IOWA STATE UNIVERSITY
Digital Repository

2001

Palladium-catalyzed annulations, ternary couplings, and migration chemistry

Daniel Edward Emrich
Iowa State University

INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Palladium-catalyzed annulations, ternary couplings, and migration chemistry

by

Daniel Edward Emrich

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Major Professor: Richard C. Larock

Iowa State University

Ames, Iowa

2001

UMI Number: 3016703

UMI®

Graduate College
Iowa State University

This is to certify that the Doctoral dissertation of

Daniel Edward Emrich

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

Eor the Major Program

Signature was redacted for privacy.

For the Grdduate College

To Rebecca

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

atm	atmosphere
aq	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
br s	broad singlet
Bu	butyl
C	Celsius
cat.	catalytic
calcd	calculated
d	days
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMA	N,N-dimethylacetamide
DME	ethylene glycol dimethyl ether
DMF	N,N-dimethylformamide
DMG	N,N-dimethylglycine
DMSO	dimethyl sulfoxide
DPPB	1,2-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPM	1,2-bis(diphenylphosphino)methane

DPPP	1,3-bis(diphenylphosphino)propane
EDG	electron-donating group
EI	Electron Ionization
eq	equation
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
eV	electron volts
EWG	electron-withdrawing group
g	gram
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
h	hours
H	hydrogen
Hex	hexanes
HRMS	High-Resolution Mass Spectrometry
Hz	Hertz
IR	infrared
m	multiplet
m	meta
Me	methyl
mg	milligram
MHz	megaHertz

mL	milliliters
mmol	millimole(s)
mol	mole(s)
mp	melting point
nm	nanometer
NMP	1-methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
NOSEY	Two-Dimensional Nuclear Overhauser Spectroscopy
o	ortho
p	para
Pd(0)	palladium(0)
Ph	phenyl
PPh_3	triphenylphosphine
q	quartet
s	singlet
S_N1	substitution, nucleophilic, unimolecular
soln	solution
t	triplet
t or *tert*	tertiary
t-Bu	*tert*-butyl
temp	temperature
Tf	trifluoromethanesulfonyl

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tt	triplet of triplets
UV	ultraviolet

GENERAL INTRODUCTION

Over the past decades, synthetic organic chemists have taken advantage of organometallics in their synthetic methodologies. Methodologies which employ an organometallic have proven useful for the formation of carbon-carbon single bonds—a typically difficult bond to form in synthetic chemistry in good yield under mild conditions. Organolithium and organomagnesium (or Grignard reagents) have been used extensively to form carbon-carbon single bonds. Typically these organometallic reagents are employed in stoichiometric amounts.

Additionally, organotransition metal chemistry has been used extensively in organic synthesis; however, transition metals are usually (but not always) employed in catalytic amounts. These reagents consist of a transition metal and organic group bonded directly by either a σ or π metal-carbon bond. One example of these reagents is the organocopper compounds, which have been used a lot with Grignard reagents. Other organometallic compounds, such as organonickel, organomercury, and organoiron compounds, have also been widely used to form carbon-carbon bonds. Even organoruthenium and organorhodium compounds, which are typically employed as hydrogenation catalysts, have recently been used to form carbon-carbon bonds.

Similarly, organopalladium compounds have progressed from being used in hydrogenation reactions to being employed in forming carbon-carbon single bonds. Much attention has been focused on palladium in synthetic chemistry due to its low toxicity, high tolerance of functional groups, and ability to be employed catalytically in reactions.

Although palladium is expensive, it is still attractive in organic synthesis, because it can be used in a small amount catalytically.

The current literature is full of synthetic methodologies where palladium has been used to form carbon-carbon bonds both regio- and sterioselectively, some of which have familiar names, such as the Heck, Sonogashira, Suzuki, and Stille reactions.

The Larock group has done extensive, basic research on organopalladium methodologies. These methodologies have involved palladium-catalyzed annulations of organic halides onto 1,2-, 1,3-, and 1,4-dienes, as well as alkynes, for the synthesis of carbo- and heterocycles. This dissertation serves to expand the scope and utility of earlier methodologies. The dissertation is organized into three different papers, which are suitable for publication, and the author of the publication was the primary investigator and author of the papers.

