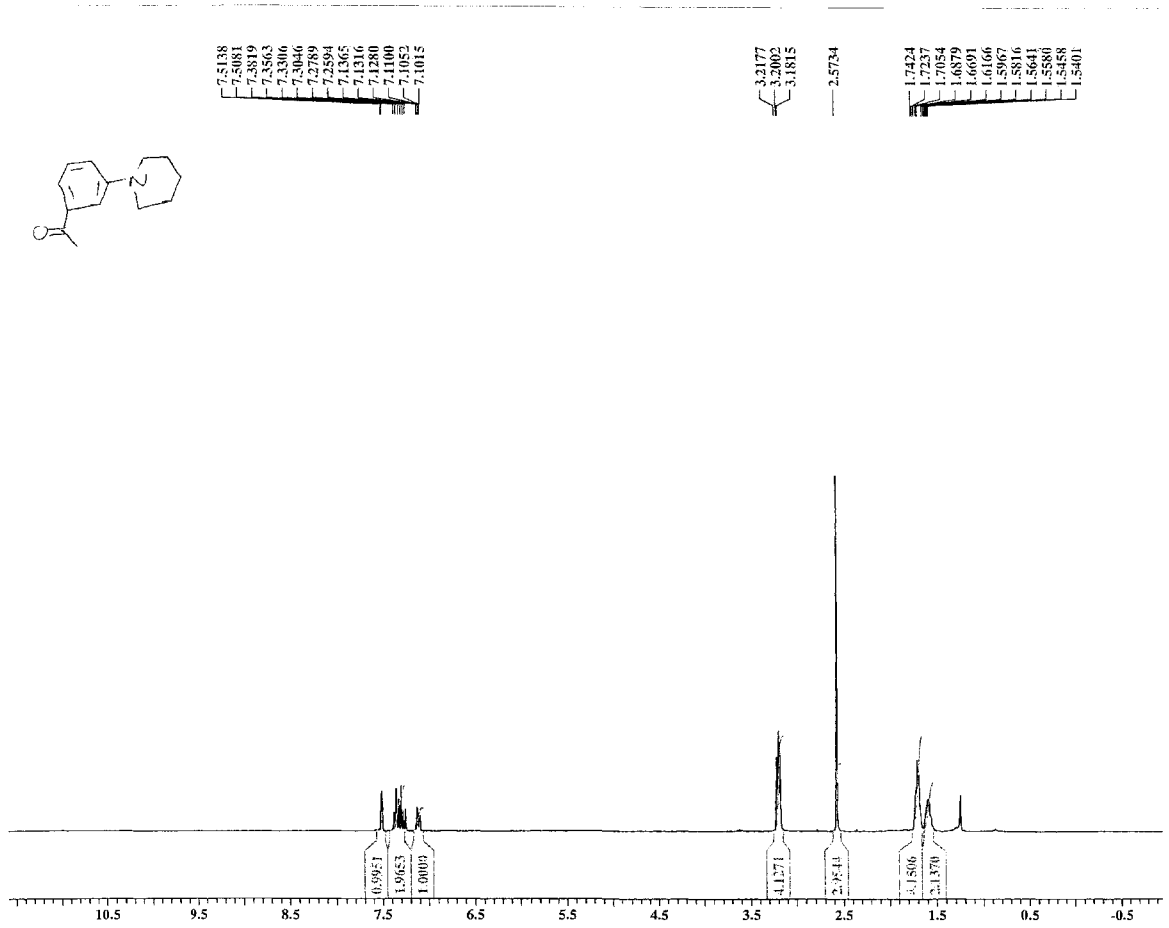
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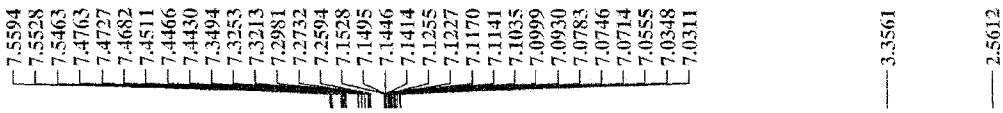
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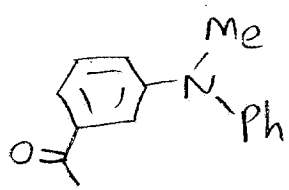
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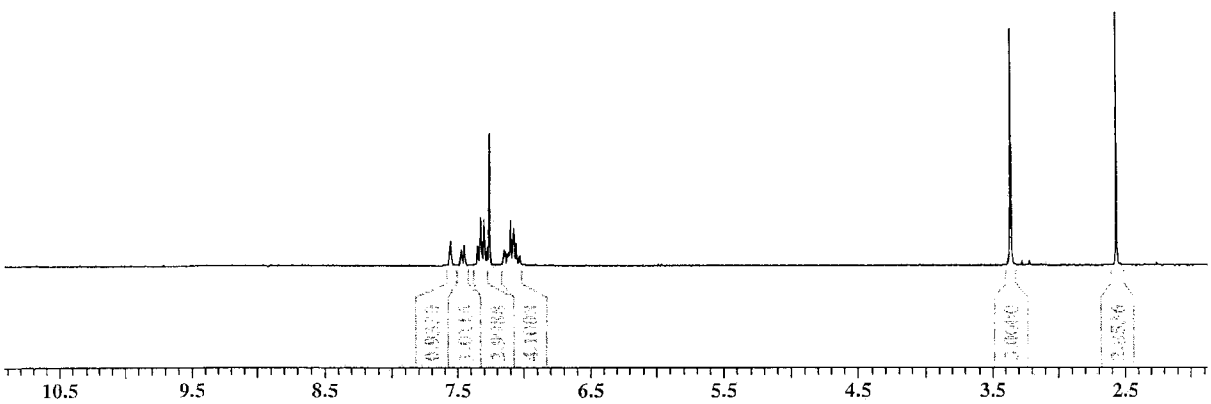
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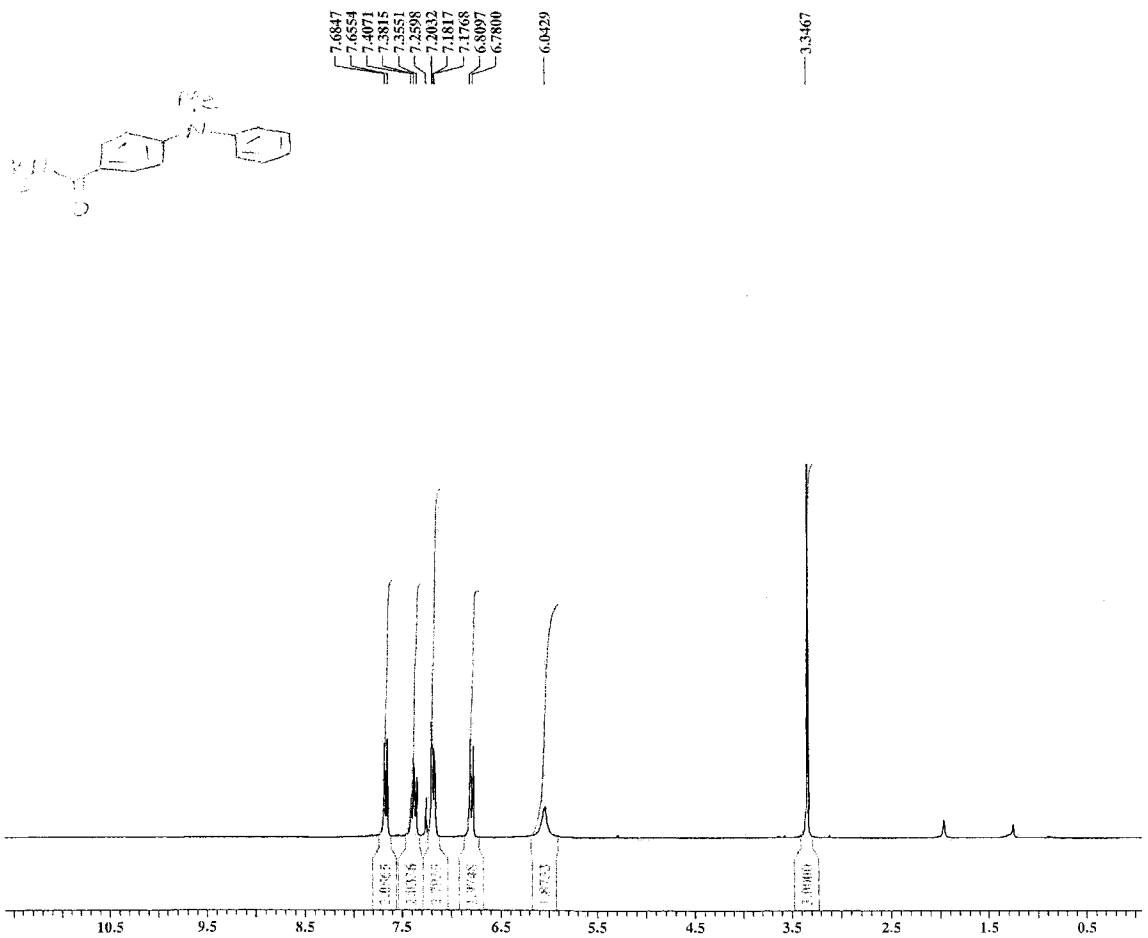
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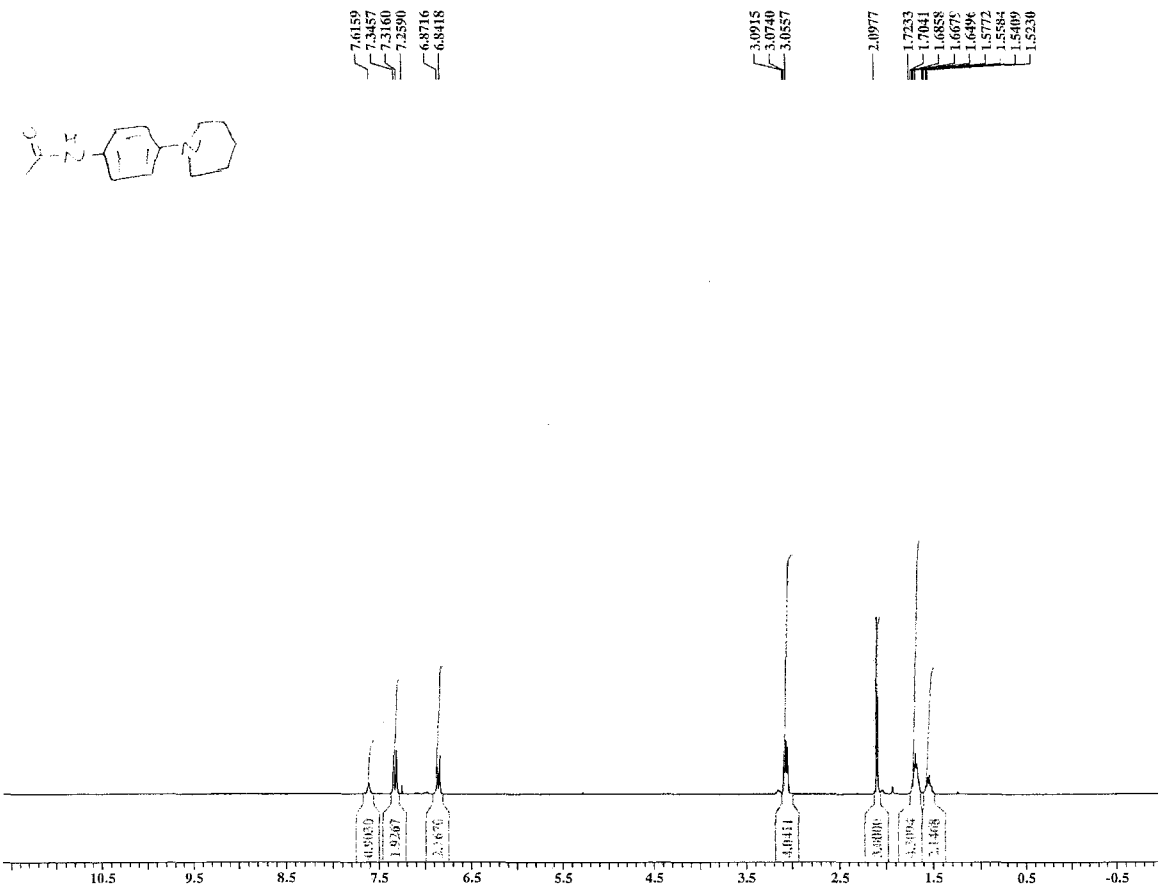
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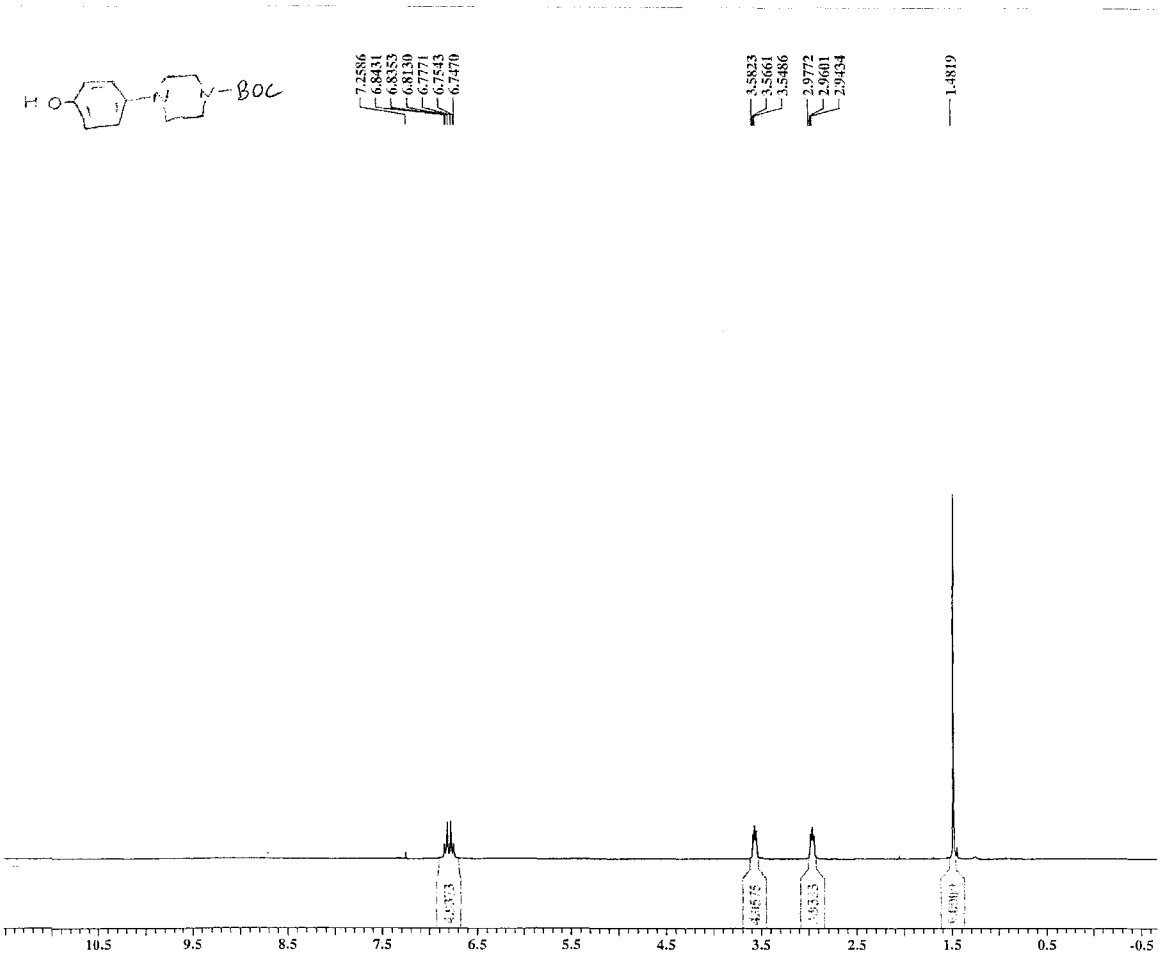
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APPENDIX E

CHAPTER 6

General Considerations

References for known compounds

^{1}H NMR spectra for reaction products

^{13}C NMR spectra for previously unknown reaction products

^{31}P NMR spectra for phosphorus containing previously unknown reaction products

General Considerations

All reactions were performed under an atmosphere of argon in oven-dried glassware. Toluene was collected from a Solvent Purification System and stored over 4 Å molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates and visualized with short wavelength UV light (254 nm). Silica gel 60 (9385, 230-400 mesh) was used for column chromatography. The yields reported are isolated yields and are the average of at least two runs. All commercially available reagents were used as received. For convenience, a stock solution of 3 in toluene (2 mM) was prepared and stored under argon. All compounds described in Tables 1-4 are known in the literature and were characterized by comparing their ^{1}H and ^{13}C NMR or mass spectra to the previously reported data. In all cases, the comparisons were very favorable.

References for known compounds

***N*-Methyl-*N*-(4-cyanophenyl)aniline** (Table 1, entry 1). Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

***N*-(4-*tert*-Butylphenyl)morpholine** (Table 1, entry 2). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N,N*-Dibutyl-4-*tert*-butylaniline** (Table 1, entry 3). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-*tert*-Butylphenyl)diphenylamine** (Table 1, entry 4). Creason, S. C.; Wheeler, J.; Nelson, R. F. *J. Org. Chem.* **1972**, *37*, 4440.

***N*-(4-*tert*-Butylphenyl)-*p*-anisidine** (Table 1, entry 5). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-Methoxyphenyl)morpholine** (Table 1, entry 6). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-(4-Methoxyphenyl)piperidine** (Table 1, entry 7). Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829.

***N,N*-Dibutyl-*p*-anisidine** (Table 1, entry 8). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(4-Methoxyphenyl)diphenylamine** (Table 1, entry 9). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-Methyl-*N*-(4-methoxyphenyl)aniline** (Table 1, entry 10). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(4-Methylphenyl)-*p*-anisidine** (Table 1, entry 11). Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

***N*-(2,6-Dimethylphenyl)-*p*-anisidine** (Table 1, entry 12). Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029.

***N*-(2',4',6'-Trimethylphenyl)-2,6-dimethylaniline** (Table 1, entry 13). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-(2-Pyridyl)morpholine** (Table 1, entry 14). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N,N*-Dibutyl-2-aminopyridine** (Table 1, entry 15). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(2-Pyridyl)diphenylamine** (Table 1, entry 16). Kanemaru, T.; Nagahara, S.; Senoo, A. Eur. Pat. Appl. 449742, 1991; *Chem. Abstr.* **1991**, *116*, 204473.

***N*-Methyl-*N*-(3-pyridyl)aniline** (Table 1, entry 17). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N*-(4-Nitrophenyl)morpholine** (Table 2, entry 1). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-Methyl-*N*-(4-nitrophenyl)aniline** (Table 2, entry 2). Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.

***N*-(3-Carbomethoxy)morpholine** (Table 2, entry 3). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(3-Carbomethoxy)pyrrolidine** (Table 2, entry 4). Semple, G.; Ryder, H.; Rooker, D. P.; Batt, A. R.; Kendrick, D. A.; Szelke, M.; Ohta, M.; Satoh, M.; Nishida, A.; Akuzawa, S.; Miyata, K. *J. Med. Chem.* **1997**, *40*, 331.

***N*-(4-Carbomethoxy)morpholine** (Table 2, entry 5). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-*tert*-Butylphenyl)-*m*-nitroaniline** (Table 2, entry 6). Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett.* **1998**, *39*, 7979.

***N*-(4-Cyanophenyl)morpholine** (Table 3, entry 1). Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

***N*-(4-Cyanophenyl)-*p*-toluidine** (Table 3, entry 3). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-Nitrophenyl)-*p*-anisidine** (Table 3, entry 4). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-Nitrophenyl)diphenylamine** (Table 3, entry 5). Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791.

***N*-Methyl-*N*-(4-carbomethoxyphenyl)aniline** (Table 3, entry 8). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(3-Carbomethoxy)piperidine** (Table 3, entry 10). Semple, G.; Ryder, H.; Rooker, D. P.; Batt, A. R.; Kendrick, D. A.; Szelke, M.; Ohta, M.; Satoh, M.; Nishida, A.; Akuzawa, S.; Miyata, K. *J. Med. Chem.* **1997**, *40*, 331.

***N*-Methyl-*N*-(3-carbomethoxyphenyl)aniline** (Table 3, entry 11). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-(4-Methylphenyl)morpholine** (Table 3, entry 13). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-(3-Methoxyphenyl)morpholine** (Table 3, entry 15). Kataoka, N.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

***N*-(3-Methoxyphenyl)piperidine** (Table 3, entry 16). Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029.

***N*-(3-Methoxyphenyl)-*p*-toluidine** (Table 3, entry 17). Beard, R. L.; Teng, M.; Colon, D. F.; Duong, T. T.; Chandraratna, R. A. U.S. Patent 5739338, 1998; *Chem. Abstr.* **1998**, 128, 282789.

***N*-(4-Pyridyl)morpholine** (Table 3, entry 19). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-Methyl-*N*-(4-pyridyl)aniline** (Table 3, entry 20). Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

***N*-Methyl-*N*-(4-chlorophenyl)aniline** (Table 4, entry 1). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-Methyl-*N*-(4-carboethoxyphenyl)aniline** (Table 4, entry 2). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

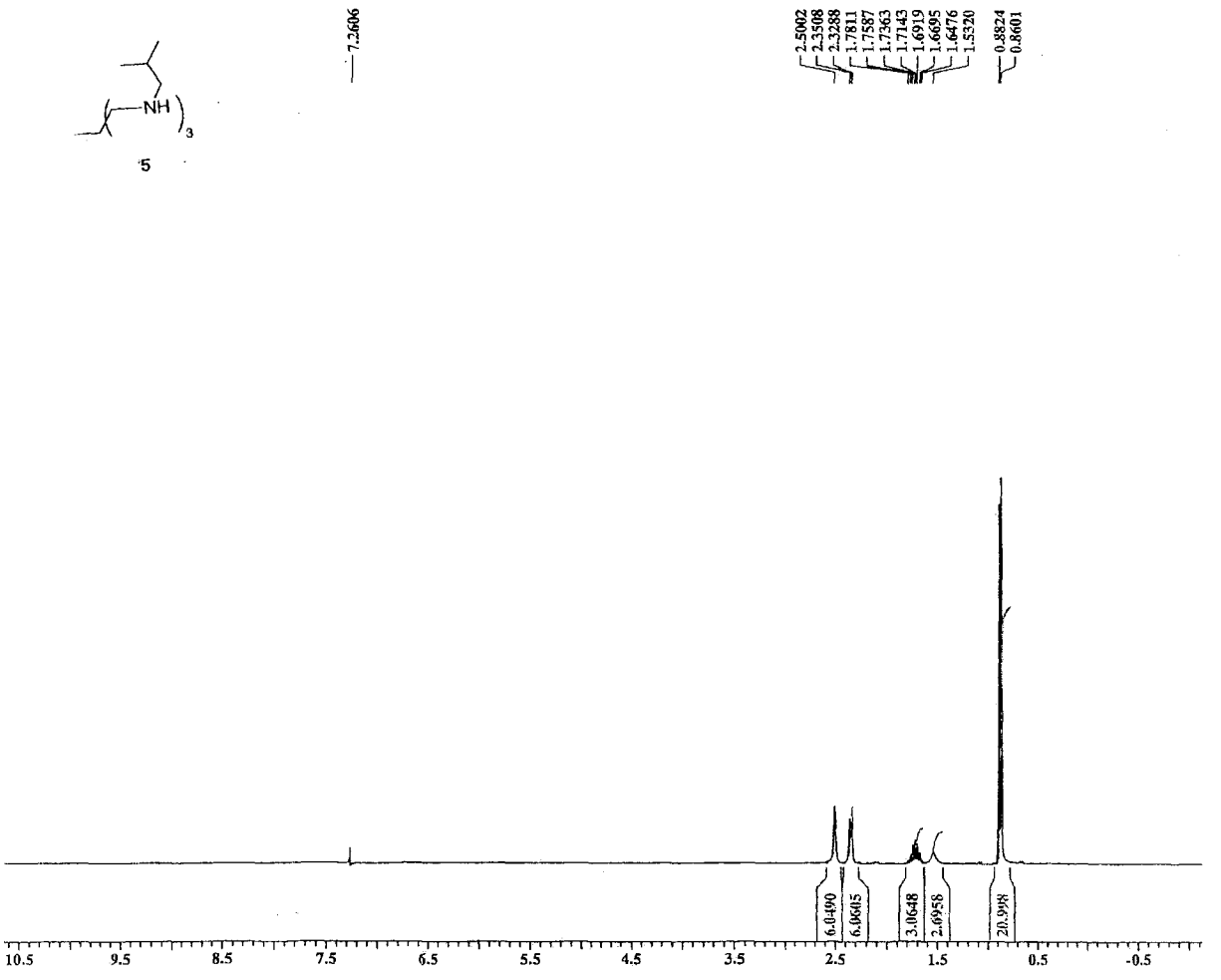
***N*-(4-Carboethoxy)morpholine** (Table 4, entry 3). Belfield, A. J.; Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron* **1999**, *55*, 13285.

***N,N*-Dibutyl-4-carboethoxyaniline** (Table 4, entry 4). Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.

***N*-(4-Methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane** (Table 4, entry 6). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-(4-Methylphenyl)-2',6'-Dimethylaniline** (Table 4, entry 7). Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

***N,N*-Dibutyl-*p*-toluidine** (Table 4, entry 8). Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.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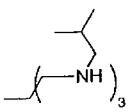
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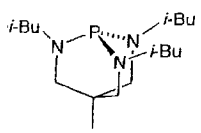
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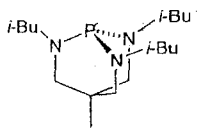
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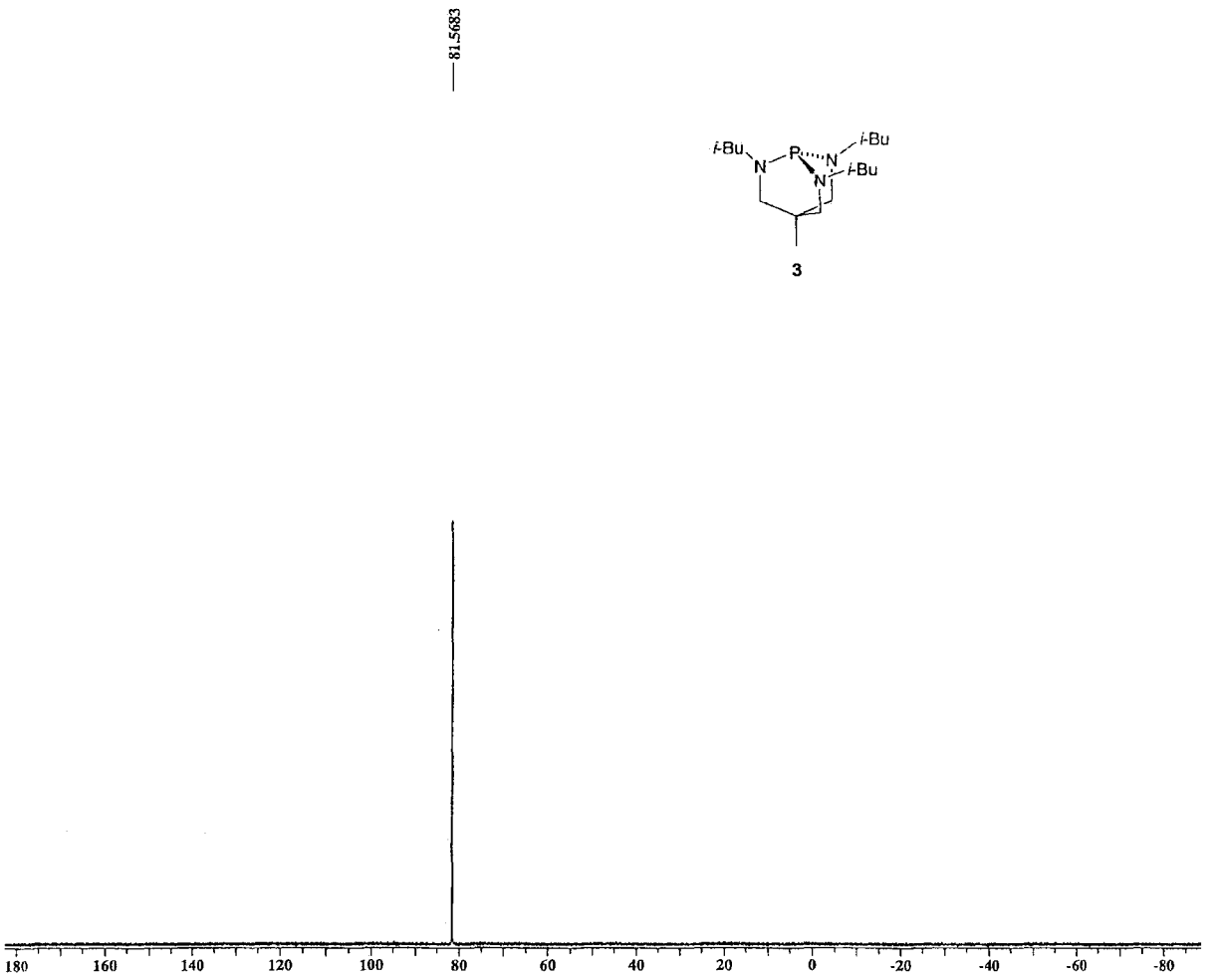
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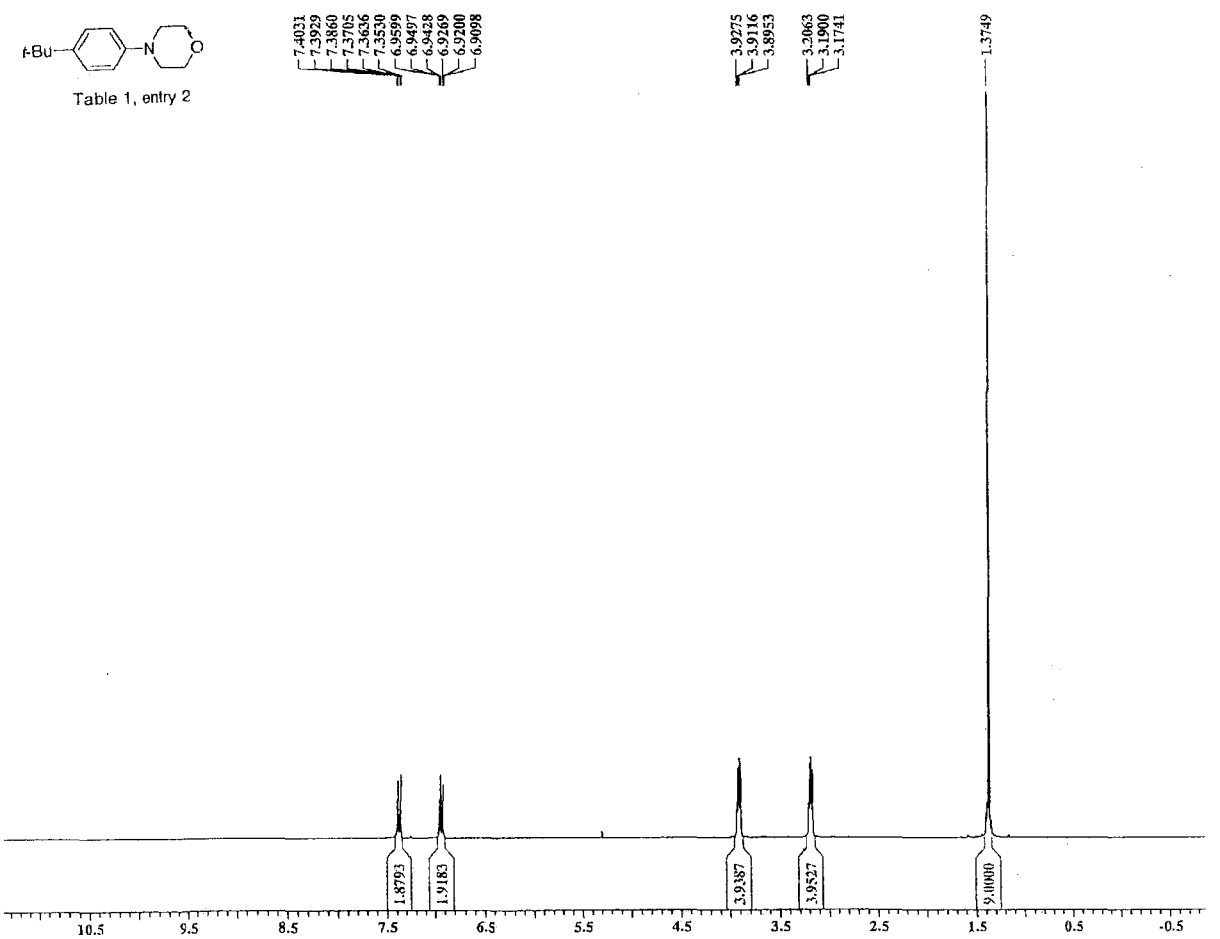
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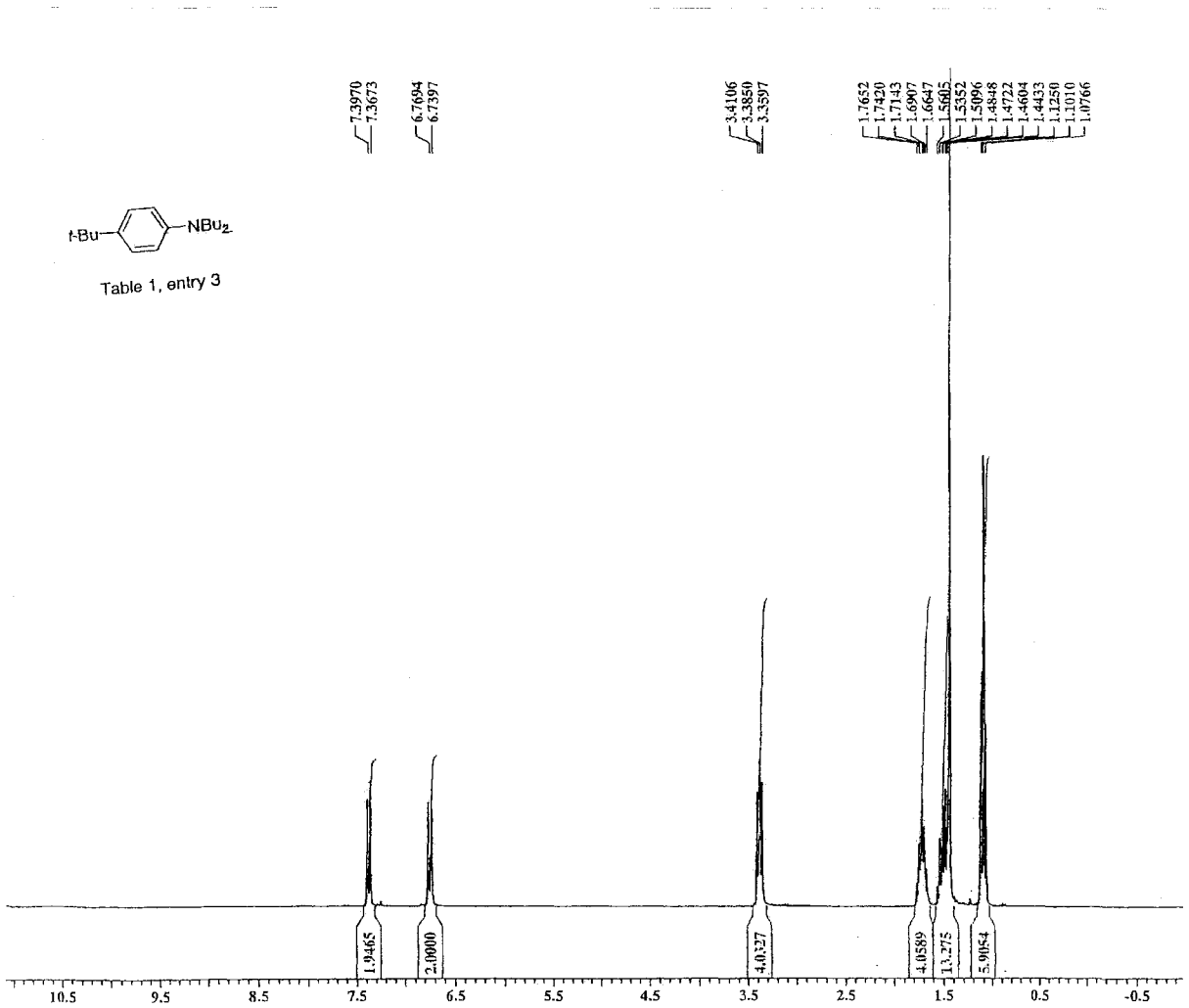
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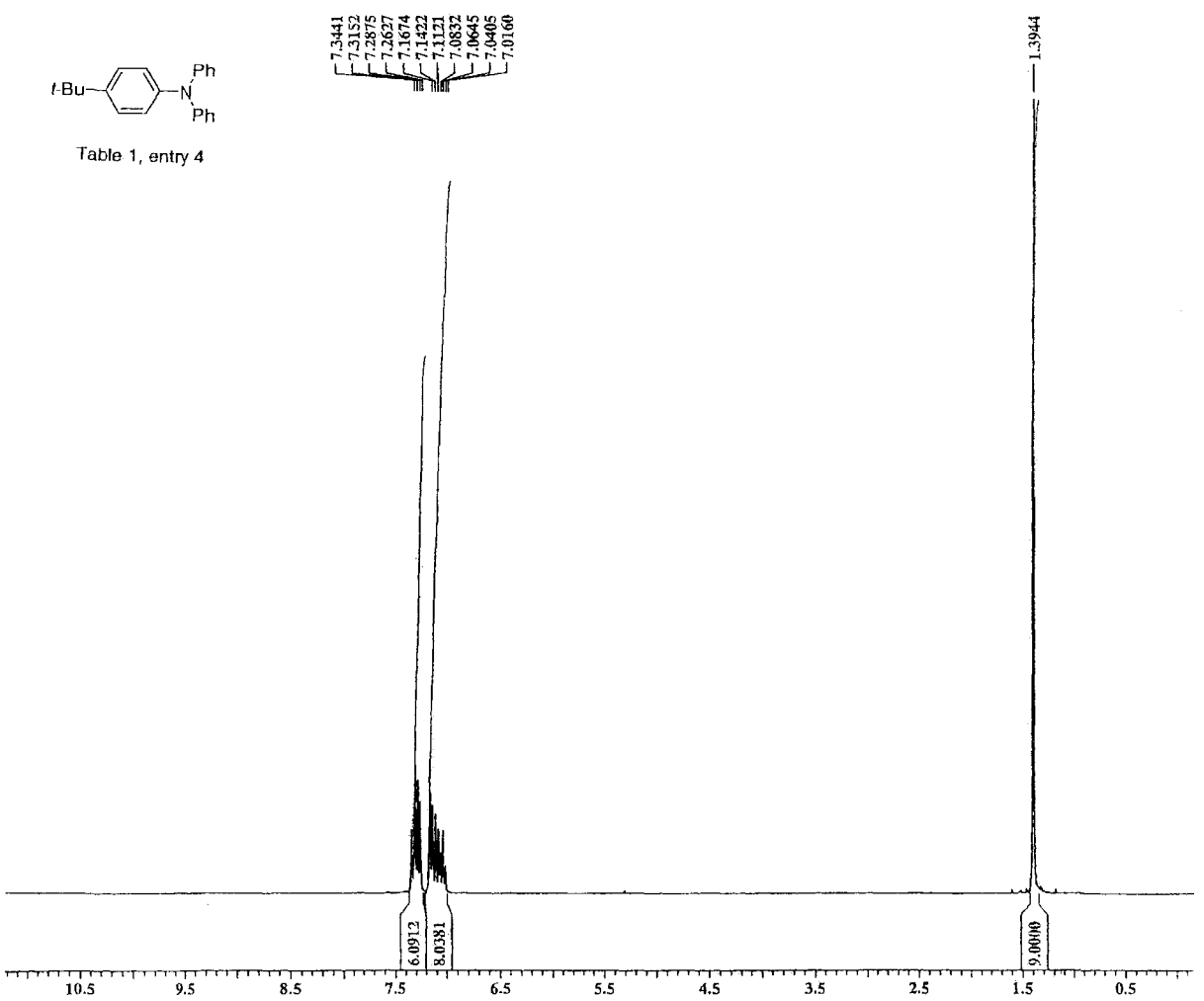
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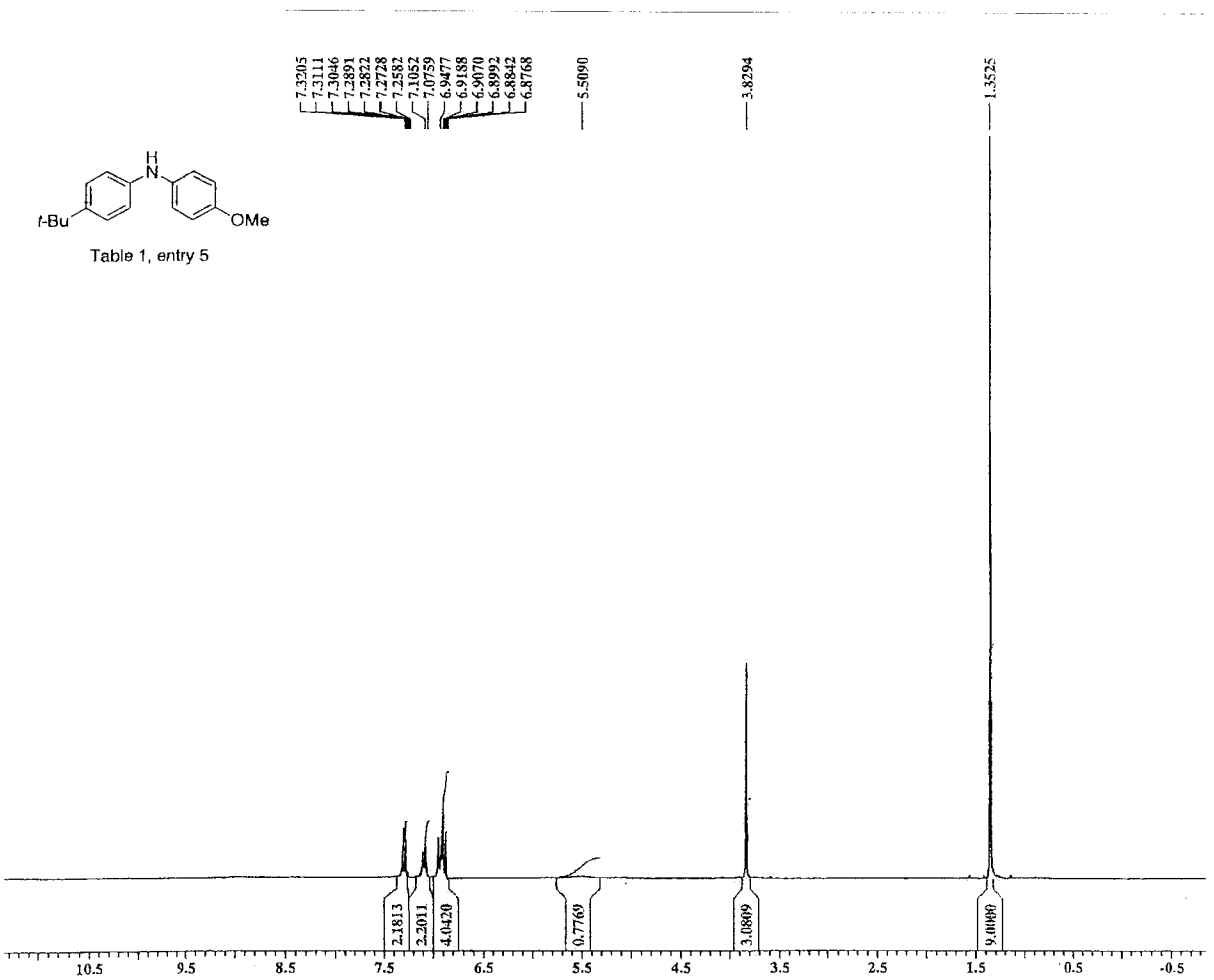
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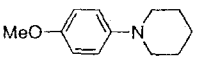

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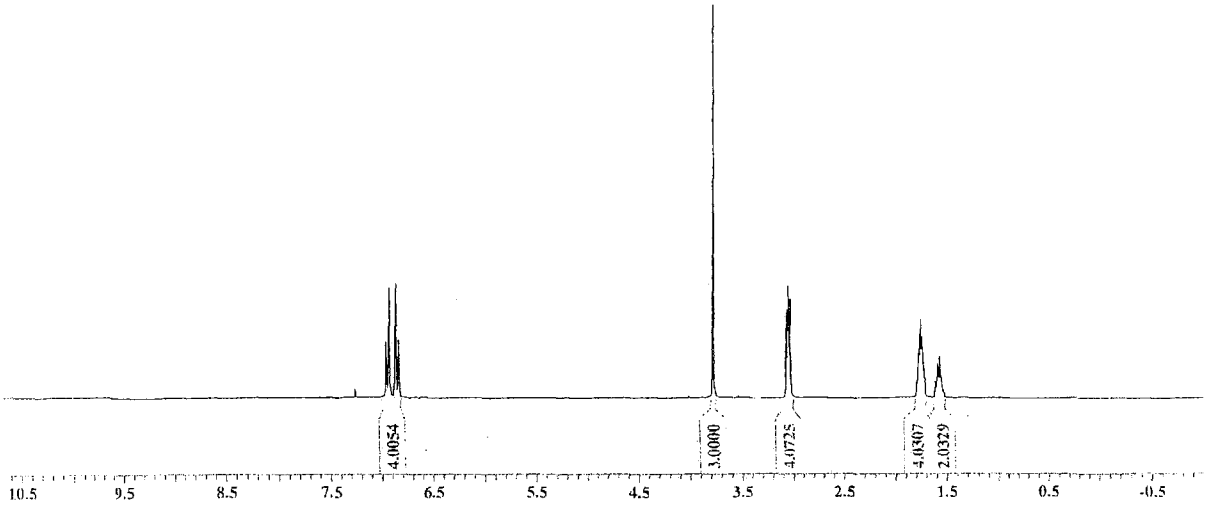

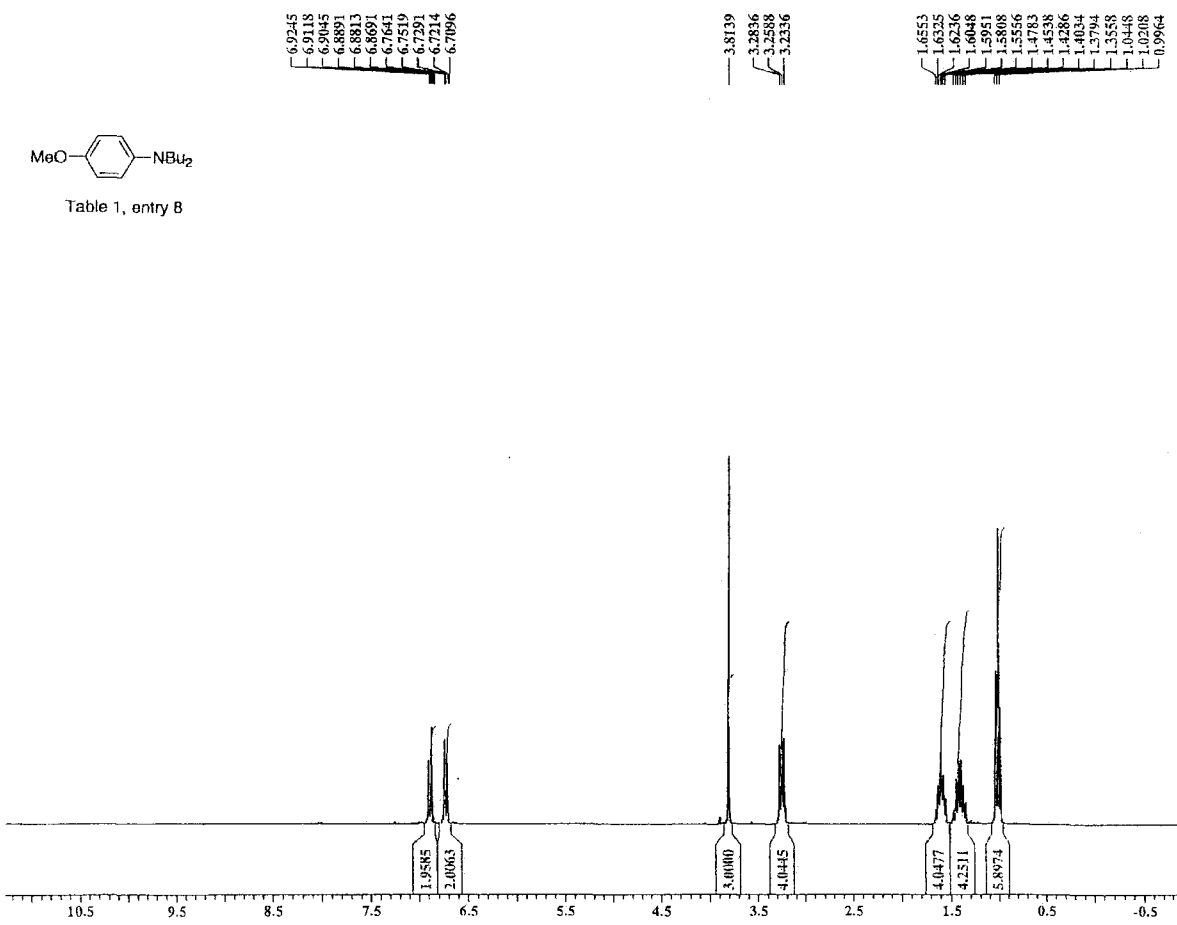

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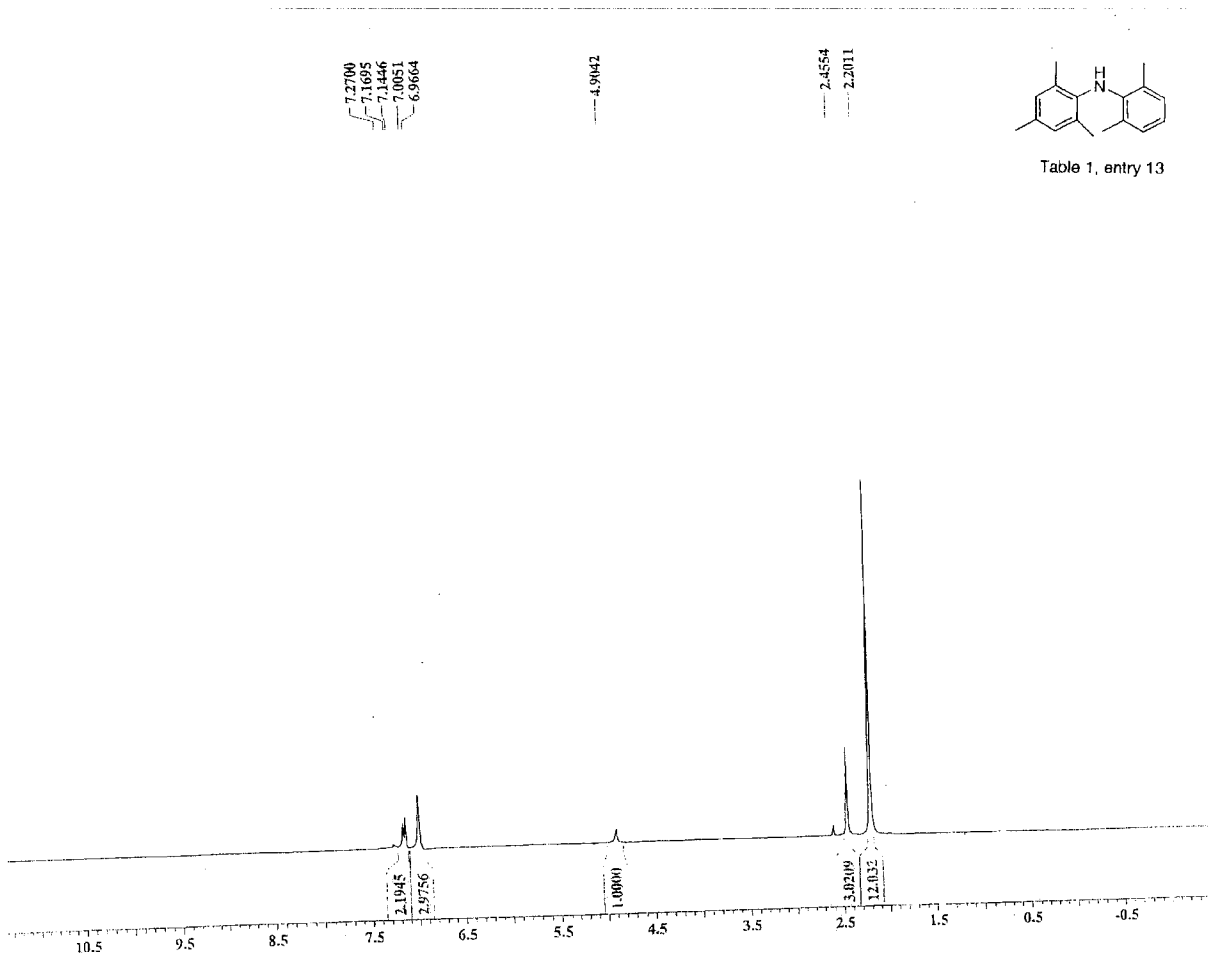

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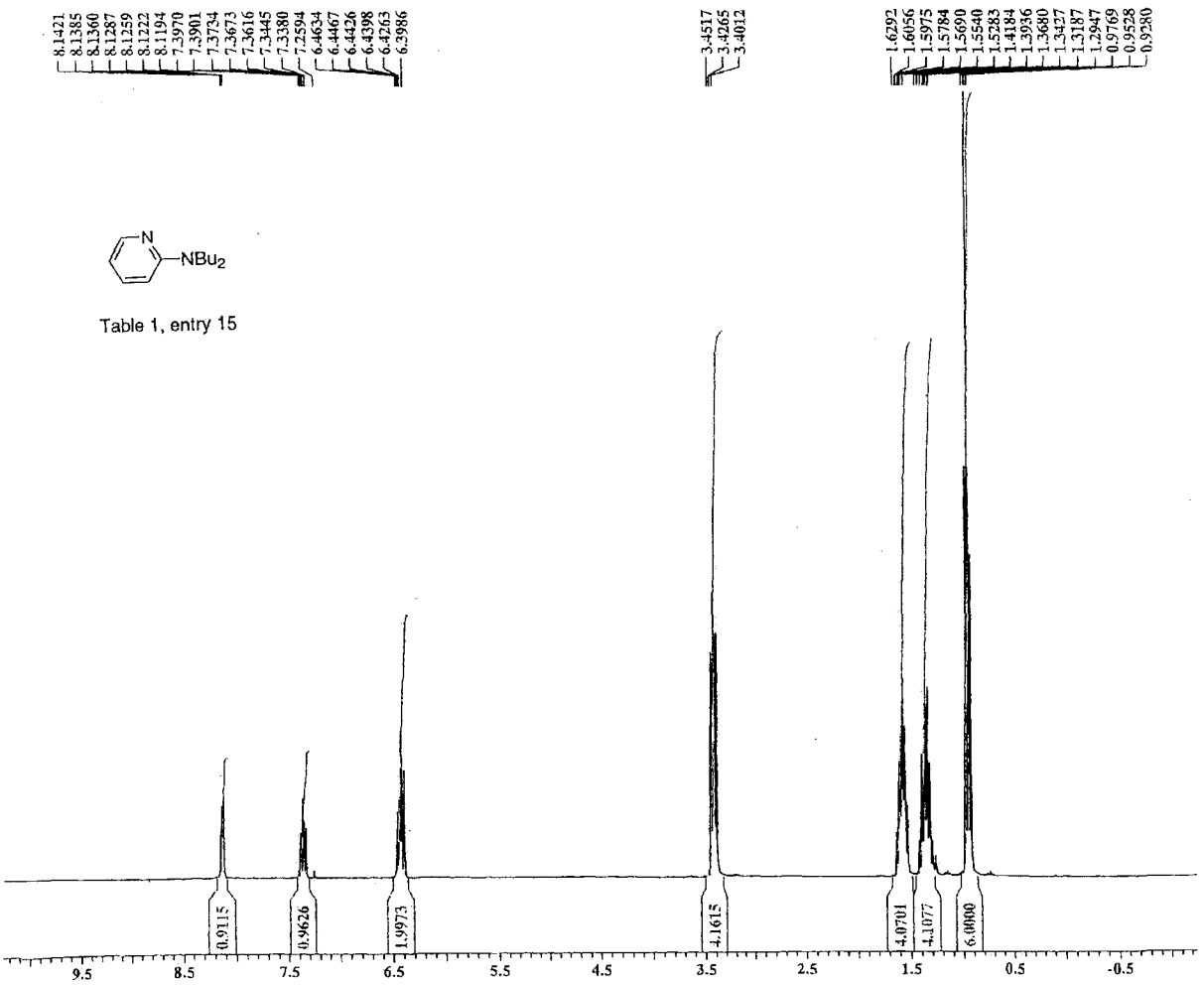
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NBu2
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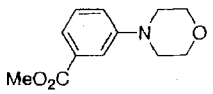

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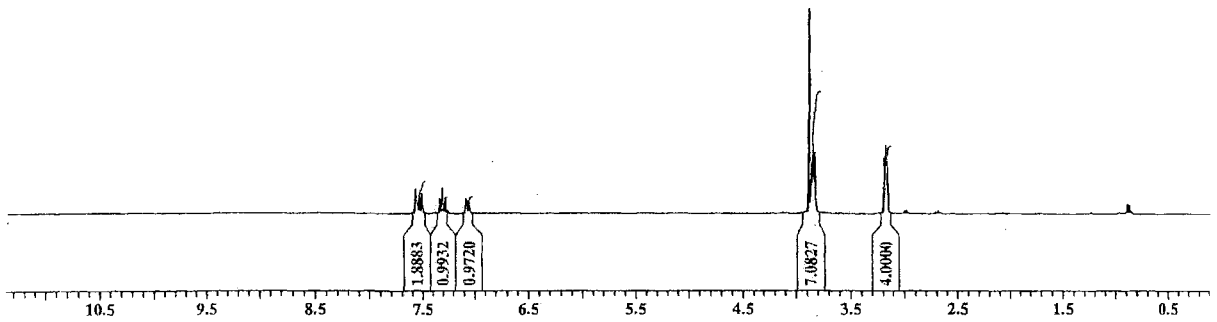

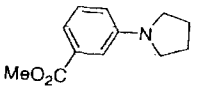

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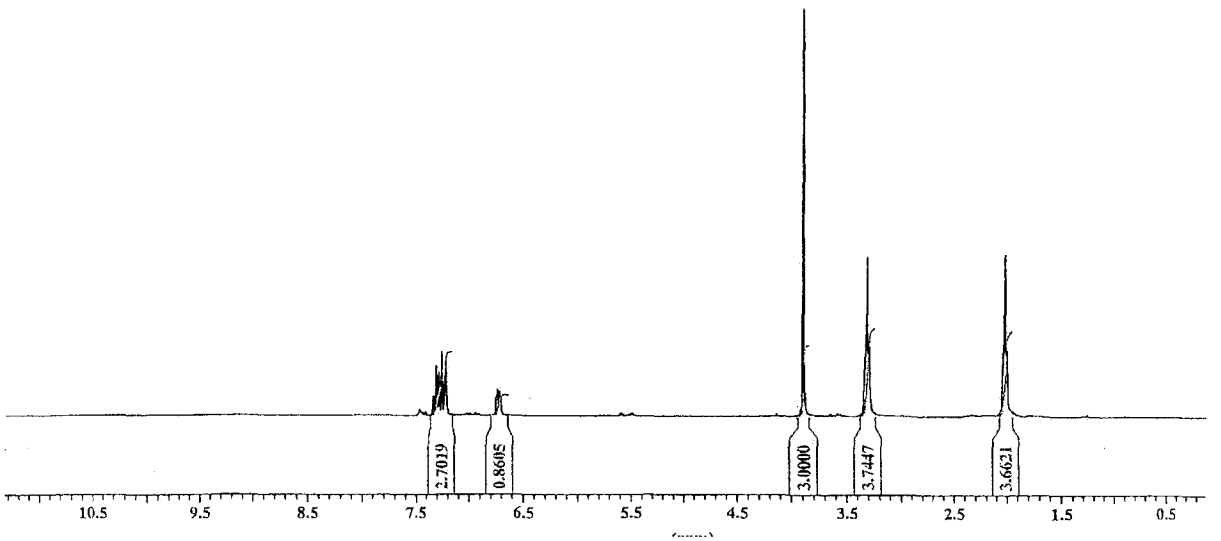

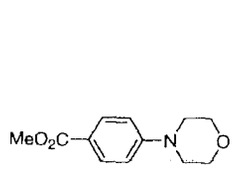

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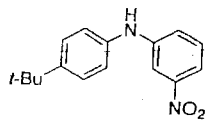

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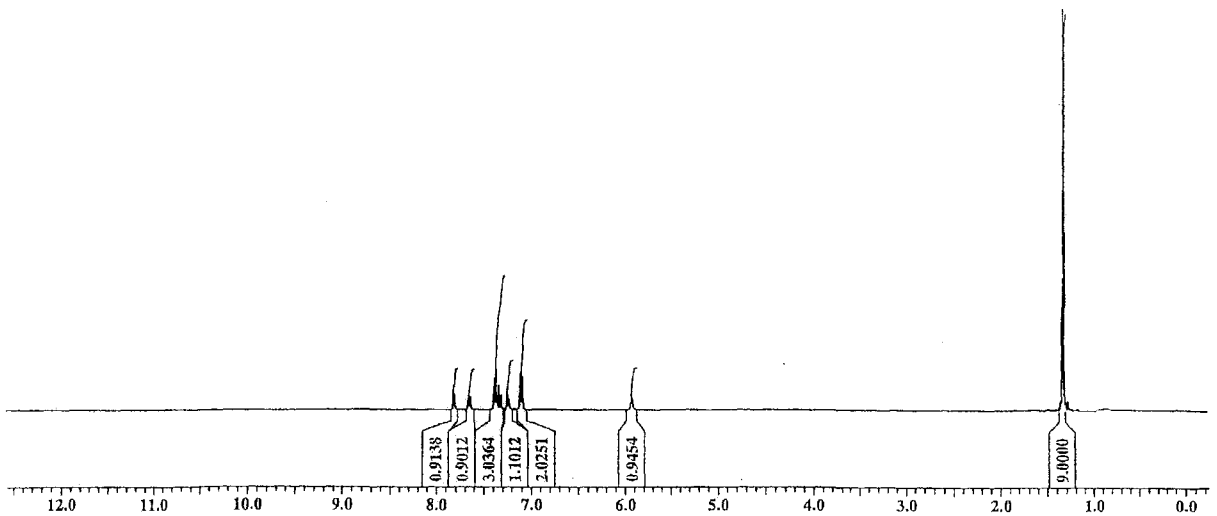

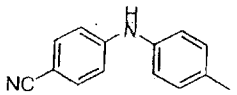

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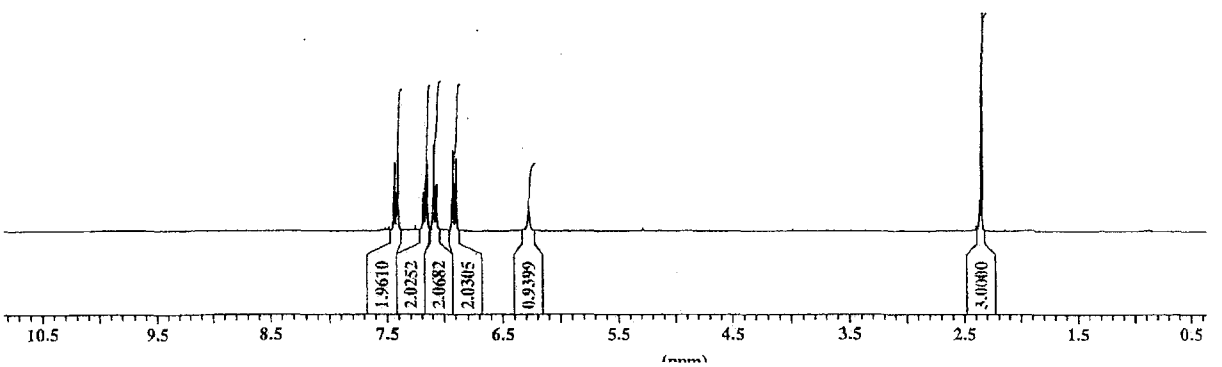

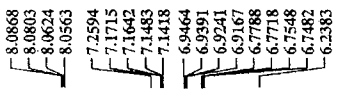

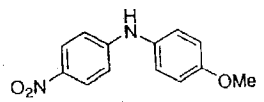

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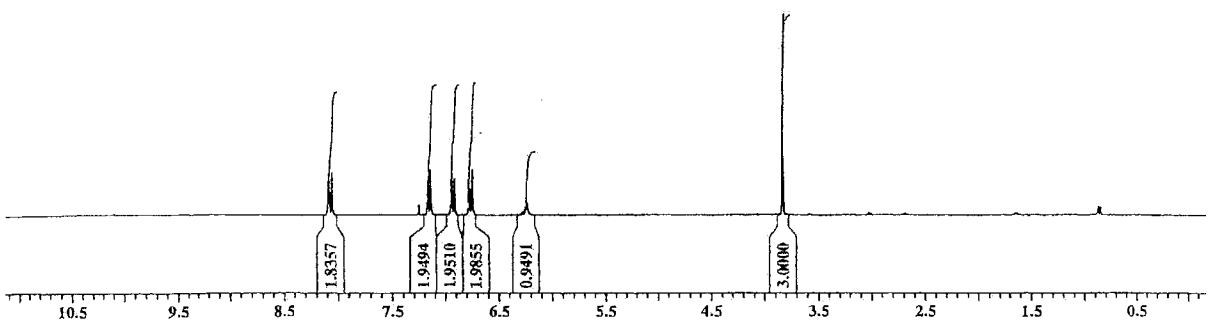

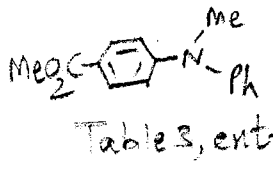

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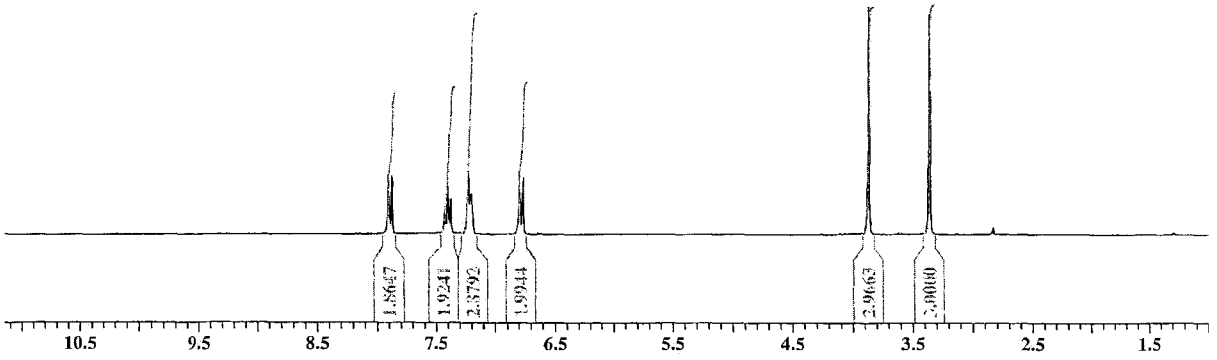

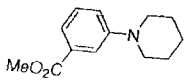

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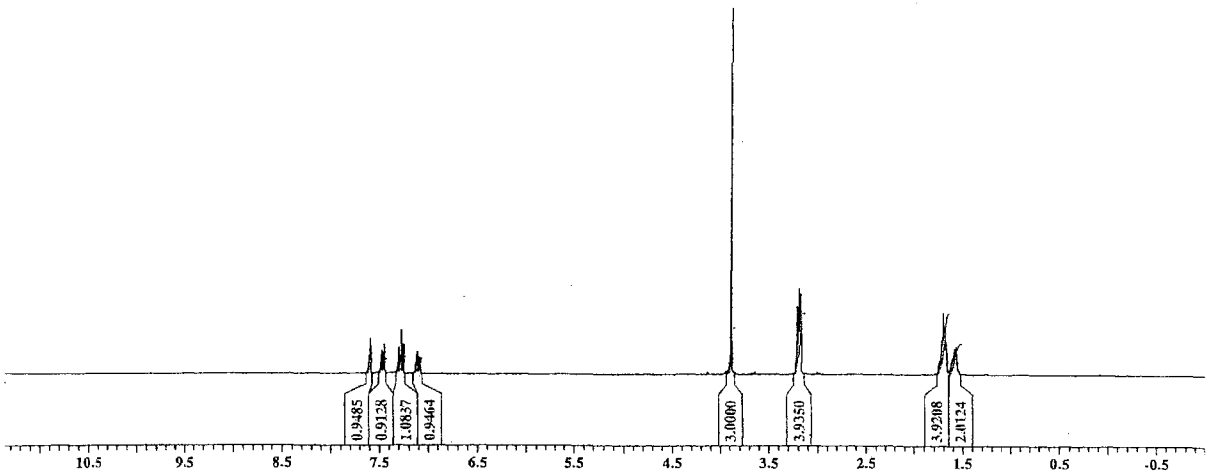

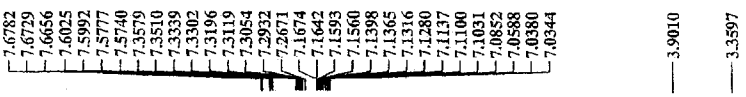

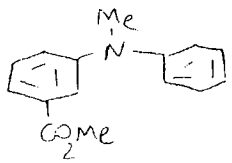

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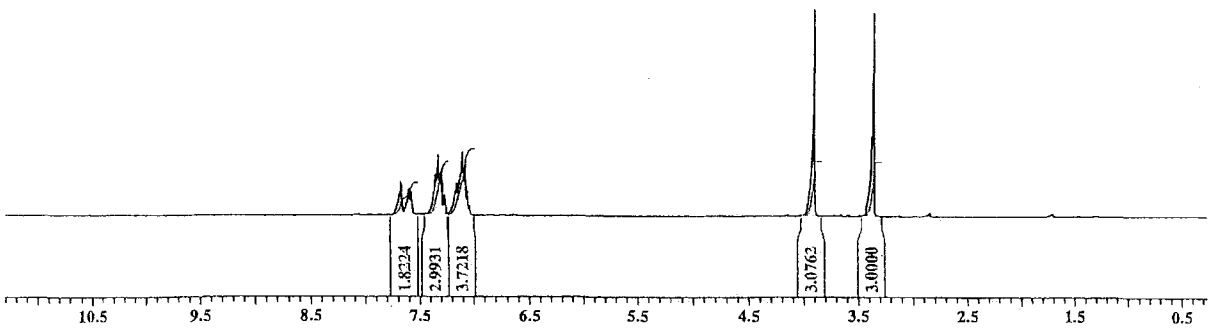

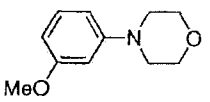

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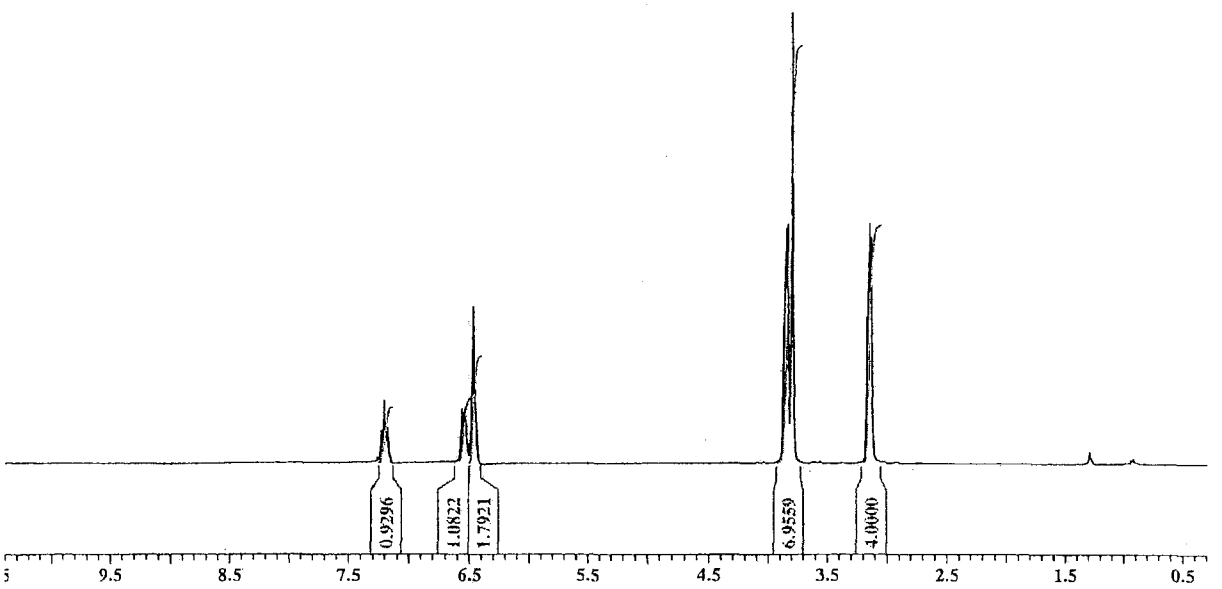

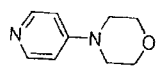

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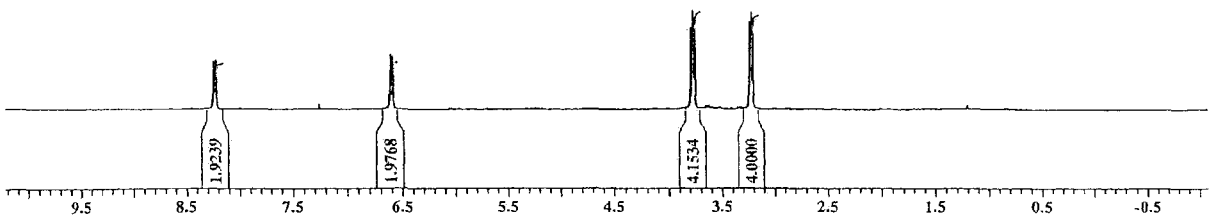

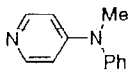

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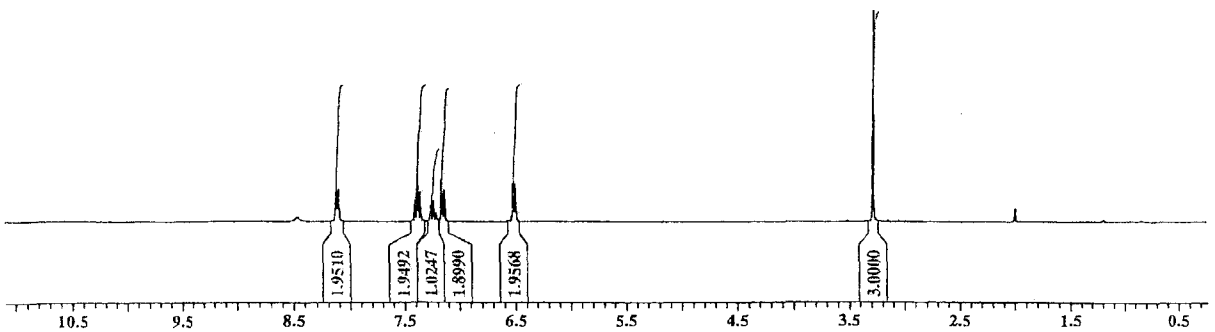

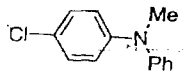

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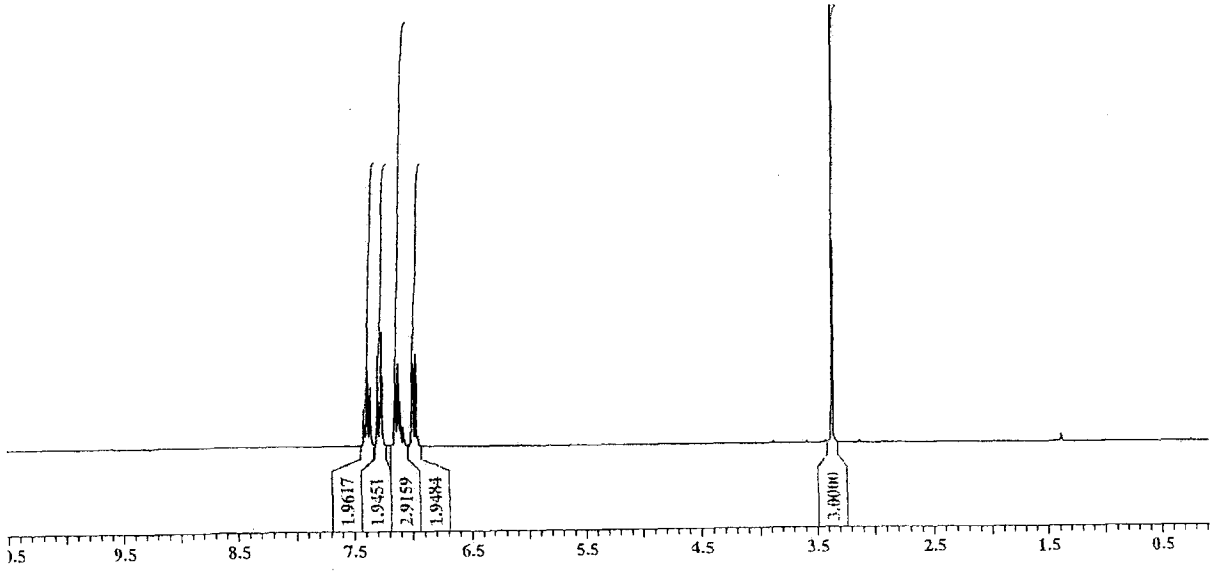

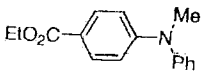

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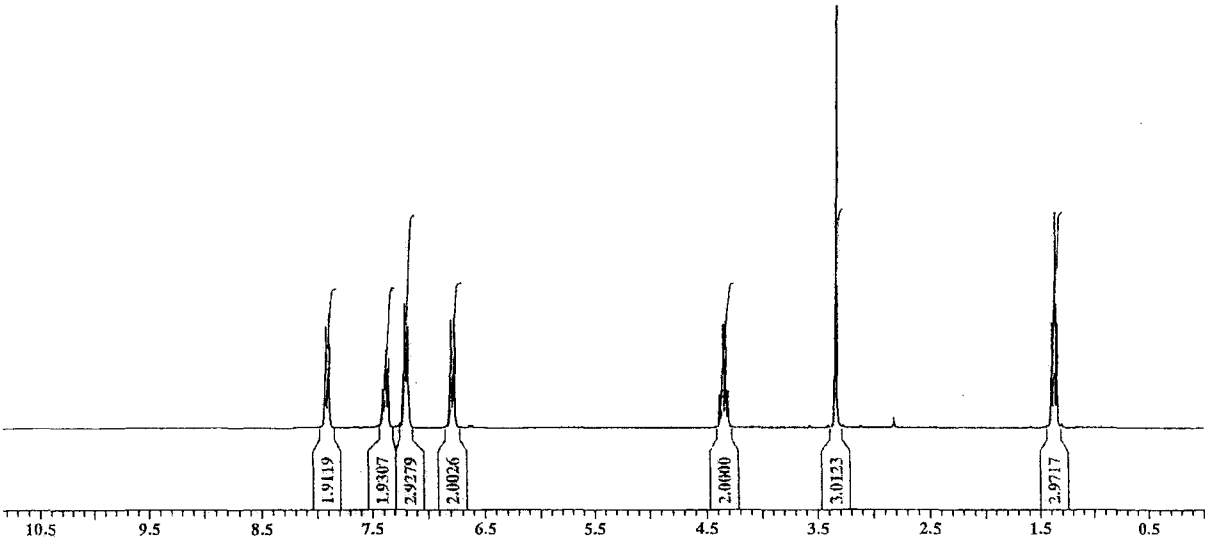

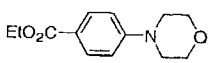

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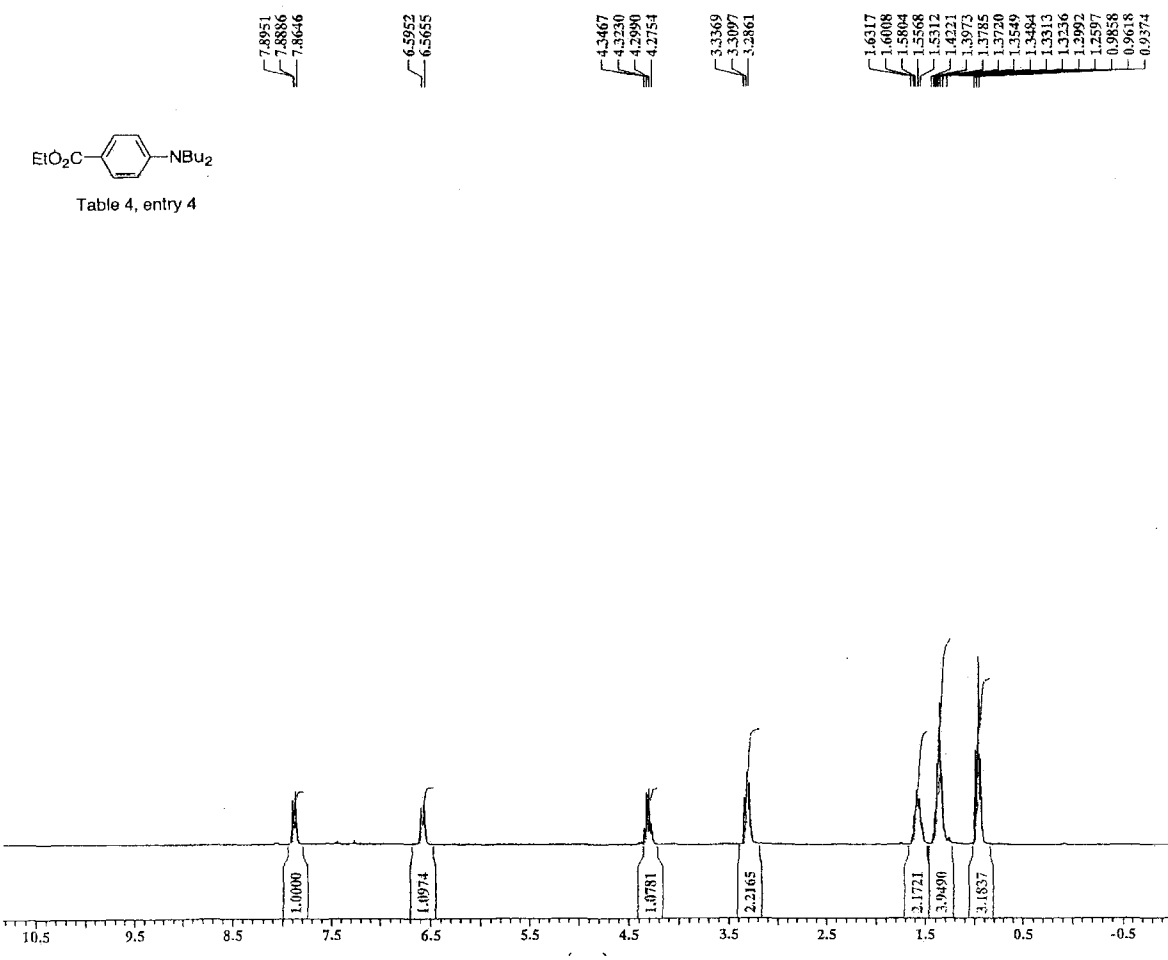

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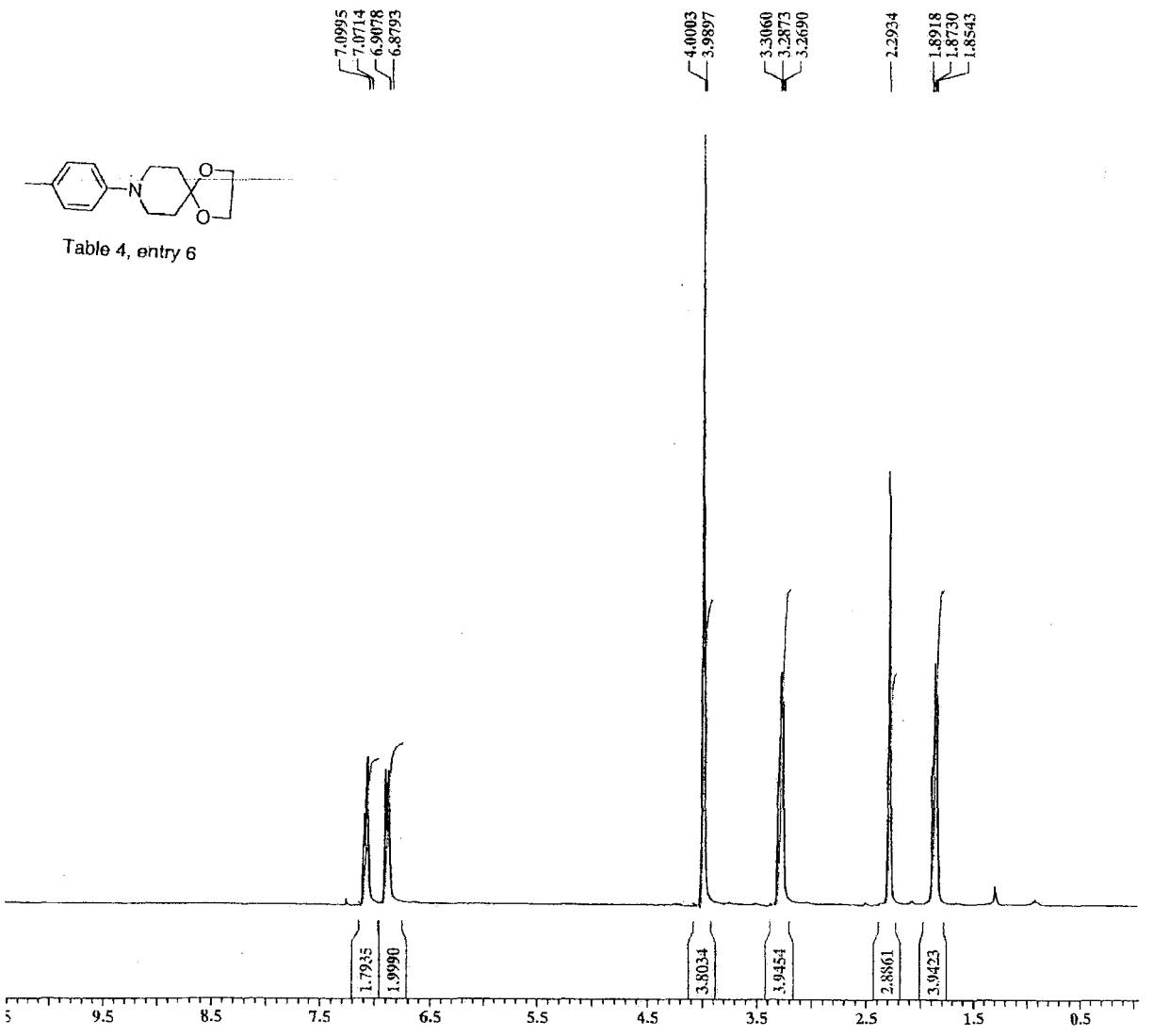


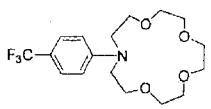
Table 4, entry 6

APPENDIX F

CHAPTER 7

^{1}H NMR spectra for reaction products

^{13}C NMR spectra for previously unknown reaction products



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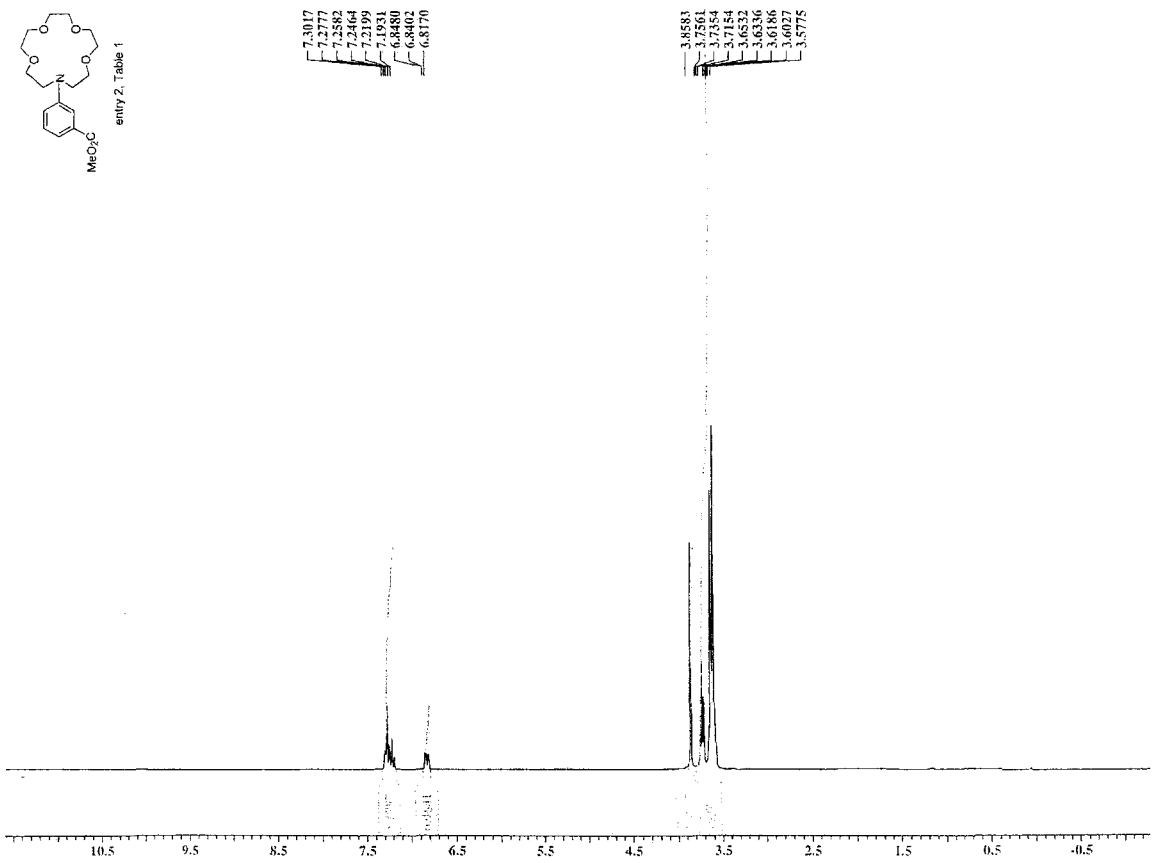
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6.8402
6.8170
3.8583
3.7561
3.7354
3.7154
3.6532
3.6336
3.6186
3.6027
3.5775
10.5
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-0.5

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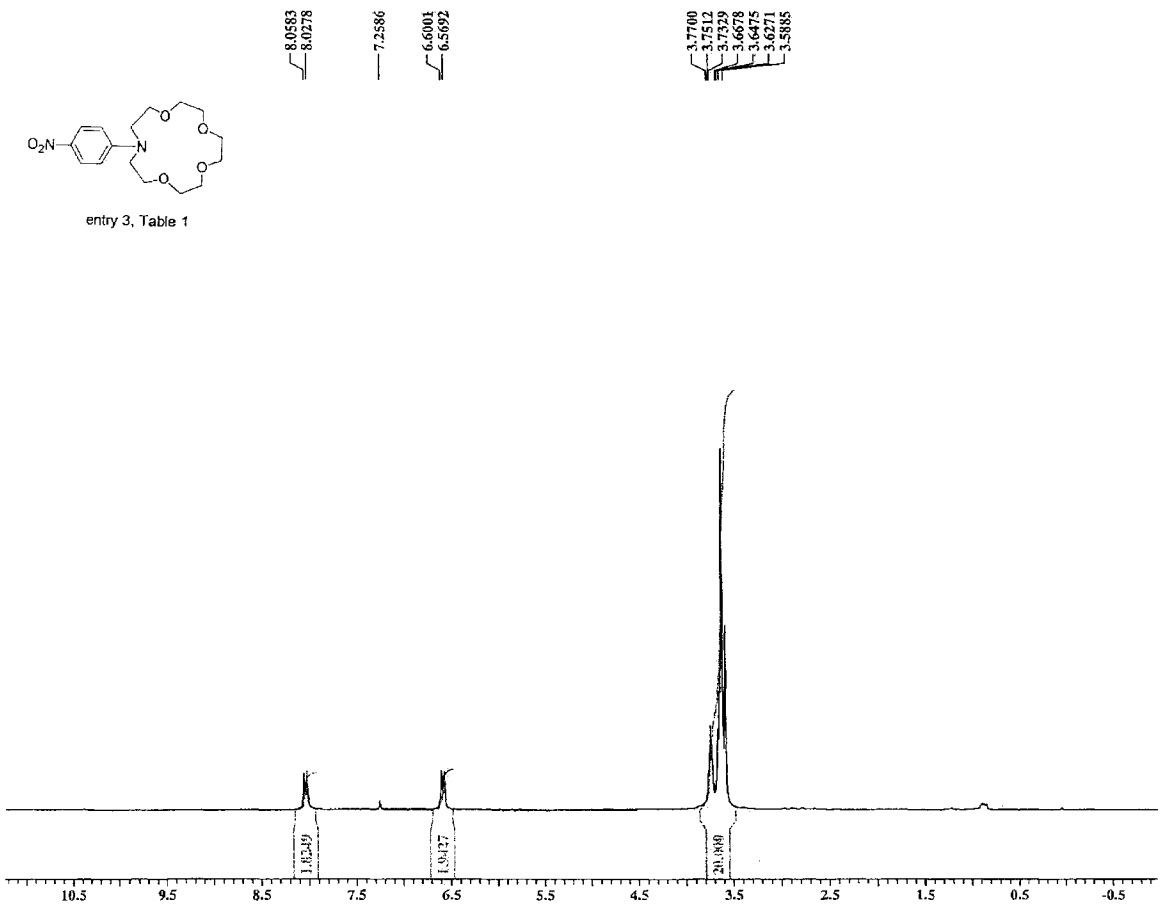

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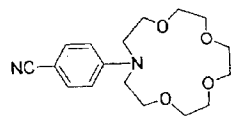
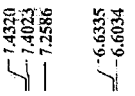
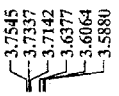
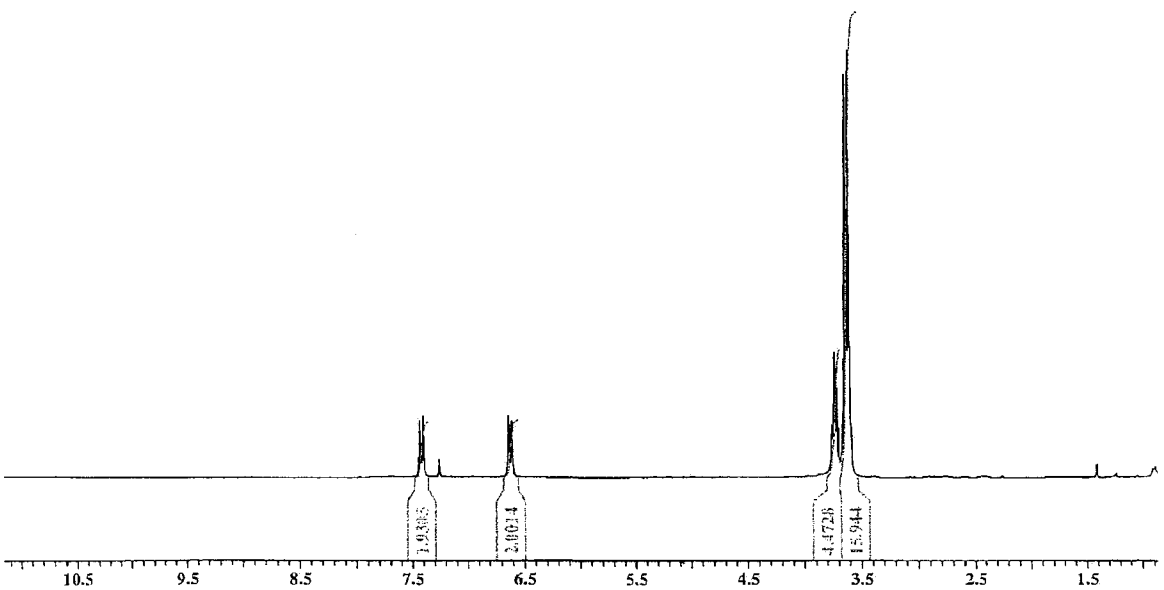
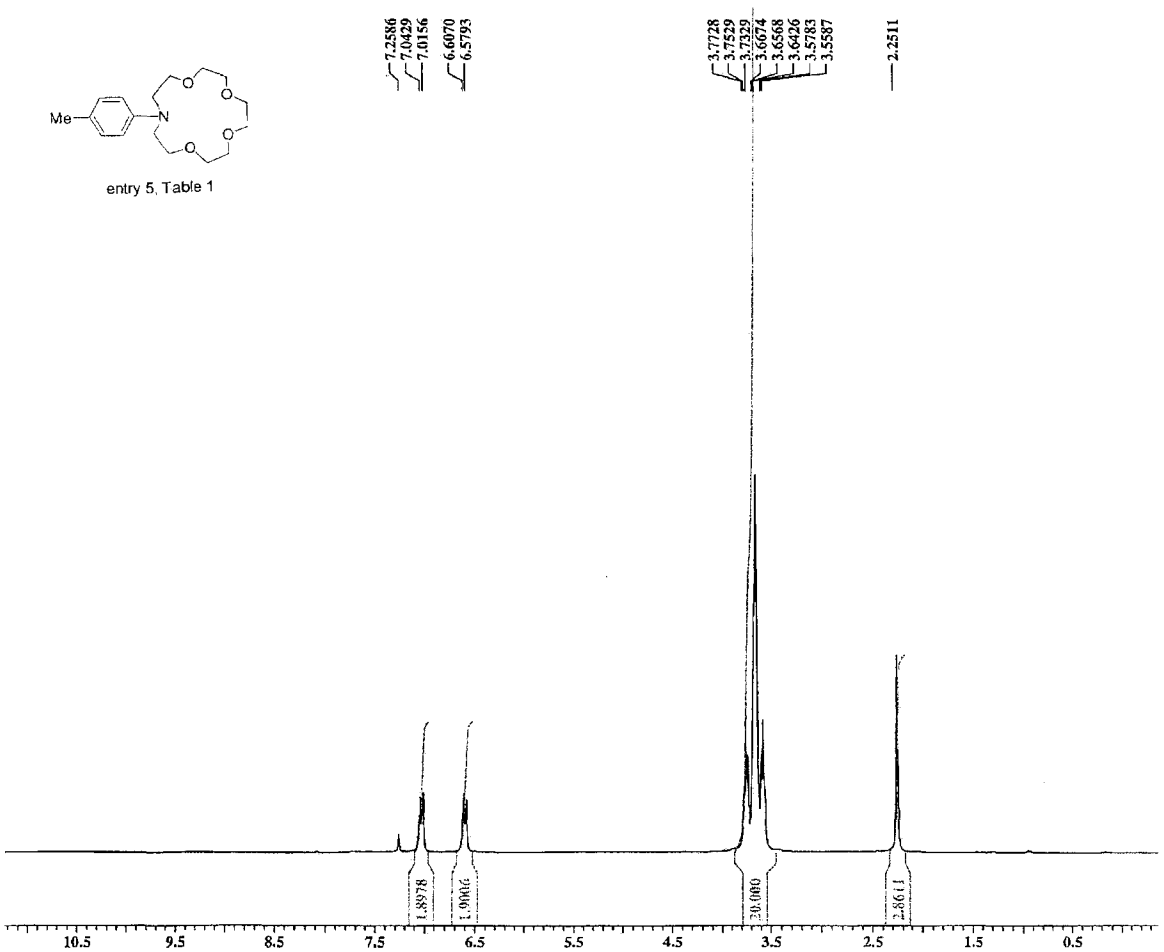