Dissertation Organization

This dissertation is divided into three chapters, and each chapter is written as an independent paper following the guidelines for the *Journal of Organic Chemistry*. The papers are composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgements, and references.

Chapter 1 extends earlier Larock group, palladium-catalyzed methodology. *o*-Amino- and *o*-hydroxyaryl iodides, which were previously annulated onto norbornene and bicyclo[2.2.2]oct-2-ene, are annulated onto other cyclic and bicyclic alkenes. The reaction has been optimized, and a reaction mechanism is proposed.

Chapter 2 presents preliminary results on new palladium-catalyzed methodology for the synthesis of tetrasubstituted alkenes. These alkenes are formed via the ternary coupling of aryl iodides, alkynes, and organometallics. The reaction conditions are optimized and the scope and limitations of the reaction are discussed. A reaction mechanism is proposed, and the regio- and stereoselectivity of the reaction is investigated.

Chapter 3 presents work on palladium migration chemistry wherein the palladium migrates from an aryl group to an acyl group. Different substrates, which undergo this new kind of palladium migration, are investigated. The reaction conditions are optimized, and a reaction mechanism is proposed.

General conclusions and acknowledgements are included.

CHAPTER 1. PALLADIUM(0)-CATALYZED HETEROANNULATION OF CYCLIC AND BICYCLIC ALKENES BY FUNCTIONALLY-SUBSTITUTED ARYL IODIDES

A paper to be submitted to the *Journal of Organic Chemistry*

Daniel E. Emrich and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Abstract

A palladium(0) catalyst has been employed to affect the heteroannulation of *o*-amino- and *o*-hydroxyaryl iodides onto cyclic and bicyclic alkenes, which prevent β-hydride elimination in the key organopalladium intermediate. The best yields for the heteroannulation of *o*-aminoaryl iodides onto alkenes to form indoline derivatives are obtained by using 5 mol % of Pd(OAc)$_2$, 1 equiv of *n*-Bu$_4$NCl, 2 equivs of NaOAc, 1 equiv of dimethylglycine (DMG), 1 equiv of the *o*-aminoaryl iodide, and 2 equivs of the alkene in ethylene glycol at 100 °C for 1 day. The best results for the heteroannulation of alkenes by *o*-hydroxyaryl iodides to form 2,3-dihydrobenzofurans are obtained by employing 5 mol % of Pd(OAc)$_2$, 15 mol % of *n*-Bu$_4$NCl, 1 equiv of Na$_2$CO$_3$, 1 equiv of the *o*-hydroxyaryl iodide, and 2 equivs of the alkene in *N,N*-dimethylformamide (DMF) at 100 °C for 1 day. The reaction appears to involve (1) oxidative addition of the carbon-iodide bond of the aryl iodide to the palladium catalyst, (2) arylpalladation of the olefin carbon-carbon double bond,

(3) possible coordination of the internal nucleophile to the palladium, (4) formation of a six-membered palladacycle by loss of hydrogen iodide, and (5) reductive elimination of the organopalladium intermediate to regenerate Pd(0) and the heteroannulation product.

Introduction

Heteroannulation processes allow for the rapid construction of a wide variety of heterocycles.[1] In our laboratories, it has been shown that the palladium(0)-catalyzed annulation of 1,2-, 1,3-, and 1,4-dienes, as well as alkynes, can be employed for the synthesis of indoles,[2] benzofurans,[3] benzopyrans,[3] isocoumarins,[3] α-pyrones,[3] indenones,[4] polycyclic aromatic hydrocarbons,[5] isoquinolines,[6] and isoindoloindoles.[7]

We hoped to be able to extend these annulation processes to cyclic and bicyclic alkenes to produce a variety of carbazole,[8] indoline,[9] and benzofuran[10] derivatives. These classes of compounds are of interest due to their importance in pharmaceuticals and their appearance in a large number of natural products. Typically, synthetic routes to benzofuran[11] and indoline[12] derivatives involve multi-step procedures or harsh reaction conditions. We desired to develop a one-step palladium(0)-catalyzed route to these important heterocycles.