entry 4, Table 1





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N
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O
O
O
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6.5793
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3.7529
3.7329
3.6674
3.6568
3.6426
3.5783
3.5587
2.2511
1.8978
1.9066
20.000
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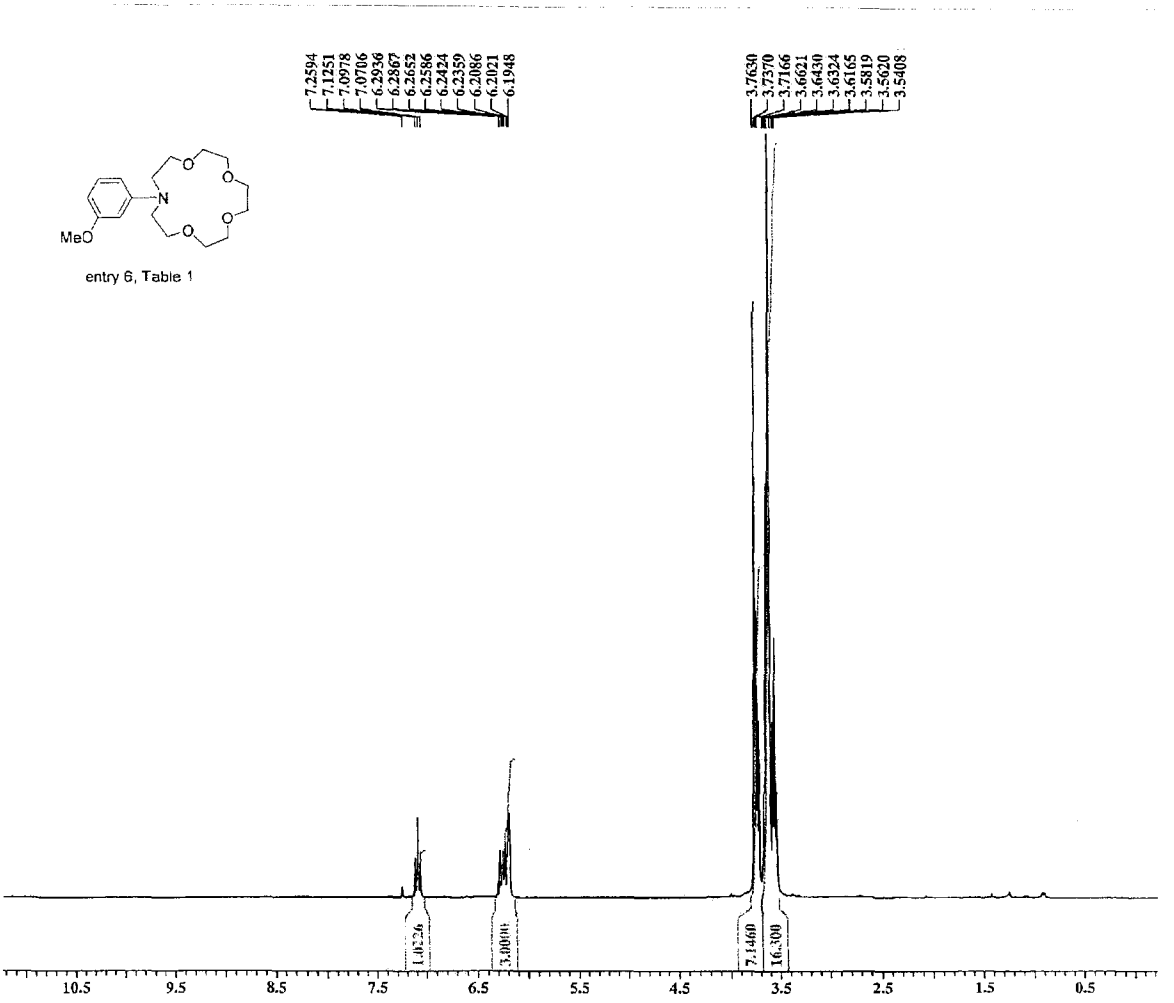
1.5
0.5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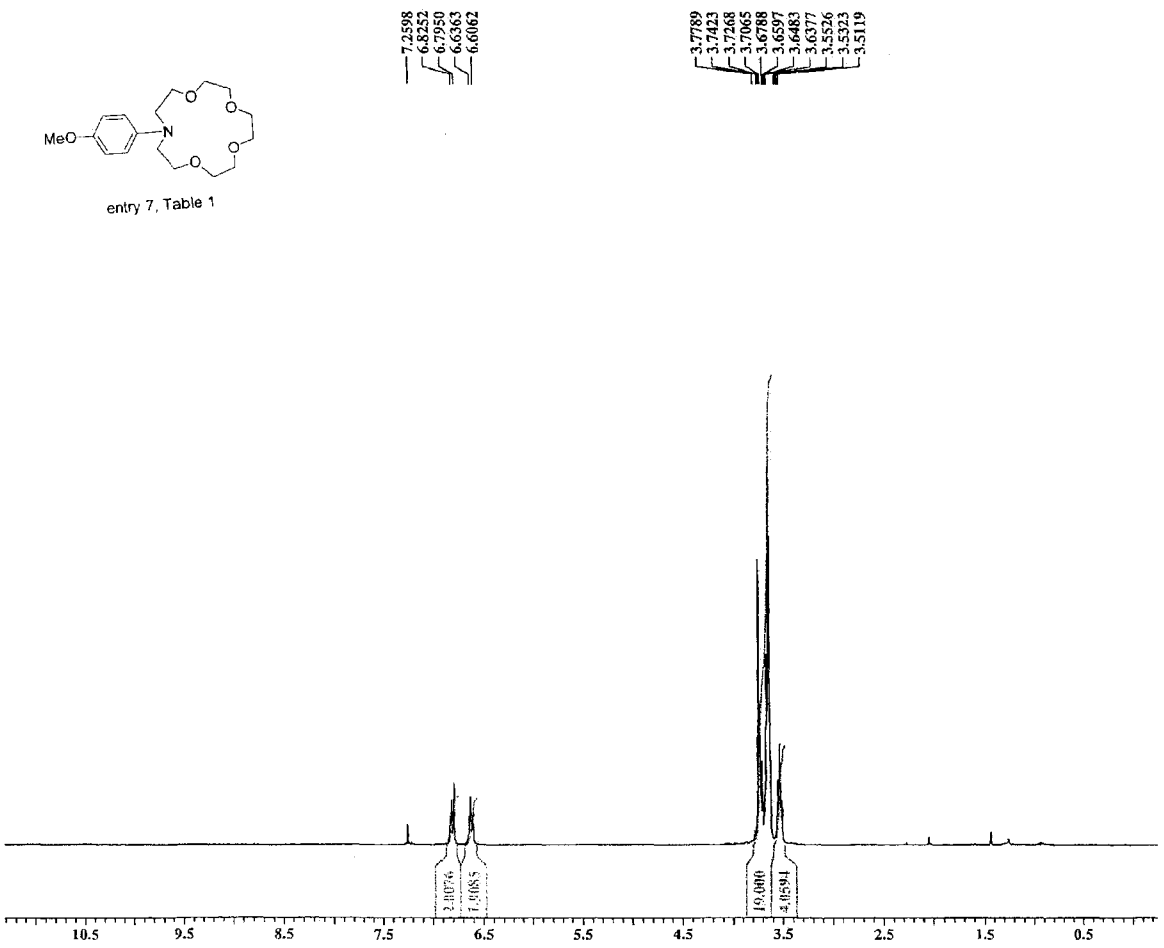
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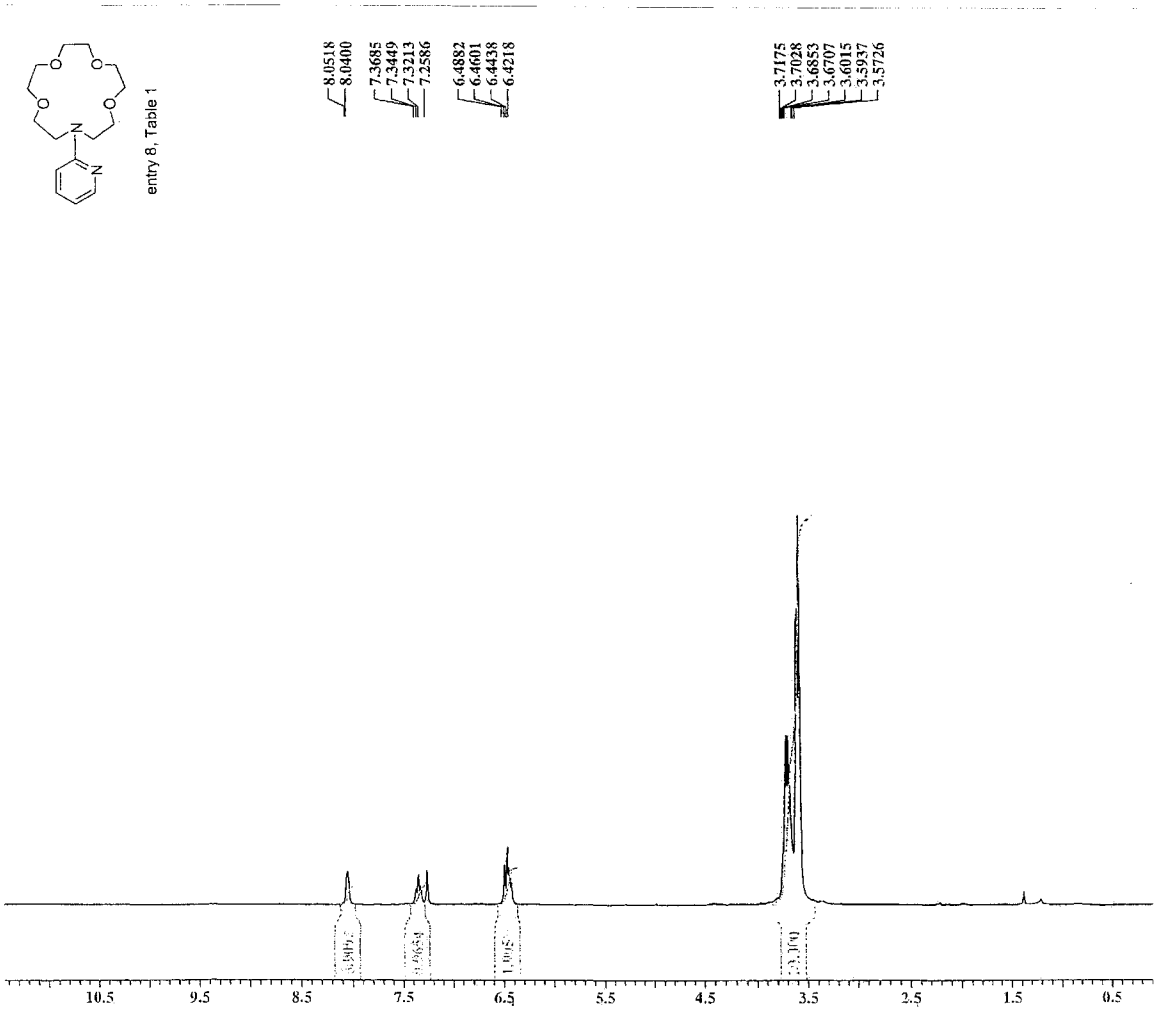
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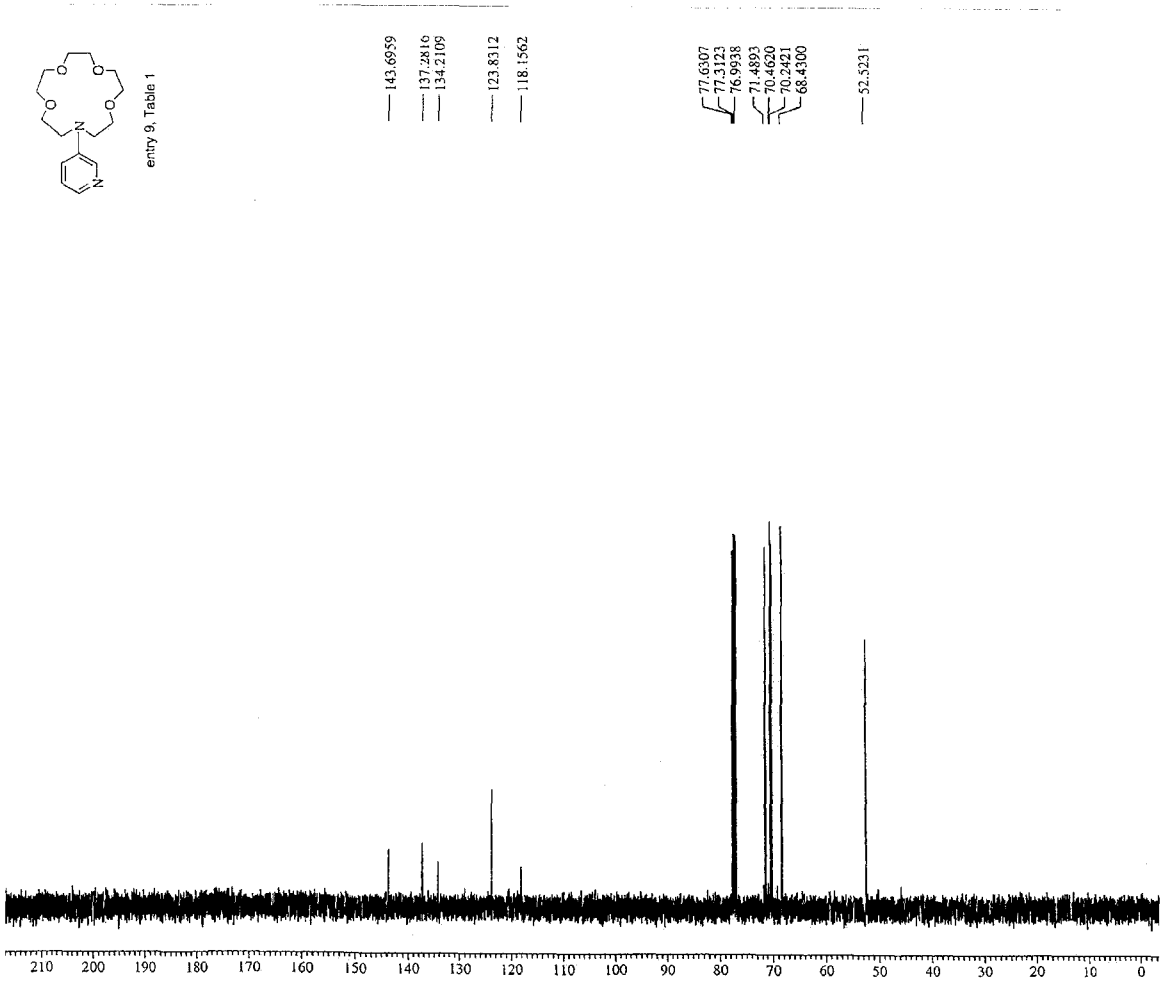
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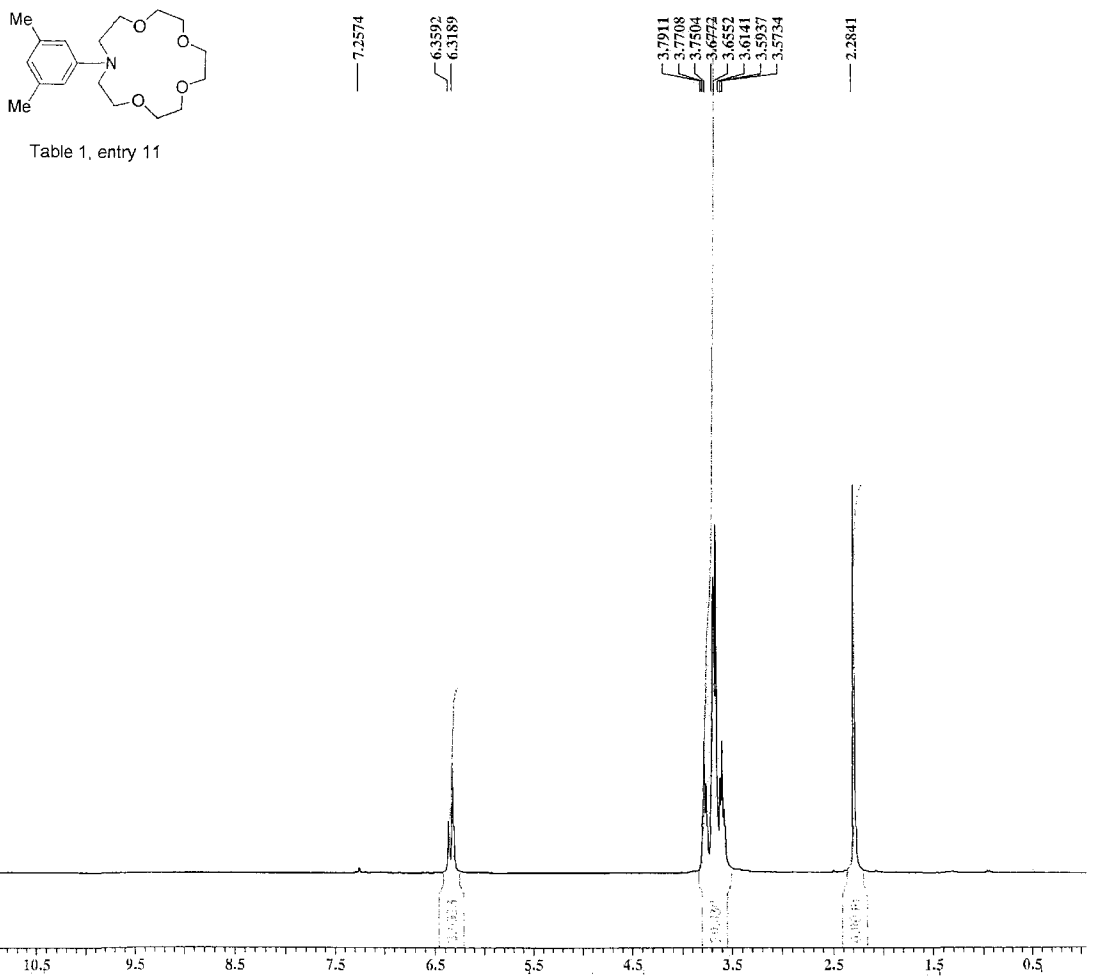

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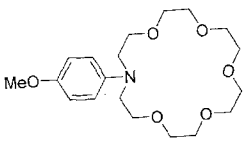

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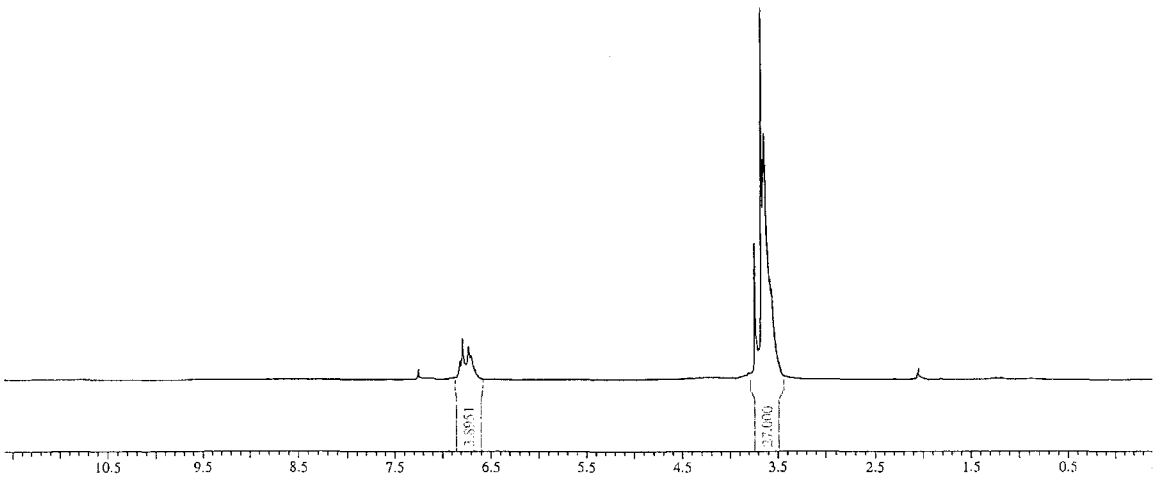

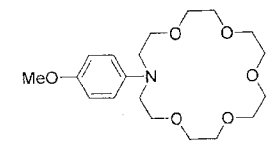

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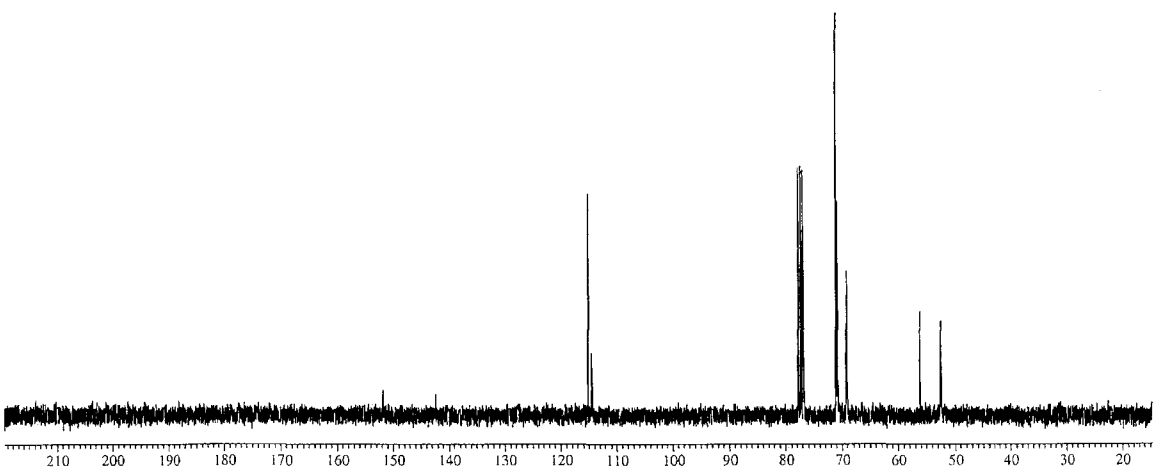

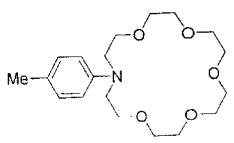

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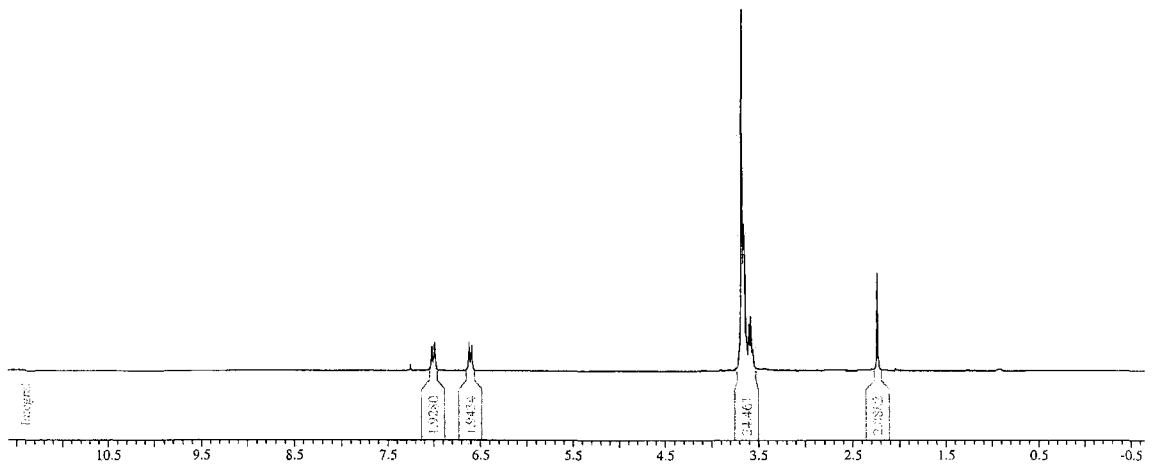
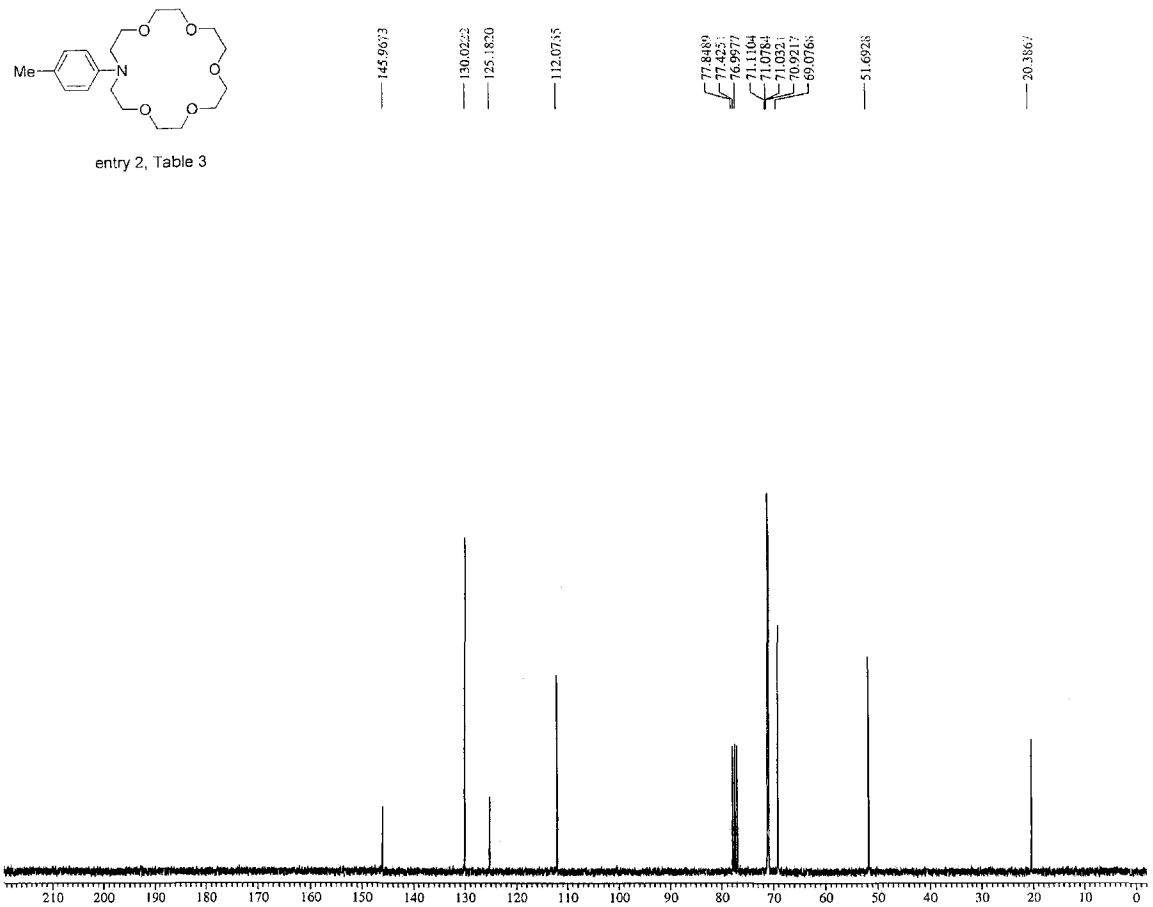




entry 2, Table 3

APPENDIX G

CHAPTER 8

General Considerations

References

General Considerations

$Pd_2(dba)_3$, CsF, Me_4NF, and KF were purchased from Aldrich and used without further purification. Anhydrous dioxane was purchased from Aldrich in Sure/Seal® bottles and further distilled under argon from sodium/benzophenone. All other reagents were commercially available and used without further purification. Although commercially available,[1] ligands **1a**, **1b**, and **1d** were prepared according to previously reported procedures.[2] All other ligands were synthesized according to previously reported methods.[2] For convenience, stock solutions of **1** in dioxane (2 mM) were prepared and stored under argon. All reactions were performed under an atmosphere of argon in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, unless otherwise noted. The yields reported are isolated yields and are the average of two runs.

General Procedure for the Stille Cross-Coupling of Aryl Chlorides. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (1.5 mol %) and CsF or Me_4NF (2.2 mmol). If the aryl chloride (1.0 mmol) was a solid, it was also added at this time. The flask was capped with a rubber septum and removed from the glove box. Ligand **1** (6.0 mol %) was then added via syringe from a stock solution (2 mM in dioxane). Aryl chloride (if a liquid, 1.0 mmol), tin reagent (1.1 mmol), and dioxane (2 mL) were then successively added via syringe. Under a positive pressure of argon, the flask was sealed with a Teflon screw-cap and the reaction mixture was heated at the temperature indicated (see Tables 1-3) until the starting material had been completely consumed as judged by TLC. The mixture was then cooled to room temperature, diluted with ether or acetone, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

4-Methylbiphenyl[3] (Product in Table 1). The general procedure was followed using 4-chlorotoluene (105 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexanes) to afford 116 mg (84%) of the desired product as a white solid.

4-Trifluoromethylbiphenyl[3] (Table 2, entry 1). The general procedure was followed using 4-chlorobenzotrifluoride (150 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol),

CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 1% ethyl acetate/hexanes) to afford 173 mg (96 %) of the desired product as a white solid.

Methyl-4-phenylbenzoate[4] **(Table 2, entry 2).** The general procedure was followed using methyl-4-chlorobenzoate (140 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 2% ethyl acetate/hexanes) to afford 164 mg (95 %) of the desired product as a white solid.

4-Nitrobiphenyl[3] **(Table 2, entry 3).** The general procedure was followed using 1-chloro-4-nitrobenzene (130 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 2% ethyl acetate/hexanes) to afford 140 mg (86 %) of the desired product as a light yellow solid.

4-Cyanobiphenyl[3] **(Table 2, entry 4).** The general procedure was followed using 4-chlorobenzonitrile (113 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 2% ethyl acetate/hexanes) to afford 140 mg (96 %) of the desired product as a white solid.

4-Phenylbenzaldehyde[5] **(Table 2, entry 5).** The general procedure was followed using 4-chlorobenzaldehyde (118 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 3% ethyl acetate/hexanes) to afford 133 mg (89 %) of the desired product as a white solid.

4-Phenylbenzophenone[5] **(Table 2, entry 6).** The general procedure was followed using 4-chlorobenzophenone (179 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 3% ethyl acetate/hexanes) to afford 196 mg (93 %) of the desired product as a white solid.

2-Phenylpyridine[6] **(Table 2, entry 7).** The general procedure was followed using 2-chloropyridine (94 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg,

1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 108 mg (85 %) of the desired product as a light yellow liquid. **3-Phenylpyridine**[7] **(Table 2, entry 8).** The general procedure was followed using 3-chloropyridine (94 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 30% ethyl acetate/hexanes) to afford 126 mg (99%) of the desired product as a light yellow liquid. **2,5-Dimethylbiphenyl**[8] **(Table 2, entry 9).** The general procedure was followed using 2-chloro-*p*-xylene (116 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexanes) to afford 134 mg (90%) of the desired product as colorless liquid.

2,6-Dimethylbiphenyl[6] **(Table 2, entry 10).** The general procedure was followed using 2-chloro-*m*-xylene (118 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexanes) to afford 141 mg (95%) of the desired product as a colorless liquid.

2,6-Dimethylbiphenyl (Table 2, entry 11). The above procedure was followed with Me_4NF (170mg, 1.8 mmol) to afford 146 mg (98%) of the desired product.

4-Methoxybiphenyl[6] **(Table 2, entry 12).** The general procedure was followed using 4-chloroanisole (117 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexanes) to afford 107 mg (71%) of the desired product as a white solid.

4-Methoxybiphenyl (Table 2, entry 13). The above procedure was followed using Me_4NF (170 mg, 1.8 mmol) to afford 136 mg (90%) of the desired product.

Methyl-4-vinylbenzoate[9] **(Table 3, entry 1).** The general procedure was followed using methyl-4-chlorobenzoate (140 mg, 0.816 mmol), vinyltributyltin (0.27 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), **1d** (16.8 mg, 0.049 mmol). The

reaction mixture was purified by column chromatography on silica gel (eluent: 1% ethyl acetate/hexanes) to afford 123 mg (93%) of the desired product as a white solid.

4-Allyl-benzoic acid methyl ester[10] **(Table 3, entry 2).** The general procedure was followed using methyl-4-chlorobenzoate (140 mg, 0.816 mmol), allyltributyltin (0.31 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 3% ethyl ether/pentane) to afford 141 mg (98%) of desired allylation product (minor) and its conjugated isomer (major) as a white solid.

2,5-Dimethylstyrene[7] **(Table 3, entry 3).** The general procedure was followed using 2-chloro-*p*-xylene (116 mg, 0.816 mmol), vinyltributyltin (0.27 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexanes) to afford 37 mg (34%) of the desired product as colorless liquid.

2,5-Dimethylstyrene (Table 3, entry 4). The above procedure was followed using Me_4NF (mg, mmol) to afford 78 mg (72%) of the desired product.

2-Allyl-*p*-xylene[11] **(Table 3, entry 5).** The general procedure was followed using 2-chloro-*p*-xylene (116 mg, 0.816 mmol), allyltributyltin (0.31 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexanes) to afford 113 mg (95%) of desired allylation product (major) and its conjugated isomer (minor) as a colorless liquid.

4-Vinylanisole[7] **(Table 3, entry 6).** The general procedure was followed using 4-chloro-anisole (117 mg, 0.816 mmol), vinyltributyltin (0.27 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (1 % ethyl ether/pentane) to afford 25 mg (23%) of the desired product as colorless liquid.

4-Vinylanisole (Table 3, entry 7). The above procedure was followed using vinyltributyltin (0.36 mL, 1.22 mmol) and Me_4NF (232 mg, 2.45 mmol) to afford 58 mg (53%) of the desired product.

4-Vinylanisole (Table 3, entry 8). The above procedure was followed using vinyltributyltin (0.36 ml, 1.22 mmol), Me_4NF (232 mg, 2.45 mmol), and **1e** (21.8 mg, 0.049 mmol) to afford 97 mg (89%) of the desired product.

4-Allylanisole[7] **(Table 3, entry 9).** The general procedure was followed using 4-chloroanisole (117 mg, 0.816 mmol), allyltributyltin (0.31 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 1 % ethyl ether/pentane) to afford 114 mg (94%) of desired allylation product (major) and its conjugated isomer (minor) as a colorless liquid.

1-(1-Ethoxyvinyl)-4-methoxybenzene[7] **(Table 3, entry 10).** The general procedure was followed using 4-chloroanisole (117 mg, 0.816 mmol), 1-ethoxyvinyltributyltin (0.34 mL, 0.898 mmol), CsF (272 mg, 1.8 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), and **1d** (16.8 mg, 0.049 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: 2.5% triethylamine/hexanes) to afford 141 mg (97%) of the desired product as a light yellow liquid.

References

1. Available from Aldrich and Strem Chemicals.

2. (a) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467. (b) Laramay,M. A. H.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163. (c) Laramay, M. A. H.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421. (d) Wu, W.; Verkade, J. G. Manuscript in preparation.

3. Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830.

4. Riggleman, S.; Deshong, P. *J. Org. Chem.* **2003**, *68*, 8106.

5. Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

6. Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660.

7. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

8. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

9. Gomes, P.; Gosmini, C.; Perichon, J. *Tetrahedron* **2003**, *59*, 2999.

10. Gomes, P.; Gosmini, C.; Perichon, J. *J. Org. Chem.* **2003**, *68*, 1142.

11. Ichihara, J. *Chem. Commun.* **1997**, 1921.

APPENDIX H

CHAPTER 9

General Considerations

^{1}H NMR spectra for reaction products

^{13}C NMR spectra for previously unknown reaction products

^{31}P NMR spectra for phosphorus containing reaction products

General Considerations

2-Mesityltributylstannane,[1] *o*-tolytributylstannane,[1] 4-(tributylstannyl)nitrobenzene,[2] 4-*tert*-butylphenyltrifluoromethanesulfonate,[3] bis(2-aminoethyl)(2-benzylaminoethyl)amine,[4] bis[2-benzylamino)ethyl](2-aminoethyl)amine,[4] and tris[2-(benzylamino)ethyl]amine[5] were prepared following literature procedures. All other reagents were commercially available and were used as received unless otherwise noted. Cesium fluoride (Aldrich) was ground to fine powder and then dried under vacuum at 100 °C for 12 h prior to use. THF, 1,4-dioxane, and pentane were distilled from Na/benzophenone under argon and degassed prior to use. Acetonitrile was distilled from CaH_2 under argon. Anhydrous DMF was purchased from Aldrich. For convenience, stock solutions of **1** and **2** in 1,4-dioxane (2 mM) were prepared and stored under argon. All reactions were performed under an atmosphere of argon in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, unless otherwise noted. The yields reported are isolated yields and are the average of two runs.

Synthesis of Ligand 2. To a solution of 20.9 g (88.56 mmol) of bis(2-aminoethyl)(2-benzylaminoethyl)amine in 30 mL of methanol was added 17.2 g (238.89 mmol) of *iso*-butyraldehyde through a dropping funnel over 20 minutes. The mixture was allowed to stir for 3 h after which 200 mL of methanol was added. The resulting solution was allowed to cool to 0 °C in an ice bath and then 11.1 g of sodium borohydride was added portion-wise over 1 h. The reaction mixture was allowed to stir overnight. Removal of solvent in vacuo afforded a white residue, which was dissolved by the addition of 200 mL of water and extracted with CH_2Cl_2 (3 x 150 mL). The organic extracts were combined, washed with brine (50 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the resulting liquid was distilled under vacuum (135-142 °C/210 mTorr) to afford 29.4 g of bis[(2-*iso*-butylamino)ethyl][(2-benzylamino)ethyl]amine.

A solution of 29.4 g (84.5 mmol) of bis[(2-*iso*-butylamino)ethyl][(2-benzylamino)ethyl]amine in 50 mL of CH_3CN was added to 84.4 mmol of $ClP(NMe_2)_2$ uner argon, prepared *in situ* in 100 mL of CH_3CN by the slow addition of 2.52 mL (28.1 mmol) of PCl_3 to 10.3 mL (56.3 mmol) of $P(NMe_2)_3$ at 0 °C in an ice bath. A white solid was formed in the beginning of reaction, and dissolved as the reaction progressed. The reaction mixture

was stirred for 0.5 h at 0 °C, then overnight at room temperature. Removal of solvent under vacuum resulted in a viscous oil which was dissolved in 30 mL of THF. Addition of 200 mL of hexanes to the resulting solution afforded a white precipitate from which the solvent was decanted. The obtained precipitate was washed with ether (3 x 80 mL) and dried under vacuum to give 29.8 g of $[HP(Me_2CHNCH_2CH_2)_2(PhCH_2NCH_2CH_2)N]Cl$ as a white solid.

To a mixture of 29.8 g (72.2 mmol) of $[HP(Me_2CHNCH_2CH_2)_2(PhCH_2NCH_2CH_2)N]Cl$ and 16.2 g (144.6 mmol) of *t*-BuOK in a 500 mL Schlenk flask was added 150 mL of dry THF under argon. The reaction mixture was stirred overnight and then THF was distilled off under vacuum. Pentane (2 x 150 mL) was added to the remaining residue under argon and the mixture was stirred for 1 h and then allowed to settle for 3 h. The clear upper layer was transferred through cannula into a 500 mL Schlenk flask. The combined organic extracts were concentrated in vacuo to give a light yellow oil which was further purified by vacuum distillation (150 °C/140 mTorr) to afford a 16.6 g of **2** as a pale yellow oil (overall yield: 58 %). ^{1}H NMR (C_6D_6): δ 7.35 (d, J = 7.4 Hz, 2H), 7.21-7.16 (m, 2H), 7.09-7.04 (m, 2H), 4.08 (d, J = 8.9 Hz, 2H), 2.78-2.63 (overlapping region, 16H), 1.81 (septet, J = 6.7 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.5 Hz, 6H). ^{13}C NMR (C_6D_6): δ 141.9 (d, J = 6.2 Hz), 128.4, 128.3, 126.8, 58.3 (d, J = 37.0 Hz), 53.5 (d, J = 42.2 Hz), 51.4 (d, J = 3.0 Hz), 51.2 (d, J = 3.0 Hz), 46.6 (d, J = 6.7 Hz), 45.3 (d, J = 6.7 Hz), 28.6 (d, J = 5.1 Hz), 20.7 (d, J = 1.6 Hz), 20.69 (d, J = 1.6 Hz). ^{31}P NMR (C_6D_6): δ 130.0. HRMS *m/z* Calcd for $C_{21}H_{37}N_4P$: 376.27559. Found: 376.27508. Anal. Calcd. for $C_{21}H_{37}N_4P$: C, 66.97; H, 9.91; N, 14.89. Found: C, 67.13; H, 9.81; N, 14.83.

Synthesis of Ligand 3. To a solution of 15.58 g (47.6 mmol) of bis[(2-benzylamino)ethyl] (2-aminoethyl)amine in 30 mL of methanol was added 4.43 g (61.5 mmol) of isobutyraldehyde through a dropping funnel over 20 minutes. The mixtrure was allowed to stir for 3 h after which 200 mL of methanol was added. The resulting solution was allowed to cool to 0 °C in an ice-bath and then 3.8 g of sodium borohydride was added portion-wise over 0.5 h. The reaction mixture was allowed to stir overnight. Removal of solvent under reduced pressure afforded a white residue, which was dissolved by the addition of 200 mL of water. The reaction mixture was extracted with methylene chloride (3 x 150 mL). The organic extracts were combined and washed with brine (50 mL), dried over anhydrous

sodium sulfate and concentrated under reduced pressure to give light yellow oil. The crude material was purified by chromatography on silica gel (CH_2Cl_2/MeOH, v:v = 6:4) to afford 16 g of bis [(2-benzylamino)ethyl] [(2-*iso*-butylamino)ethyl]amine.

A procedure analogous to that for synthesis of **2** from bis[(2-*iso*-butylamino)ethyl] -[(2-benzylamino)ethyl]amine was followed for the preparation of **3** from bis[(2-benzylamino)ethyl] [(2-*iso*-butylamino)ethyl]amine. The quantities were as follows: the reaction of 16 g (41.88 mmol) of bis[(2-benzylamino)ethyl] [(2-*iso*-butylamino)ethyl]amine with 1.25 mL (13.9 mmol) of PCl_3 and 5.1 mL (27.84 mmol) of $P(NMe_2)_3$ afforded 15.2 g (34.1 mmol) of $[HP(Me_2CHNCH_2CH_2)(PhCH_2NCH_2CH_2)_2N]Cl$, which was deprotonated with 7.64 g (68.2 mmol) of *t*-BuOK to give **3**. The crude product was recrystallized from pentane to afford 13.0 g of **3** as a white solid (overall yield: 66%). ^1H NMR (C_6D_6): δ 7.36 (d, J = 7.2 Hz, 4H), 7.21-7.16 (m, 4H), 7.07-7.05 (m, 2H), 4.11 (d, J = 9.1 Hz, 4H), 2.81-2.75 (m, 2H), 2.69-2.58 (m, 12H), 1.80 (septet, J = 6.7 Hz, 1H), 0.93 (d, J = 6.7, 6H). ^{13}C NMR (C_6D_6): δ 141.7 (d, J = 6.2 Hz), 128.43 (s), 128.27 (d, J = 2.1 Hz), 126.92 (s), 57.9 (d, J = 36.6 Hz), 53.4 (d, J = 41.4 Hz), 51.36 (d, J = 11.8 Hz), 51.07 (d, J = 2.7 Hz), 46.55 (d, J = 6.7 Hz), 45.35 (d, J = 6.7 Hz), 28.6 (d, J = 5.1 Hz), 20.73 (d, J = 1.6 Hz). ^{31}P NMR (C_6D_6): δ 128.9. HRMS *m/z* Calcd for $C_{24}H_{35}N_4P$: 410.25299. Found: 410.26040. Anal. Calcd. for $C_{24}H_{35}N_4P$: C, 70.20; H, 8.60; N, 13.66. Found: C, 70.25; H, 8.44; N, 13.56.

Synthesis of Ligand 4. A procedure analogous to that for synthesis of **2** from bis(2-*iso*-butylaminoethyl)(2-benzylaminoethyl)amine was followed for the preparation of **4** from tris[2-(benzylamino)ethyl]amine. The reaction of 32 g (76.94 mmol) of tris[(2-benzylamino)ethyl]amine with 2.3 mL (25.6 mmol) of PCl_3 and 9.4 mL (51.3 mmol) of $P(NMe_2)_3$ afforded 30 g (62.4 mmol) of $[HP(PhCH_2NCH_2CH_2)_3N]Cl$, which was deprotonated with 14.0 g (125 mmol) of *t*-BuOK to give **4**. The crude product was recrystallyzed from pentane to afford 24.9 g (56.2 mmol) of **4** as off-white solid (overall yield: 73%). ^1H NMR (C_6D_6): δ 7.36 (d, J = 5.5 Hz, 6H), 7.35-7.17 (m, 6H), 7.11-7.09 (m, 3H), 4.13 (d, J = 6.9 Hz, 6H), 2.66-2.63 (m, 6H), 2.56-2.54 (m, 6H). ^{13}C NMR (C_6D_6): δ 141.6 (d, J = 5.9 Hz), 128.5 (s), 128.3 (d, J = 2.1 Hz), 127.0 (s), 53.1 (d, J = 41.1 Hz), 51.0 (d, J = 2.7 Hz), 45.4 (d, J = 6.7 Hz). ^{31}P NMR (C_6D_6): δ 127.9. HRMS *m/z* Calcd for $C_{27}H_{33}N_4P$: 444.24429. Found: 444.24510.

General Procedure for Stille Cross-Coupling reaction Using Ligand 1 (Procedure A). In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol, 1.5 mol %) CsF (272 mg, 1.8 mmol). The tube was fitted with a rubber septum and removed out of the glove box. One mL of 1,4-dioxane, stock solution of ligand **1** in dioxane (16.8 mg, 0.049 mmol, 6 mol %), aryl chloride (1.0 equiv, aryl chloride if solid was added inside the glove box), and organotin reagent (1.1 equiv) were added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred for 30 minutes at room temperature then heated with stirring at the indicated temperature for the indicated time. The reaction mixture was cooled to room temperature, diluted with ether or acetone, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

General Procedure for Stille Cross-Coupling Reaction Using Ligand 4 (Procedure B). In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol, 1.5 mol %), CsF (272 mg, 1.8 mmol), and ligand **4** (11 mg, 0.025 mmol, 3.5 mol %). The tube was fitted with a rubber septum and removed out of the glove box. One mL of 1,4-dioxane, aryl chloride (1.0 equiv, aryl chloride if solid was added inside the glove box), and organotin reagent (1.1 equiv) were added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred for 30 minutes at room temperature then heated with stirring at the indicated temperature for the indicated time. The reaction mixture was cooled to room temperature, diluted with ether or acetone, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

General Procedure For the Synthesis of Sterically Hindered Biaryls Using Ligand 3 (Procedure C). In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (7 mg, 0.0075 mmol, 1.5 mol %), CsF (168 mg, 1.1 mmol), and ligand **3** (7.2 mg, 0.0175 mmol, 3.5 mol %). The tube was fitted with a rubber septum and removed out of the glove box. Aryl halide (1.0 equiv), 1,4-dioxane (1 mL), and organotin reagent (1.1 equiv) were added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred for 30 minutes at room temperature then heated with stirring at the indicated temperature for the indicated time. The reaction mixture was cooled to room

temperature, diluted with ether or acetone, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

General procedure For Room-Temperature Stille reactions of Aryl Bromides Using Ligand 4 (Procedure D). In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol, 1.5 mol %), CsF (272 mg, 1.8 mmol), and ligand **4** (11 mg, 0.025 mmol, 3.0 mol %). The tube was fitted with a rubber septum and removed out of the glove box. One mL of THF, aryl bromide (1.0 equiv) and organotin reagent (1.1 equiv) were added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred at room temperature for the indicated time, and then diluted with ether or acetone, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

Methyl 4-vinylbenzoate[6] (Table 1, entry 1). Procedure A was followed using methyl 4-chlorobenzoate (140 mg, 0.816 mmol) and vinyltributyltin (0.27 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford 123 mg (93%) of the desired product as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 6.74 (dd, J =17.5, 11.0 Hz, 1H), 5.86 (d, J = 17.5 Hz, 1H), 5.38 (d, J = 11.0 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.1, 142.1, 136.2, 130.1, 129.5, 126.3, 116.7, 52.3.

4-Nitrobiphenyl[7] (Table 1, entry 2). Procedure A was followed using 1-chloro-4-nitrobenzene (130 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford 140 mg (86%) of the desired product as light yellow solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

4-Phenylbenzaldehyde (Table 1, entry 3). Procedure A was followed using 4-chlorobenzaldehyde (118 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (3% ethyl acetate/hexanes) to afford 133 mg (89%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1} H and ^{13} C NMR spectra.

4-Phenylbenzophenone (Table 1, entry 4) Procedure A was followed using 4-chlorobenzophenone (179 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol).

The reaction mixture was purified by column chromatography on silica gel (3% ethyl acetate/hexanes) to afford 196 mg (93%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1} H and ^{13} C NMR spectra.

2-Phenylpyridine (Table 1, entry 5). Procedure A was followed using 2-chloropyridine (94 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (10% ethyl acetate/hexanes) to afford 108 mg (85%) of the desired product as light yellow liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

3-Phenylpyridine (Table 1, entry 6). Procedure A was followed using 3-chloropyridine (94 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (30% ethyl acetate/hexanes) to afford 126 mg (99%) of the desired product as light yellow liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

2-Allyl-*p*-xylene[8] (Table 1, entry 7). Procedure A was followed using 2-chloro-*p*-xylene (116 mg, 0.816 mmol) and allyltributyltin (0.31 mL, 0.898 mmol) The reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 113 mg (95%) of the mixture of the desired product with its double bond migrating isomer as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2,6-Dimethylbiphenyl[1] (Table 1, entry 8). Procedure A was followed using 2-chloro-*m*-xylene (118 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 141 mg (95%) of the desired product as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

4-Methoxybiphenyl (Table 1, entry 9). Procedure A was followed using 4-chloroanisole (117 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 107 mg (71%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

1-(1'-Ethoxyvinyl)-4-methoxybenzene[1] (Table 1, entry 10). Procedure A was followed using 4-chloro-anisole (117 mg, 0.816 mmol) and 1-ethoxyvinyltributyltin (0.34 mL, 0.898

mmol). The reaction mixture was purified by column chromatography on silica gel (2.5% triethylamine/hexanes) to afford 141 mg (97%) of the desired product as light yellow liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2-Cyanobiphenyl[9] (Table 1, entry 11). Procedure A was followed using 2-chloro-benzonitrile (114 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (4% ethyl acetate/hexanes) to afford 135 mg (91%) of the desired product as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

Methyl 4-biphenylcarboxylate[10] (Table 2, entry 1). Procedure B was followed using 4-chlorobenzoate (142 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford 164 mg (95%) of the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

4-Nitrobiphenyl[7] (Table 2, entry 2). Procedure B was followed using 1-chloro-4-nitrobenzene (130 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford 158 mg (98%) of the desired product as light yellow solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

4-Phenylbenzaldehyde (Table 2, entry 3). Procedure B was followed using 4-chlorobenzaldehyde (118 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (3% ethyl acetate/hexanes) to afford 138 mg (93%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

4-Phenylbenzophenone (Table 2, entry 4). Procedure B was followed using 4-chlorobenzophenone (179 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (3% ethyl acetate/hexanes) to afford 207 mg (98%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

4-Cyanobiphenyl[7] (Table 2, entry 5). Procedure B was followed using 4-chlorobenzonitrile (114 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture

was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford 143 mg (98%) of the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

4-Trifluoromethylbiphenyl[7] (Table 2, entry 6). Procedure B was followed using 4-chlorobenzotrifluoride (150 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 180 mg (99%) of the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

Methyl 3-biphenylcarboxylate[11] (Table 2, entry 7). Procedure B was followed using 3-chlorobenzoate (142 mg, 0.816 mmol) and phenyltributyltin (0.30 mL, 0.898 mmol). The reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford 164 mg (95%) of the desired product as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

4-Methoxybiphenyl (Table 3, entry 1). Procedure B was followed using 4-chloroanisole (117 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 131 mg (87%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

2,5-Dimethylbiphenyl[12] (Table 3, entry 2). Procedure B was followed using 2-chloro-*p*-xylene (116 mg, 0.816 mmol), phenyltributyltin (0.30 ml, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 127 mg (85%) of the desired product as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

3,4-Methylenedioxybiphenyl[13] (Table 3, entry 3). Procedure B was followed using 5-chloro-1,3-benzodioxole (130 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 146 mg (90%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H), 7.44-7.42 (m, 2H), 7.39-7.31 (m, 1H), 7.08 (m, 2H), 6.00 (s, 2H). ^{13} C NMR (75.5 MHz, $CDCl_3$): δ 148.3, 147.3, 141.1, 135.8, 128.9, 127.1, 127.1, 120.8, 108.8, 107.9, 101.3.

3-Phenylpyridine (Table 3, entry 4). Procedure B was followed using 3-chloropyridine (94 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (30% ethyl acetate/hexanes) to afford 123 mg (97%) of the desired product as light yellow liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

2-Phenylpyridine (Table 3, entry 5). Procedure B was followed using 2-chloropyridine (94 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (10% ethyl acetate/hexanes) to afford 81 mg (64%) of the desired product as light yellow liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

3-Phenylthiophene (Table 3, entry 6). Procedure B was followed using 3-chlorothiophene (94 mg, 0.816 mmol), phenyltributyltin (0.30 mL, 0.898 mmol), and **1** (16.8 mg, 0.048 mmol, 6 mol %). The reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 91 mg (69%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

4-Vinylanisole (Table 4, entry 1). Procedure B was followed using 4-chloro-anisole (117 mg, 0.816 mmol), vinyltributyltin (0.27 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 62mg (57%) of the desired product as colorless liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

1-(1'-Ethoxyvinyl)-4-methoxybenzene[1] (Table 4, entry 2). Procedure B was followed using 4-chloroanisole (117 mg, 0.816 mmol), 1-ethoxyvinyltributyltin (0.34 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (2.5% triethylamine/hexanes) to afford 139 mg (96%) of the desired product as light yellow liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

4-Allylanisole (Table 4, entry 3). Procedure B was followed using 4-chloroanisole (117 mg, 0.816 mmol), allyltributyltin (0.31 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 116 mg (95%) of the mixture of the desired product with its double bond migrating isomer as colorless liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

2-(4'-Methoxyphenyl)thiophene[14] (Table 4, entry 4). Procedure B was followed using 4-chloroanisole (117 mg, 0.816 mmol), (tributylstannyl)thiophene (0.27 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 105 mg (67%) of the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2-(4'-Methoxyphenyl)furan[15] (Table 4, entry 5). Procedure B was followed using 4-chloroanisole (117 mg, 0.816 mmol), (tributylstannyl)furan (0.27 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). The reaction mixture was purified by column chromatography on silica gel (1 % ethyl acetate /hexanes) to afford 140 mg (97%) of the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2,5,2'-Trimethylbiphenyl[16] (Table 5, entry 1). Procedure C was followed using 2-chloro-*p*-xylene (71 mg, 0.5 mmol), *o*-tolytributylstannane (210 mg, 0.55 mmol). After the reaction was run for 48 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 97 mg (99%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.24 (m, 3H), 7.22-7.11 (m, 3H), 6.99 (s, 1H), 2.39 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.0, 141.7, 136.0, 135.1, 132.9, 130.2, 130.0, 129.9, 129.5, 128.1, 127.3, 125.8, 21.2, 20.1, 19.6.

2,4,6,2',5'-Pentamethylbiphenyl (Table 5, entry 2). Procedure C was followed using 2-chloro-*p*-xylene (71 mg, 0.5 mmol), 2-mesityltributylstannane (225 mg, 0.55 mmol). After the reaction was run for 48 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 98 mg (88%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J = 7.7 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 6.95 (s, 2H), 6.85 (s, 1H), 2.35 (s, 6H), 1.94 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 140.6, 138.6, 136.4, 135.9, 132.8, 129.9, 128.2, 127.8, 21.3, 21.3, 20.5, 19.2. HRMS *m/z* Calcd for $C_{17}H_{20}$: 224.15650. Found 224.15692.

2,6,2'-Trimethylbiphenyl[1] (Table 5, entry 3). Procedure C was followed using 2-chloro-*m*-xylene (72.5 mg, 0.5 mmol), *o*-tolytributylstannane (210 mg, 0.55 mmol). After the reaction was run for 60 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 95 mg (97%) of the desired product as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2,4,6,2',6'-Pentamethylbiphenyl[1] (Table 5, entry 4). Procedure C was followed using 2-chloro-*m*-xylene (72.5 mg, 0.5 mmol), 2-mesityltributylstannane (225 mg, 0.55 mmol). After the reaction was run for 60 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 91 mg (81%) of the desired product as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

1-(2'-Methylphenyl)naphthalene[17] (Table 5, entry 5). Procedure C was followed using 1-chloronaphthalene (90 mg, 0.5 mmol), *o*-tolyltributylstannane (210 mg, 0.55 mmol). After the reaction was run for 40 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 107 mg (98%) of the mixture of the desired product with 2-(2'-Methylphenyl)naphthalene (which came from 2-chloronaphthalene in the starting material) as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

1-(2',4',6'-Trimethylphenyl)naphthalene[18] (Table 5, entry 6). Procedure C was followed using 1-chloronaphthalene (90 mg, 0.5 mmol), 2-mesityltributylstannane (225 mg, 0.55 mmol). After the reaction was run for 40 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 119 mg (97%) of the mixture of the desired product with 2-(2',4',6'-Trimethylphenyl)naphthalene (which came from 2-chloronaphthalene in the starting material) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95-7.65 (m, 2H), 7.57-7.50 (m, 2H), 7.39-7.29 (m, 3H), 7.05 (s, 2H), 2.43 (s, 3H), 1.92 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.0, 137.1, 137.06, 136.9, 133.9, 132.2, 128.3, 127.3, 126.9, 126.2, 125.9, 125.7, 21.4, 20.5.

2-Methyl-1-(2'-methylphenyl)-naphthalene[19] (Table 5, entry 7) Procedure C was followed using 1-bromo-2-methyl-naphthalene (123 mg, 0.5 mmol), *o*-tolyltributylstannane (210 mg, 0.55 mmol). After the reaction was run for 48 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 99 mg (86%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.46-7.25 (m, 7H), 7.14 (d, J = 6.7 Hz, 1H), 2.19 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.4, 137.7, 137.0, 133.3, 132.7, 132.2, 130.2, 130.2, 128.8, 128.1, 127.6, 127.3, 126.2, 126.1, 125.9, 124.9, 20.6, 19.8.

2-Methyl-1-(2',4',6'-trimethylphenyl)-naphthalene (Table 5, entry 7). Procedure C was followed using 1-bromo-2-methyl-naphthalene (123 mg, 0.5 mmol), 2-mesityltributylstannane (225 mg, 0.55 mmol). After the reaction was run for 48 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 100 mg (77%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.46-7.38 (m, 2H), 7.34-7.22 (m, 2H), 7.04 (s, 2H), 2.41 (s, 3H), 2.14 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 136.8, 136.7, 135.7, 133.3, 132.45, 132.40, 128.9, 128.4, 128.1, 127.1, 126.2, 125.3, 125.0, 21.4, 20.1, 20.0. HRMS *m/z* Calcd for $C_{20}H_{20}$: 260.1565. Found: 260.1572.

2,4,6-Triisopropyl-2'-methylbiphenyl[20] (Table 5, entry 9). Procedure C was followed using 1-bromo-2, 4, 6-triisopropylbenzene (142 mg, 0.5 mmol), *o*-tolyltributylstannane (210 mg, 0.55 mmol), **3** (14.4 mg, 0.035 mmol, 7 mol %), and $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol, 3 mol %). After the reaction was run for 60 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 130 mg (88%) of the desired product as white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.19 (m, 3H), 7.08-7.05 (m, 3H), 2.95 (septet, J = 7.0 Hz, 1H), 2.44 (septet, J = 6.8 Hz, 2H), 2.00 (s, 3H), 1.31 (d, J = 7.0 Hz, 6H), 1.12 (d, J = 7.0 Hz, 6H), 1.03 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ147.9, 146.3, 140.4, 136.9, 136.0, 130.3, 129.7, 126.9, 125.5, 120.8, 34.4, 30.5, 25.1, 24.3, 23.7, 20.5. HRMS *m/z* Calcd for $C_{22}H_{30}$: 294.2347. Found: 294.2350.

4-*tert*-Butylstyrene (Table 6, entry 1). Procedure D was followed using 1-bromo-4-*tert*-butylbenzene (177 mg, 0.816 mmol) and vinyltributyltin (0.27ml, 0.898 mmol). After the reaction was run for 10 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 129 mg (99%) of the desired product as colorless liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

4-Allyl-*tert*-butylbenzene[21] (Table 6, entry 2). Procedure D was followed using 1-bromo-4-*tert*-butylbenzene (177 mg, 0.816 mmol), allyltributyltin (0.31 mL, 0.898 mmol). After the reaction was run for 10 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 124 mg (87%) of the desired product as colorless liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2-(4'-*tert*-Butylphenyl)furan[22] (Table 6, entry 3). Procedure D was followed using 1-bromo-4-*tert*-butylbenzene (177 mg, 0.816 mmol), (tributylstannyl)furan (0.27 mL, 0.898 mmol). After the reaction was run for 10 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 157 mg (97%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 6.6 Hz, 2H), 7.63-7.42 (m, 3H), 6.63 (d, J = 3.3 Hz, 1H), 6.49-6.47 (m, 1H), 1.367 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 154.4, 150.6, 141.9, 128.4, 125.8, 123.8, 111.7, 104.5, 34.8, 31.5.

4-*tert*-Butylbiphenyl[23] (Table 6, entry 4). Procedure D was followed using 1-bromo-4-*tert*-butylbenzene (177 mg, 0.816 mmol), tributylphenyltin (0.30 mL, 0.898 mmol). After the reaction was run for 10 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 168 mg (98%) of the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

3-Methyl-4-vinyl-anisole[24] (Table 6, entry 5). Procedure D was followed using 4-bromo-3-methylanisole (167 mg, 0.816 mmol), vinyltributyltin (0.27 mL, 0.898 mmol). After the reaction was run for 14 h, the reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 117 mg (97%) of the desired product as pale yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 17.5, 11.0 Hz, 1H), 6.77-6.71 (m, 2H), 5.56 (dd, J = 17.4, 1.3 Hz, 1H), 5.20 (dd, J = 10.9, 1.35 Hz), 3.81 (s, 3H),

2.36 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ159.3, 137.1, 134.3, 129.8, 126.7, 115.6, 113.3, 111.8, 55.4, 20.2.

3-Methyl-4-allyl-anisole (Table 6, entry 6). Procedure D was followed using 4-bromo-3-methylanisole (167 mg, 0.816 mmol), allylltributyltin (0.31 mL, 0.898 mmol). After the reaction was run for 14 h, the reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 128 mg (97%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, J = 8.04 Hz, 1H), 6.74-6.69 (m, 2H), 5.99-5.88 (m, 1H), 5.07-4.94 (m, 2H), 3.79 (s, 3H), 3.32 (d, J = 6.21 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 158.2, 137.8, 137.3, 130.5, 130.3, 116.0, 115.5, 111.2, 55.4, 37.1, 19.8. HRMS *m/z* Calcd for $C_{11}H_{14}O$: 162.10447. Found:162.10480.

2-(2'-Methyl-4'-methoxyphenyl)furan (Table 6, entry 7). Procedure D was followed using 4-bromo-3-methylanisole (167 mg, 0.816 mmol), (tributylstannyl)furan (0.27 mL, 0.898 mmol). After the reaction was run for 14 h, the reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 150 mg (98%) of the desired product as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 1.2 Hz, 1H), 7.59-7.47 (m, 1H), 6.81-6.79 (m, 2H), 6.49-6.41 (m, 2H), 3.83 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.0, 153.3, 141.3, 136.6, 141.3, 136.6, 128.8, 123.6, 116.6, 111.5, 111.4, 107.3, 55.5, 22.2. HRMS *m/z* Calcd for $C_{12}H_{12}O_2$: 188.0837. Found: 188.0845.

2-(2'-Methyl-4'-methoxyphenyl)thiophene (Table 6, entry 8). Procedure D was followed using 4-bromo-3-methylanisole (167 mg, 0.816 mmol), (tributylstannyl)thiophene (0.27 mL, 0.898 mmol). After the reaction was run at 50 °C for 14 h, the reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 165 mg (99%) of the desired product as pale yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.30 (m, 2H), 7.11-7.08 (m, 1H), 7.03-7.02 (m, 1H), 6.85-6.77 (m, 2H), 3.84 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.4, 143.3, 137.9, 131.9, 127.2, 127.0, 126.3, 124.9, 116.3, 111.4, 55.5, 21.6. HRMS *m/z* Calcd for $C_{12}H_{12}OS$: 204.0609. Found: 206.0604.

4-(*N*,*N*-dimethylamino)styrene[25] (Table 6, entry 9). Procedure D was followed using 4-bromo-*N*,*N*-dimethylaniline (168 mg, 0.816 mmol), vinyltributyltin (0.27 mL, 0.898 mmol). After the reaction was run for 14 h, the reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford 117 mg (97%) of the desired product as pale yellow liquid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2-(4'-*N*,*N*-Dimethylaminophenyl)furan[26] (Table 6, entry 10). Procedure D was followed using 4-bromo-*N*,*N*-dimethylaniline (168 mg, 0.816 mmol), (tributylstannyl)furan (0.27 mL, 0.898 mmol). After the reaction was run for 14 h, the reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford 142 mg (93%) of the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.

2,2'-Bithiophene (Table 6, entry 11). Procedure D was followed using 2-bromo-thiophene (136 mg, 0.816 mmol), (tributylstannyl)thiophene (0.27 mL, 0.898 mmol). After the reaction was run at 50 °C for 30 h, the reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 132 mg (98%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

2-(2'-Thienyl)furan (Table 6, entry 12). Procedure D was followed using 2-bromo-thiophene (136 mg, 0.816 mmol), (tributylstannyl)furan (0.27 mL, 0.898 mmol). After the reaction was run at 50 °C for 30 h, the reaction mixture was purified by column chromatography on silica gel (1% ethyl ether/pentane) to afford 132 mg (98%) of the desired product as colorless liquid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

2-Phenylthiophene (Table 6, entry 13). Procedure D was followed using 2-bromo-thiophene (136 mg, 0.816 mmol), tributylphenyltin (0.30 mL, 0.898 mmol). After the reaction was run at 50 °C for 30 h, the reaction mixture was purified by column chromatography on silica gel (hexanes) to afford 119 mg (91%) of the desired product as white solid. The product was identical with an authentic material (Aldrich) by ^{1}H and ^{13}C NMR spectra.

Room-Temperature Synthesis of 1-(2'-Methylphenyl)naphthalene[17] Using ligand 3 (eq 1). In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (7 mg, 0.0075 mmol, 1.5 mol %), CsF (168 mg, 1.1 mmol), and ligand **3** (6.2 mg, 0.015 mmol, 3 mol %). The tube was fitted with a rubber septum and removed out of the glove box. One mL of 1,4-dioxane, 1-bromonaphthalene (103.5 mg, 0.5 mmol), and *o*-tolytributylstannane (210 mg, 0.55 mmol) were added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred at room temperature for 48 h, and then diluted with ether, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes) to afford 88 mg (81%) of the desired product as white solid. The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.

Room-Temperature Synthesis of 2-Methyl-1-(2-methylphenyl)-naphthalene[19] (eq 2). The above procedure for eq 1 was followed with 1-bromo-2-methyl-naphthalene (123 mg, 0.5 mmol). The desired product was obtained in 57% yield (66 mg). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.

Stille Cross-Coupling of 4-Bromoanisole with 4-(Tributylstannyl)nitrobenzene (eq 3). In a glove box, the Schlenk tube equipped with a stir bar was charged with $PdCl_2$ (2.7 mg, 0.015 mmol, 3 mol %), CsF (168 mg, 1.1 mmol), CuI (3.8 mg, 0.02 mmol), and ligand **4** (6.7 mg, 0.015 mmol, 3 mol %). The tube was fitted with a rubber septum and removed out of the glove box. One mL of anhydrous DMF, 1-bromonanisole (94 mg, 0.5 mmol) and 4-(tributylstannyl)nitrobenzene (0.195 mL, 0.55 mmol) were added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred at room temperature for 20 h, and then diluted with ether, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (5 % ethyl acetate / hexanes) to afford 87 mg (76%) of 4-methoxy-4'-nitro-1, 1'-biphenyl [27] as light yellow solid. The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.

Stille Cross-Coupling of 4-*tert*-Butylphenyltriflate with Tributylphenyltin Using Ligands 1-4 (eq 4). In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol, 1.5 mol %) and CsF (272 mg, 1.8 mmol). The tube was fitted with a rubber septum and removed out of the glove box. One mL of 1,4-dioxane,

ligand **1** (or **2**) (solid ligands **3** and **4** were added inside the glove box), 4-*tert*-butylphenyltriflate (0.19 mL, 0.816 mmol), and tributylphenyltin (0.30 mL, 0.898 mmol) were added in turn to the Schlenk tube through rubber septum using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred for 30 minutes at room temperature, then, heated with stirring at 90 °C for 36 h. The reaction mixture was cooled to room temperature, diluted with ether, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes) to afford the desired product as white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[23]

Competition Experiment Between Aryl Triflate and Aryl Bromide (eq 5) In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol, 1.5 mol %), CsF (272 mg, 1.8 mmol), and **4** (10.9 mg, 0.024 mmol, 3 mol %). The tube was fitted with a rubber septum and removed out of the glove box. One mL of 1,4-dioxane, 4-bromotoluene (0.1 mL, 0.816 mmol), 4-*tert*-butylphenyl triflate (0.19 mL, 0.816 mmol), and tributylphenyltin (0.27 mL, 0.816 mmol) were then added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was stirred at room temperature for 16 h, and then diluted with ether, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes) to afford 115 mg (84%) of 4-methylbiphenyl as a white solid. The product was identical with an authentic material obtained from Aldrich by ^{1}H and ^{13}C NMR spectra.

Competition Experiment Between Aryl Triflate and Aryl Chloride (eq 6) In a glove box, the Schlenk tube equipped with a stir bar was charged with $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol, 1.5 mol %), CsF (272 mg, 1.8 mmol), and **4** (10.9 mg, 0.024 mmol, 3 mol %). The tube was fitted with a rubber septum and removed out of the glove box. One mL of 1,4-dioxane, 4-chlorotoluene (0.1 mL, 0.816 mmol), 4-*tert*-butylphenyltriflate (0.19 mL, 0.816 mmol) and tributylphenyltin (0.27 mL, 0.816 mmol) were then added successively using syringes. The tube was sealed with a Teflon screwcap. The reaction mixture was initially stirred for 30 minutes at room temperature then heated with stirring at 90 °C for 36 h. The reaction mixture was cooled to room temperature, diluted with ether, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes) to afford 163

mg (95%) of 4-*tert*-butylbiphenyl as a white solid. The ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[23]

1-Phenylcyclopentene[28] (Table 7, entry 1) Procedure B was followed using 1-chloro-1-cyclopentene (86 mg, 0.816 mmol), tributylphenyltin (0.30 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). After the reaction was run at 100 °C for 40 h, the crude product was purified by column chromatography on silica gel (pentane) to afford 117 mg (91%) of the desired product as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, J = 7.2 Hz, 2H), 7.35- 7.22 (m, 3H), 6.20 (t, J = 1.95 Hz, 1H), 2.76-2.73 (m, 2H), 2.57-2.52 (m, 2H), 2.09-1.99 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.6, 137.0, 128.5, 127.0, 126.3, 125.8, 33.6, 33.4, 23.6.

1-(2'-Thiophenyl)cyclopentene[29] (Table 7, entry 2) Procedure B was followed using 1-chloro-1-cyclopentene (86 mg, 0.816 mmol), (tributylstannyl)thiophene (0.27 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). After the reaction was run at 100 °C for 40 h, the crude product was purified by column chromatography on silica gel (pentane) to afford 102 mg (83%) of the desired product as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16-7.14 (m, 1H), 6.99-6.92 (m, 2H), 6.05-6.03 (m, 1H), 2.70-2.68 (m, 2H), 2.55-2.50 (m, 2H), 2.08-2.00 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 141.5, 136.9, 127.4, 126.0, 123.9, 123.5, 34.5, 33.5, 23.6.

1-(2'-Furyl)cyclopentene[29] (Table 7, entry 3) Procedure B was followed using 1-chloro-1-cyclopentene (86 mg, 0.816 mmol), (tributylstannyl)furan (0.27 mL, 0.898 mmol), and **4** (12.7 mg, 0.029 mmol, 3.5 mol %). After the reaction was run at 100 °C for 40 h, the crude product was purified by column chromatography on silica gel (pentane) to afford 101 mg (93%) of the desired product as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J = 1.4 Hz, 1H), 6.38-6.36 (m, 1H), 6.17 (d, J = 3.3 Hz, 1H), 6.09-6.08 (m, 1H), 2.65-2.60 (m, 2H), 2.59-2.49 (m, 2H), 2.04-1.94 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 152.8, 141.7, 133.1, 125.1, 111.1, 106.0, 33.4, 32.6, 23.5.

References

(1) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(2) Kosugi, M.; Miyajima, Y.; Nakanish, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jap.* **1989**, *62*, 3383.

(3) Seganish, W. M.; Deshong, P. *J. Org. Chem.* **2004**, *69*, 1137.

(4) Thomas, E. W.; Cudahy, M. M.; Spilman, C. H.; Dinh, D. M.; Watkins, T. L.; Vidmar, T. J. *J. Med. Chem.* **1992**, *35*, 1233.

(5) Naiini, A. A.; Menge, W. M. P. B. Verkade, J. G. *Inorg. Chem.* **1991**, *30*, 5009.

(6) Bergmann, E. D.; Blum, J. *J. Org. Chem.* **1959**, *24*, 549.

(7) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830.

(8) Ochiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Chemical & Pharmaceutical Bulletin* **1982**, *30*, 3994.

(9) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.

(10) Riggleman, S.; Deshong, P. *J. Org. Chem.* **2003**, *68*, 8106.

(11) Kang, S.–K.; Kim, J.–S.; Yoon, S.–K.; Lim, K,-H.; Yoon, S. S. *Tetrahedron Lett.* **1998**, *39*, 3011.

(12) Rao, M. S. C.; Rao, G. S. K. *Synthesis* **1987**, 231.

(13) Nakao, Y.; Oda, T.; Sahoo, A. K.; Hiyama, T. *J. Organomet. Chem.* **2003**, *687*, 570.

(14) Takahashi, K.; Suzuki, T.; Akiyama, K.; Ikegami, Y.; Fukazawa, Y. *J. Am. Chem. Soc.* **1993**, *113*, 4576.

(15) Tanis, S. T.; Deaton, M. V.; Dixon, L. A.; Mcwilliams, M. C.; Raggon, J. W., Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914.

(16) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690.

(17) Terao, Y.; Wakhi, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

(18) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jap.* **1976**, *49*, 1958.

(19) Riguet, E.; Alami, M.; Cahiez, G. *J. Organometal. Chem.* **2001**, *624*, 376.

(20) Walker, S. D.; Barder, T. E.; Martineli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(21) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242.

(22) Feherrari, A. F.; Kagumba, L.; Hadjikyriacou, S.; Chen, F.; Gaudiana, R. *J. App. Poly. Sci.* **2003**, *87*, 1634.

(23) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(24) Vinutha, A. R.; Von Rudloff, E. *Can. J. Chem.* **1968**, *46*, 3743.

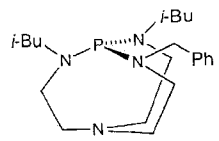
(25) Peyroax, E.; Berthiol, F.; Doucet, H.; Santeli, M. *Eur. J. Org. Chem.* **2004**, *5*, 1075.

(26) Guizzardi, B.; Mella, M.; Fagnoni, M.; Albini, A. *Tetrahedron* **2000**, *56*, 9383.

(27) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571.

(28) Miller, J. A. *Tetrahetron Lett.* **2002**, *43*, 7111.

(29) Brown, H. C.; Gupta, A. K.; Rangaishenvi, M. V.; Prased, J. V. N. V. *Heterocycles* **1989**, *28*, 283.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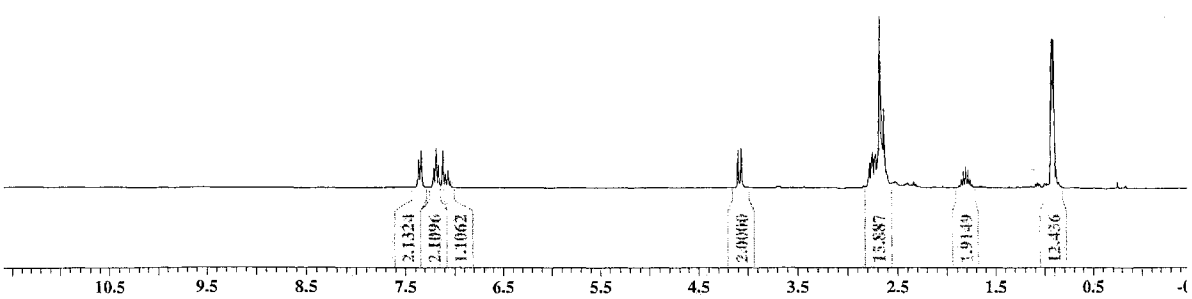
1.7628
1.7404
0.9362
0.9244
0.9142
0.9028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13.887
1.9149
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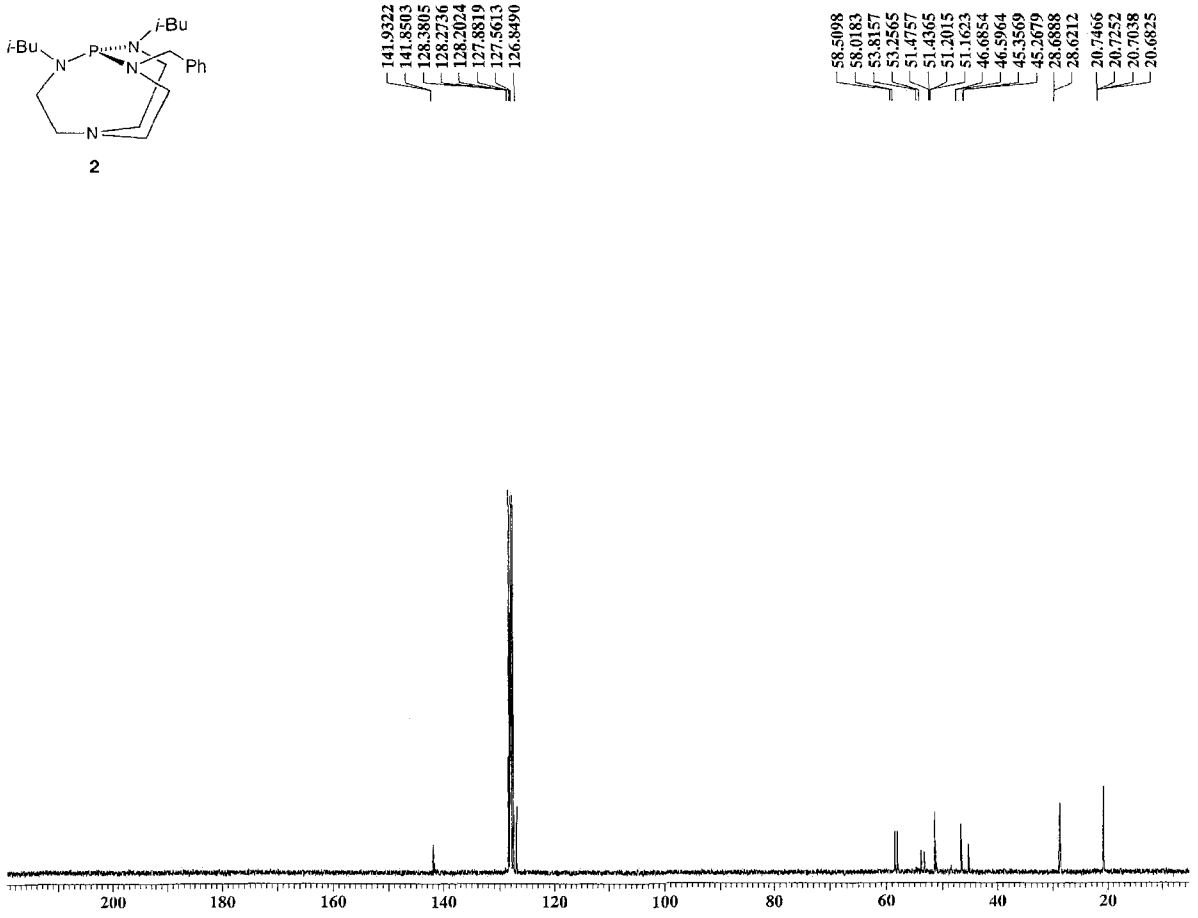
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5


i-Bu
i-Bu
Ph
2
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126.8490
58.5098
58.0183
53.8157
53.2565
51.4757
51.4365
51.2015
51.1623
46.6854
46.5964
45.3569
45.2679
28.6888
28.6212
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20.7252
20.7038
20.6825
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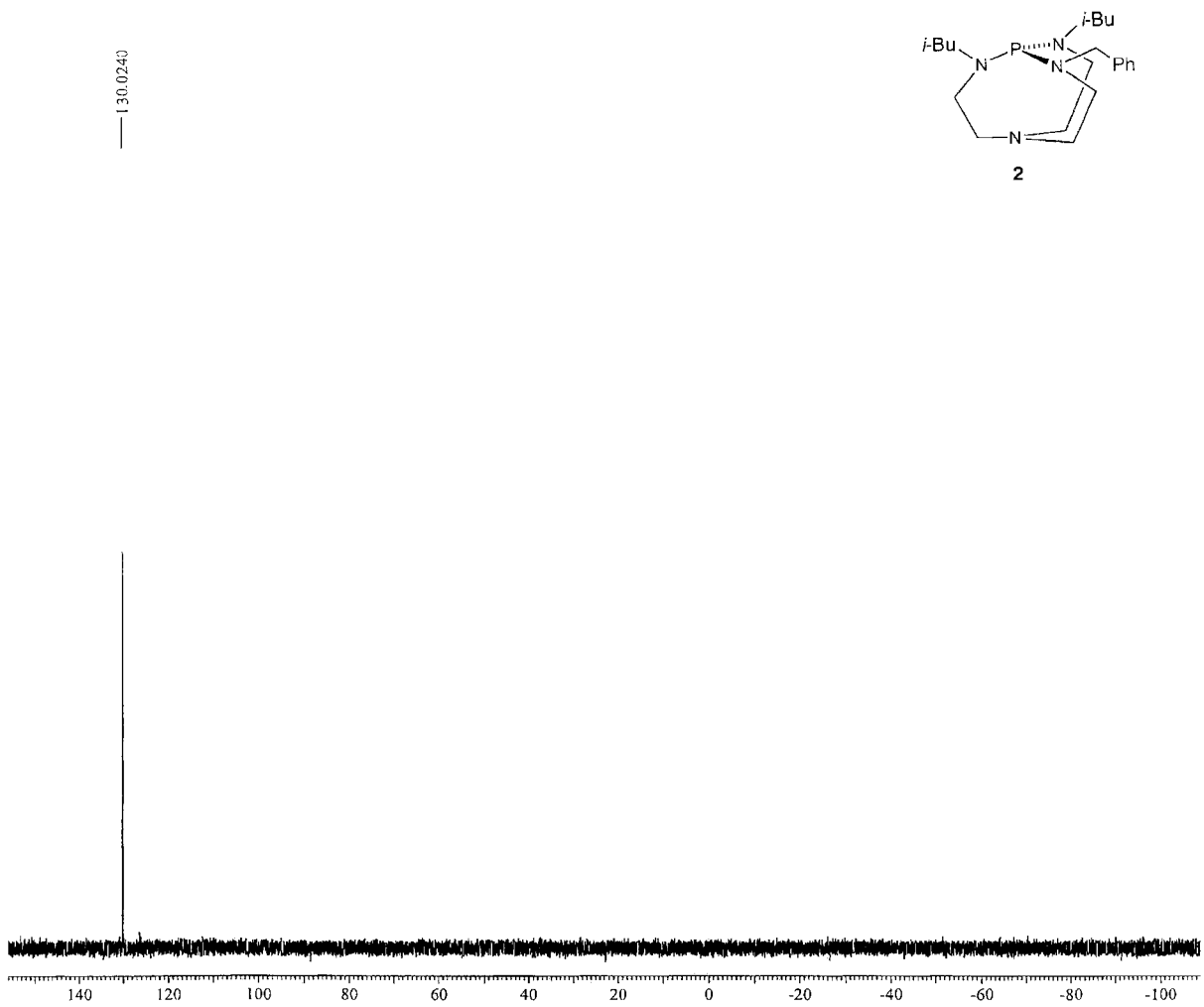
120
100
80
60
40
20


130.0240
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i-Bu
N
P
N
N
Ph
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2
140
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60
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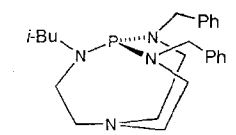
20
0
-20
-40
-60
-80
-100


i-Bu
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P
N
N
Ph
Ph
N

3


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7.3490
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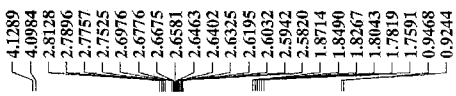
7.1911
7.1654
7.1174
7.0775
7.0531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4.0984
2.8128
2.7896
2.7757
2.7525
2.6976
2.6776
2.6675
2.6581
2.6463
2.6402
2.6325
2.6195
2.6032
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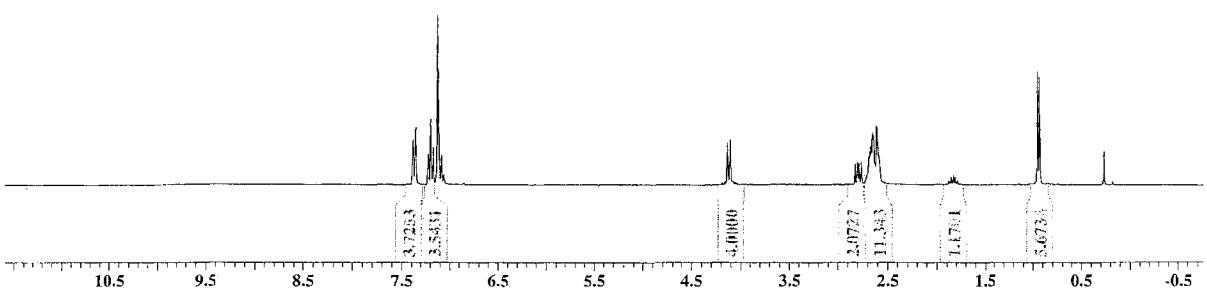
1.8714
1.8490
1.8267
1.8043
1.7819
1.7591
0.9468
0.9244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4.0000
2.0727
11.3483
1.1761
5.6737
10.5
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8.5
7.5
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5.5
4.5
3.5
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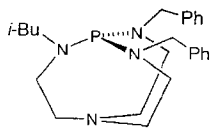
1.5
0.5
-0.5



3

141.7791
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128.2594
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127.5720
126.9202

58.2355
57.7512
53.6376
53.0891
51.3831
51.3439
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46.5964
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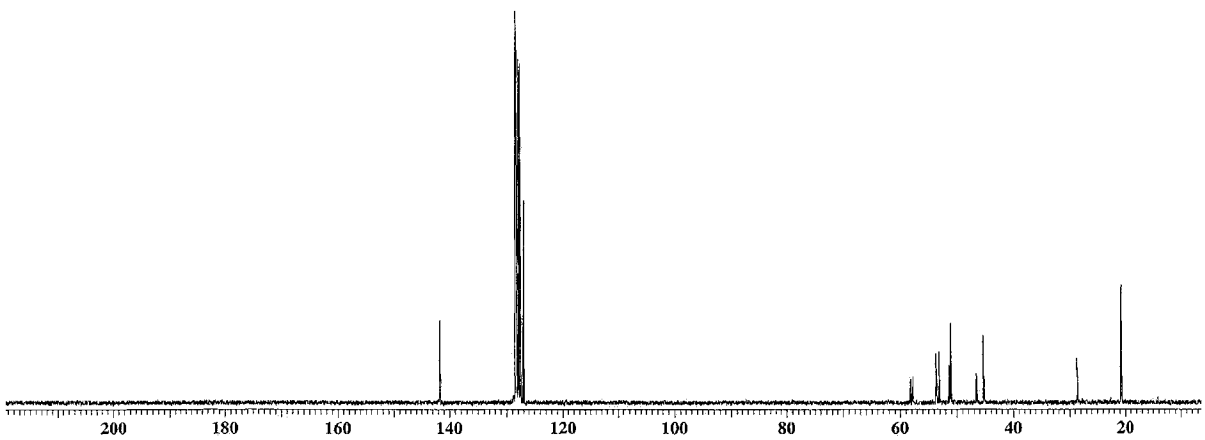
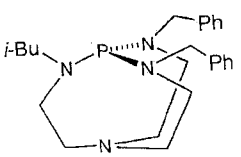
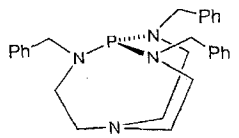
45.3926
45.3035
28.6425
28.5749
20.7430
20.7216





3


Ph
Ph
Ph
P
N
N
N
N

4


7.3717
7.3533
7.2135
7.1952
7.1758
7.1138
7.1122
7.0927


4.1457
4.1226


2.6634
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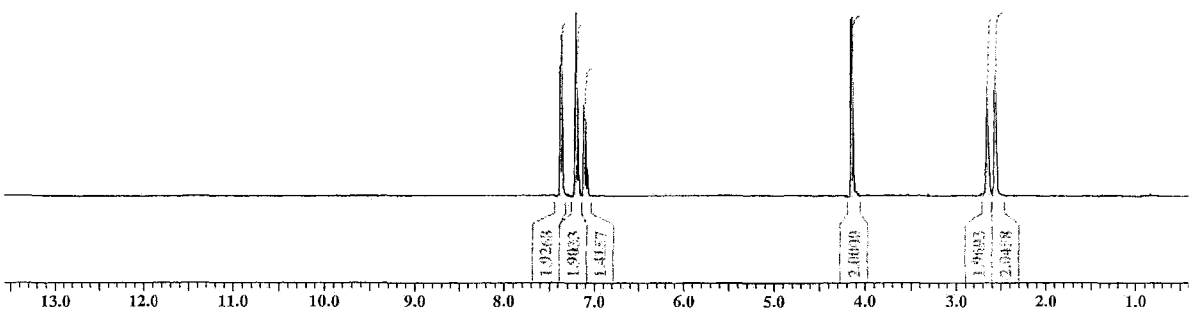
2.6392
2.6268
2.5616
2.5552
2.5481
2.5376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1.44577
2.00000
1.96082
2.04238
13.0
12.0
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10.0
9.0
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7.0
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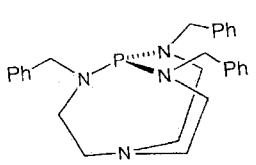
2.0
1.0


Ph
N
P
N
Ph
N
Ph
N

4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141.5618
128.4838
128.3057
128.2772
128.2202
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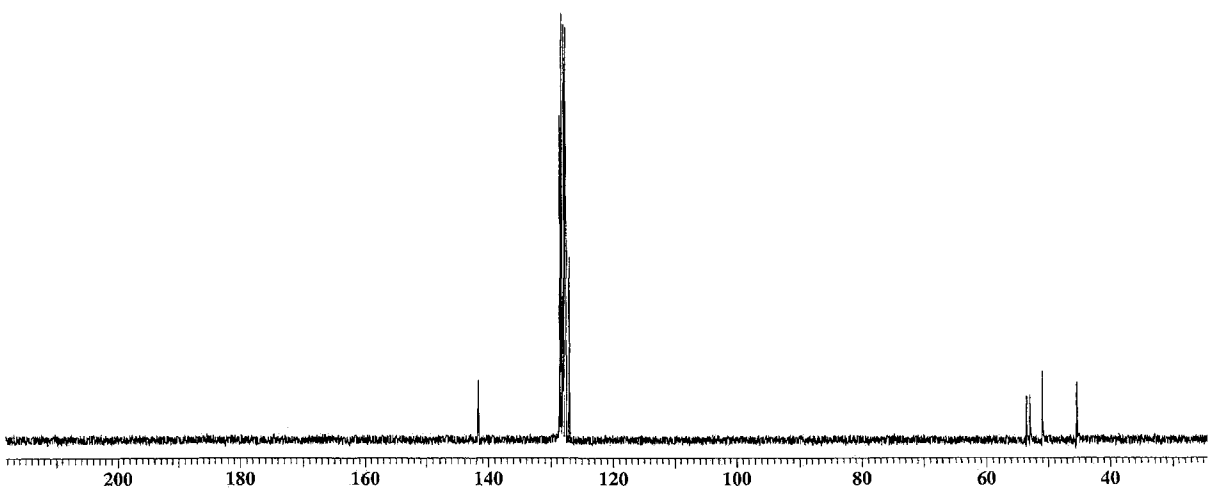
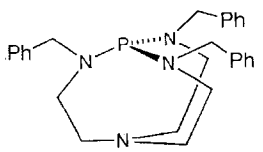
127.5791
126.9915

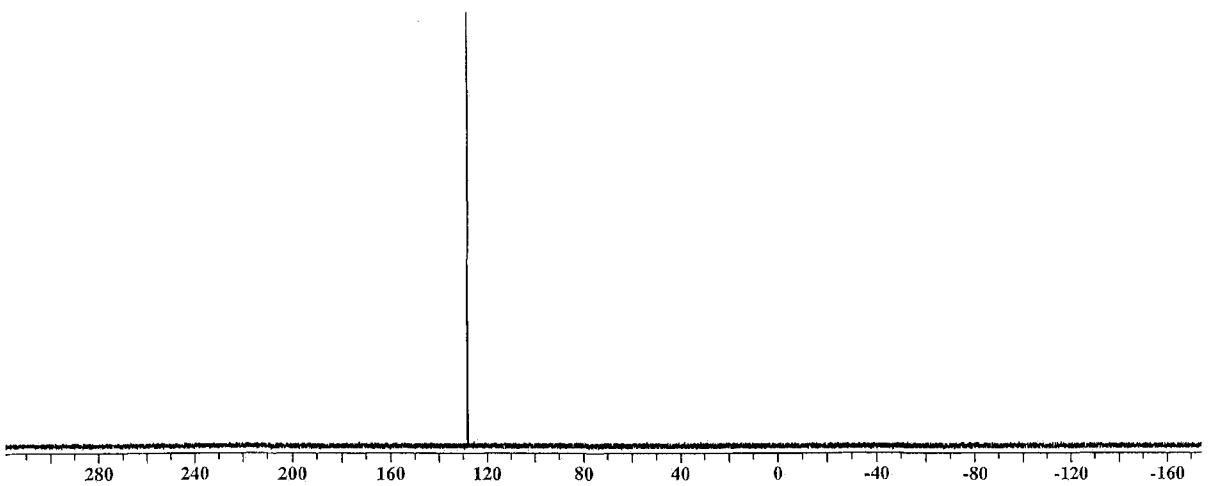

53.4274
52.8825
50.9878
50.9522
45.4211
45.3320

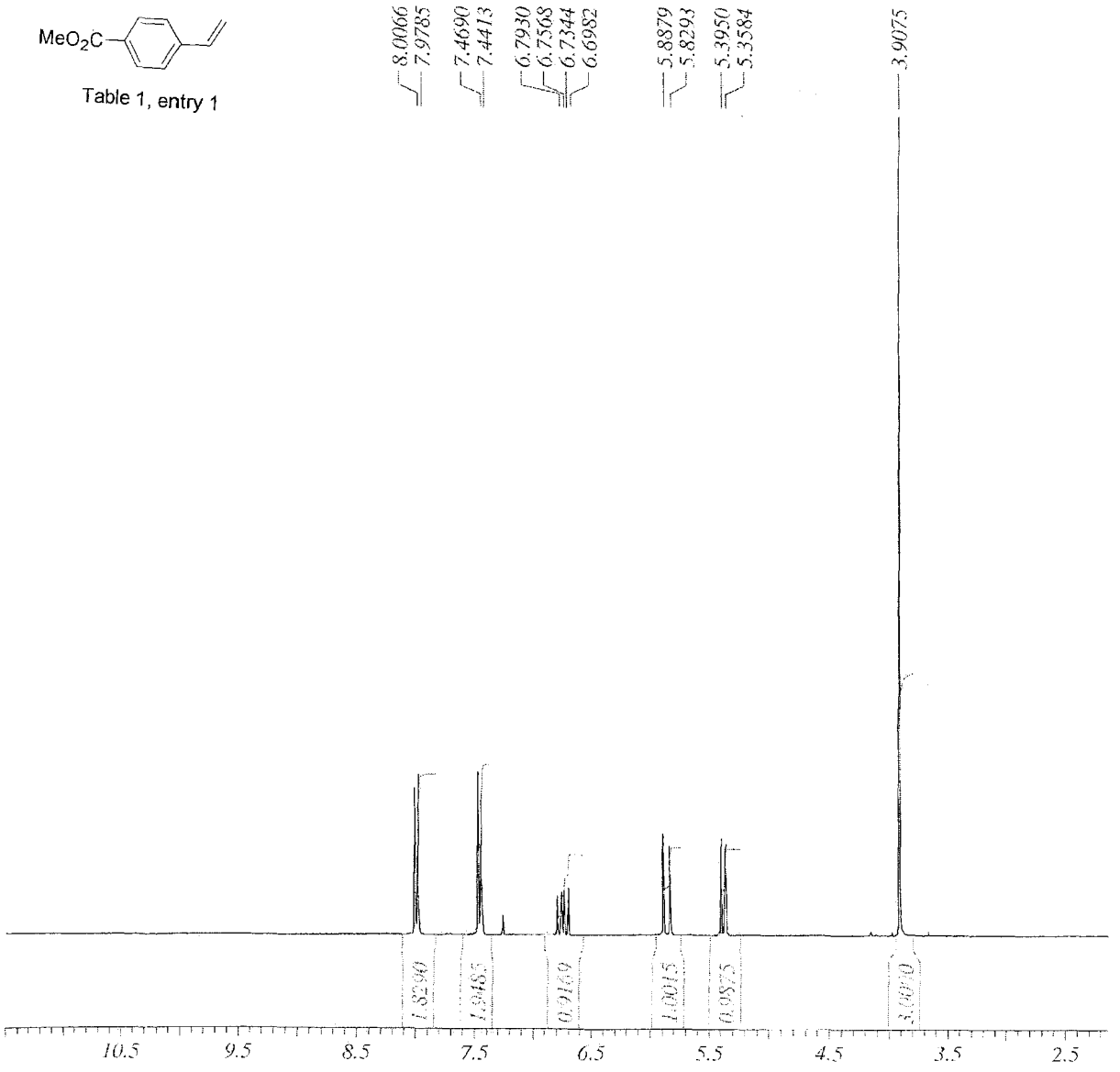

200
180
160
140
120
100
80
60
40



4

127.9667




MeO2C
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7.4690
7.4413
6.7930
6.7568
6.7344
6.6982
5.8879
5.8293
5.3950
5.3584
3.9075
1.8290
1.9485
0.9169
1.0015
0.9875
3.0070
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5

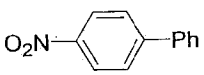
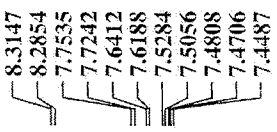
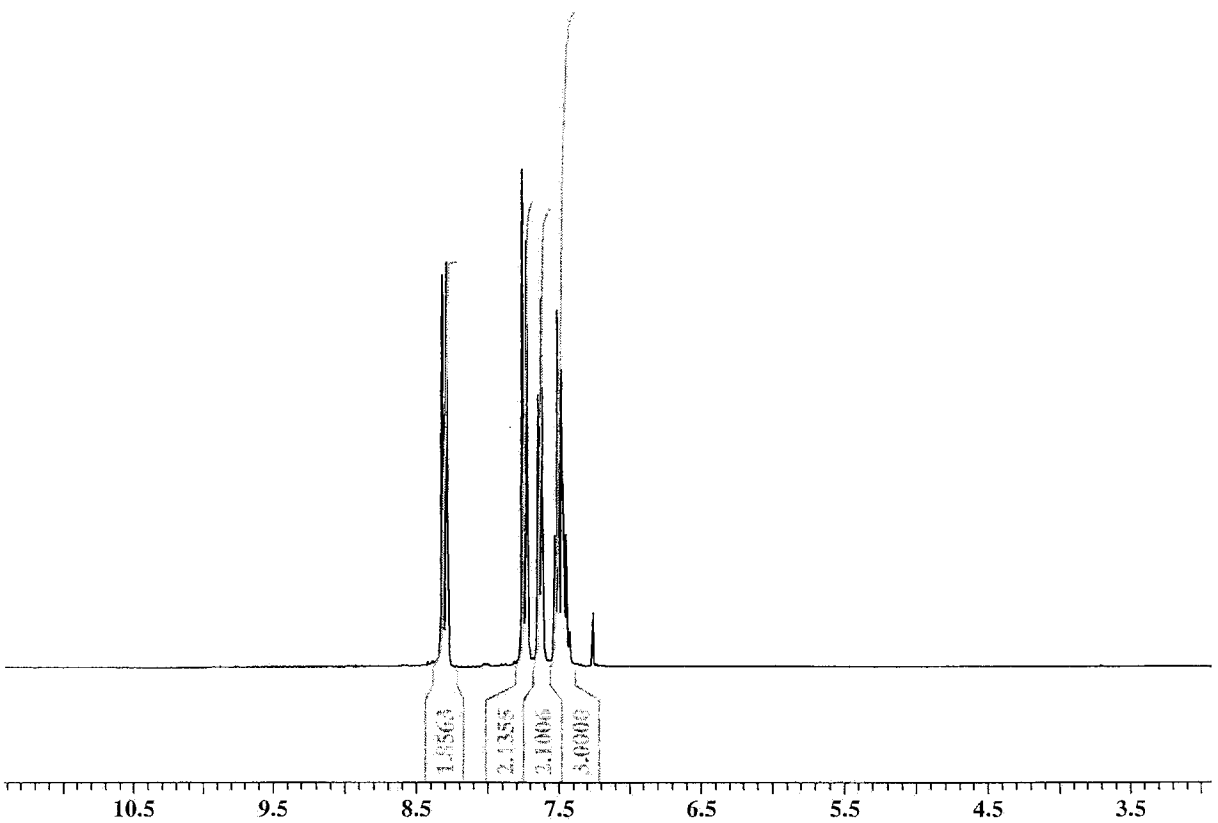
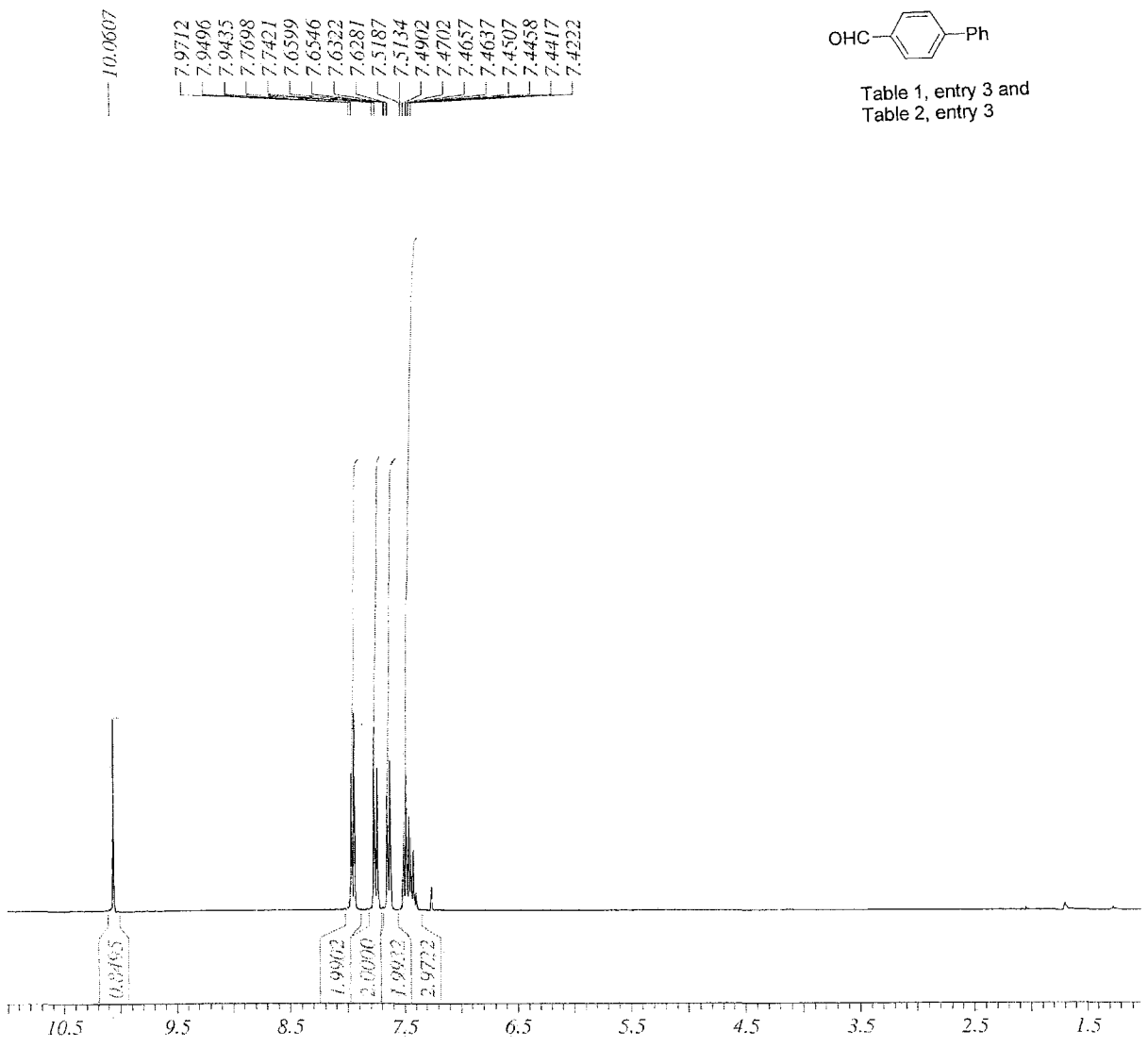


Table 1, entry 2 and
Table 2, entry 2



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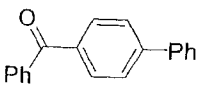
7.9435
7.7698
7.7421
7.6599
7.6546
7.6322
7.6281
7.5187
7.5134
7.4902
7.4702
7.4657
7.4637
7.4507
7.4458
7.4417
7.4222
OHC
Ph
Table 1, entry 3 and
Table 2, entry 3
0.9465
1.9962
2.0000
1.9932
2.9722
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5



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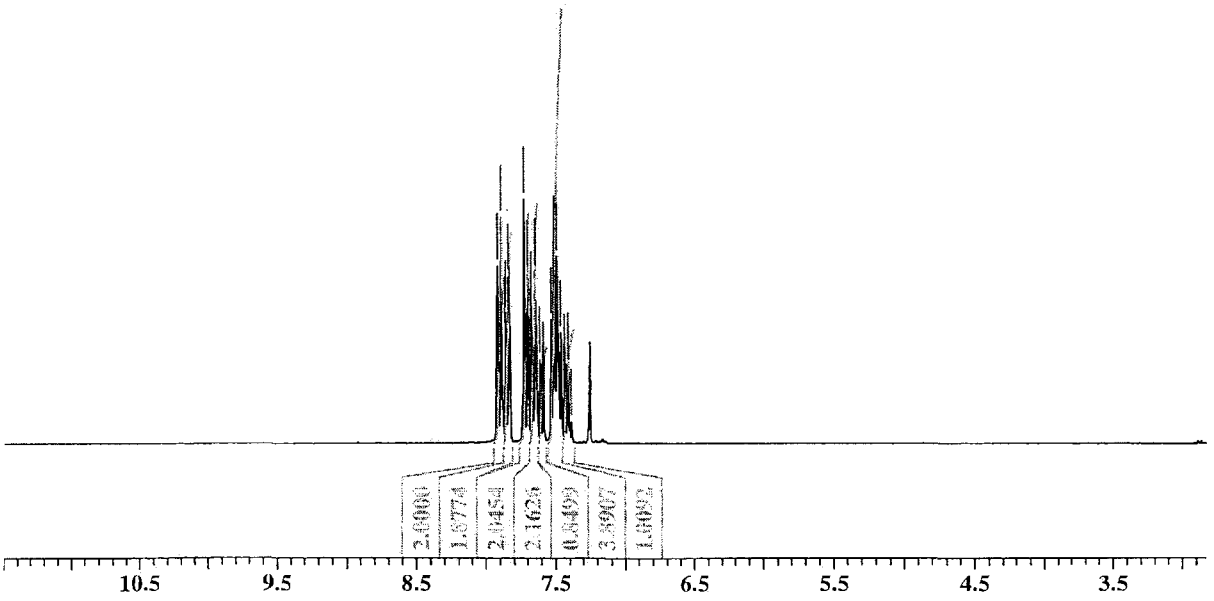
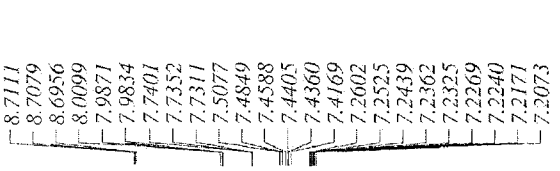




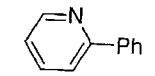
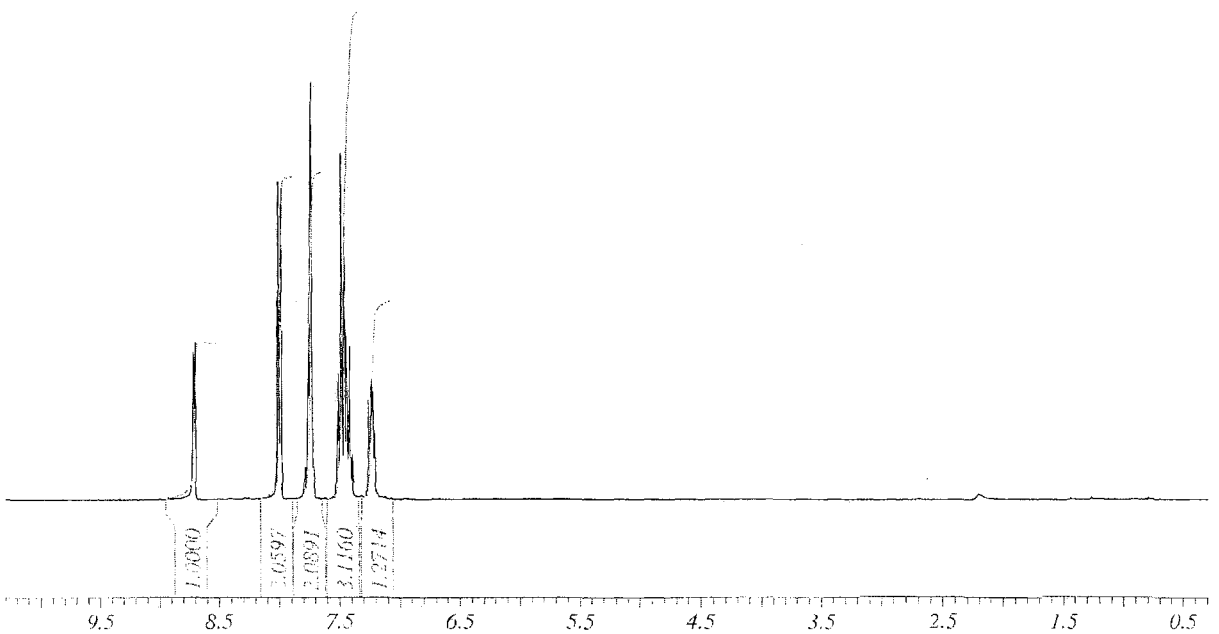


Table 1, entry 5 and
Table 3, entry 5



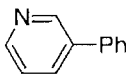
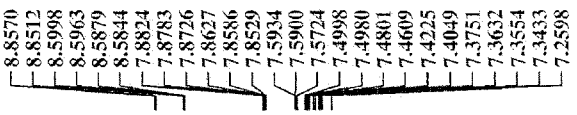
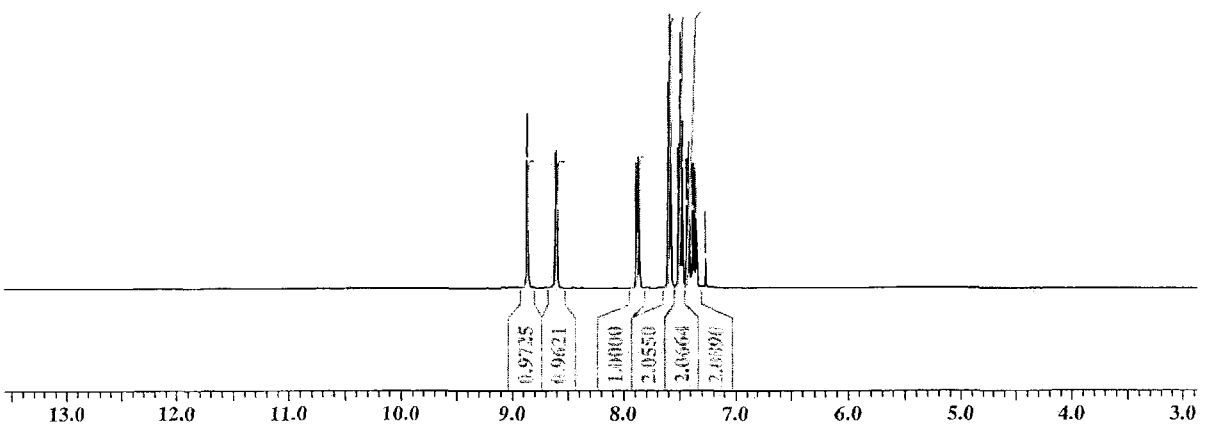
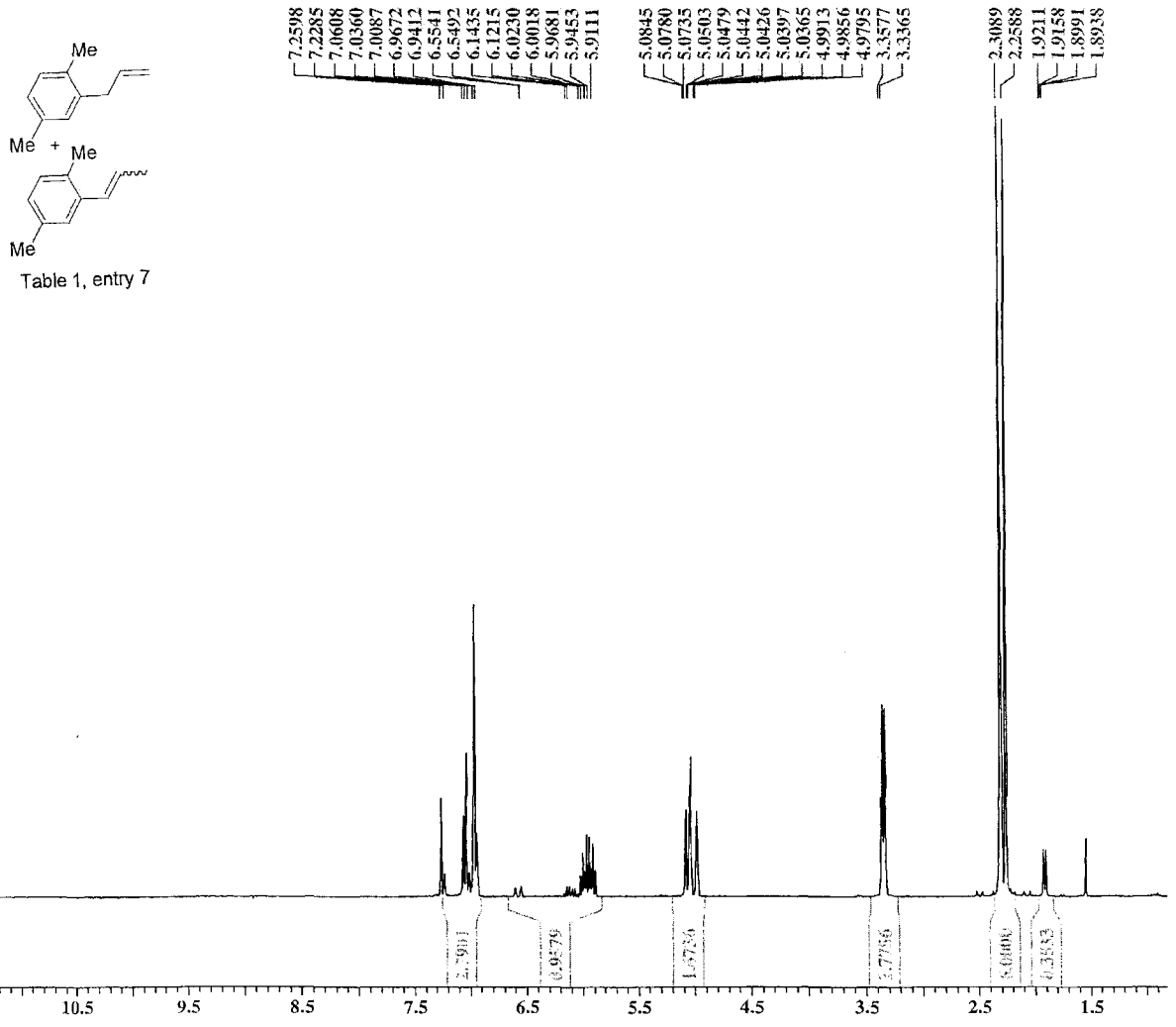