For the formation of annulation products, the cyclic and bicyclic alkenes employed must be chosen so as to prevent syn-β-hydride palladium elimination in the key organopalladium intermediate, since β-hydride elimination is known to be a very facile process which leads to the formation of Heck-type products. These Heck-type processes are prevented by employing suitably constructed alkenes, such as norbornene, due to its constrained geometry.

Norbomylpalladium species have previously been synthesized and have been well-studied.[13] Many groups have successfully demonstrated that these compounds can insert CO and then be trapped by various nucleophiles (Scheme 1).[13a-d] Other groups have reported direct intermolecular displacement of the palladium from the norbomyl group by various nucleophiles for the generation of carboxylic acid derivatives,[13e-f] nitriles,[13g-h] and cross-coupled hydrocarbons[13i-o] (eqs 1 and 2).

Scheme 1
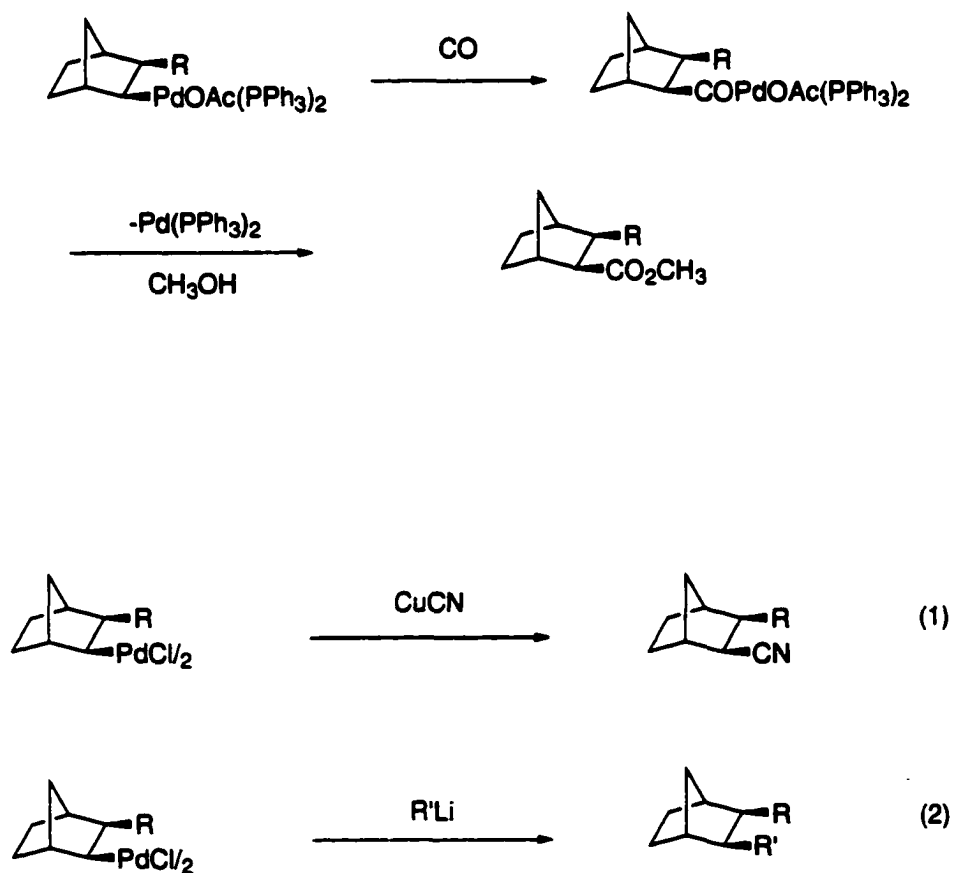
Intramolecular displacement of the palladium in such species has been reported by

Catellani, who has successfully formed hexahydromethanobiphenyls.[14] They are generated

from intermediate 1 by intramolecular η^2-coordination of the aryl group to the

norbornylpalladium intermediate, electrophilic aromatic substitution, and subsequent

reductive elimination to generate the four-membered annulation product 2 (Scheme 2).

Scheme 2
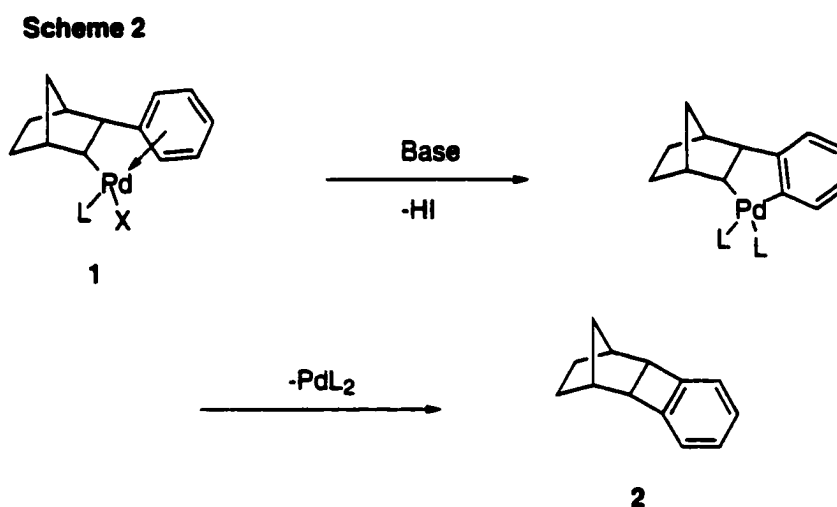
Catellani has also reported the formation of heterocycles from norbornene and

norbornadiene by palladium-catalyzed annulation using o-hydroxy- and o-aminoaryl

iodides.[15] She has postulated that her observed products arise by oxidative addition of the

aryl iodide to palladium(0), alkene insertion, coordination of the o-hydroxy or o-amino group

to the palladium (generating palladacycle 3), followed by reductive elimination of palladium

to form the observed heterocycles with simultaneous regeneration of Pd(0) (Scheme 3).

However, Catellani's research was not extended to other alkenes or to other o-aryl iodides.

Scheme 3

$n = 1,2$

$X = Br, I$
$YH = OH, NH_2$

cat. Pd(0)

3

$-PdL_2$
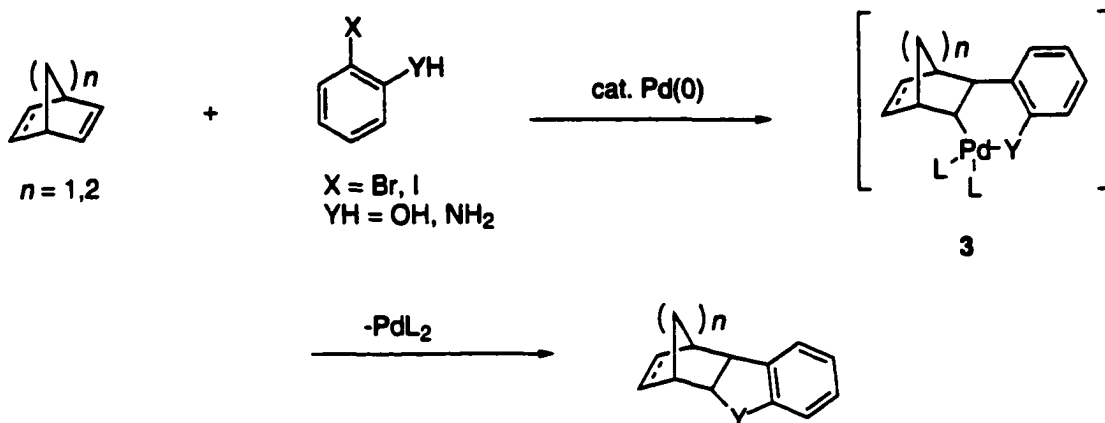
Dr. C. Jia in the Larock group simultaneously observed the same process. Like the products of Catellani's work, Jia's heteroannulation products result from the carbopalladation of bicyclic alkenes, such as norbornene, norbornadiene, bicyclo[2.2.2]oct-2-ene, and derivatives of these alkenes, which prevent intermediate palladium β-hydride elimination (eq 3). Herein we report the extension of Catellani's and Jia's work to other appropriate cyclic and bicyclic alkenes for the construction of heterocycles.