Table 1, entry 6 and
Table 3, entry 4






Me
Me
+
Me
Me
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7.0608
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7.0087
6.9672
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6.1435
6.1215
6.0230
6.0018
5.9681
5.9453
5.9111
5.0845
5.0780
5.0735
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5.0426
5.0397
5.0365
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4.9795
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3.3365
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2.7991
0.9279
1.6736
3.7756
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8.5
7.5
6.5
5.5
4.5
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2.5
1.5

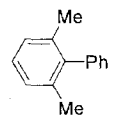
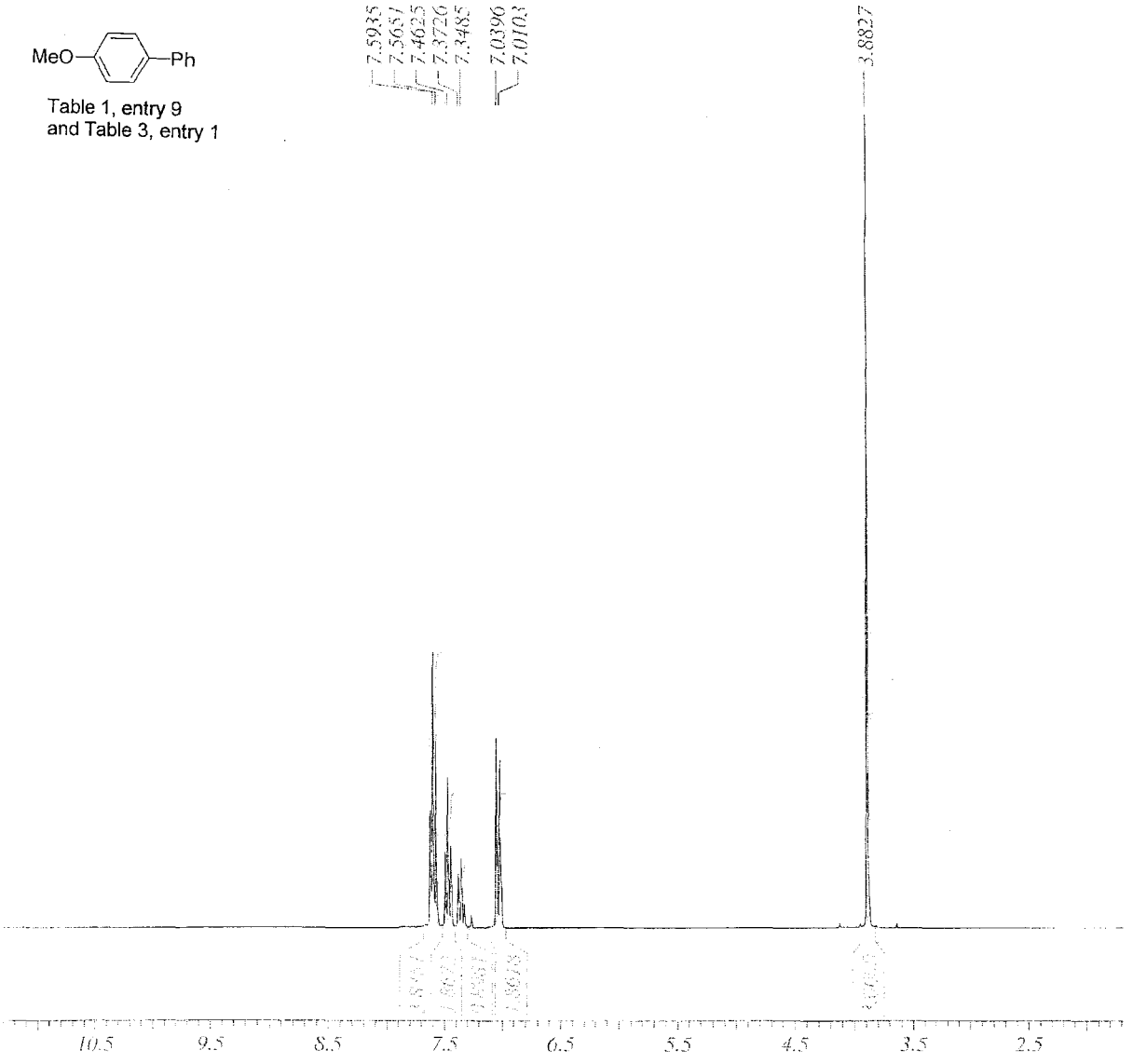


Table 1, entry 8


MeO
Ph
Table 1, entry 9
and Table 3, entry 1
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7.4625
7.3726
7.3485
7.0396
7.0103
3.8827
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8.5
7.5
6.5
5.5
4.5
3.5
2.5

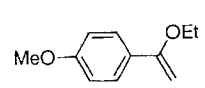
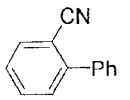


Table 1, entry 10 and
Table 4, entry 2



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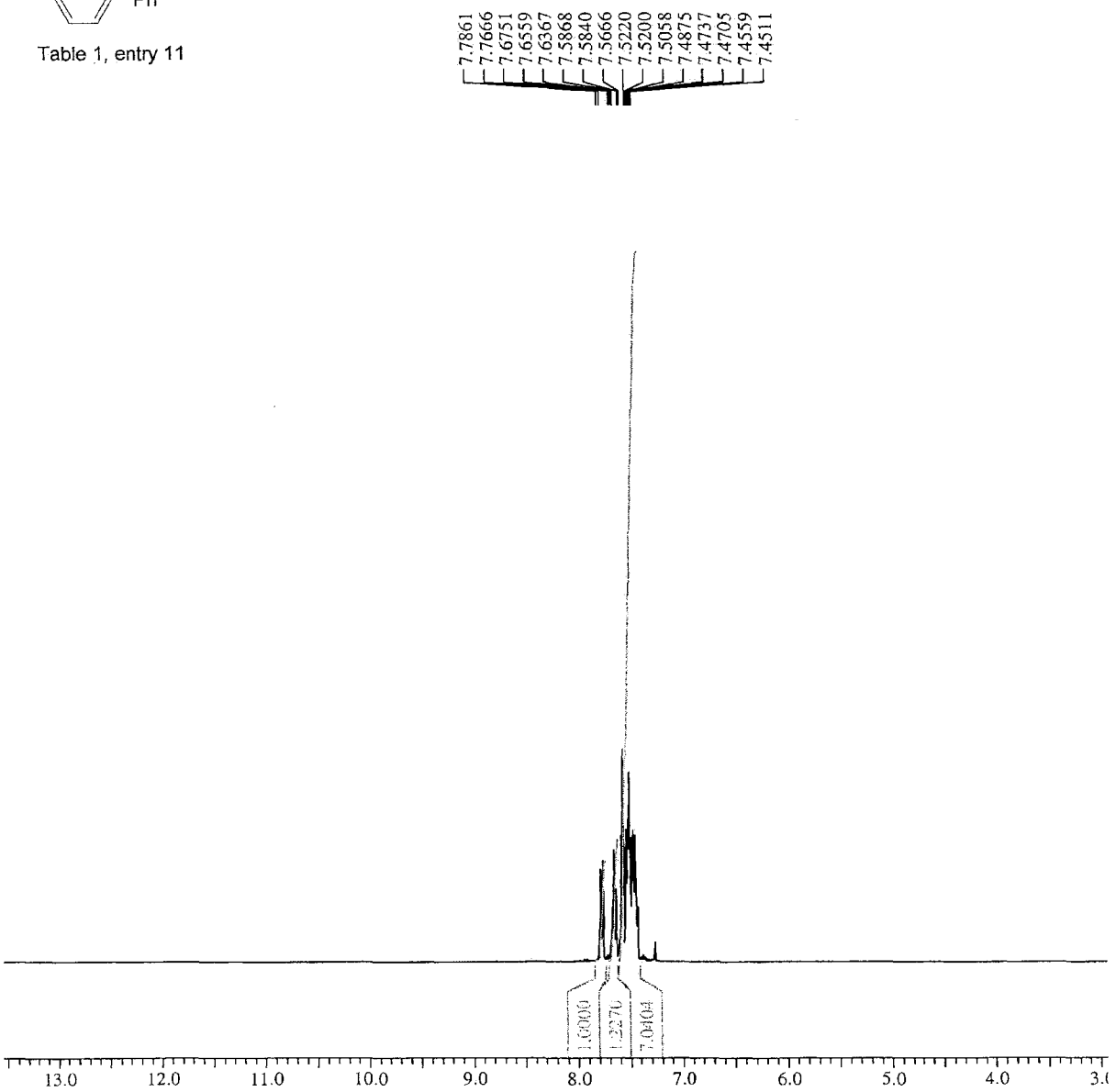

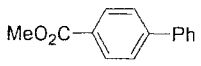

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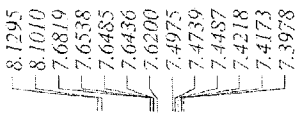
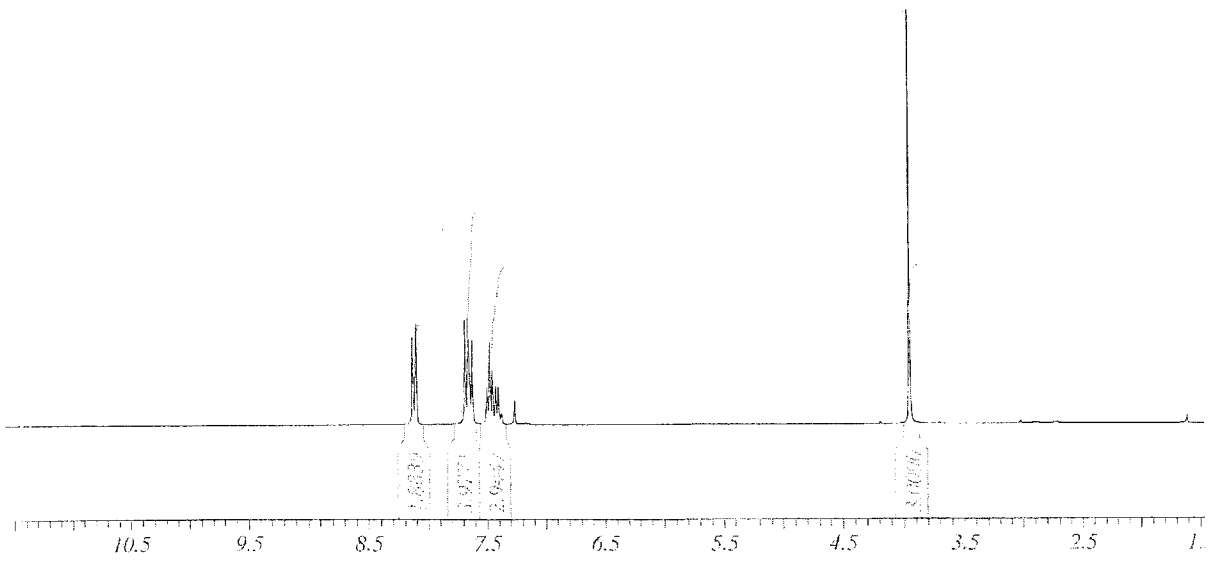




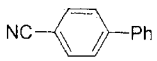
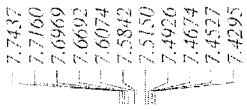
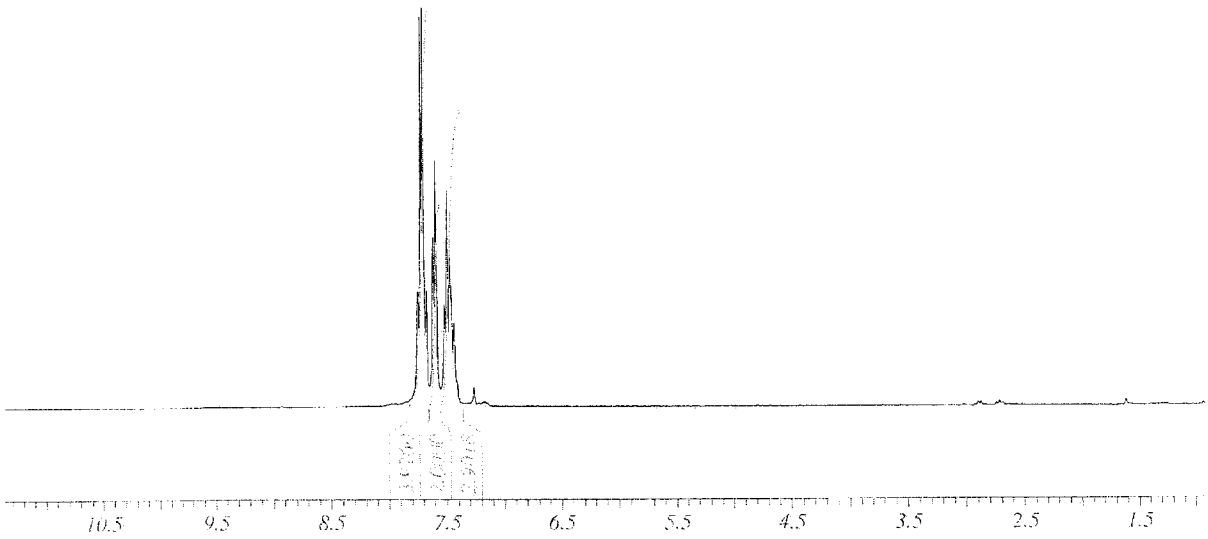
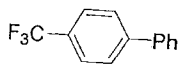


Table 2, entry 5







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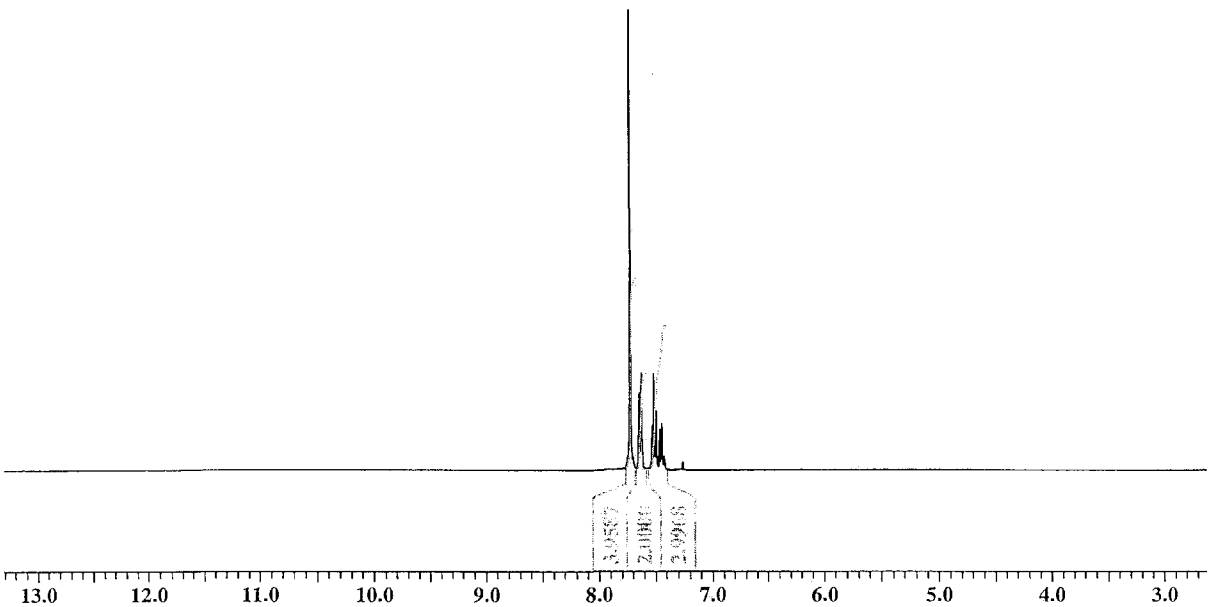

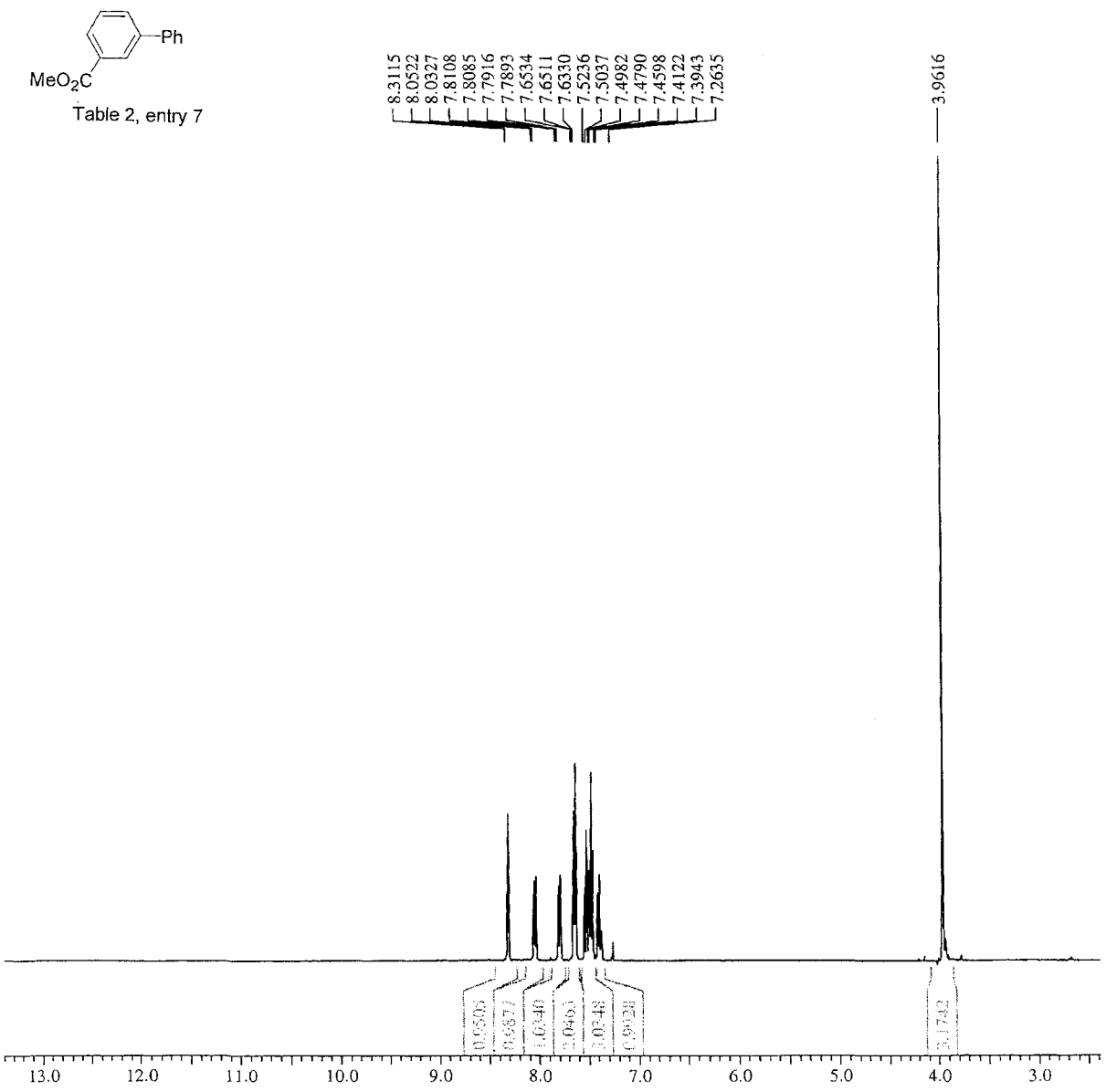
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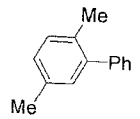

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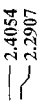

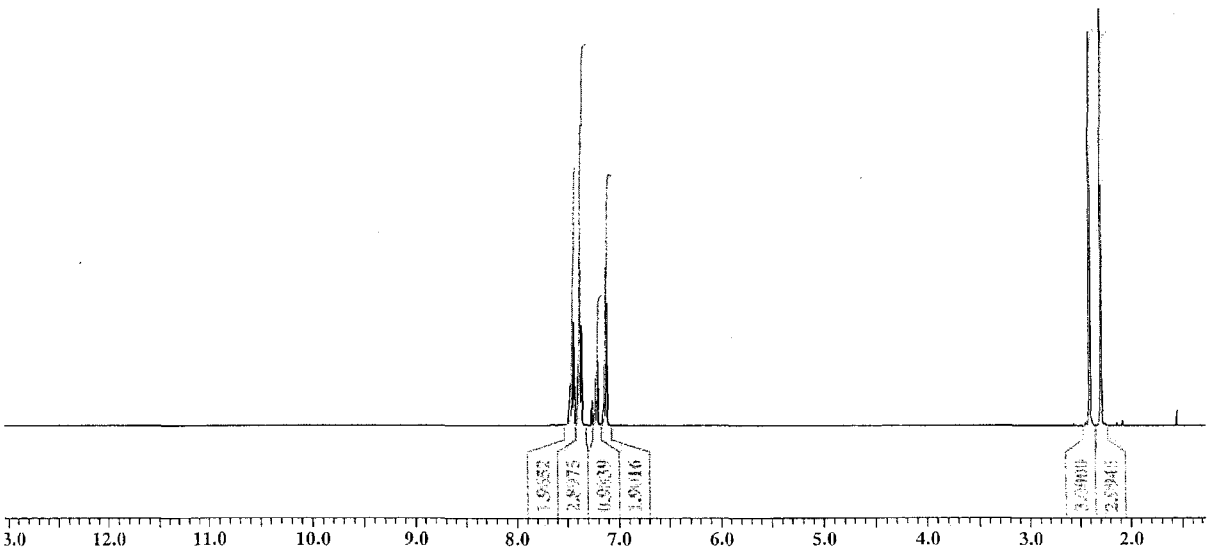

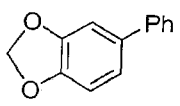

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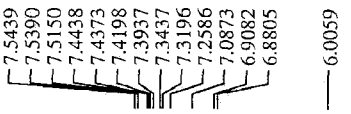

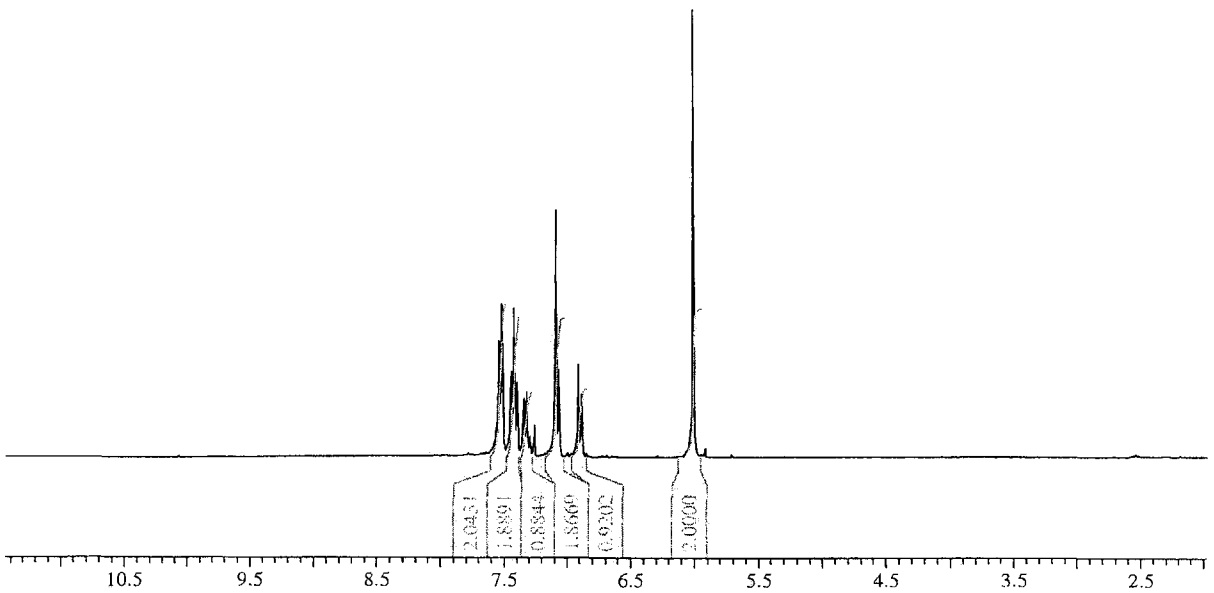

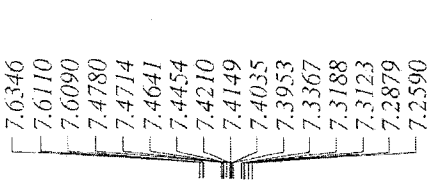

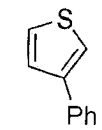

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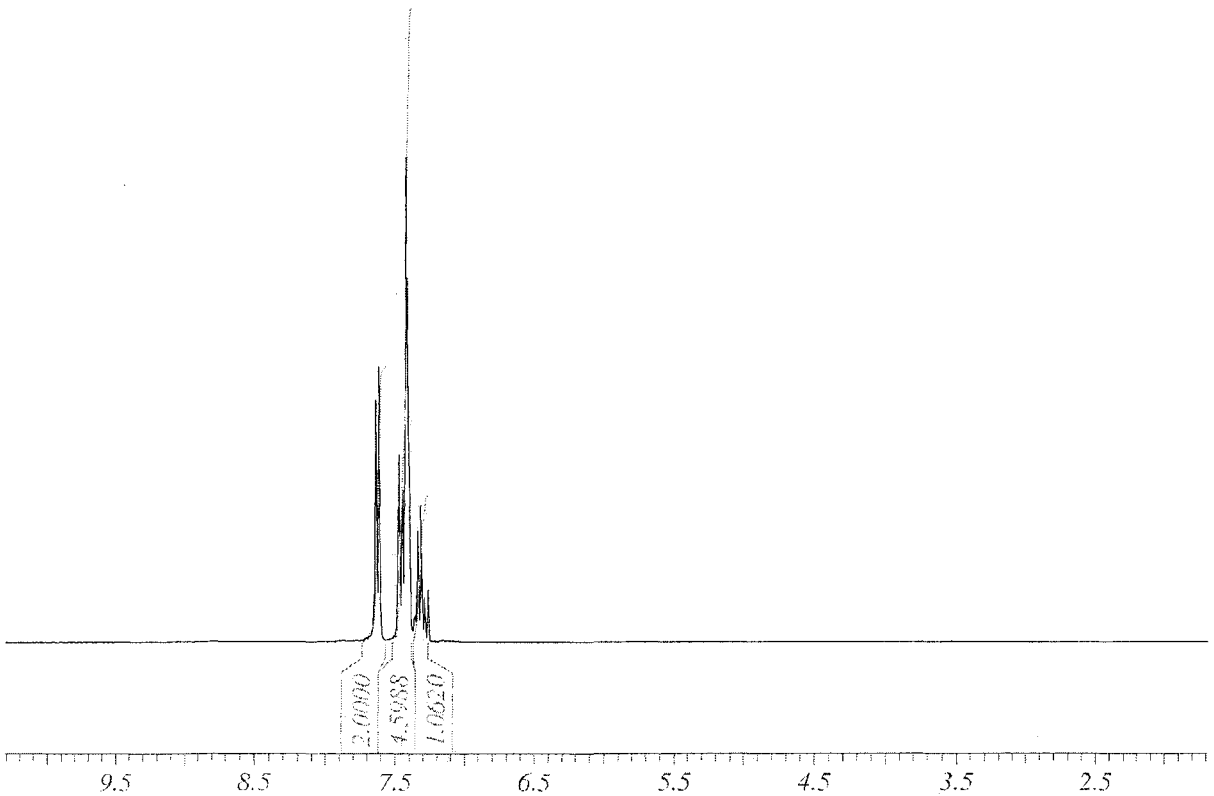

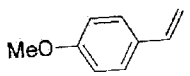

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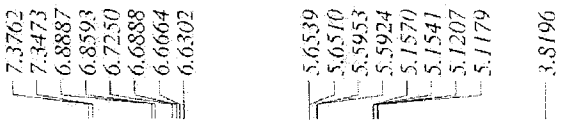

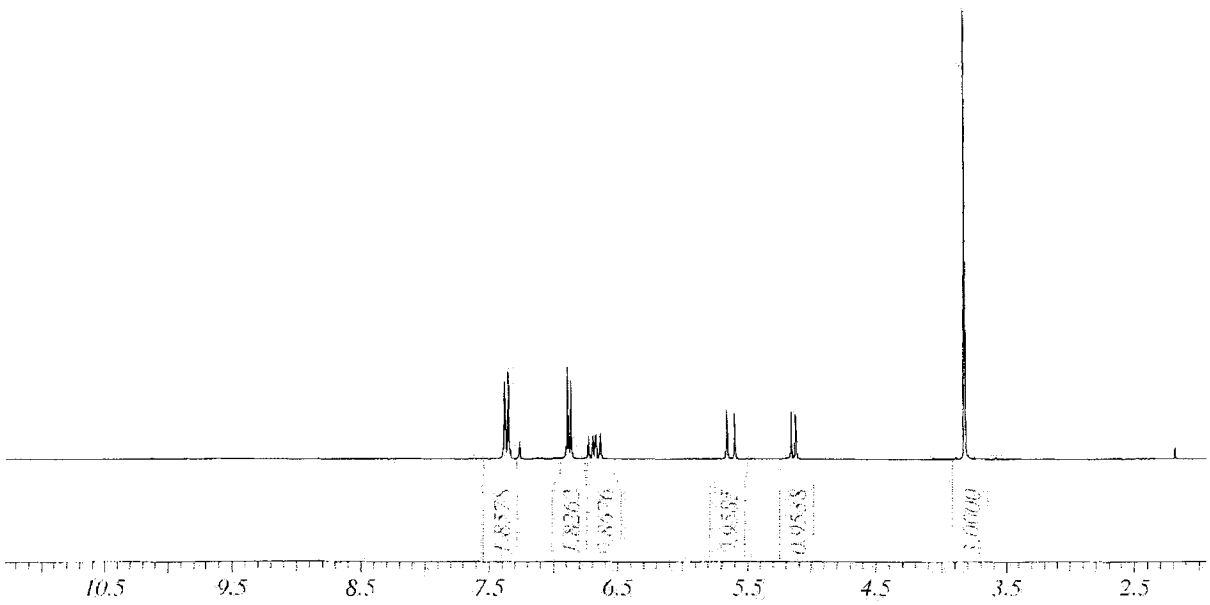

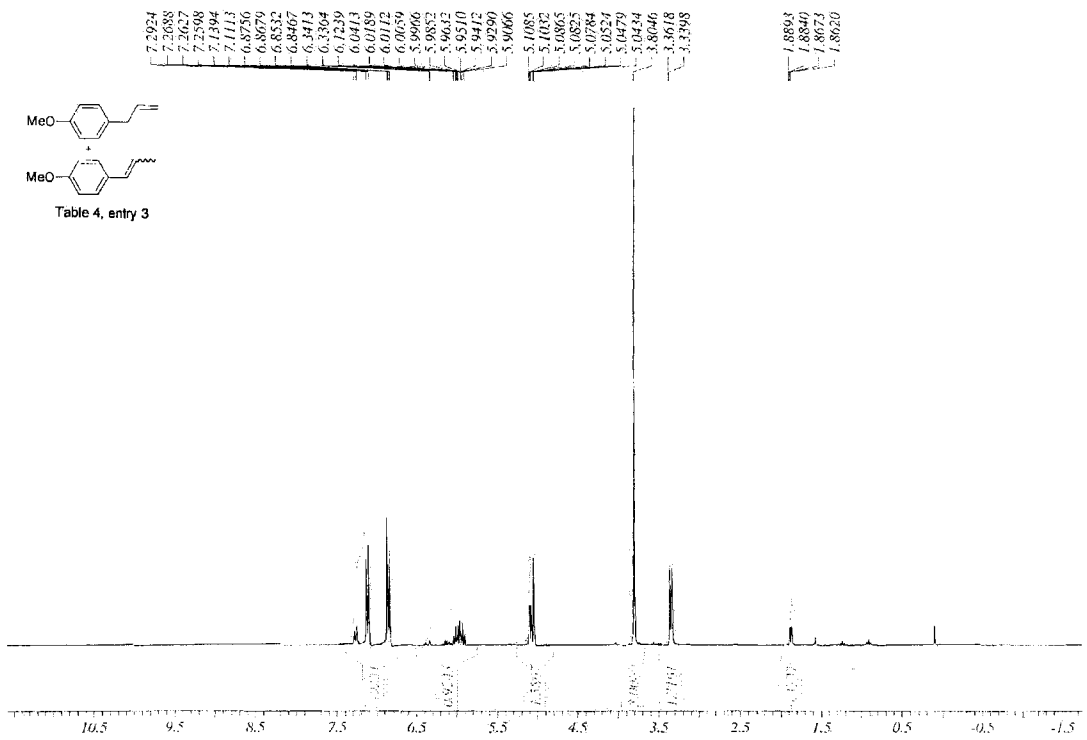
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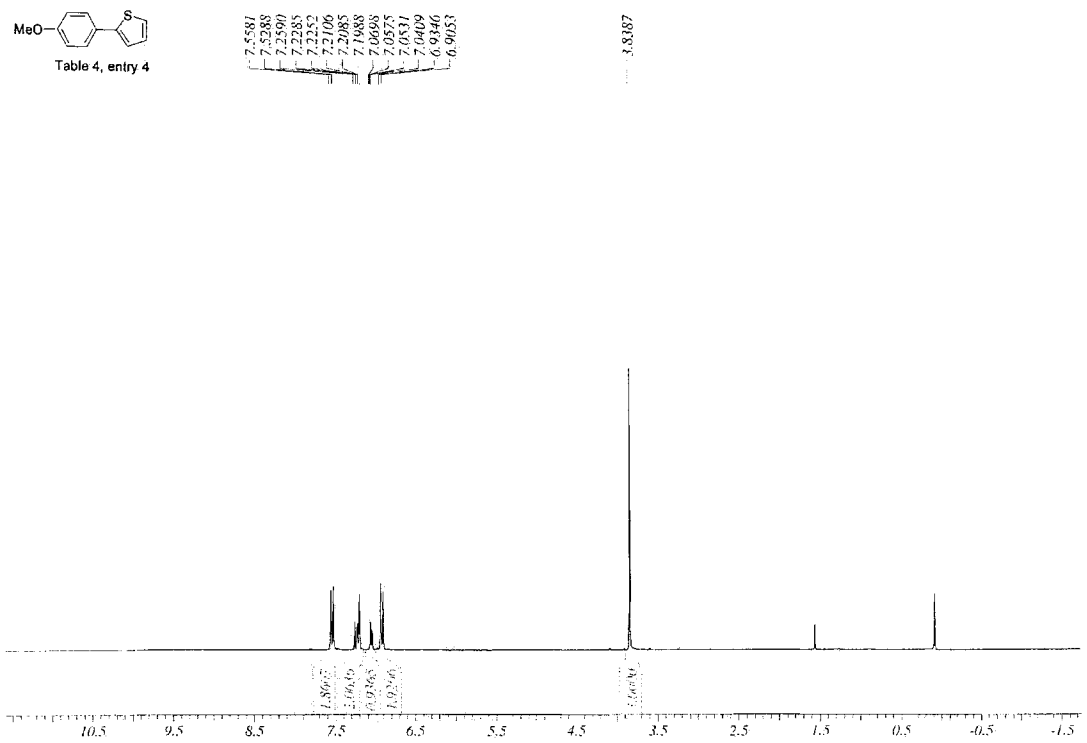
MeO
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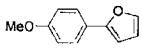

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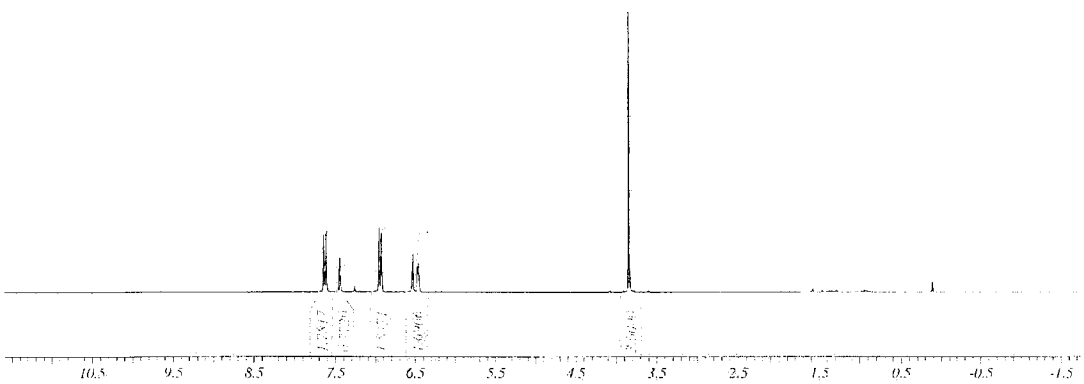

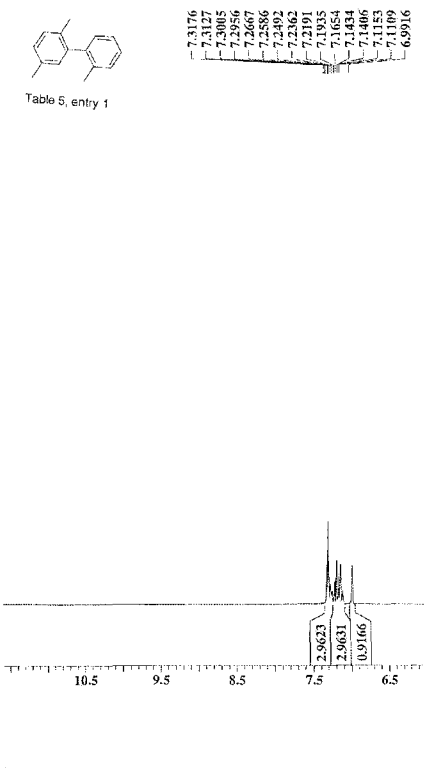
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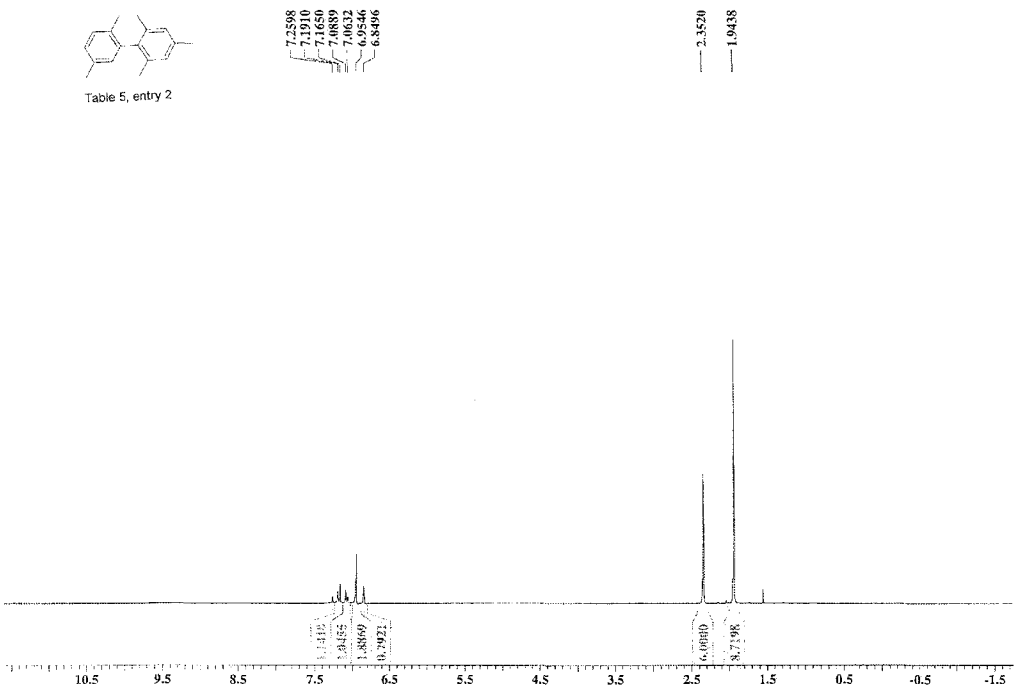

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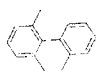

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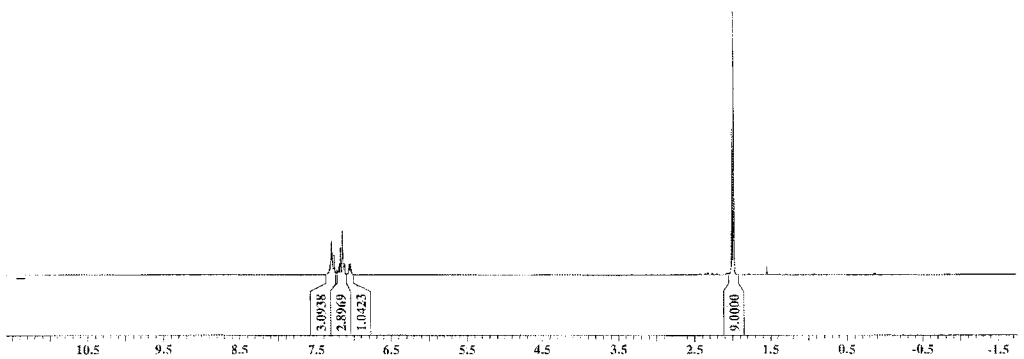

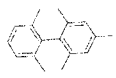

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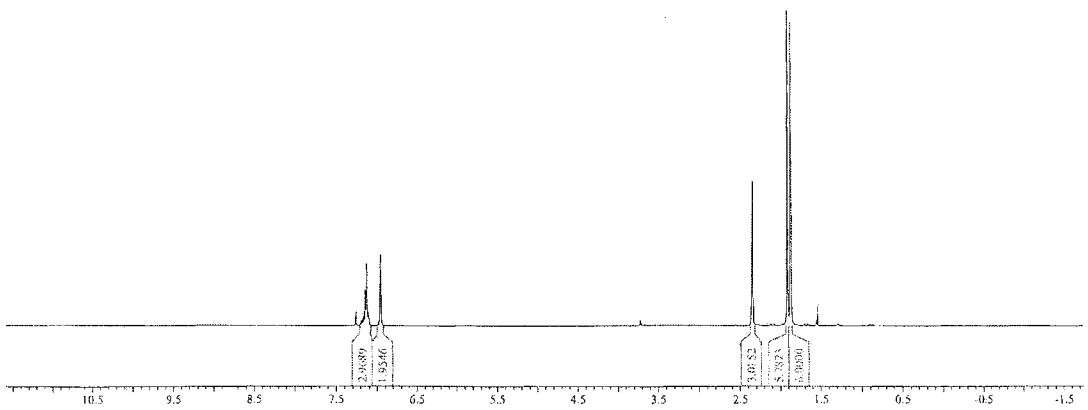

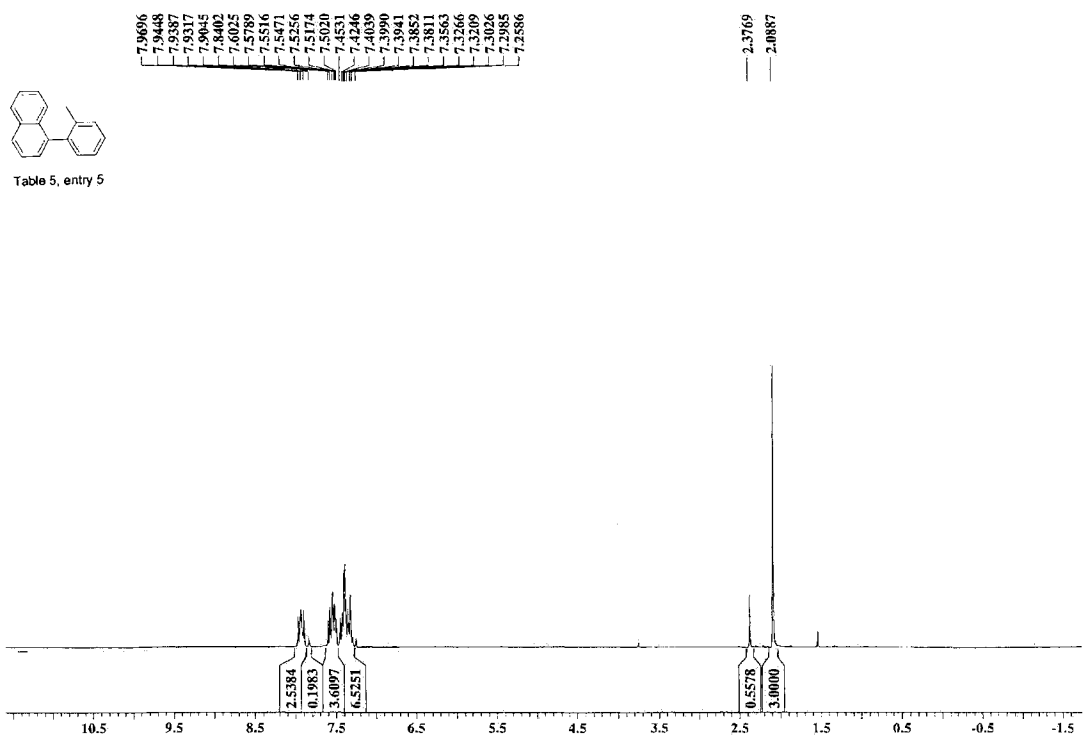

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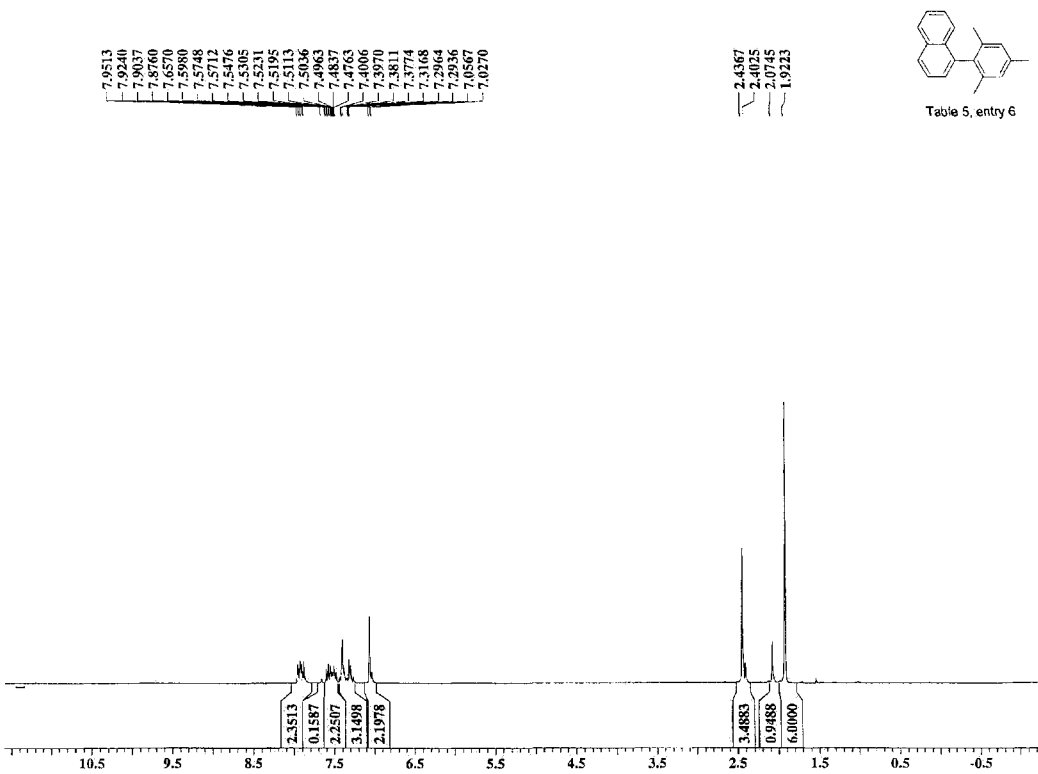
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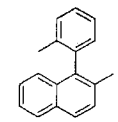

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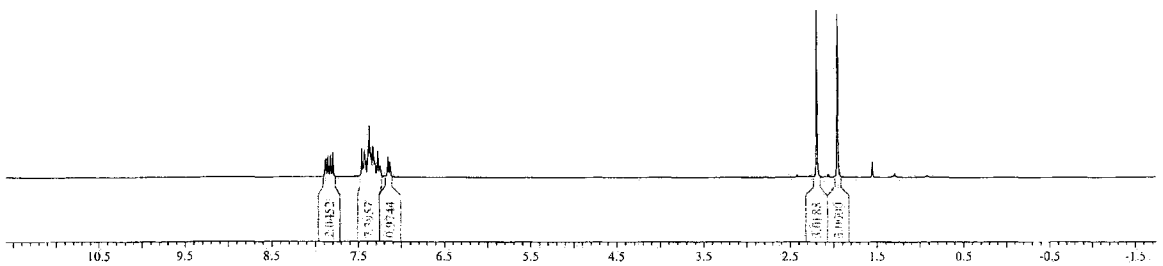

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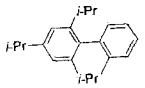

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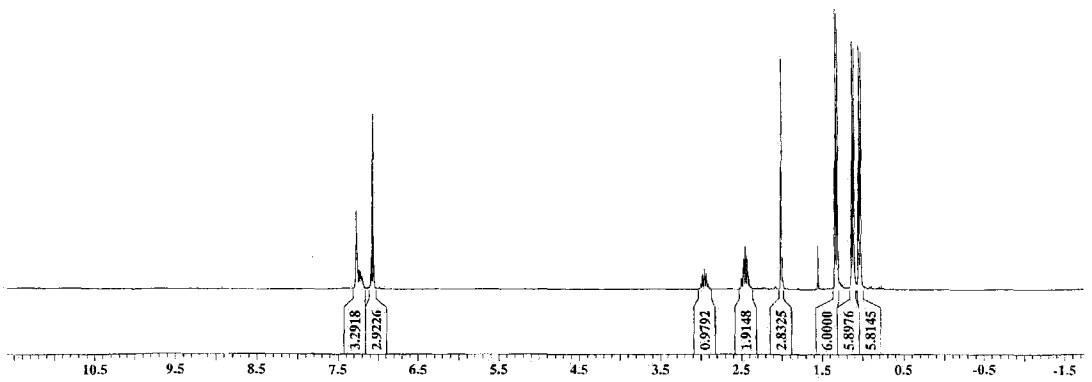