$X = O, NAc$

$n = 1$
$n = 2$

2 % Pd(OAc)$_2$
2 Na$_2$CO$_3$
15 % n-Bu$_4$NCl
DMF, 100 °C, 1 day

(3)

X	n	% yield
O	1	78
O	2	86
NAc	1	61
NAc	2	64
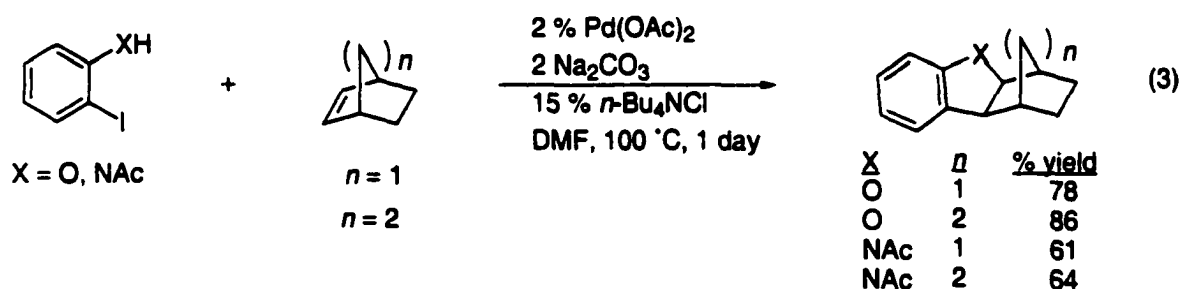
Results and Discussion

In order to extend our palladium(0)-catalyzed heteroannulation chemistry to cyclic

and bicyclic alkenes, we selected a few alkenes which preclude *syn*-β-hydride palladium

elimination (Figure 1). Jia's conditions were first applied to the reaction of 2-iodoaniline and

the cyclic alkene 2,2-dimethyl-1,3-dioxole (4) (eq 4). As shown in Table 1, entry 1, 2-

iodoaniline failed to react with 2,2-dimethyl-1,3-dioxole under these conditions. When the

solvent N,N-dimethylacetamide (DMA) was employed instead of N,N-dimethylformamide

(DMF), there was still no heteroannulation product 13 observed (Table 1, entry 2).
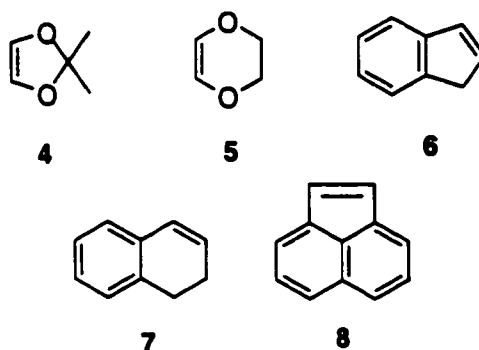
Figure 1. Cyclic and bicyclic alkenes which preclude palladium beta-hydride elimination.

(4)

9 X = NH
10 X = NAc
11 X = NTs
12 X = NMs

13 X = NH
14 X = NAc
15 X = NTs
16 X = NMs
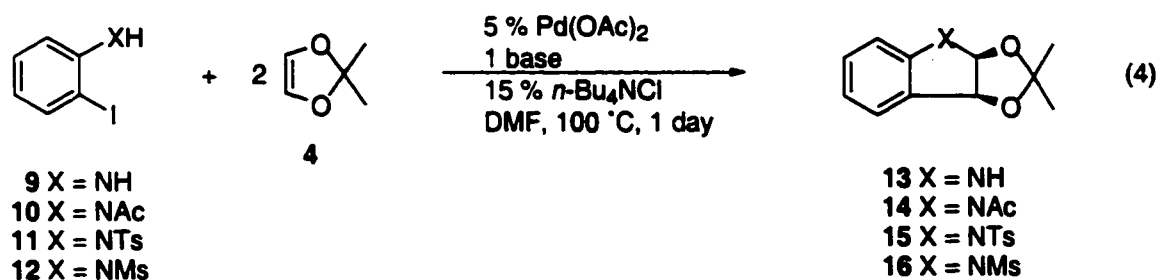
Table 1. Effect of Base on the Reaction of 2-Iodoaniline Derivatives and 2,2-Dimethyl-1,3-dioxole (eq 4).[a]