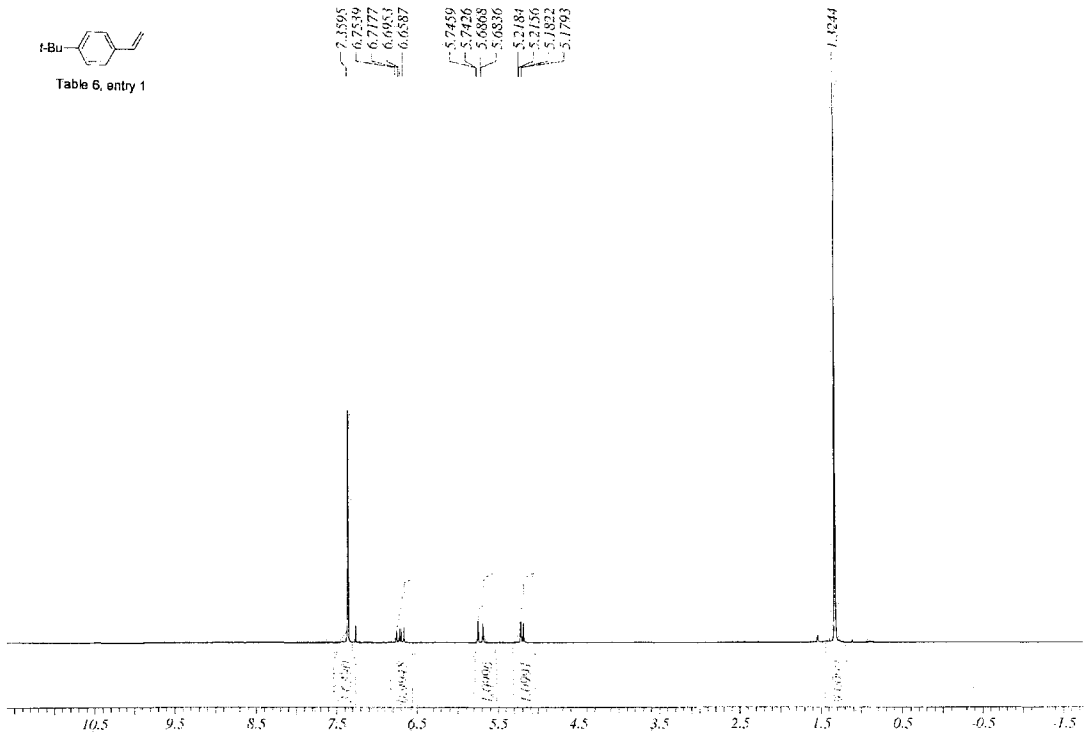
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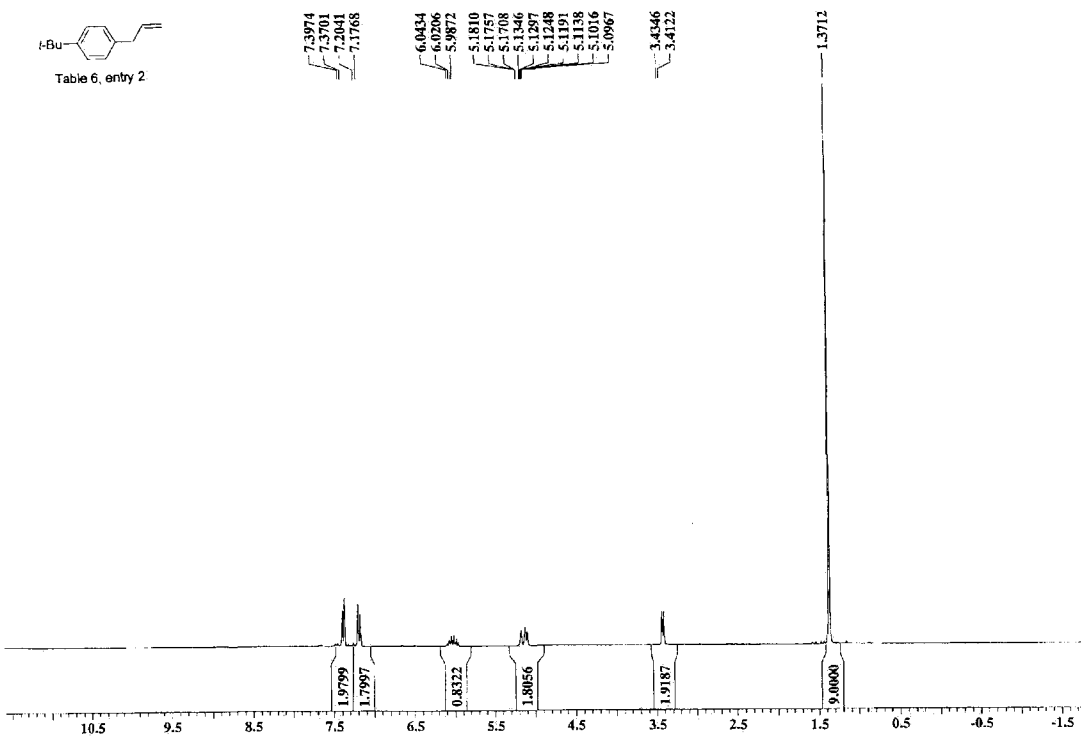
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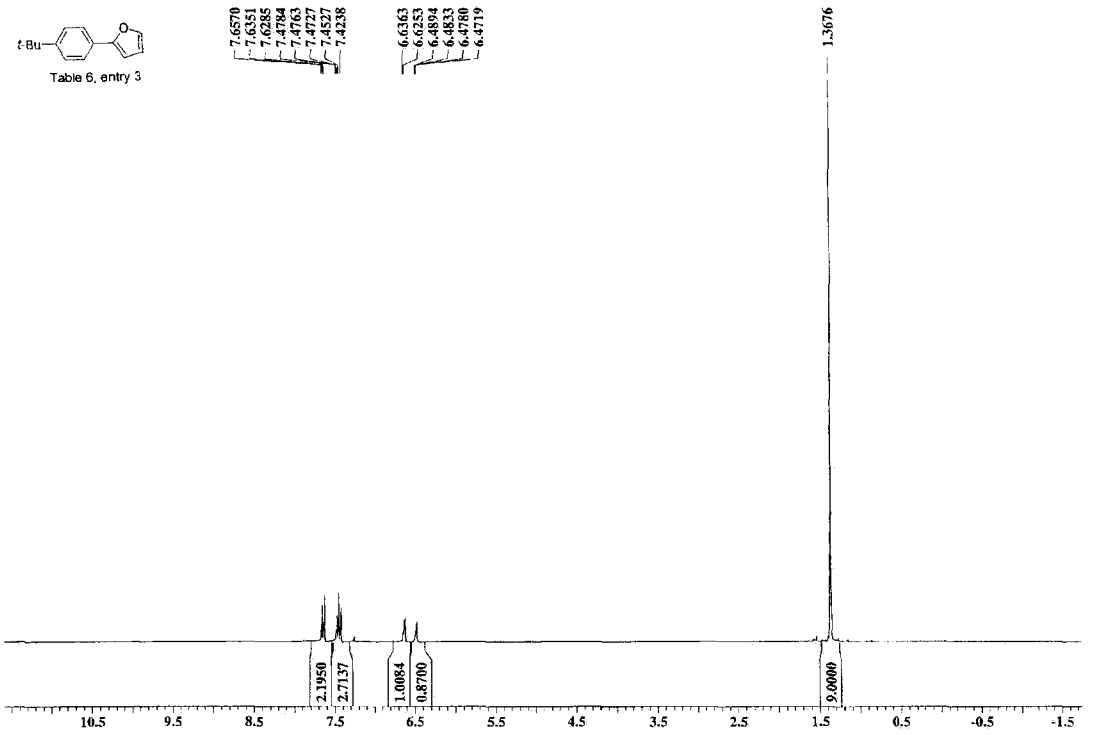
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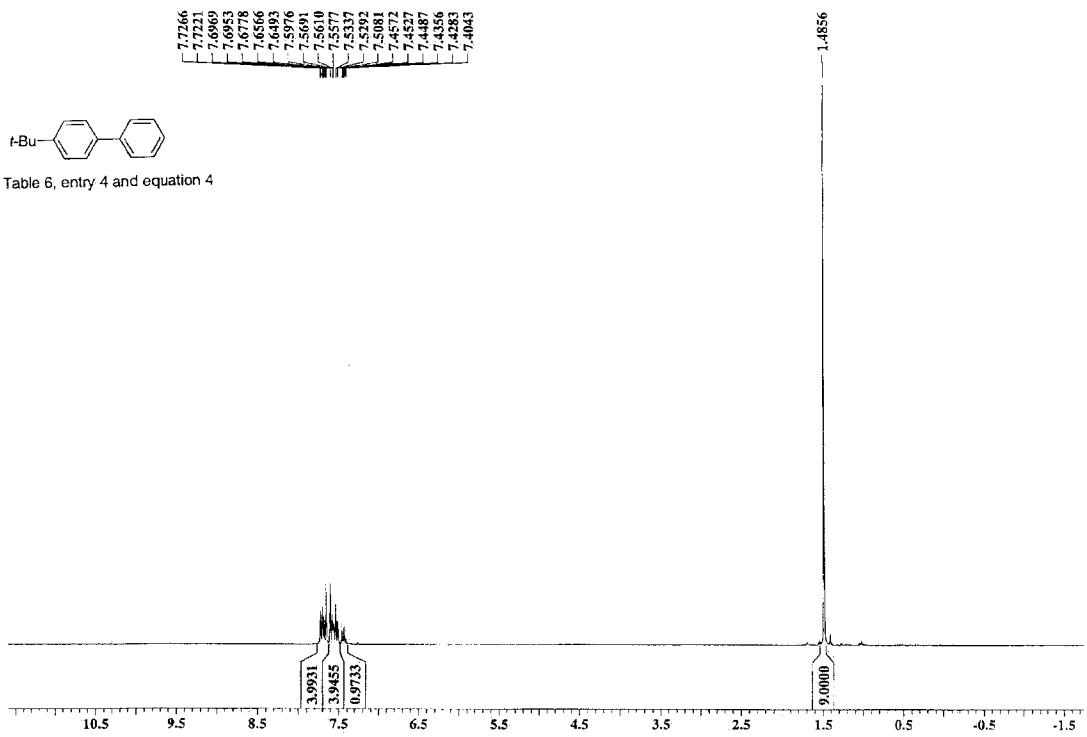

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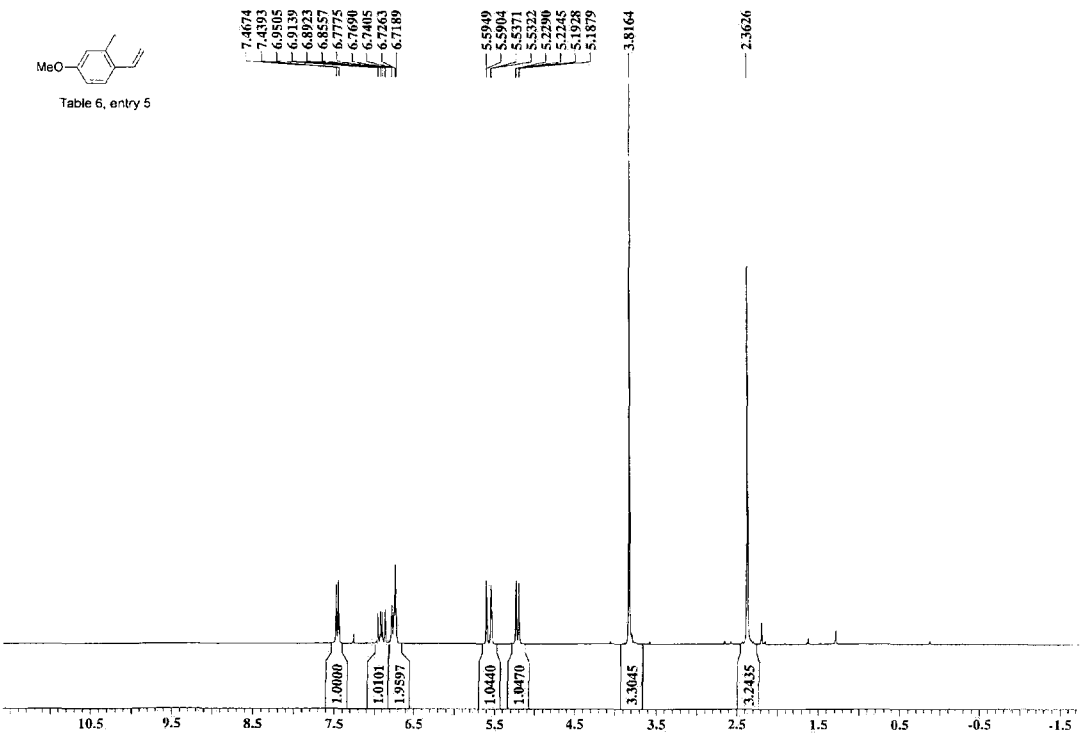
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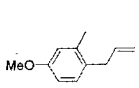

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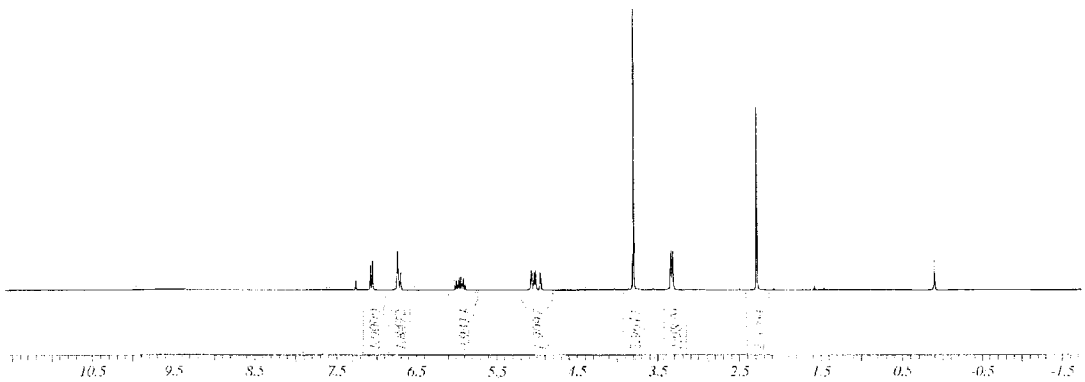

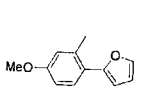

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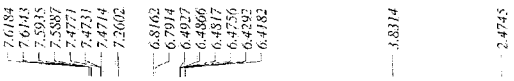

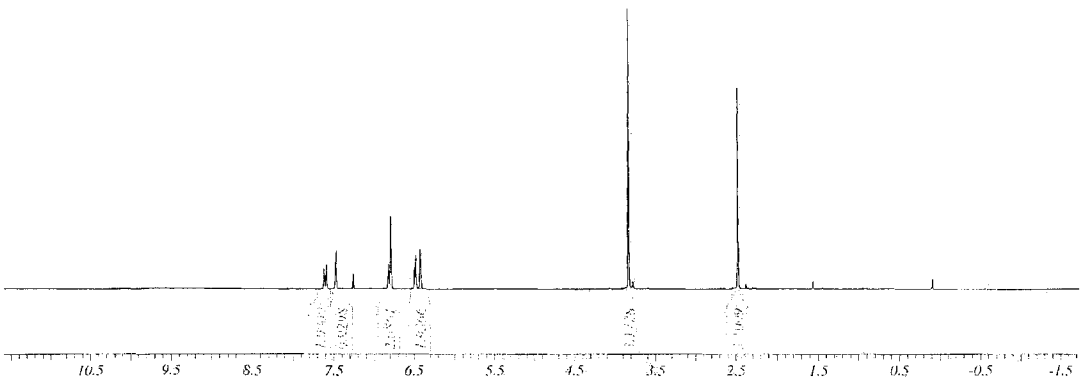

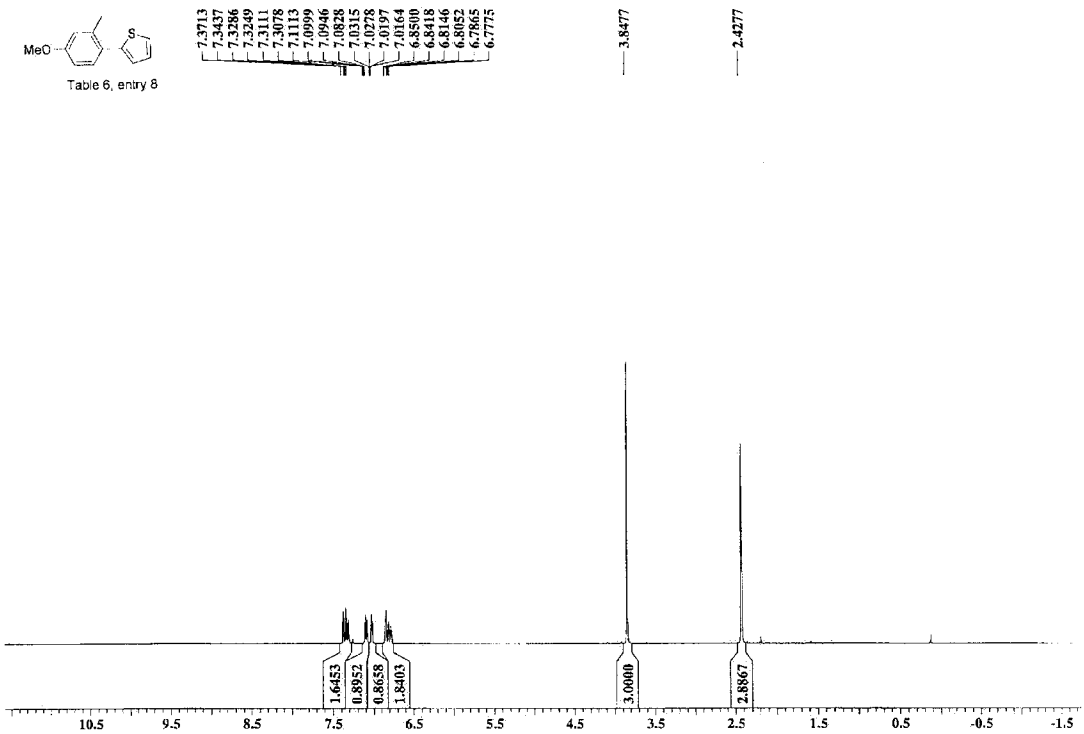
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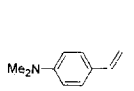

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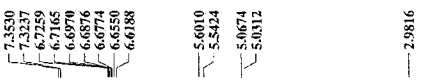

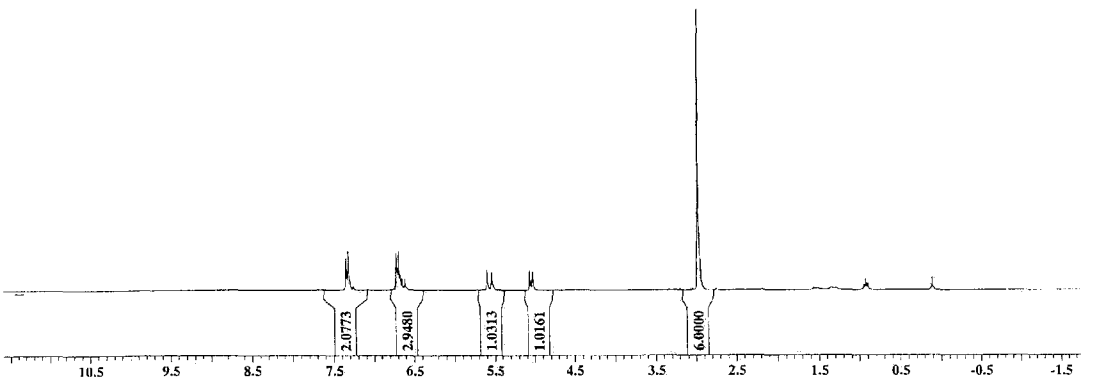

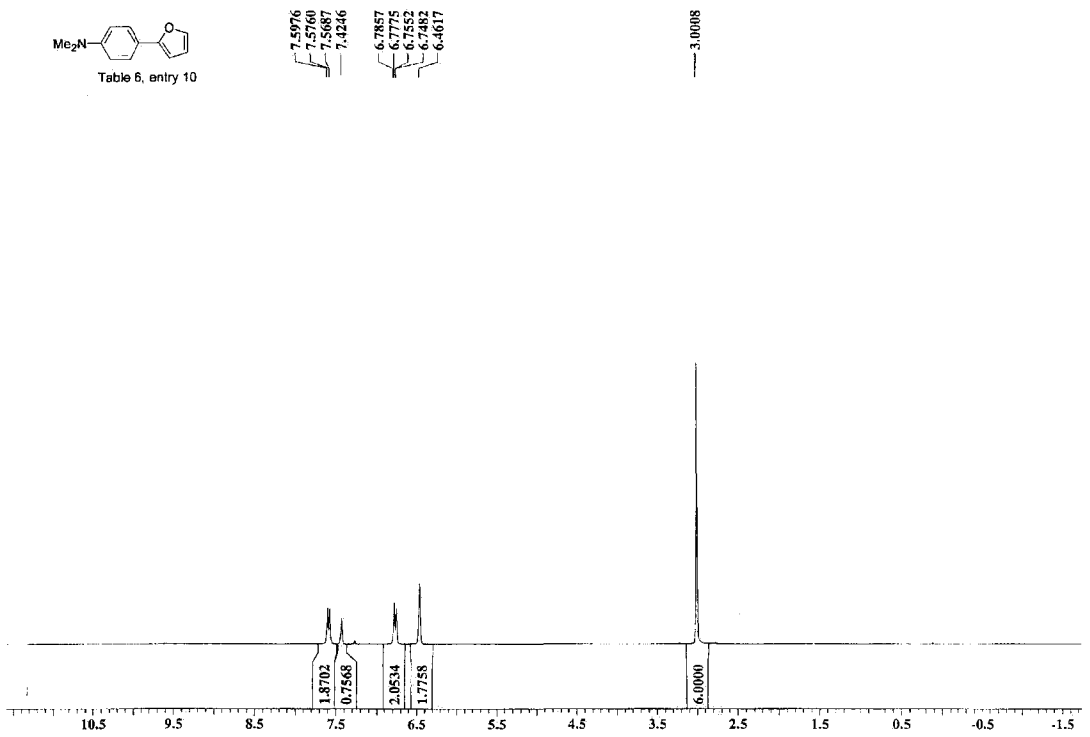
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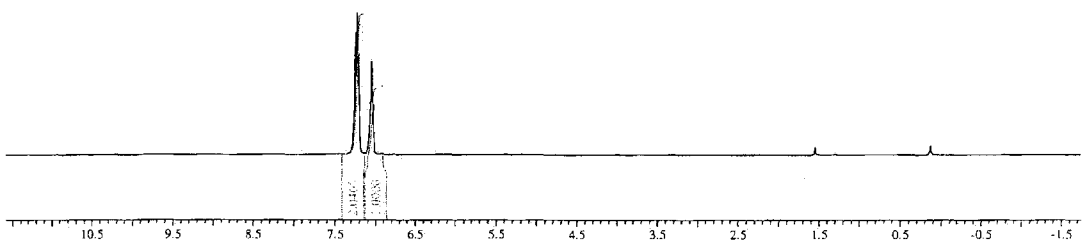

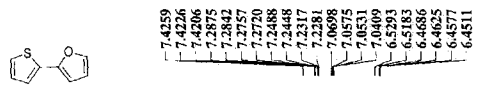

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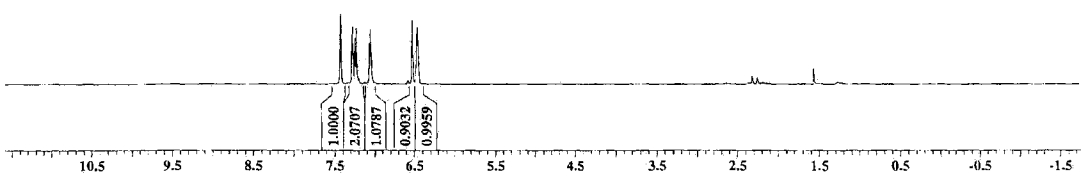

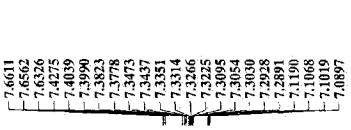

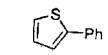

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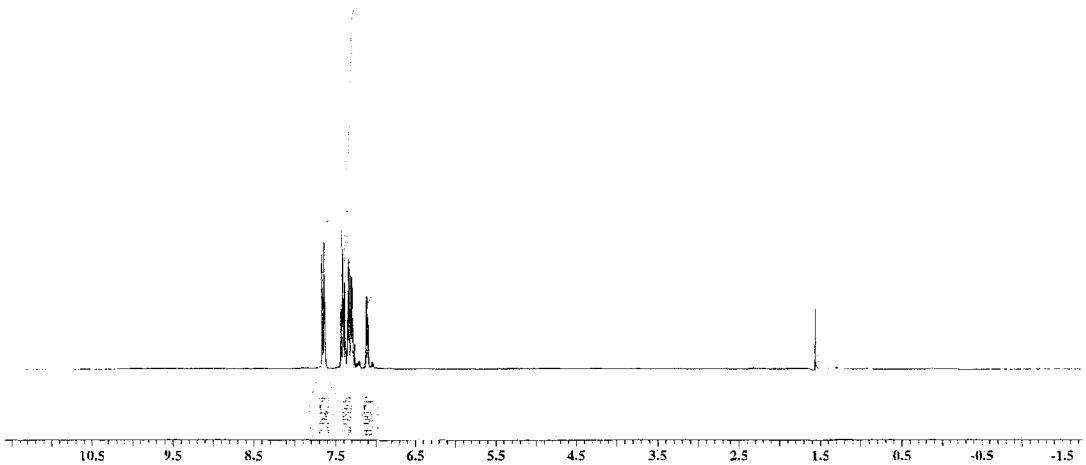

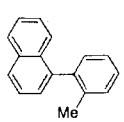
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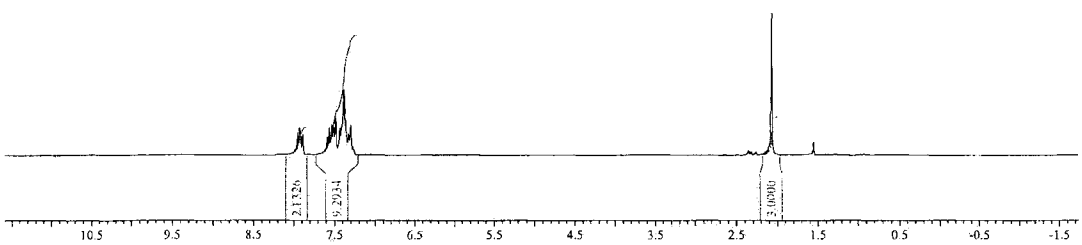
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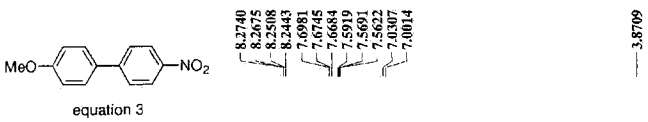
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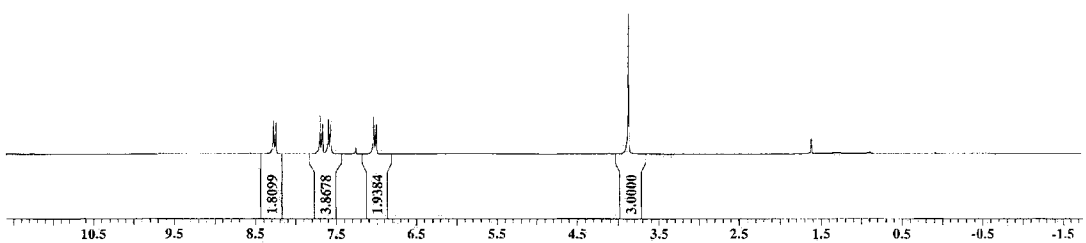
equation 3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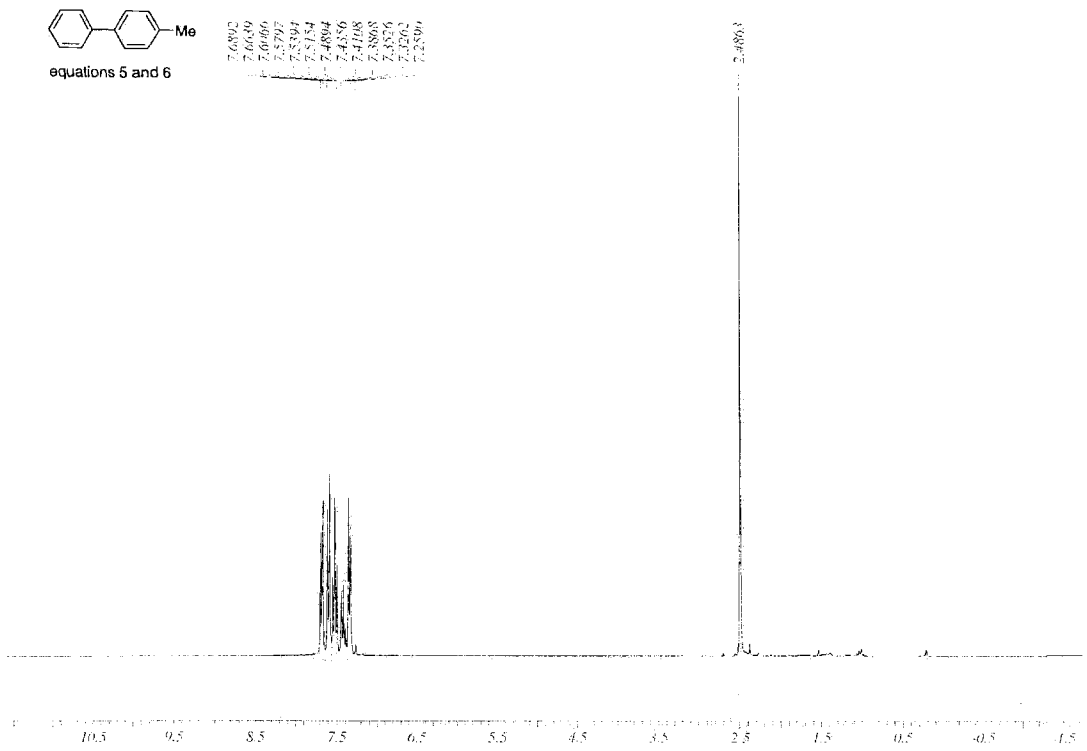
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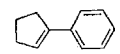

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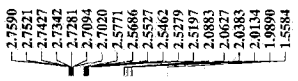

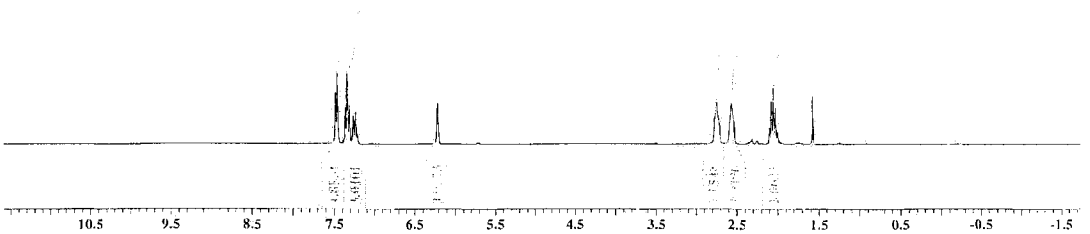

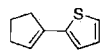

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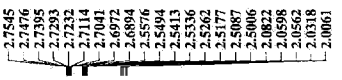

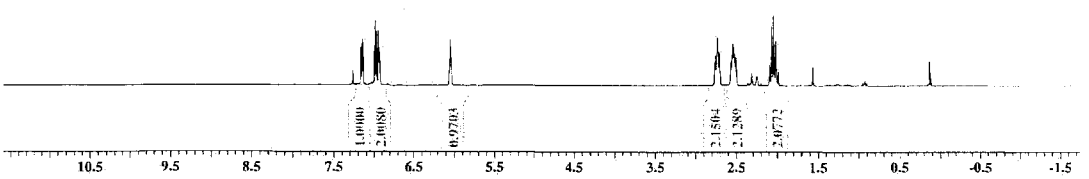

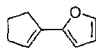

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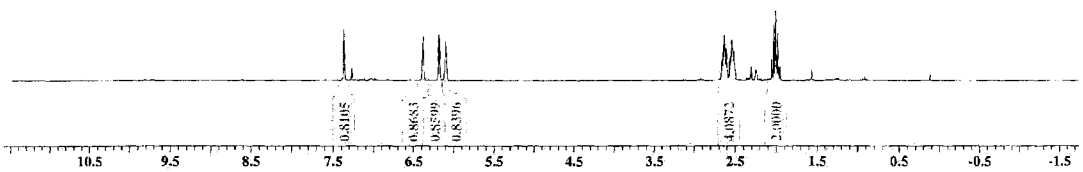


APPENDIX I

CHAPTER 10

General Considerations

Spectroscopic data

References for known compounds

^{1}H NMR spectra for reaction products

^{13}C NMR spectra for previously unknown reaction products

General Considerations

$Pd(OAc)_2$ and tetrabutylammonium acetate were purchased from Aldrich and used without further purification. Anhydrous DMF was purchased from Aldrich in Sure/Seal® bottles and dispensed by syringe. All other reagents were commercially available and used without further purification. All reactions were performed under an atmosphere of argon in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, unless otherwise noted. Alumina gel flash chromatography was performed using Fluka Basic Brockman Activity I Alumina 60-325 mesh. The yields reported are isolated yields and are the average of two runs. Compounds known in the literature were characterized by comparing their ^1H and ^{13}C NMR or mass spectra to the previously reported data. In all cases, the comparisons were very favorable. New compounds were characterized by elemental analysis, ^1H and ^{13}C NMR spectroscopy, and high resolution mass spectrometry.

General Procedure for Ligand, Copper, and Amine-Free Sonogashira Coupling of Aryl Iodides and Bromides with Terminal Alkynes.

An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with Bu_4NOAc (1.5 mmol) and $Pd(OAc)_2$ (1-3 mol %) or $Pd_2(dba)_3$ (2 mol % for aryl bromides) inside a nitrogen-filled glove box. The flask was capped with a rubber septum and then it was removed from the glove box. An aryl iodide or bromide (1.0 mmol) and then DMF (3 mL) were then added and after 5 min of stirring, the alkyne (1.0 mmol) was added. Stirring was continued at room temperature under argon for the corresponding reaction times indicated in the Tables, after which the reaction mixture was diluted with water (10 mL), and extracted with diethyl ether (4 x 10 mL). The combined ether layers were dried over Na_2SO_4, filtered, concentrated, and purified by alumina gel flash chromatography using hexanes or hexanes/ether to elute the desired coupling product.

Spectroscopy data

4-Ethoxycarbonyldiphenylacetylene[1] (Table 1, entry 1) ^1H NMR ($CDCl_3$): δ 8.05-8.02 (m, 2H), 7.60-7.53 (m, 4H), 7.38-7.26 (m, 3H), 4.42 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 166.3, 131.9, 131.7, 130.0, 129.7, 129.0, 128.7, 128.1, 122.9, 92.5, 88.9, 61.4, 14.6.

4-(Phenylethynyl)acetophenone[2] (Table 1, entry 2) ^{1}H NMR ($CDCl_3$): δ 7.94-7.91 (m, 2H), 7.61-7.53 (m, 4H), 7.37-7.35 (m, 3H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 197.5, 136.4, 132.0, 131.9, 129.1, 128.7, 128.5, 128.4, 122.9, 93.0, 88.9, 26.8.

4-Nitrodiphenylacetylene[2] (Table 1, entry 3) ^{1}H NMR ($CDCl_3$): δ 8.23-8.20 (m, 2H), 7.68-7.65 (m, 2H), 7.58-7.55 (m, 2H), 7.40-7.39 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 147.2, 132.5, 132.1, 130.5, 129.5, 128.8, 123.9, 122.3, 94.9, 87.8.

2-Methyldiphenylacetylene[2] (Table 1, entry 4) ^{1}H NMR ($CDCl_3$): δ 7.61-7.54 (m, 3H), 7.43-7.37 (m, 3H), 7.29-7.19 (m, 3H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 140.4, 132.1, 131.8, 129.7, 128.6, 128.5, 128.4, 125.9, 123.8, 123.3, 93.6, 88.6, 21.0.

3-Methoxydiphenylacetylene[3] (Table 1, entry 5) ^{1}H NMR ($CDCl_3$): δ 7.56-7.51 (m, 2H), 7.41-7.33 (m, 3H), 7.29-7.24 (m, 1H), 7.16-7.13 (m, 1H), 7.08-7.07 (m, 1H), 6.92-6.88 (m, 1H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.6, 131.9, 129.6, 128.6, 128.5, 124.5, 124.4, 123.4, 116.5, 115.2, 89.5, 89.4, 55.5.

2-Methoxydiphenylacetylene[2] (Table 1, entry 6) ^{1}H NMR ($CDCl_3$): δ 7.59-7.50 (m, 3H), 7.38-7.29 (m, 4H), 6.98-6.90 (m, 2H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 160.1, 133.8, 131.9, 130.0, 128.5, 128.3, 123.8, 120.7, 112.7, 110.9, 93.7, 85.9, 56.1.

4-Methoxydiphenylacetylene[2] (Table 1, entry 7) ^{1}H NMR ($CDCl_3$): δ 7.55-7.47 (m, 4H), 7.38-7.32 (m, 3H), 6.91-6.88 (m, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.9, 133.3, 131.7, 128.5, 128.2, 123.8, 115.6, 114.2, 89.6, 88.3, 55.5.

1-(4-Cyclohex-1-enylethynylphenyl)-ethanone[2] (Table 2, entry 1) ^{1}H NMR ($CDCl_3$): δ 7.88-7.85 (m, 2H), 7.48-7.45 (m, 2H), 6.27-6.23 (m, 1H), 2.57 (s, 3H), 2.24-2.12 (m, 4H), 1.71-1.57 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 197.5, 136.8, 135.9, 131.7, 129.0, 128.4, 120.7, 95.0, 86.4, 29.3, 26.8, 26.1, 22.5, 21.6.

1-(4'-Acetylphenyl)-1-octyne[2] (Table 2, entry 2) ^{1}H NMR ($CDCl_3$): δ 7.87-7.85 (m, 2H), 7.46-7.43 (m, 2H), 2.57 (s, 3H), 2.44-2.39 (m, 2H), 1.65-1.56 (m, 2H), 1.49-1.40 (m, 2H), 1.33-1.29 (m, 4H), 0.92-0.87 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 197.6, 135.8, 131.8, 129.4, 128.4, 94.7, 80.3, 31.6, 28.8, 28.7, 26.8, 22.8, 19.8, 14.3.

4-Nitro-1-oct-1-ynyl-benzene[2] (Table 2, entry 3) ^{1}H NMR ($CDCl_3$): δ 8.14-8.11 (m, 2H), 7.50-7.47 (m, 2H), 2.44-2.40 (m, 2H), 1.65-1.55 (m, 2H), 1.48-1.28 (m, 6H), 0.89 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 146.7, 132.4, 131.4, 123.7, 97.0, 79.5, 31.5, 28.8, 28.6, 22.8, 19.8, 14.3.

4-(5-Hydroxy-hex-1-ynyl)-nitrobenzene[4] (Table 2, entry 4) ^{1}H NMR ($CDCl_3$): δ 8.12-8.09 (m, 2H), 7.49-7.46 (m, 2H), 3.68 (t, J = 6.0 Hz, 2H), 2.49-2.45 (m, 2H), 1.94 (bs, 1H), 1.76-1.66 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 146.8, 132.4, 131.2, 123.7, 96.4, 62.4, 32.0, 25.0, 19.6.

1-Cyclohex-1-enylethynyl-4-nitrobenzene[2] (Table 2, entry 5) ^{1}H NMR ($CDCl_3$): δ 8.15 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 6.32-6.29 (m, 1H), 2.23-2.16 (m, 4H), 1.73-1.61 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 146.8, 137.9, 132.2, 131.1, 123.8, 120.4, 97.1, 85.5, 29.1, 26.1, 22.4, 21.6.

2-Methyl-1-oct-1-ynyl-benzene[2] (Table 2, entry 6) ^{1}H NMR ($CDCl_3$): δ 7.43-7.40 (m, 1H), 7.22-7.11 (m, 3H), 2.52-2.47 (m, 5H), 1.72-1.62 (m, 2H), 1.58-1.48 (m, 2H), 1.40-1.35 (m, 4H), 0.96 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 140.1, 132.0, 129.5, 127.7, 125.6, 124.1, 94.7, 79.7, 31.7, 29.2, 28.9, 22.9, 21.0, 19.8, 14.3.

1-Cyclohex-1-enylethynyl-2-methylbenzene[2] (Table 2, entry 7) ^{1}H NMR ($CDCl_3$): δ 7.43-7.40 (m, 1H), 7.21-7.11 (m, 3H), 6.25-6.22 (m, 1H), 2,46 (s, 3H), 2.30-2.15 (m, 4H), 1.76-1.61 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 140.1, 134.9, 131.9, 129.5, 128.0, 125.7, 123.7, 121.2, 95.6, 86.0, 29.6, 26.0, 22.6, 21.8, 21.0.

2-(5-Hydroxy-hex-1-ynyl)-methylbenzene (Table 2, entry 8) ^{1}H NMR ($CDCl_3$): δ 7.38-7.35 (m, 1H), 7.18-7.08 (m, 3H), 3.72-3.68 (m, 2H), 2.52-2.48 (m, 2H), 2.42 (s, 3H), 1.77-1.65 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 140.1, 132.0, 129.5, 127.8, 125.7, 123.9, 94.1, 80.0, 62.6, 32.1, 25.4, 21.0, 19.6. HRMS *m/z* Calcd for $C_{13}H_{16}O$: 188.12012. Found: 188.12030. Anal. Calcd for $C_{13}H_{16}O$: C, 82.98; H, 8.51. Found: C, 82.70; H, 8.47.

1-Cyclohex-1-enylethynyl-3-methoxybenzene (Table 2, entry 9) ^{1}H NMR ($CDCl_3$): δ 7.23-7.17 (m, 1H), 7.03-7.00 (m, 1H), 6.96-6.95 (m, 1H), 6.85-6.82 (m, 1H), 6.24-6.20 (m, 1H), 3.79 (s, 3H), 2.17-2.12 (m, 4H), 1.71-1.58 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.5, 135.6, 129.5, 125.0, 124.2, 120.9, 116.3, 114.7, 91.3, 86.9, 55.5, 29.4, 26.0, 22.6, 21.7. HRMS *m/z* Calcd for $C_{15}H_{16}O$: 212.12012. Found 212.1203. Anal. Calcd for $C_{15}H_{16}O$: C, 84.91; H, 7.55. Found: C, 84.88; H, 7.41.

3-(5-Hydroxy-hex-1-ynyl)-methoxybenzene (Table 2, entry 10) ^{1}H NMR ($CDCl_3$): δ 7.20-7.14 (m, 1H), 6.99-6.96 (m, 1H), 6.92-6.91 (m, 1H), 6.83-6.79 (m, 1H), 3.76 (s, 3H), 3.68-3.64 (m, 2H), 2.45-2.40 (m, 2H), 2.18 (bs, 1H), 1.77-1.61 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.5, 129.5, 125.1, 124.3, 116.6, 114.4, 90.1, 81.1, 62.5, 55.4, 32.1, 25.2, 19.4. HRMS *m/z* Calcd for $C_{13}H_{16}O_2$: 204.11503. Found: 204.11530. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.31; H, 7.67.

1-Cyclohex-1-enylethynyl-2-methoxybenzene[2] (Table 2, entry 11) ^{1}H NMR ($CDCl_3$): δ 7.23-7.18 (m, 1H), 7.04-7.02 (m, 1H), 6.97-6.96 (m, 1H), 6.86-6.82 (m, 1H), 6.24-6.21 (m, 1H), 3.79 (s, 3H), 2.24-2.12 (m, 4H), 1.73-1.58 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.5, 135.5, 129.5, 125.0, 124.2, 120.9, 116.4, 114.7, 91.3, 86.9, 55.4, 29.5, 26.0, 22.6, 21.8.

2-(5-Hydroxy-hex-1-ynyl)-methoxybenzene (Table 2, entry 12) ^{1}H NMR ($CDCl_3$): δ 7.37-7.34 (m, 1H), 7.25-7.20 (m, 1H), 6.89-6.82 (m, 2H), 3.85 (s, 3H), 3.71-3.67 (m, 2H), 2.52-2.48 (m, 2H), 2.41 (bs, 1H), 1.80-1.64 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 160.0, 133.8, 120.6, 113.1, 110.7, 94.5, 82.3, 62.5, 56.0, 32.1, 25.2, 19.7. HRMS *m/z* Calcd for $C_{13}H_{16}O_2$: 204.11503. Found: 204.11530. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.22; H, 7.77.

2-Methoxy-1-oct-1-ynyl-benzene[2] (Table 2, entry 13) ^{1}H NMR ($CDCl_3$): δ 7.40-7.37 (m, 1H), 7.26-7.20 (m, 1H), 6.90-6.83 (m, 2H), 3.87 (s, 3H), 2.50-2.45 (m, 2H), 1.68-1.59 (m, 2H), 1.53-1.43 (m, 2H), 1.35-1.31 (m, 4H), 0.94-0.89 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 160.0, 133.8, 129.0, 120.6, 113.4, 110.7, 94.9, 76.9, 55.9, 31.6, 29.1, 28.9, 22.8, 20.0, 14.3.

1-(5-Chloro-1-pentynyl)-4-methoxybenzene (Table 2, entry 14) ^{1}H NMR ($CDCl_3$): δ 7.35-7.32 (m, 2H), 6.83-6.80 (m, 2H), 3.79 (s, 3H), 3.73-3.69 (m, 2H), 2.61-2.57 (m, 2H), 2.09-2.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 133.1, 115.9, 114.1, 86.7, 81.5, 55.5, 44.1, 31.8, 17.1. HRMS *m/z* Calcd for $C_{12}H_{13}OCl$: 208.06549. Found: 208.06580. Anal. Calcd for $C_{12}H_{13}OCl$: C, 69.08; H, 6.24. Found: C, 69.38; H, 6.11.

4-(5-Hydroxy-hex-1-ynyl)-methoxybenzene[6] (Table 2, entry 15) ^{1}H NMR ($CDCl_3$): δ 7.34-7.29 (m, 2H), 6.82-6.77 (m, 2H), 3.78 (s, 3H), 3.71-3.66 (m, 2H), 2.45-2.40 (m, 2H), 1.80-1.61 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 159.2, 133.1, 116.2, 114.0, 88.5, 80.9, 62.7, 55.5, 32.1, 25.3, 19.4.

1-Cyclohex-1-enylethynyl-4-methoxybenzene[2] (Table 2, entry 16) ^{1}H NMR ($CDCl_3$): δ 7.38-7.35 (m, 2H), 6.84-6.81 (m, 2H), 6.19-6.17 (m, 1H), 3.79 (s, 3H), 2.22-2.13 (m, 4H), 1.72-1.58 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.4, 134.6, 133.0, 121.1, 116.1, 114.1, 90.1, 86.9, 55.5, 29.6, 26.0, 22.6. 21.8.

2-(4-Methoxyphenyl)-1-ethynyl(trimethyl)silane[7] (Table 2, entry 17) ^{1}H NMR ($CDCl_3$): δ 7.42 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 1.15 (s, 21H). ^{13}C NMR ($CDCl_3$): δ 159.8, 133.7, 116.0, 114.0, 107.4, 88.8, 55.5, 18.9, 11.6.

6-(4-Methoxyphenyl)-hex-5-ynenitrile (Table 2, entry 18) ^{1}H NMR ($CDCl_3$): δ 7.34 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 2.60-2.52 (m, 4H), 1.99-1.89 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 159.6, 133.2, 119.5, 115.5, 114.1, 85.6, 82.4, 55.5, 25.0, 18.8, 16.4. HRMS *m/z* Calcd for $C_{13}H_{13}NO$: 199.09971. Found: 199.10020. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.39; H, 6.53. Found: C, 78.66; H, 6.39.

4-(5-Hydroxy-hex-1-ynyl)-cyanobenzene (Table 3, entry 5) ^{1}H NMR ($CDCl_3$): δ 7.58-7.55 (m, 2H), 7.46-7.43 (m, 2H), 3.73-3.69 (m, 2H), 2.50-2.46 (m, 2H), 1.79-1.65 (m, 4H), 1.40 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.3, 132.1, 129.2, 118.8, 110.8, 95.5, 79.9, 62.2, 32.0, 25.0, 19.5. HRMS *m/z* Calcd for $C_{13}H_{13}NO$: 199.09971. Found: 199.10010. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.39; H, 6.53. Found: C, 78.21; H, 6.59.

2-(4-Cyanophenyl)-1-ethynyl(trimethyl)silane (Table 3, entry 6) ^{1}H NMR ($CDCl_3$): δ 7.60-7.52 (m, 4H), 1.13 (s, 21 H). ^{13}C NMR ($CDCl_3$): δ 132.7, 132.1, 128.5, 118.7, 105.3, 96.5, 18.8, 11.4. HRMS *m/z* Calcd for $C_{18}H_{25}NSi$: 283.17563. Found: 283.17620. Anal. Calcd for $C_{18}H_{25}NSi$: C, 76.32; H, 4.59. Found: C, 76.08; H, 4.53.

4-Cyanodiphenylacetylene[8] (Table 3, entry 7) ^{1}H NMR ($CDCl_3$): δ 7.65-7.59 (m, 4H), 7.57-7.55 (m, 2H), 7.40-7.38 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 132.2, 132.3, 131.9, 129.3, 128.7, 128.4, 122.3, 118.7, 111.6, 93.9, 87.9.

References for known compounds

(1) Datta, A.; Plenio, H. *Chem. Commun.* **2003**, 1504.

(2) Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 3317.

(3) Shen, W.; Wang. L. *J. Org. Chem.* **1999**, *64*, 8873.

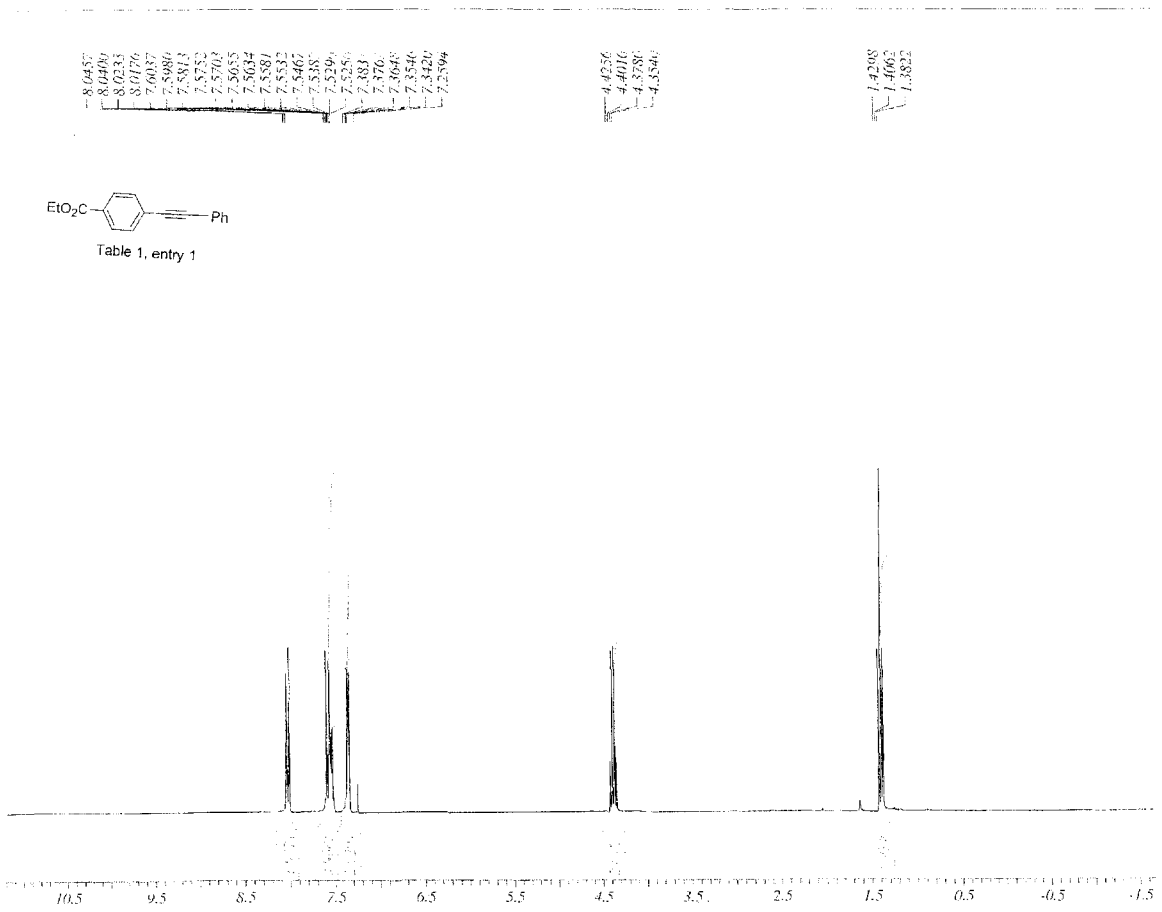
(4) Nguefack, J.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* **1996**, *37*, 5527.

(5) Denmark, S. E.; Tymonko, S. A. *J. Org. Chem.* **2003**, *68*, 9151.

(6) Gapinski, M. D.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem.* **1990**, *33*, 2807.

(7) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056.

(8) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.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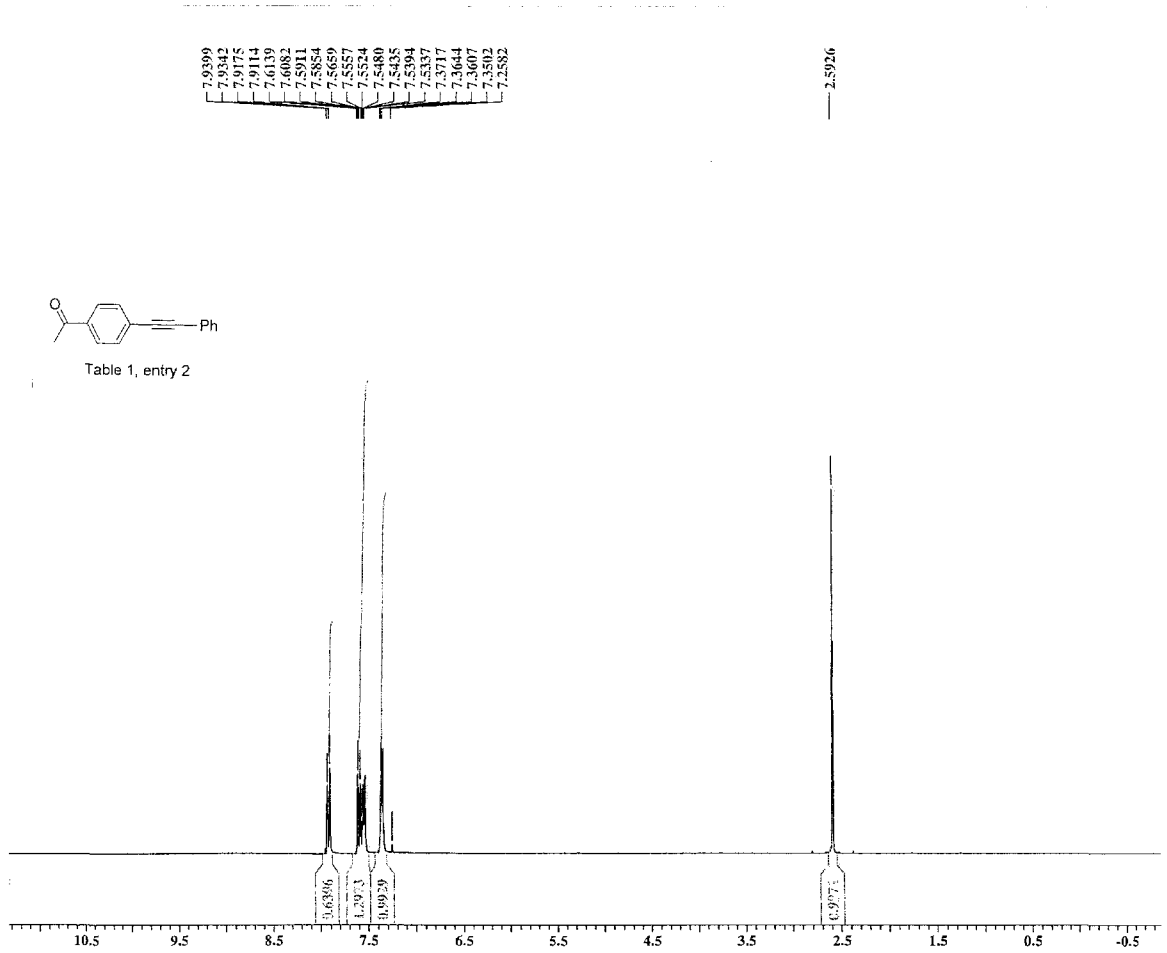
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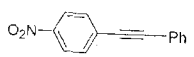

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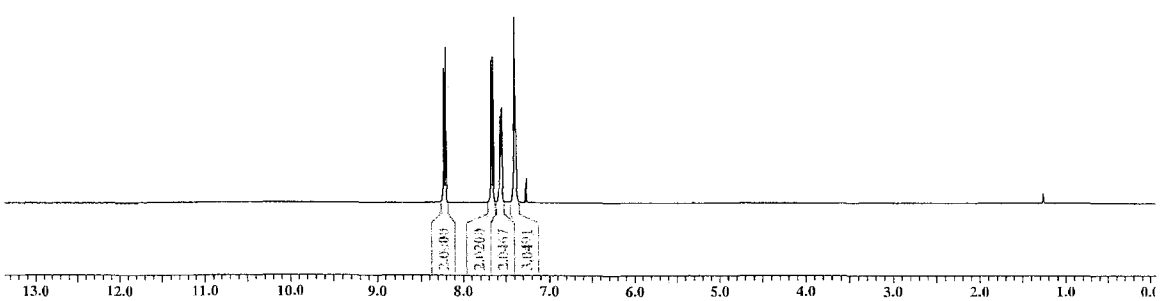

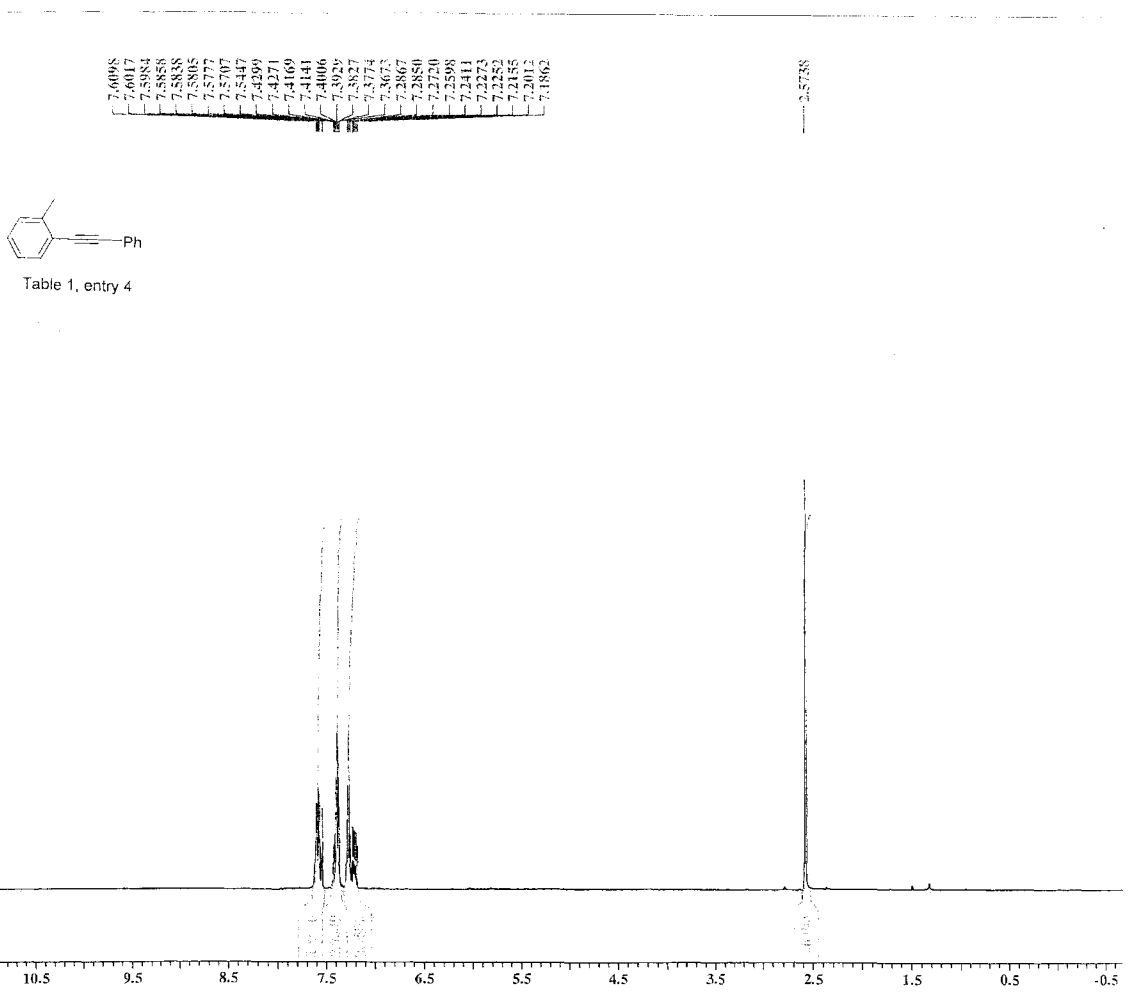

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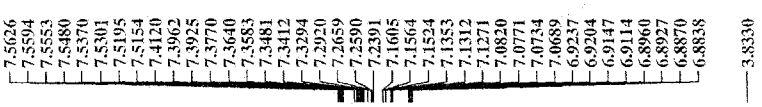

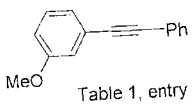

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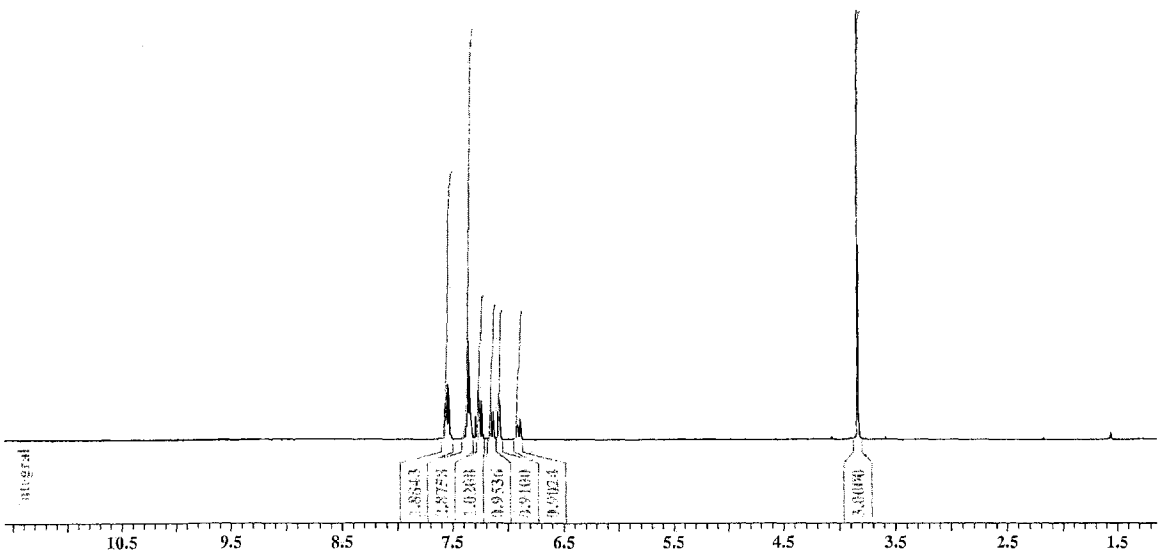

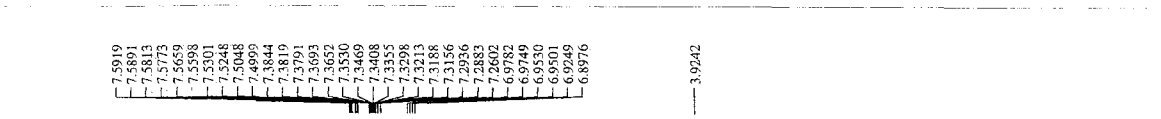

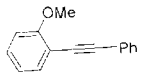

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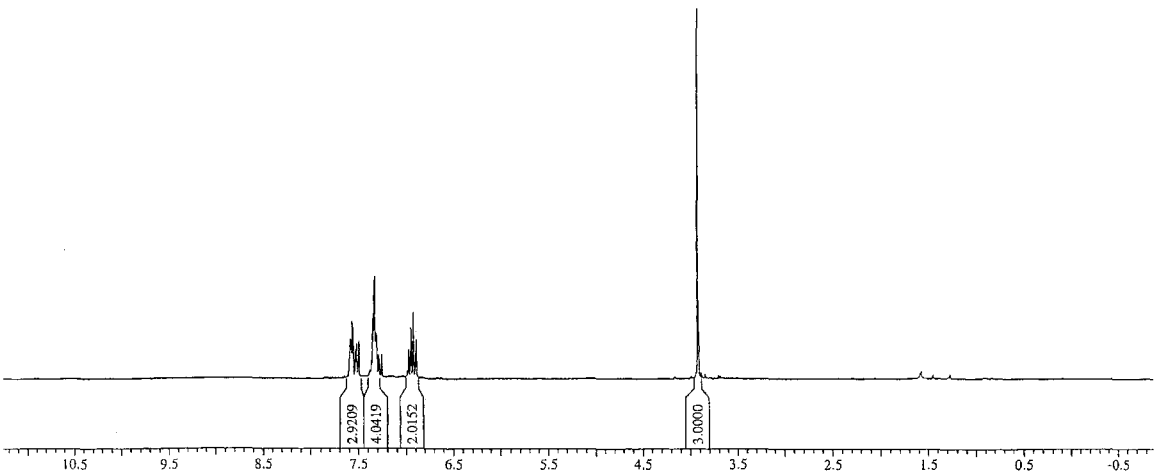

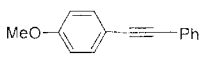

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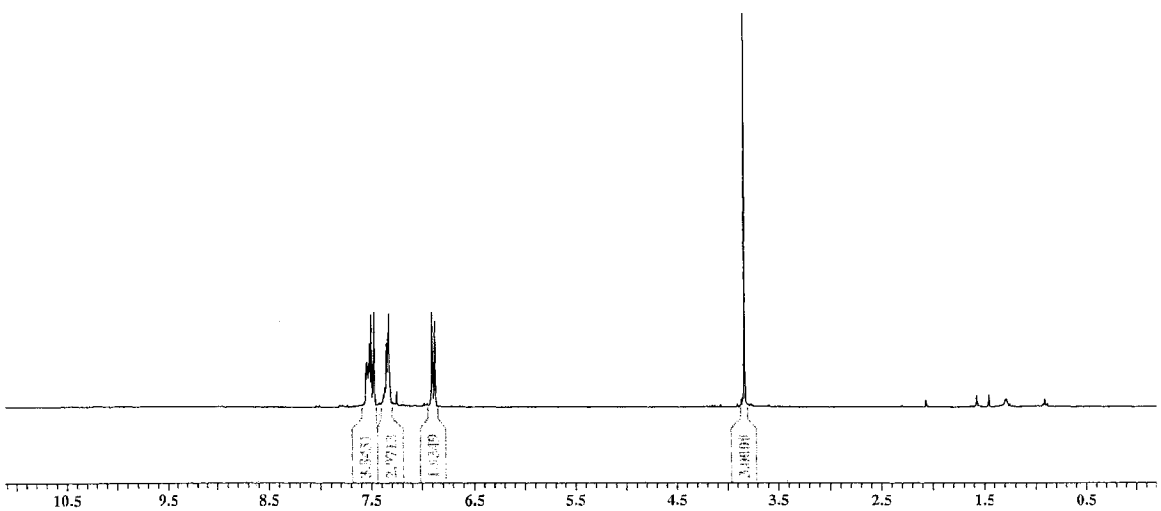

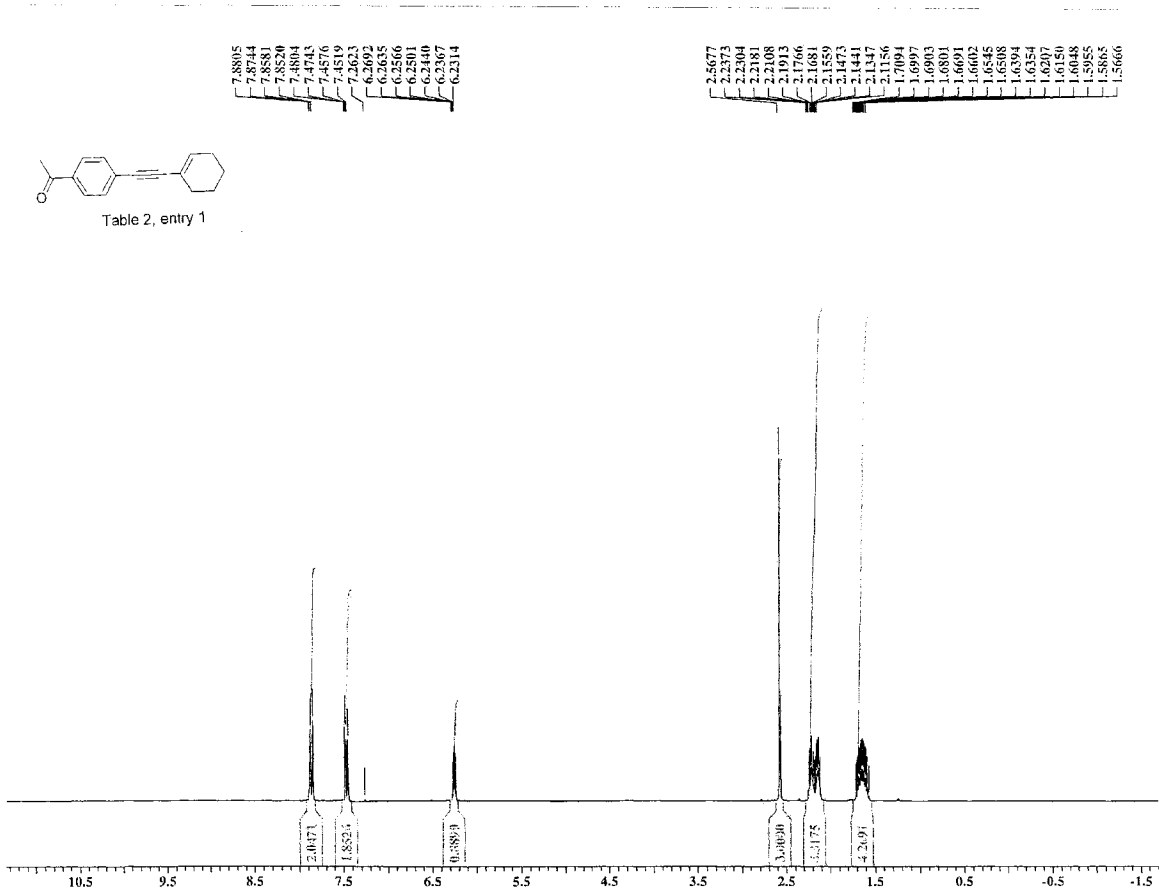

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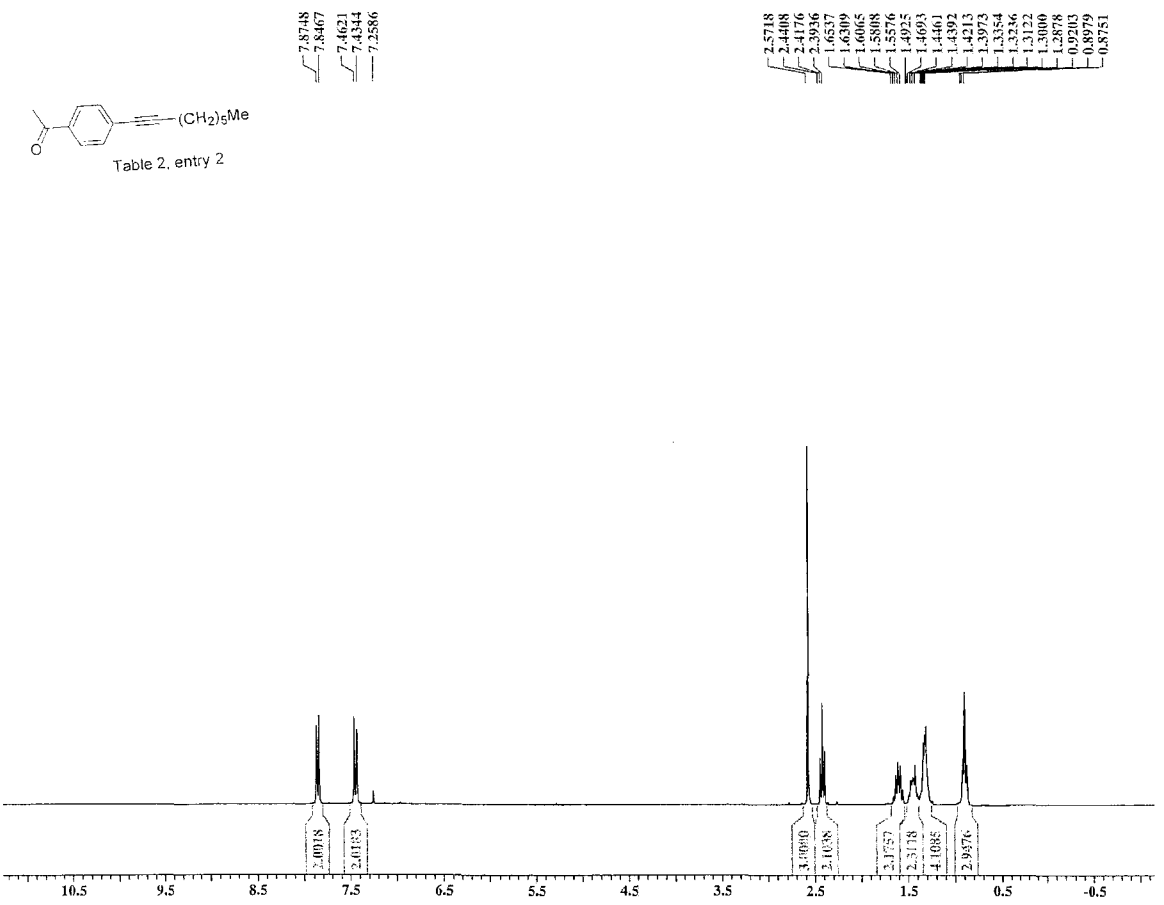
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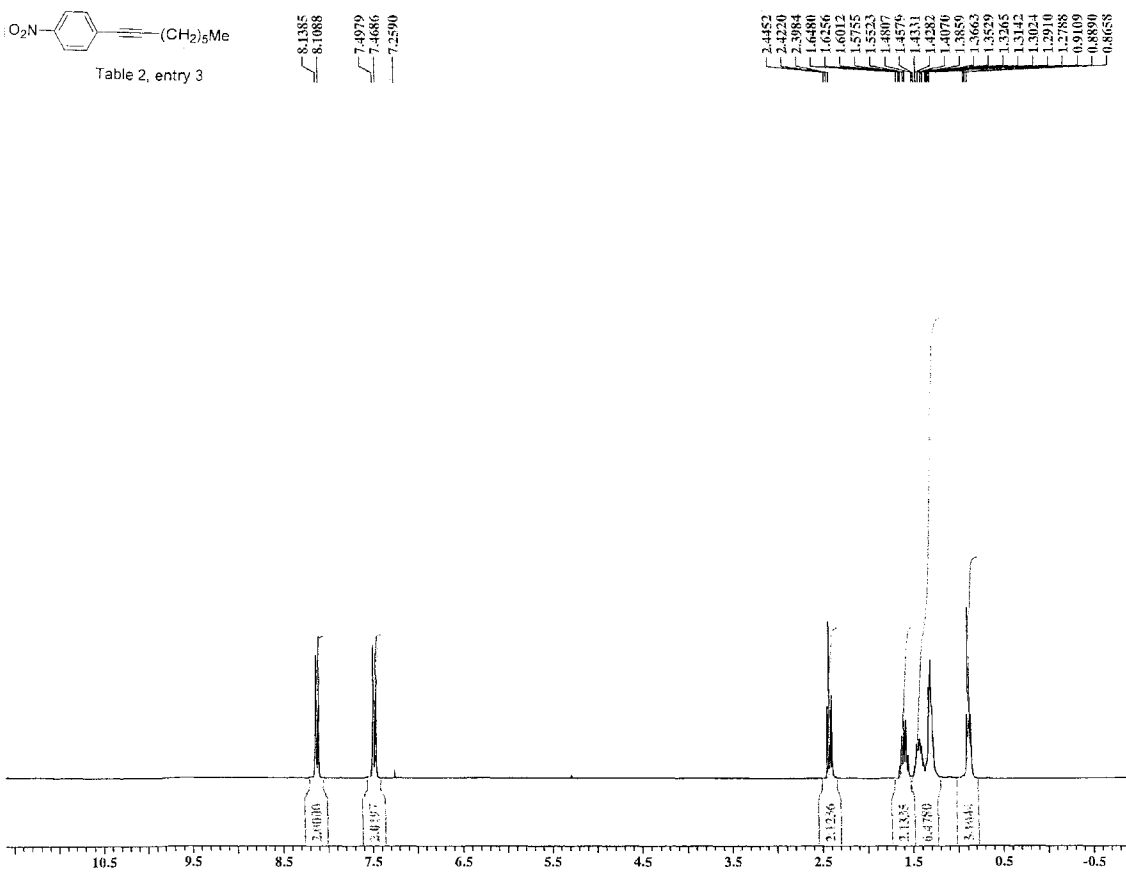
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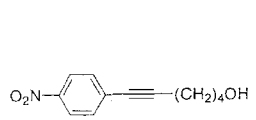

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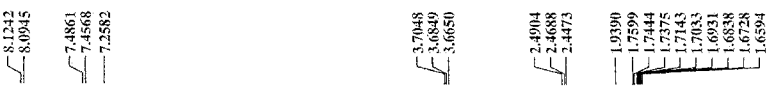

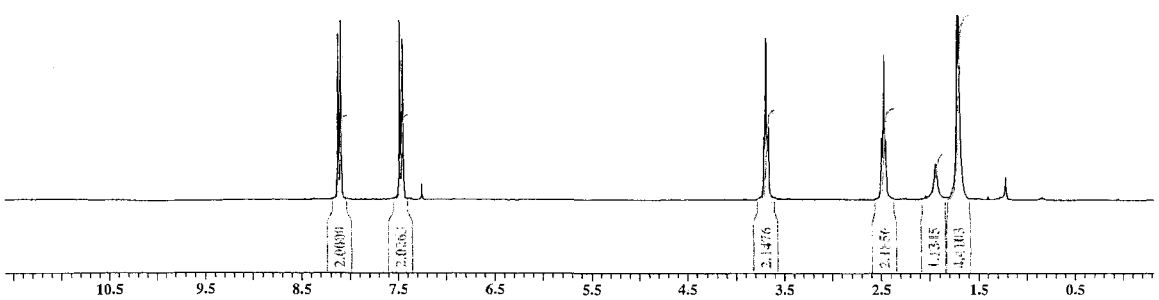

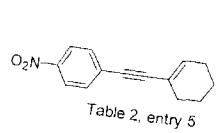

Table 2, entry 5

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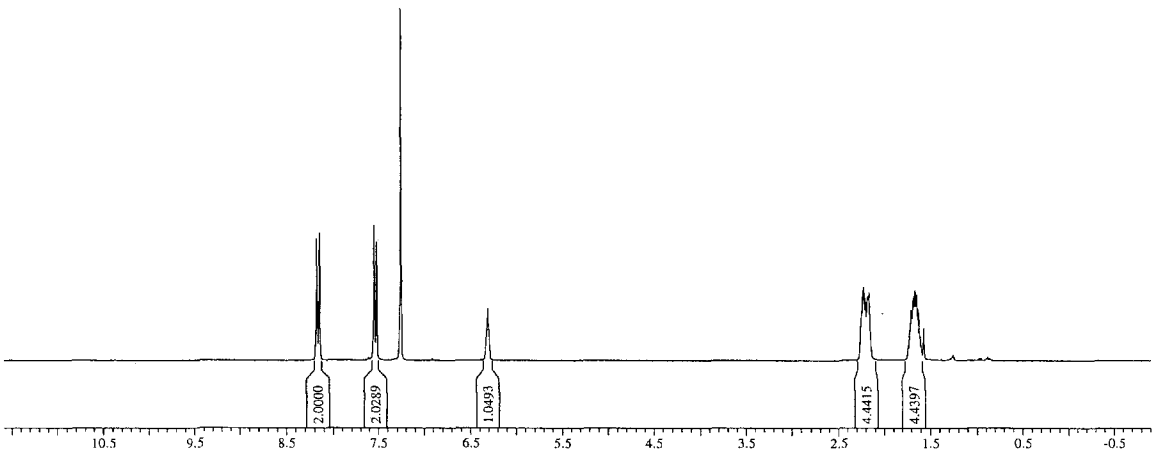
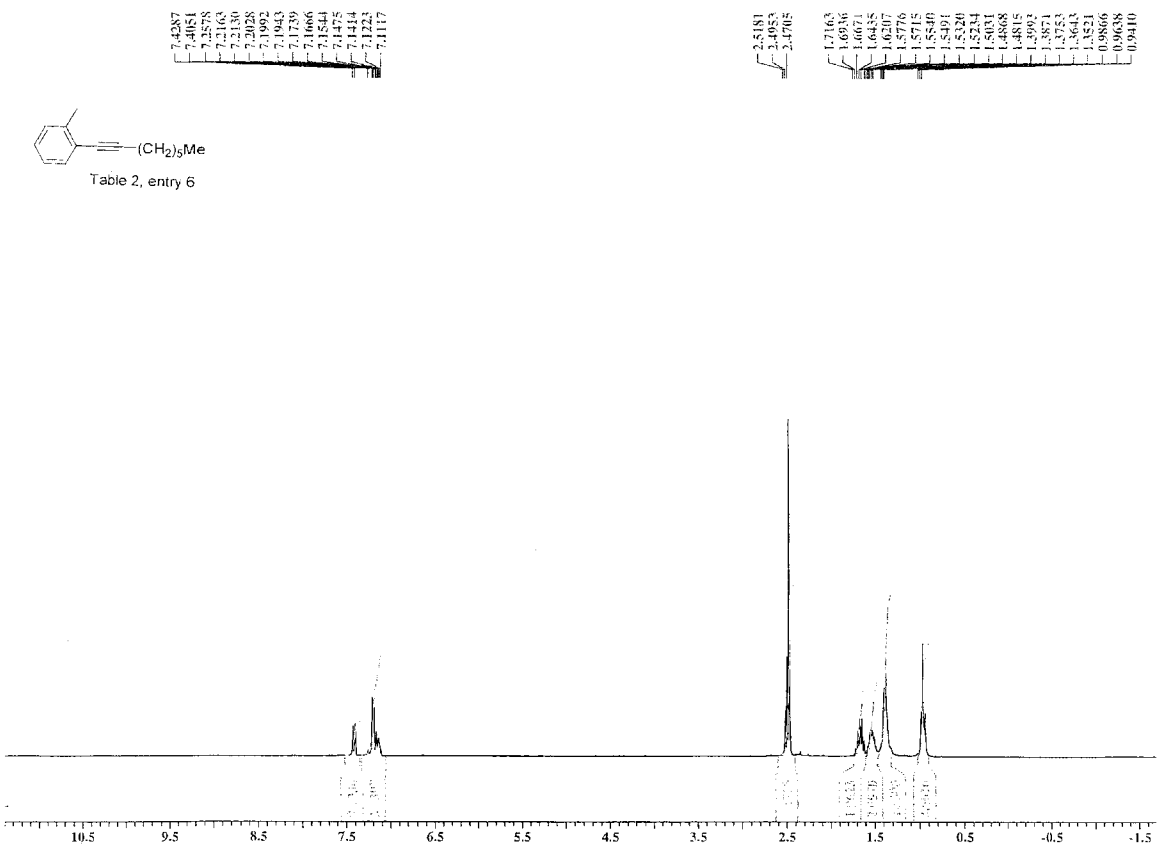
7.5170
7.2590
6.3201
6.3132
6.3071
6.3014
6.2941

2.2308
2.2238
2.2031
2.1848
2.1762
2.1648
1.7318
1.7127
1.7021
1.6931
1.6765
1.6606
1.6451
1.6276
1.6191
1.6101

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7.2578
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7.2130
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7.1992
7.1943
7.1739
7.1666
7.1544
7.1475
7.1414
7.1223
7.1117
2.5181
3.4953
2.4705
1.7163
1.6936
1.6671
1.6435
1.6207
1.5776
1.5715
1.5548
1.5491
1.5320
1.5234
1.5031
1.4868
1.4815
1.2992
1.2871
1.2753
1.2643
1.2521
0.9866
0.9638
0.9410
(CH2)5Me
Table 2, entry 6
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
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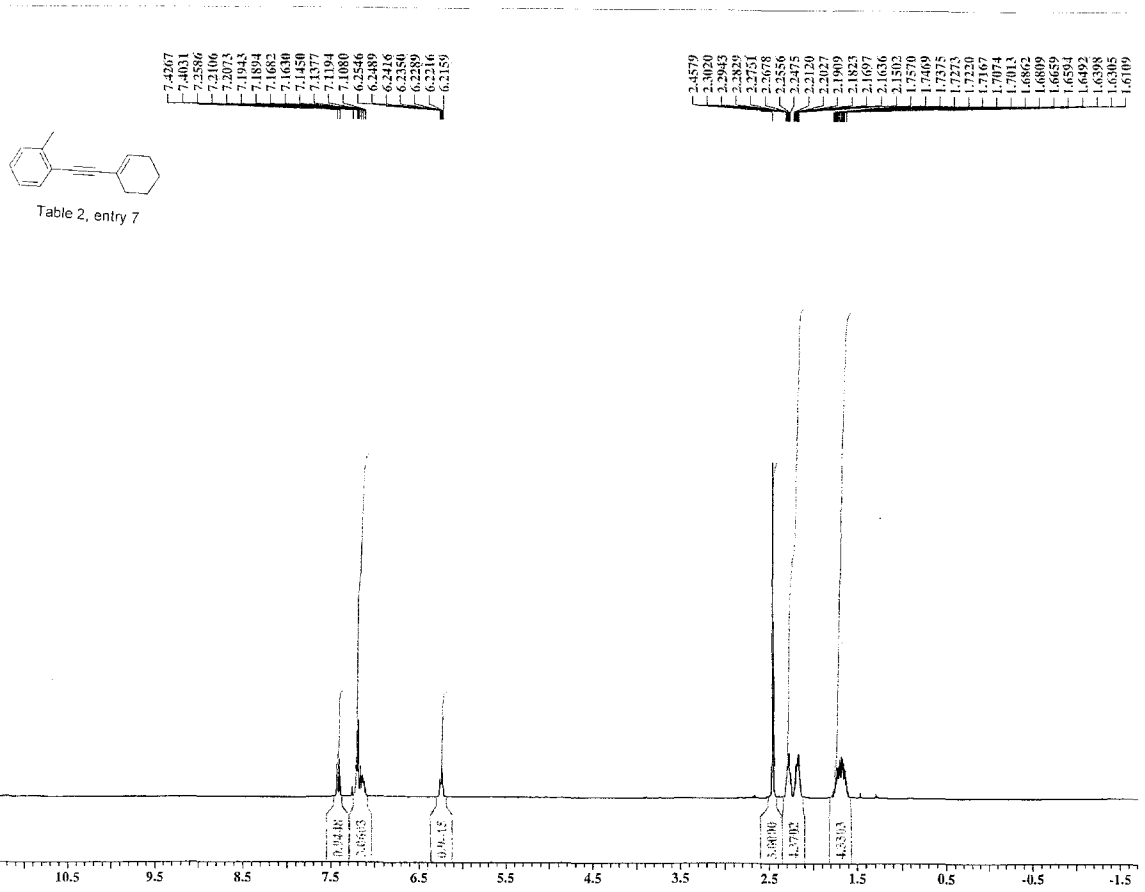
-0.5
-1.5



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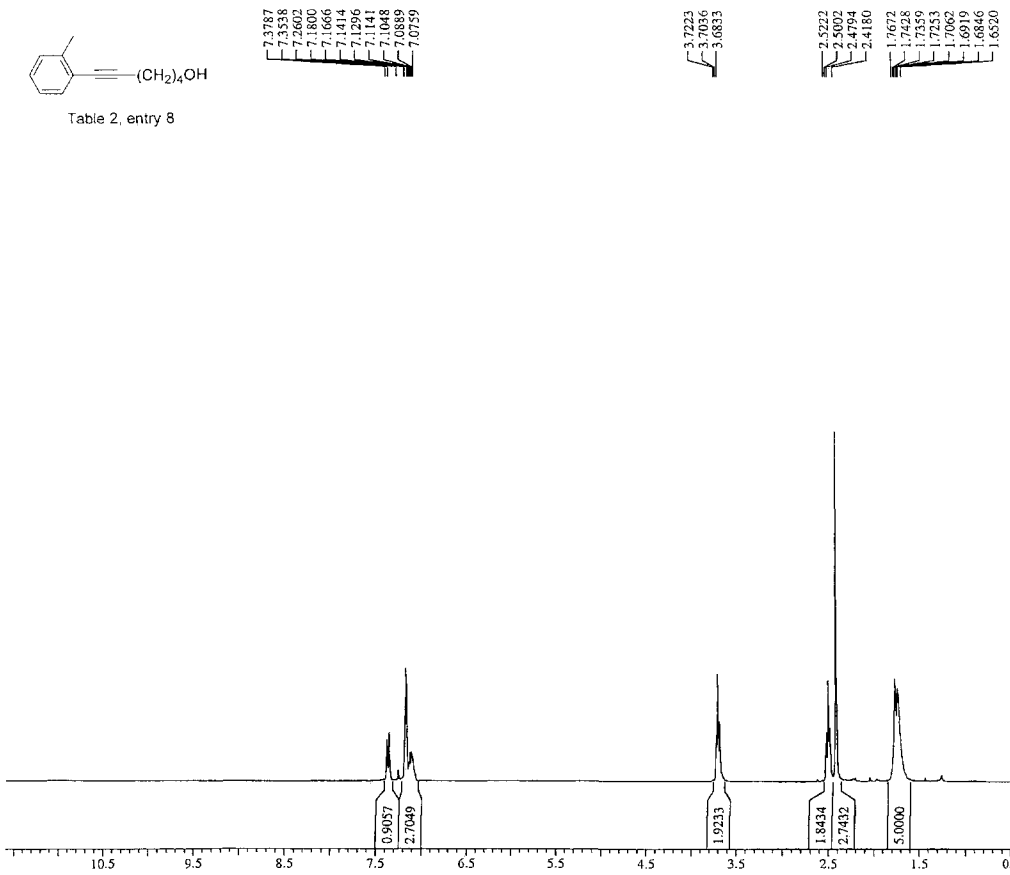

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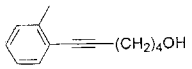
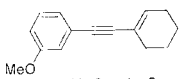


Table 2, entry 8



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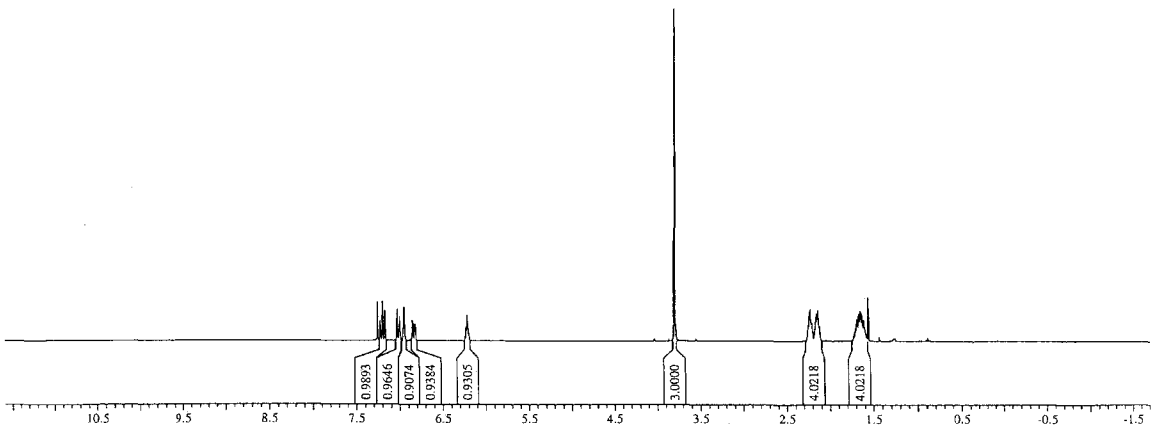


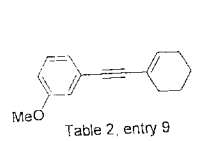
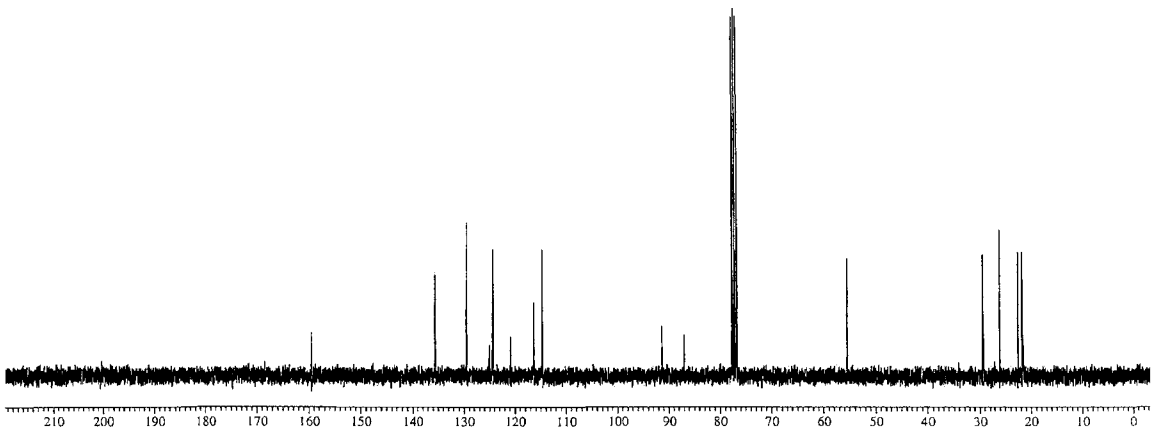
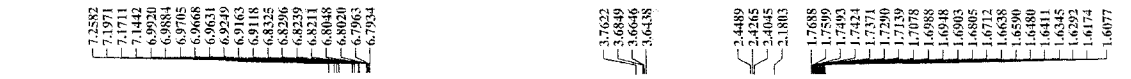
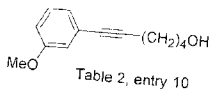


Table 2, entry 9

159.4763
135.5747
129.4808
124.9719
124.2489
120.8725
116.3494
114.6719
91.3080
86.9131
77.6673
77.2470
76.8232
55.4716
29.4366
26.0033
22.5628
21.7436







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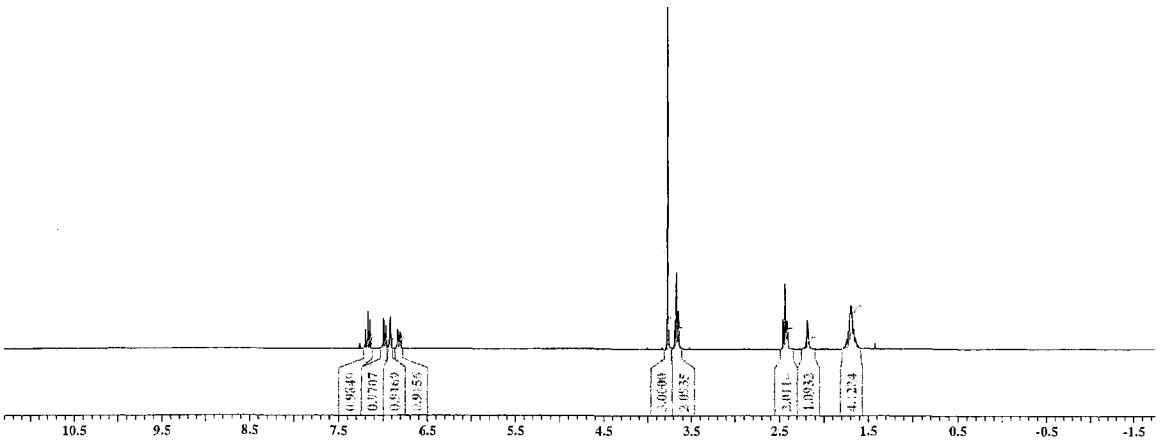

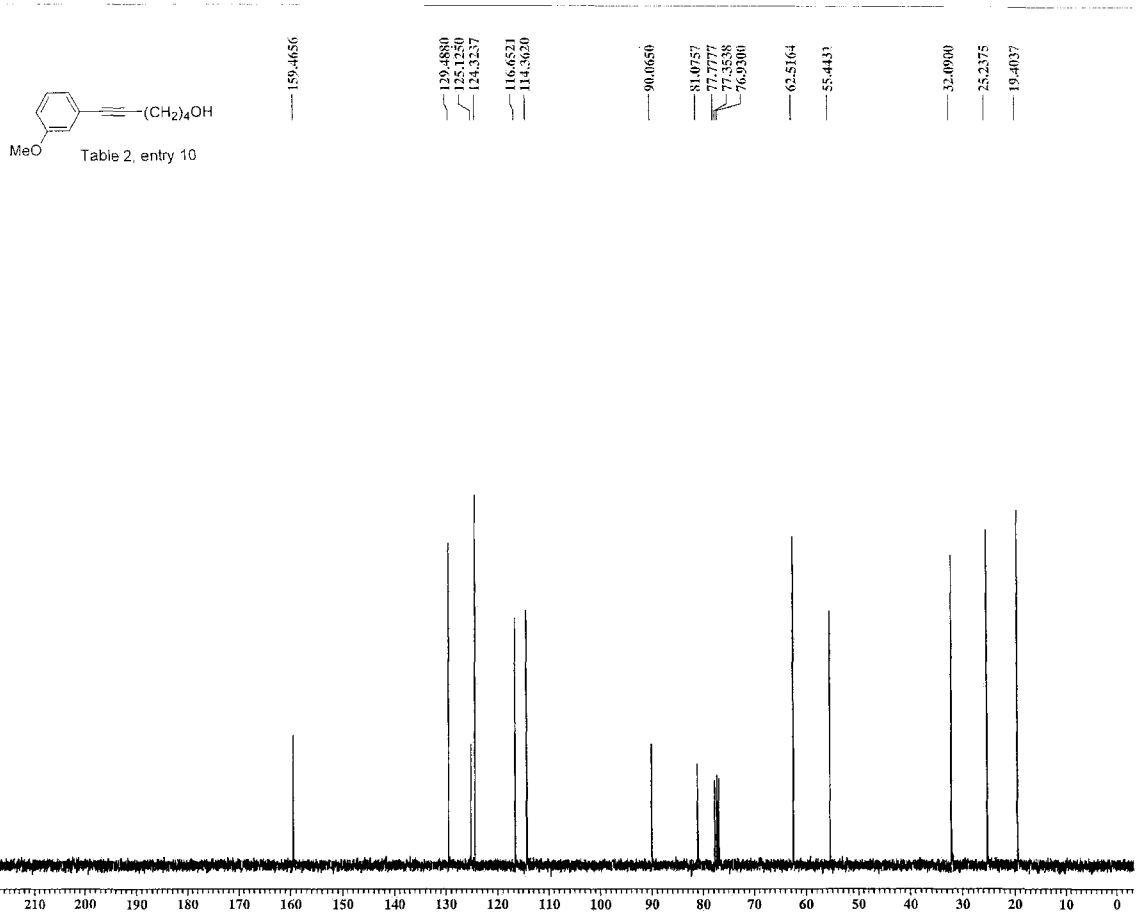
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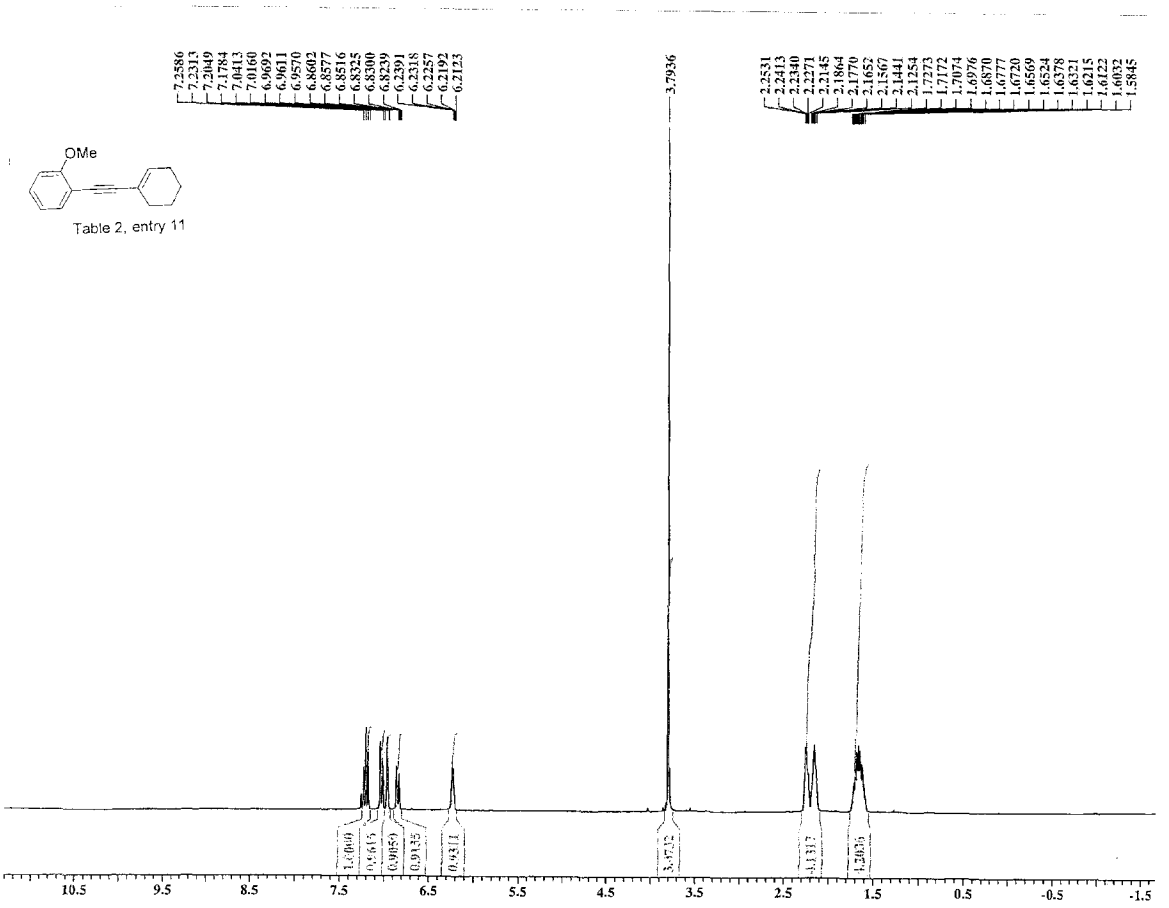
125.1250
124.3237
116.4521
114.3620
90.0650
81.0757
77.7777
77.3538
76.9300
62.5164
55.4433
32.0900
25.2375
19.4037
(CH2)4OH
MeO
Table 2, entry 10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OMe
Table 2, entry 11
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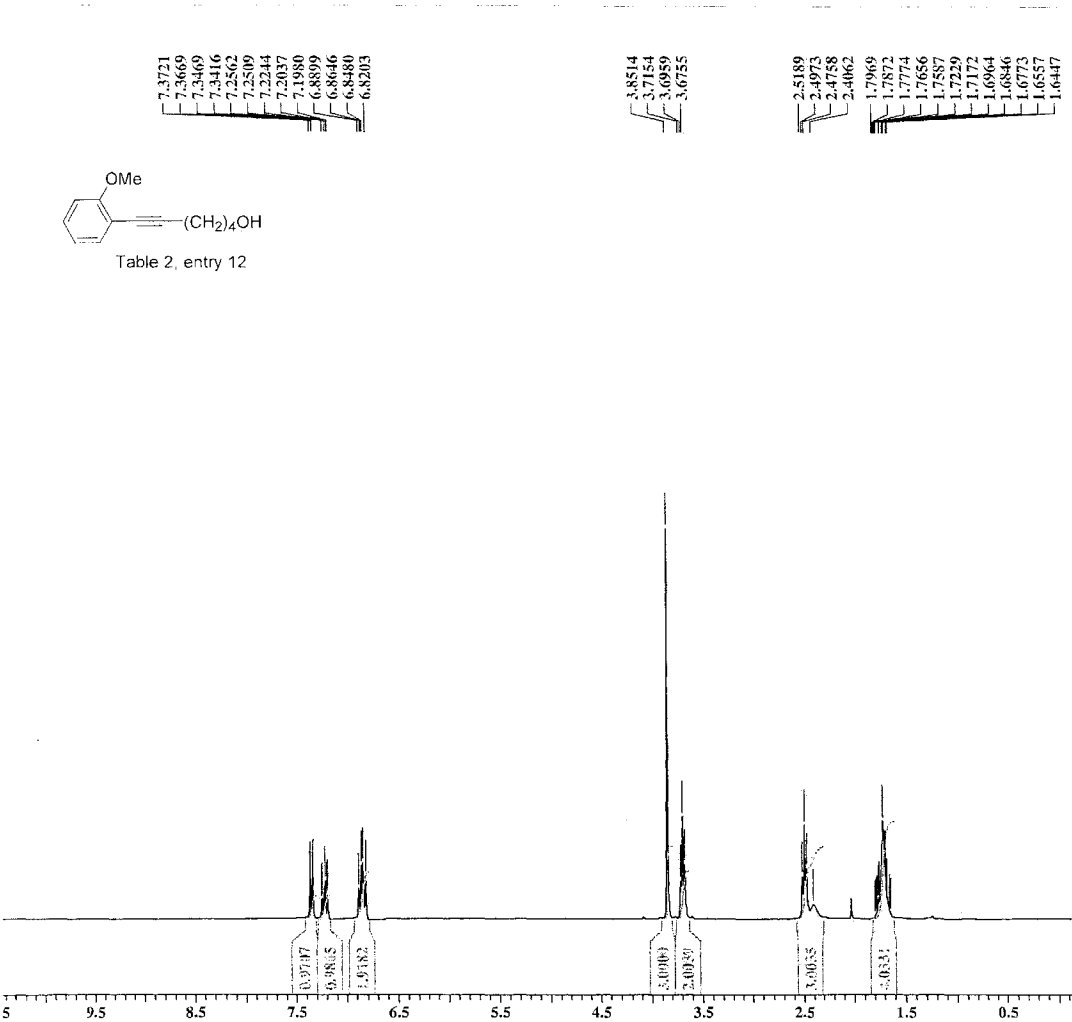
7.2313
7.2049
7.1784
7.0413
7.0160
6.9692
6.9611
6.9570
6.8602
6.8577
6.8516
6.8325
6.8300
6.8239
6.2391
6.2318
6.2257
6.2192
6.2123
3.7936
2.2531
2.2413
2.2340
2.2271
2.2145
2.1864
2.1770
2.1652
2.1567
2.1441
2.1254
1.7273
1.7172
1.7074
1.6976
1.6870
1.6777
1.6720
1.6569
1.6524
1.6378
1.6321
1.6215
1.6122
1.6032
1.5845
1.0000
0.5615
0.9085
0.9135
0.9311
3.0732
3.1317
1.2035
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5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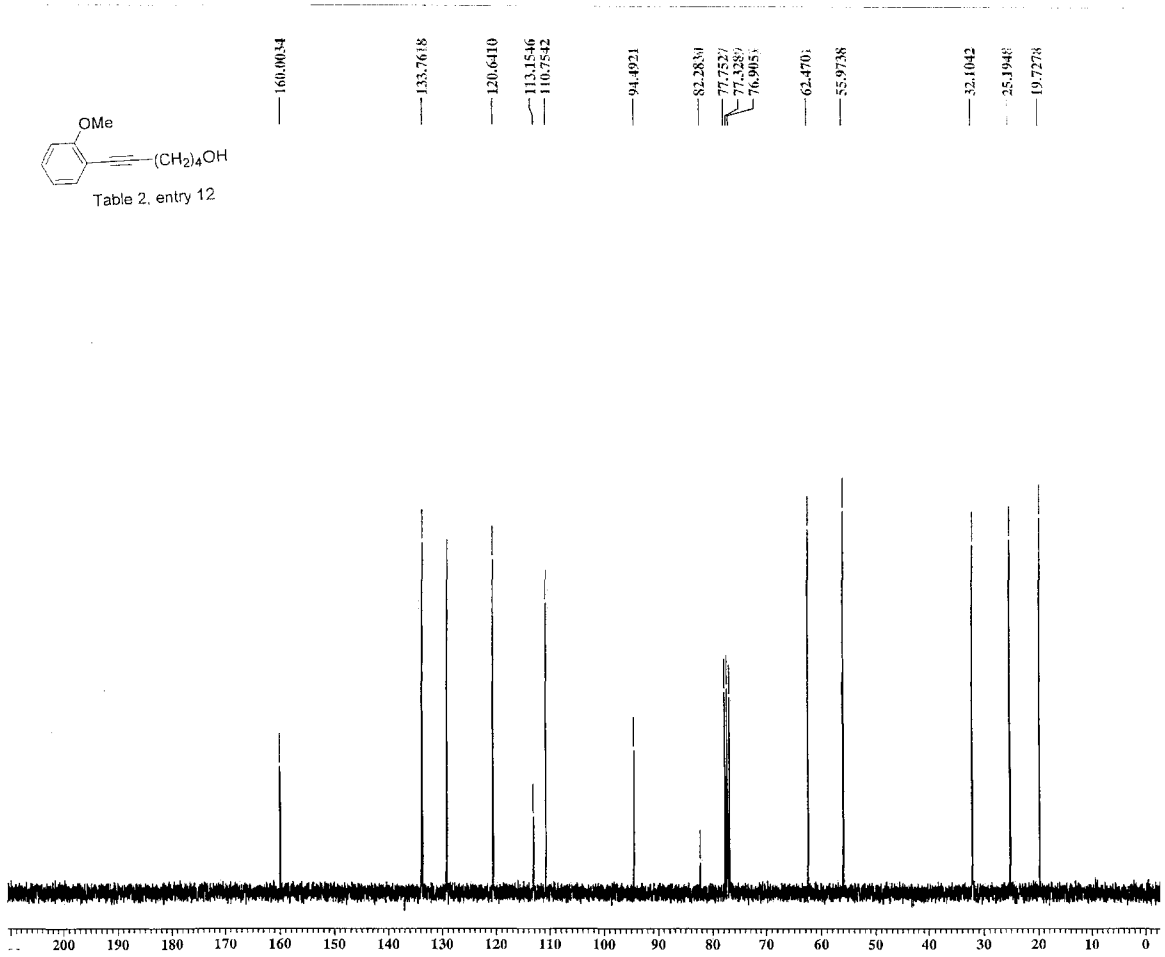
7.3669
7.3469
7.3416
7.2562
7.2509
7.2244
7.2037
7.1980
6.8899
6.8646
6.8480
6.8203
3.8514
3.7154
3.6959
3.6755
2.5189
2.4973
2.4758
2.4062
1.7969
1.7872
1.7774
1.7656
1.7587
1.7229
1.7172
1.6964
1.6846
1.6773
1.6557
1.6447
OMe
(CH2)4OH
Table 2, entry 12
0.9747
0.9865
1.0000
2.0039
3.0053
2.0633
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5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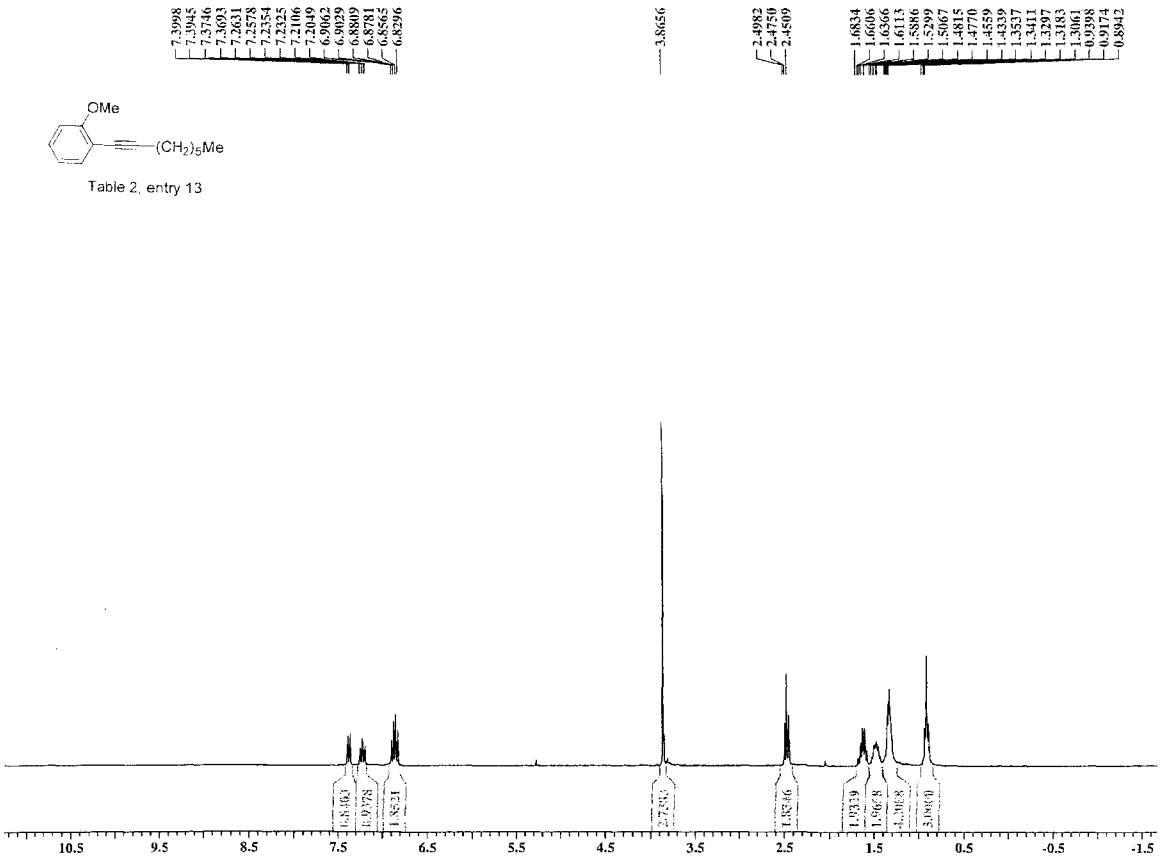
120.6410
113.1546
110.7542
94.4921
82.2836
77.7527
77.3286
76.9053
62.4701
55.9738
32.1042
25.1948
19.7278
OMe
(CH2)4OH
Table 2, entry 12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



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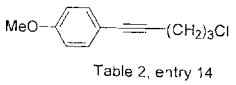
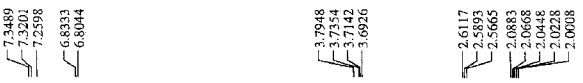
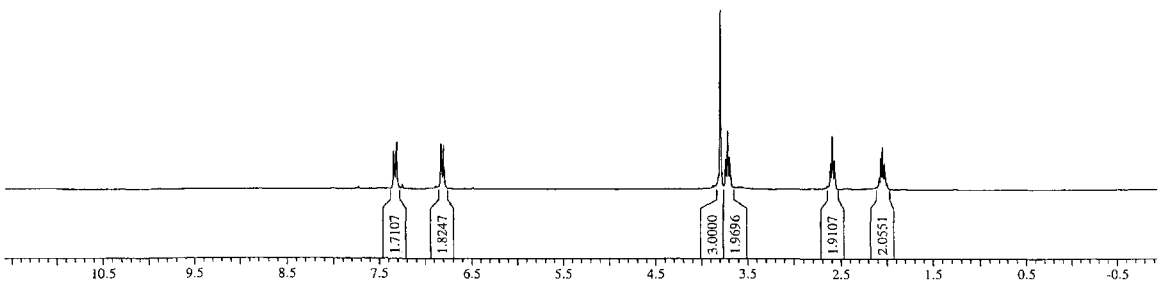


Table 2, entry 14





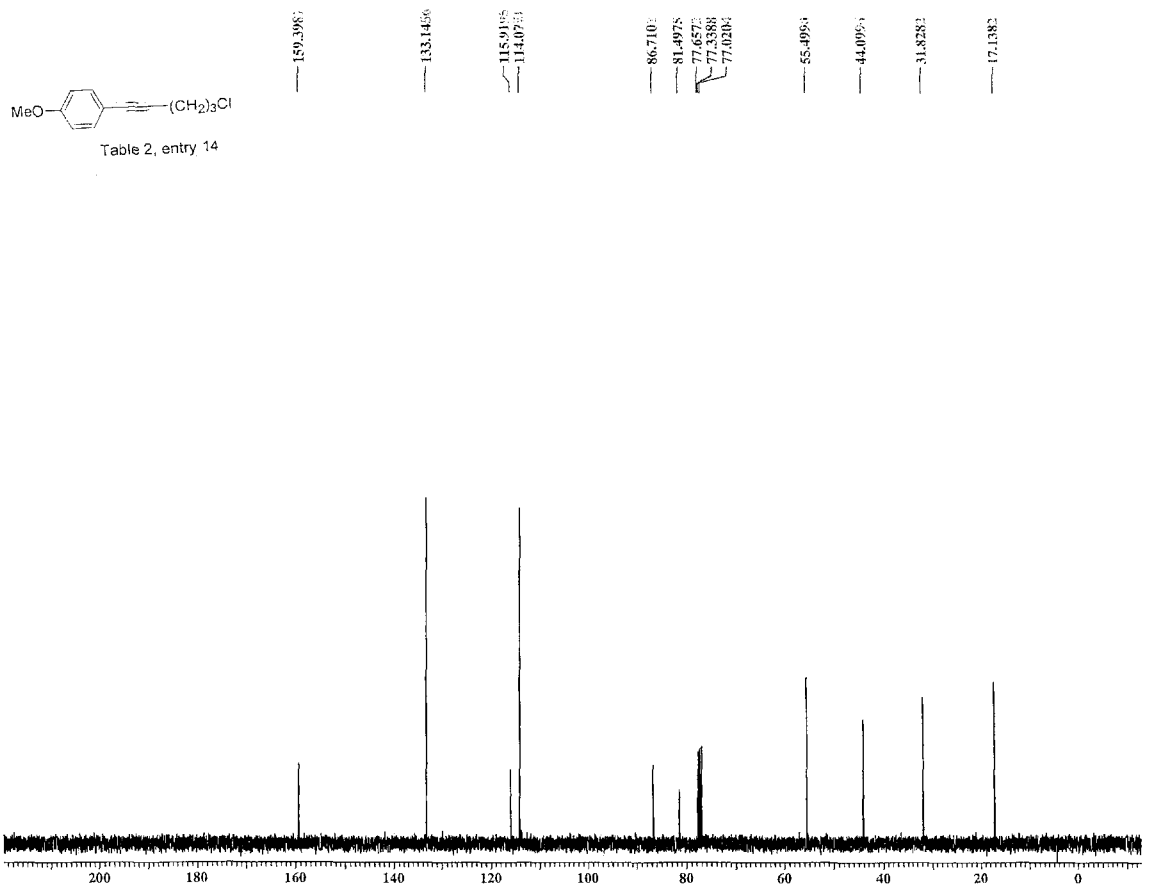
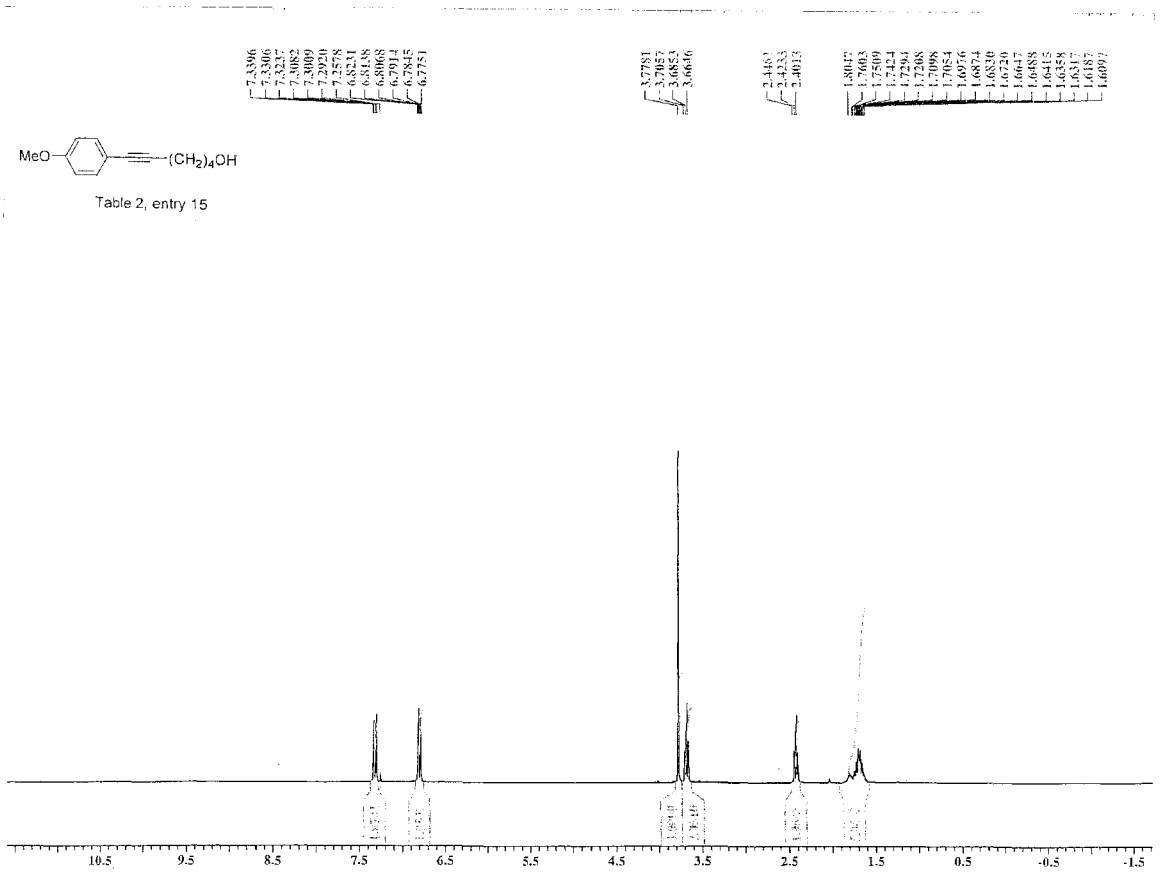


Table 2, entry 14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7.3207
7.3027
7.3002
7.2909
7.2920
7.2578
6.8221
6.8138
6.8068
6.7914
6.7845
6.7751
3.7781
3.7057
3.6853
3.6646
2.4467
2.4333
2.4013
1.8047
1.7603
1.7509
1.7424
1.7294
1.7208
1.7098
1.7054
1.6976
1.6874
1.6830
1.6720
1.6647
1.6488
1.6415
1.6358
1.6317
1.6187
1.6097
MeO
(CH2)4OH
Table 2, entry 15
10.5
9.5
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6.5
5.5
4.5
3.5
2.5
1.5
0.5
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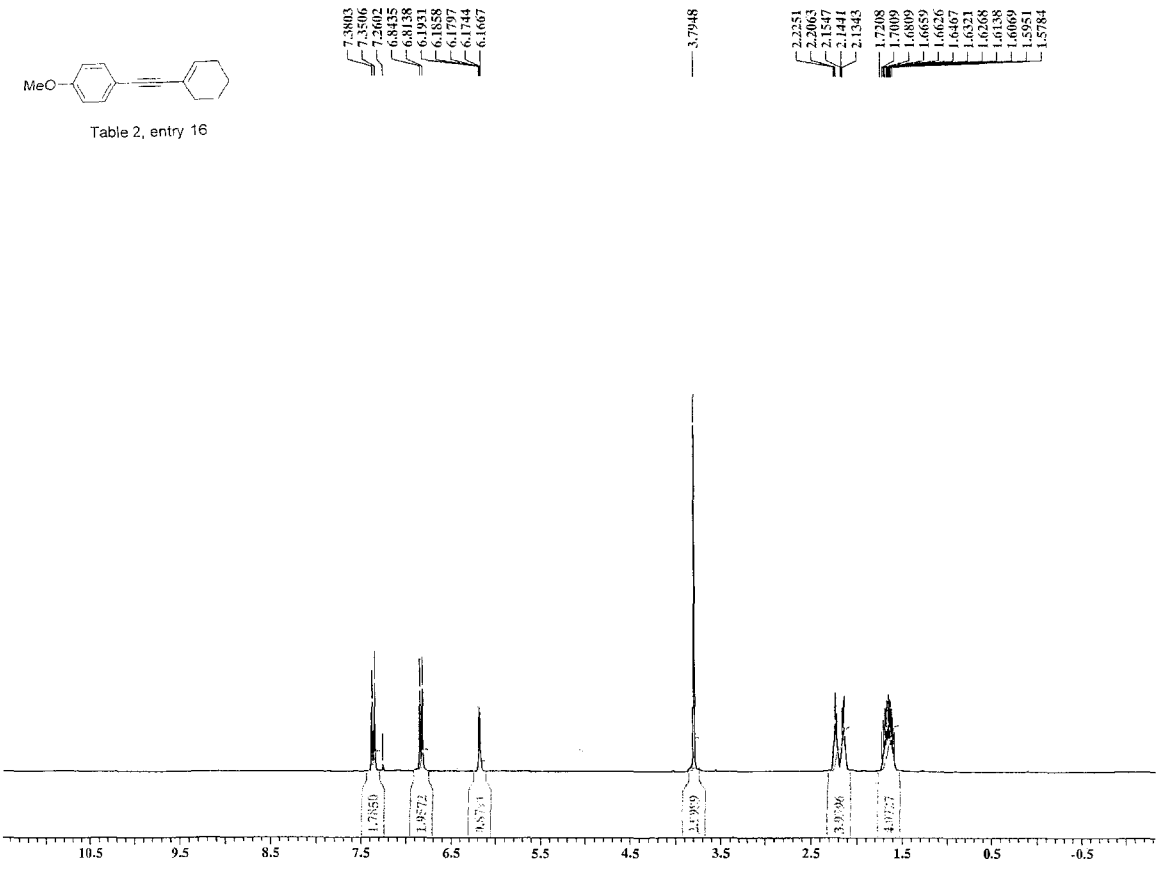
-1.5



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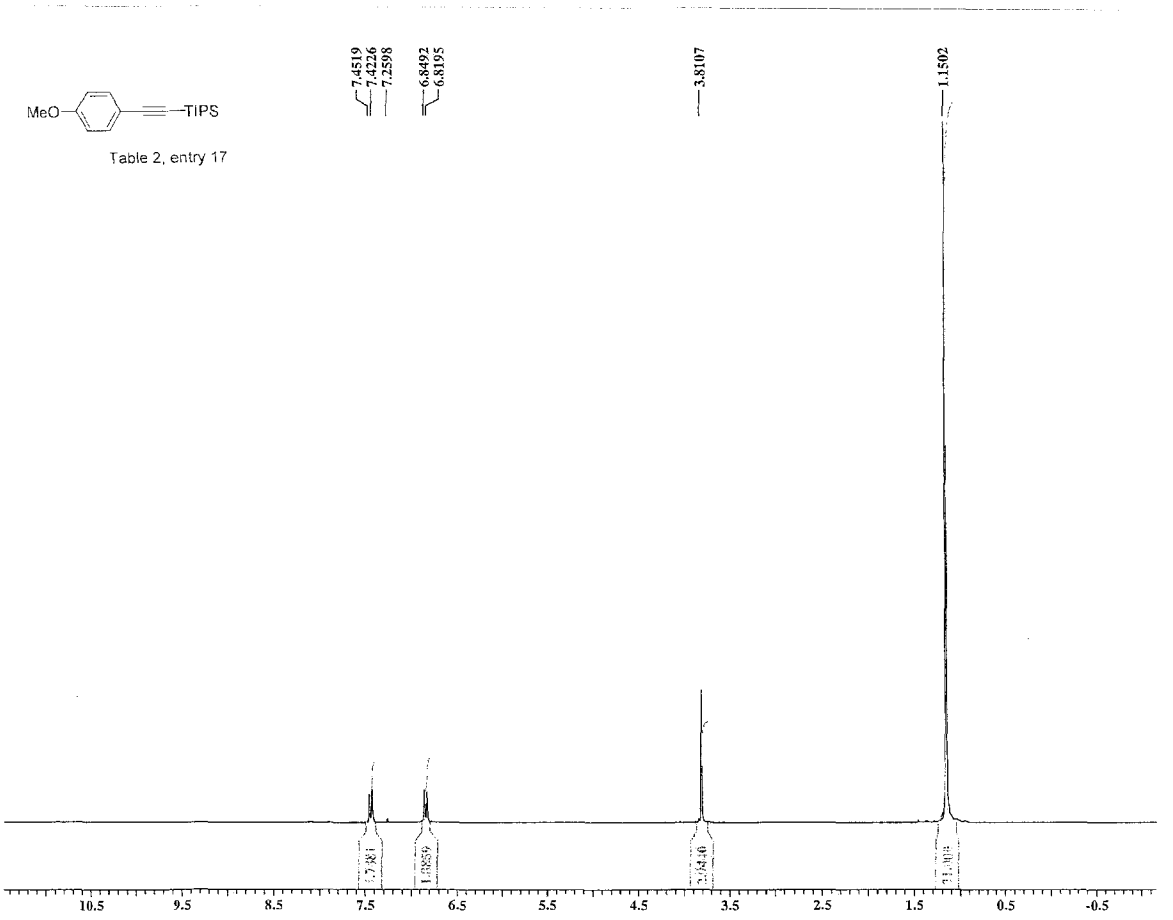
MeO
TIPS
Table 2, entry 17
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7.2598
6.8492
6.8195
3.8107
1.1502
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5

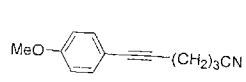
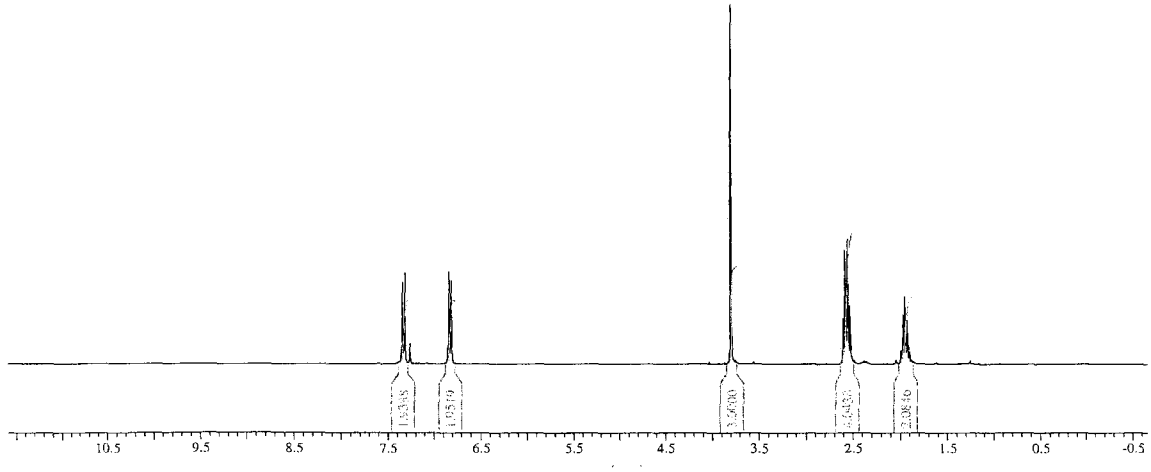
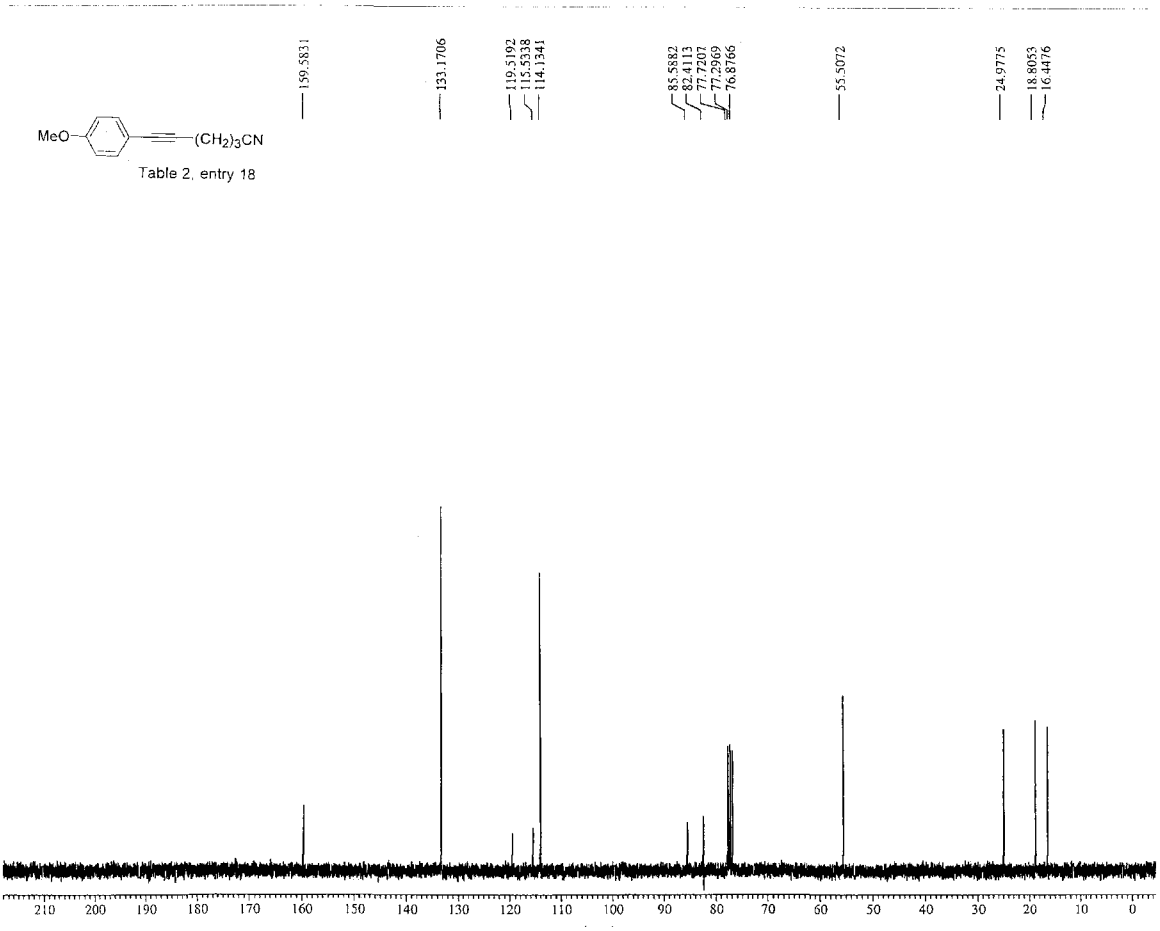


Table 2, entry 18

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133.1706
119.5192
115.5338
114.1341
85.5882
82.4113
77.7207
77.2969
76.8766
55.5072
24.9775
18.8053
16.4476
MeO
(CH2)3CN
Table 2, entry 18
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

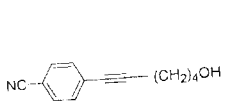
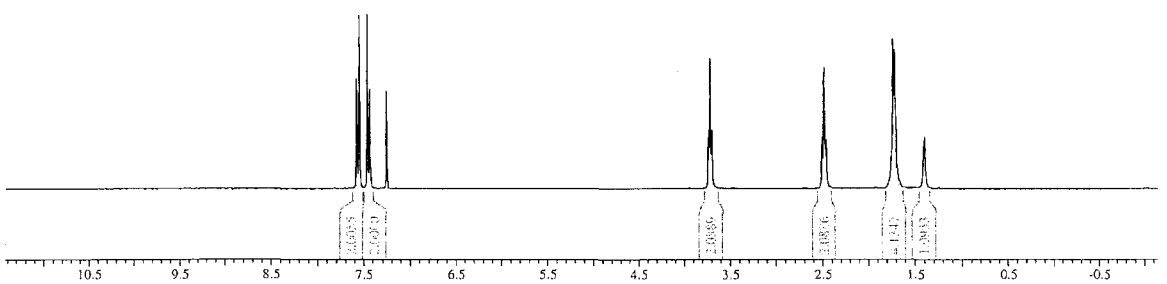


Table 3, entry 5



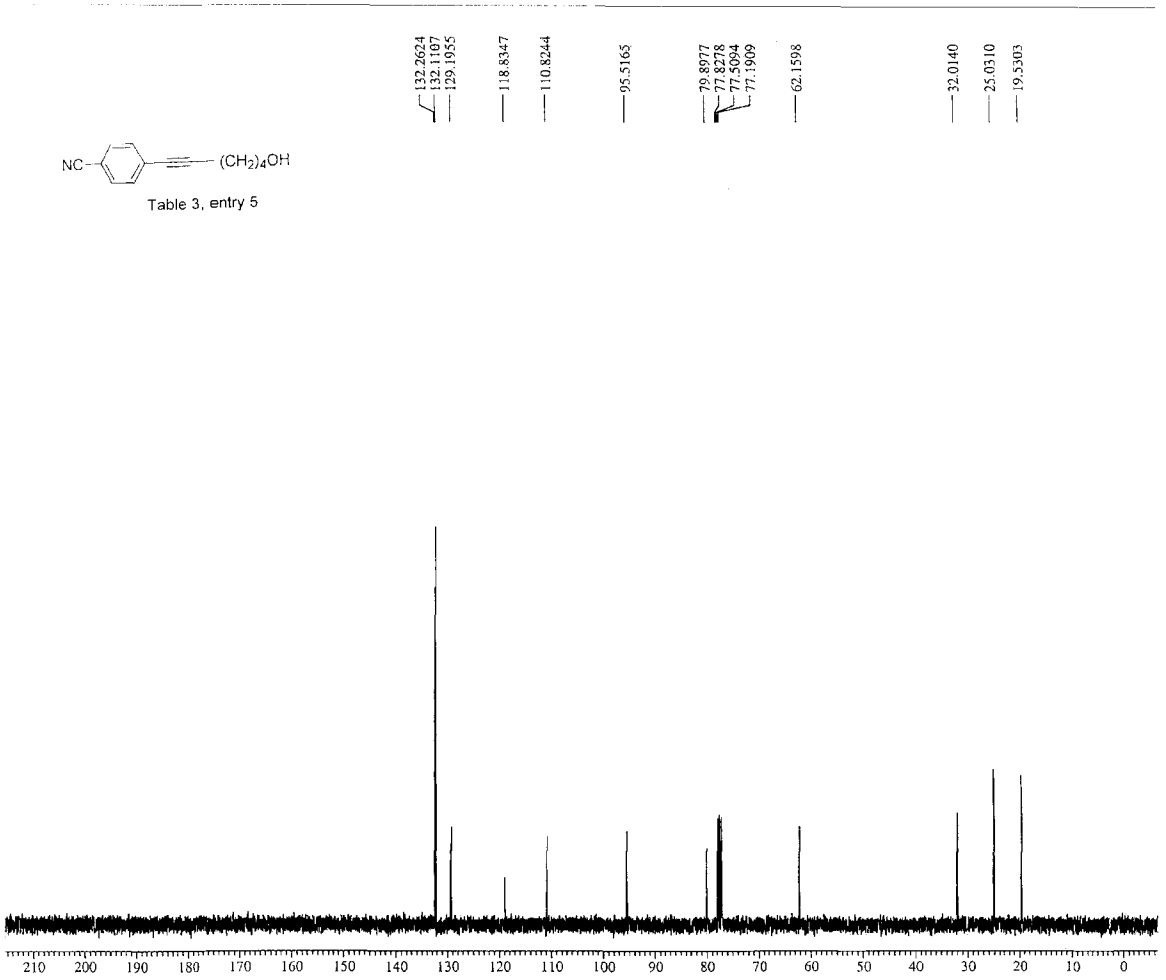
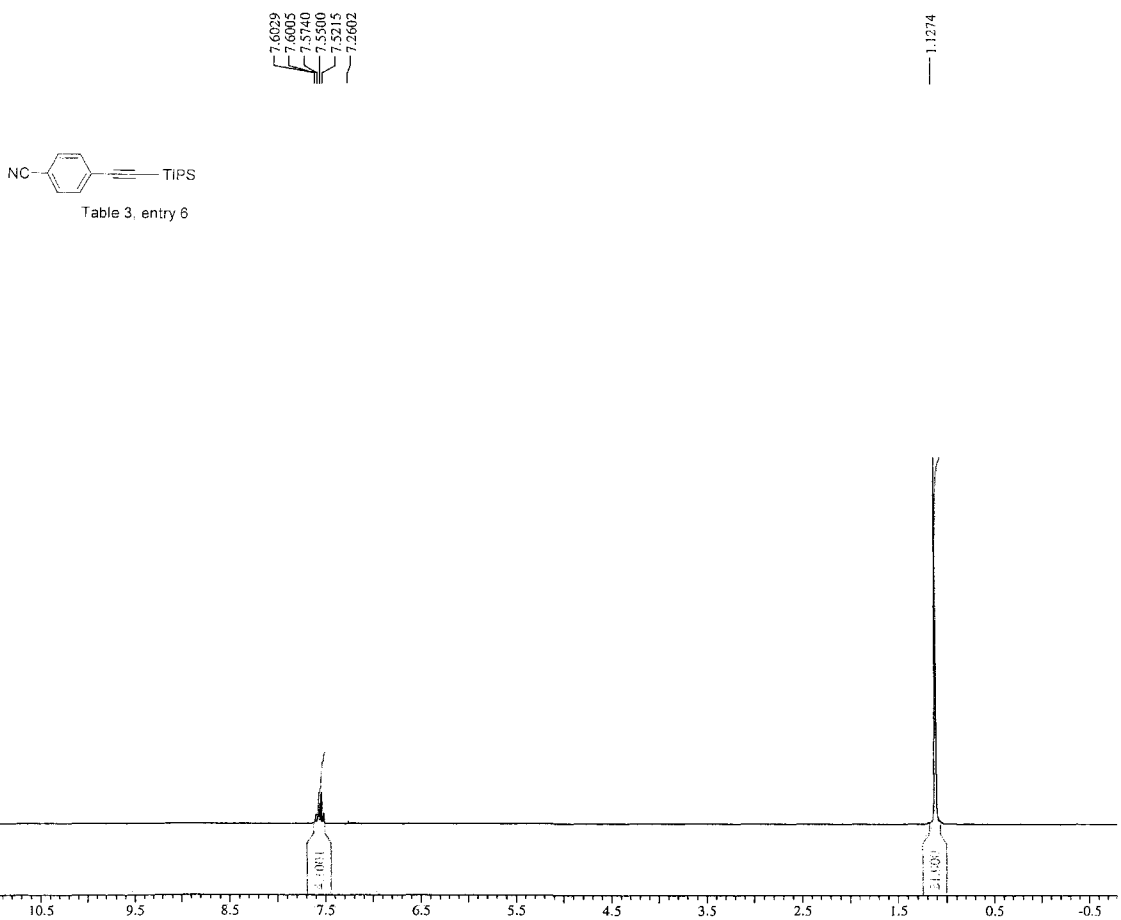


Table 3, entry 5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7.5740
7.5500
7.5215
7.2602
1.1274
NC
TIPS
Table 3, entry 6
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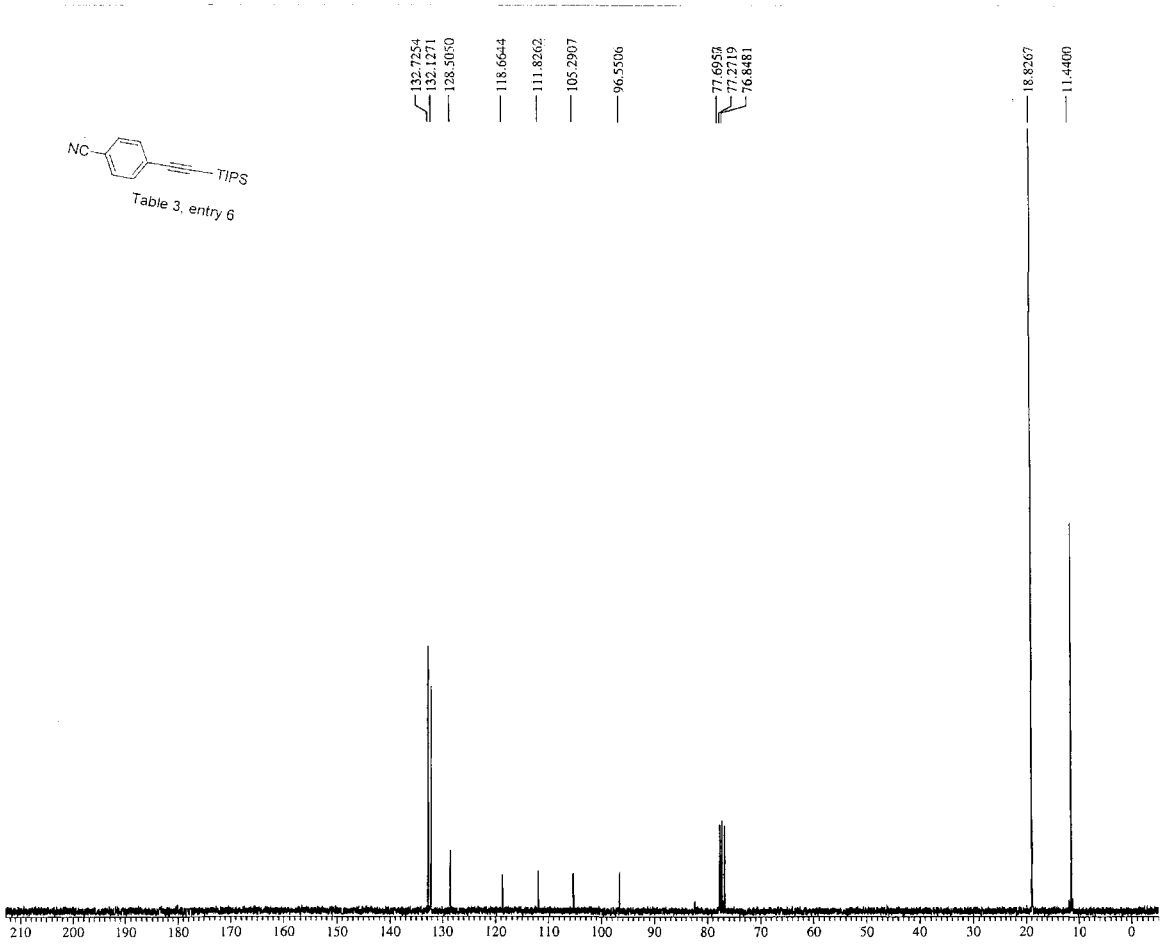
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5


NC
TIPS
Table 3, entry 6
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118.6644
111.8262
105.2907
96.5506
77.6958
77.2719
76.8481
18.8267
11.4400
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

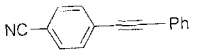
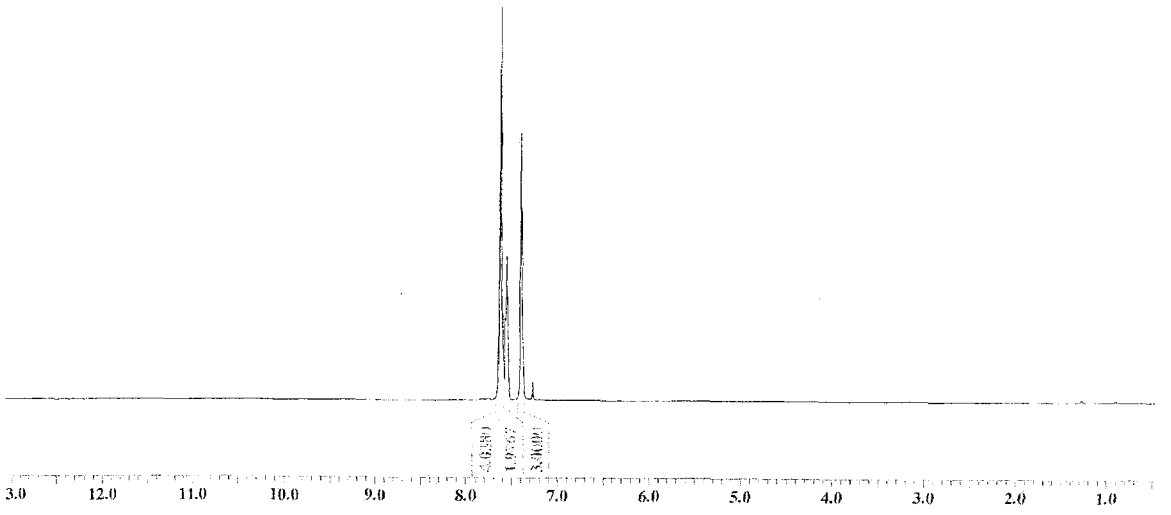


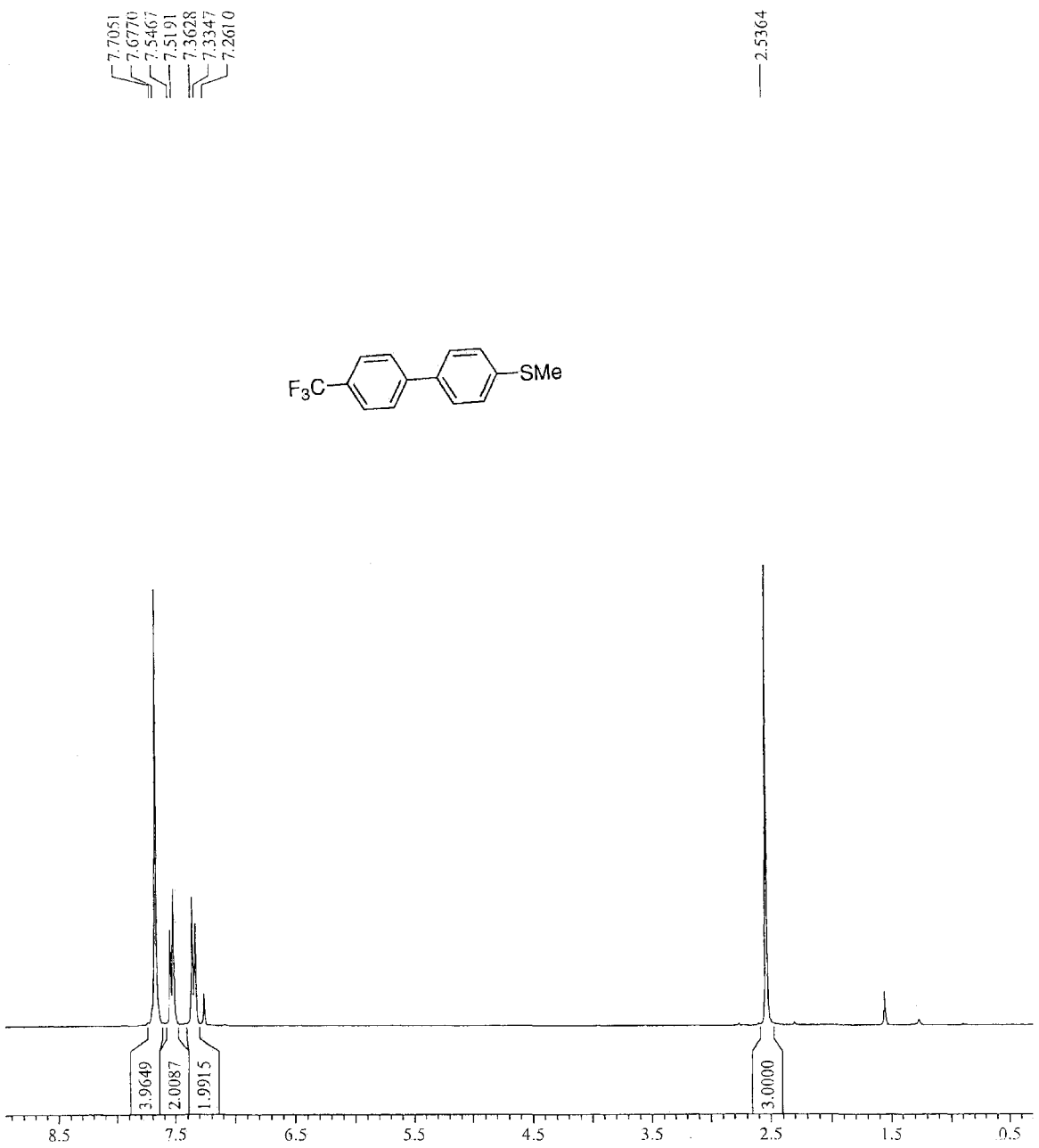
Table 3, entry 7



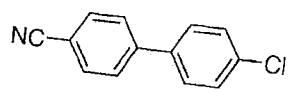
APPENDIX J

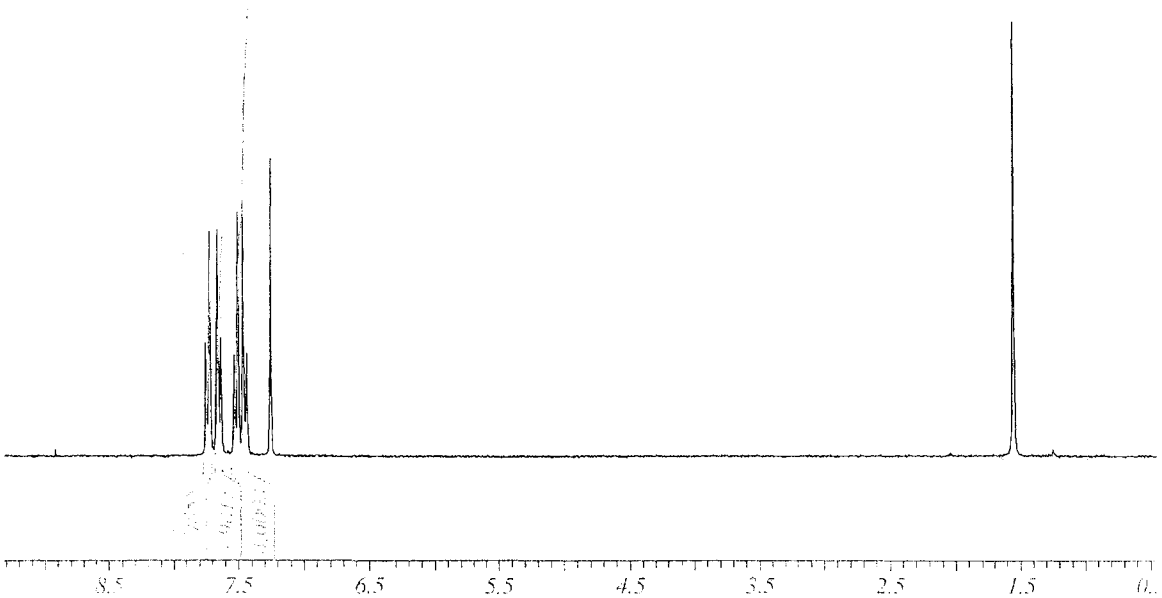
CHAPTER 11

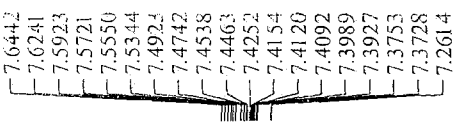
^{1}H NMR spectra for reaction products

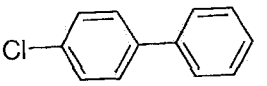

7.7051
7.6770
7.5467
7.5191
7.3628
7.3347
7.2610
2.5364
F3C
SMe
3.9649
2.0087
1.9915
3.0000
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5

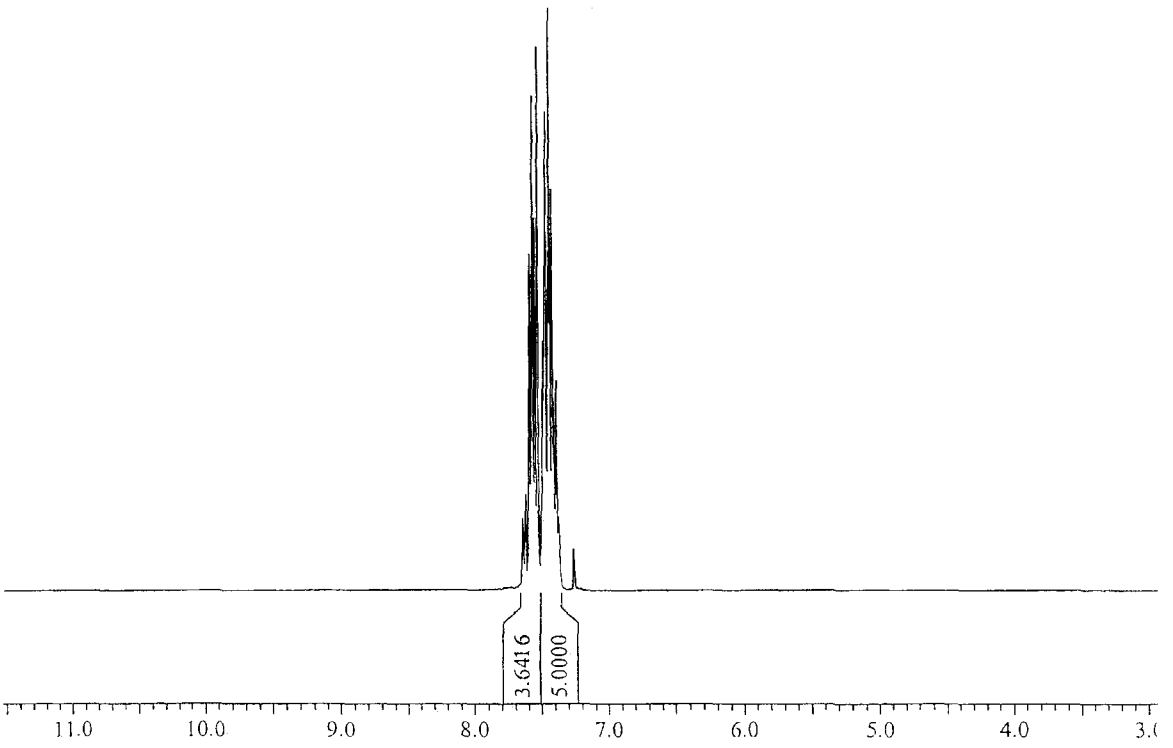

7.7470
7.7193
7.6623
7.6346
7.5366
7.5027
7.4674
7.4385

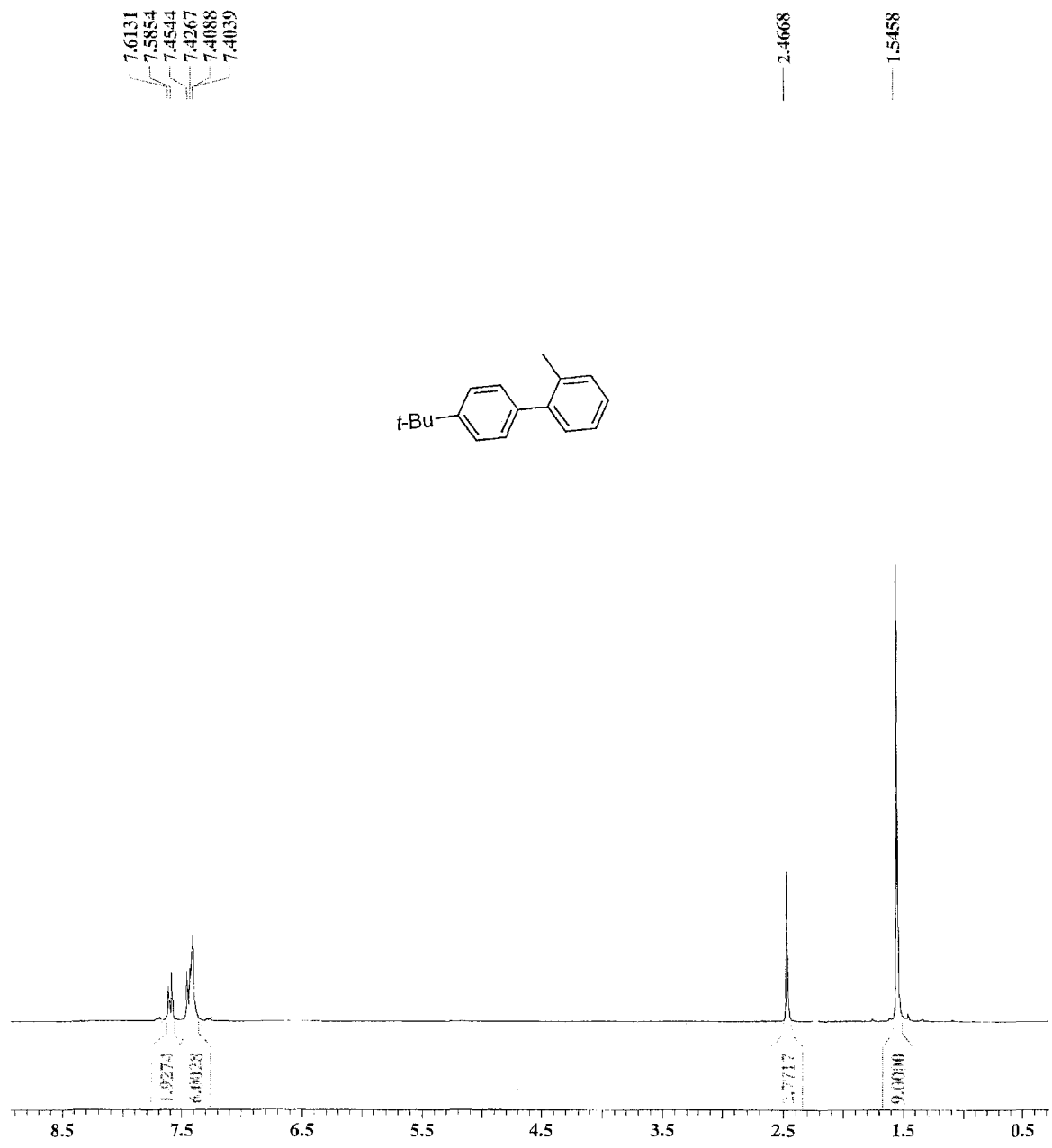

NC
Cl

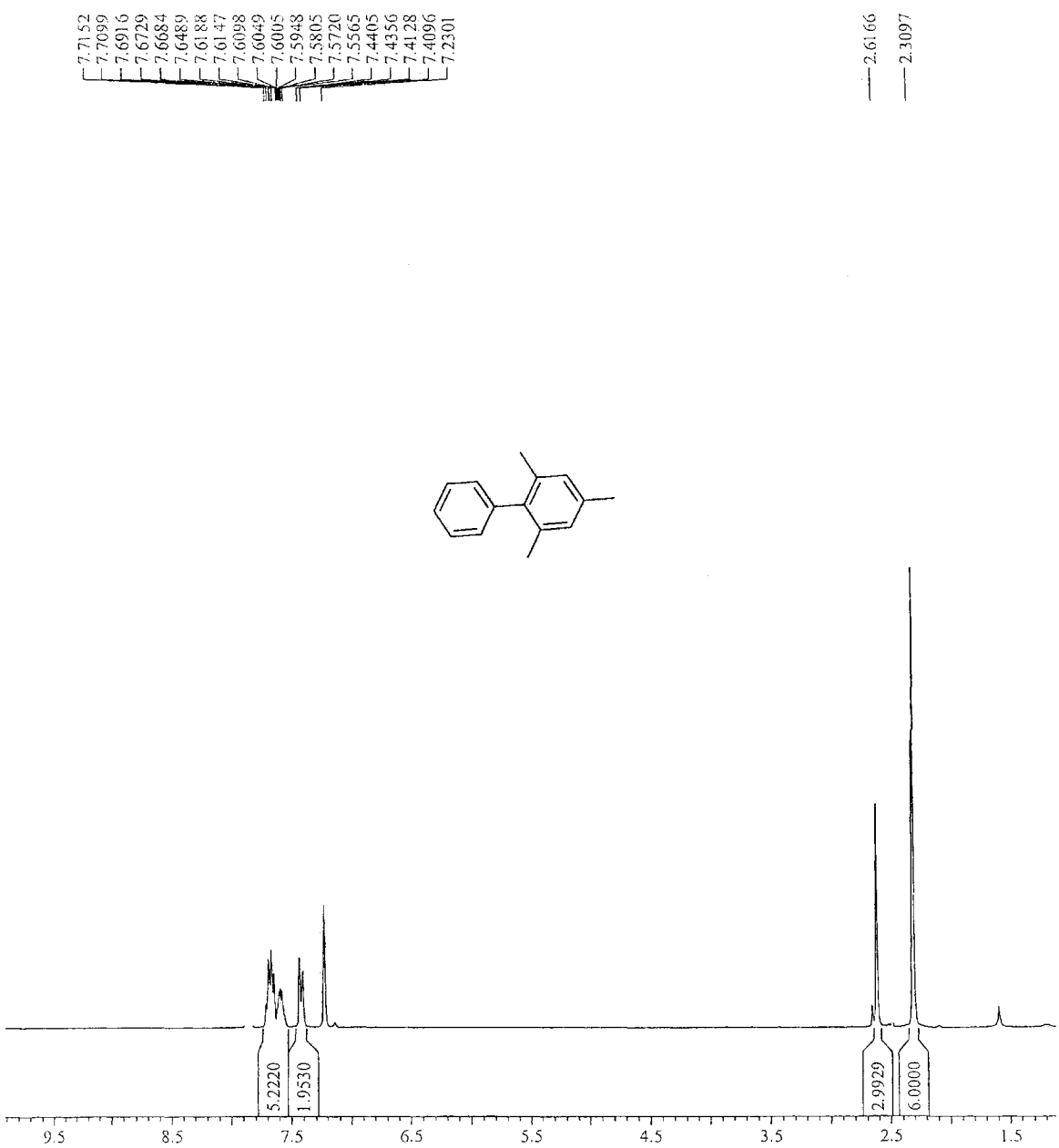

8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5


7.6241
7.5923
7.5721
7.5550
7.4742
7.4538
7.4120
7.4092
7.3989
7.3927
7.3753
7.3728
7.2614


Cl


3.6416
5.0000
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0


7.6131
7.5854
7.4544
7.4267
7.4088
7.4039
2.4668
1.5458
t-Bu
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5


7.7152
7.7099
7.6916
7.6729
7.6684
7.6489
7.6188
7.6147
7.6098
7.6049
7.6005
7.5948
7.5805
7.5720
7.5565
7.4405
7.4356
7.4128
7.4096
7.2301
2.6166
2.3097
5.2220
1.9530
2.9929
6.0000
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5