entry	X	base	% ^{1}H NMR yield of 13-16
1	NH	Na_2CO_3	0
2[b]	NH	Na_2CO_3	0
3[c]	NAc	Na_2CO_3	40
4[b]	NAc	Na_2CO_3	25
5	NAc	NaOAc	23
6	NAc	$NaHCO_3$	15
7	NAc	K_2CO_3	9
8	NAc	KOAc	36
9	NAc	$KHCO_3$	12
10[d]	NAc	Na_2CO_3	38
11[e]	NAc	Na_2CO_3	28
12[f]	NAc	Na_2CO_3	39
13[c]	NTs	Na_2CO_3	49
14[b]	NTs	Na_2CO_3	28
15	NTs	NaOAc	46
16	NTs	$NaHCO_3$	39
17	NTs	K_2CO_3	22
18	NTs	KOAc	45
19	NTs	$KHCO_3$	32
20[e]	NTs	Na_2CO_3	45

Table 1. (continued)

21[f]	NTs	Na_2CO_3	49
22[d]	NTs	Na_2CO_3	64
23[c]	NMs	Na_2CO_3	67
24[b]	NMs	Na_2CO_3	55
25	NMs	NaOAc	64
26	NMs	$NaHCO_3$	7
27	NMs	K_2CO_3	57
28	NMs	KOAc	40
29	NMs	$KHCO_3$	63
30[g]	NMs	Na_2CO_3	69
31[c,d]	NMs	Na_2CO_3	74
32[e]	NMs	Na_2CO_3	39
33[f]	NMs	Na_2CO_3	67

[a] The substituted o-aminoaryl iodide (0.45 mmol), 2,2-dimethyl-1,3-dioxole (90.0 mg, 0.90 mmol), 5 mol % of Pd(OAc)$_2$ (5.0 mg, 0.023 mmol), the base (96.0 mg, 0.90 mmol), and 15 mol % of n-Bu$_4$NCl (19.0 mg, 0.068 mmol) were reacted in 8 mL of DMF at 100 °C for 1 day.
[b] DMA was used as the solvent instead of DMF.
[c] % isolated yield instead of % ^{1}H NMR yield which were obtained using 1,4-dimethoxybenzene as the internal standard.
[d] 0.45 Mmol of the base was used instead of 0.90 mmol.
[e] No n-Bu$_4$NCl was used, and all other conditions were the same as in footnote a.
[f] 1 equiv of n-Bu$_4$NCl was used instead of 15 mol %.
[g] 0.65 Mmol of the base was used instead of 0.90 mmol.

Because 2-iodoaniline gave no heteroannulation product, the o-aminoaryl iodide

derivatives with an N-acetyl (10), N-tosyl (11), and N-mesyl (12) group were employed. We

sought to optimize the yields of these reactions by varying the conditions, including the

solvent, the base, the amount of base, and the amount of n-Bu$_4$NCl. When Jia's conditions

were applied to *N*-(2-iodophenyl)acetamide, a moderate 40% yield of product **14** was obtained (Table 1, entry 3). Running the reaction in DMA gave a lower yield than in DMF (Table 1, entry 4). Although no other solvents were employed, this preliminary result and past experience led us to believe that DMF was most likely to be the solvent of choice for this reaction.

Various inorganic bases were employed to increase the yield of **14**. None of these bases gave higher yields of **14** (Table 1, entries 5-9) than that obtained employing Na_2CO_3 under Jia's conditions. Na_2CO_3 thus proved to be the base of choice. When 1 equiv of Na_2CO_3 was employed, the yield of **14** stayed approximately the same (Table 1, entry 10).

The importance of *n*-Bu$_4$NCl was next investigated. Running the reaction without *n*-Bu$_4$NCl decreased the yield (Table 1, entry 11), proving that it is an important additive. Also, employing 1 equiv of *n*-Bu$_4$NCl did not increase the yield beyond that obtained using 15 mol % (Table 1, entry 12).

N-(2-Iodophenyl)-*p*-toluenesulfonamide (**11**) gave a moderate 49% yield of product **15** under Jia's conditions (Table 1, entry 13). We sought to optimize this yield by running the reaction in DMA, but obtained a lower yield (Table 1, entry 14). We then employed inorganic bases. NaOAc gave virtually the same yield as Na_2CO_3 (Table 1, entry 15). None of the other bases employed, namely $NaHCO_3$, K_2CO_3, KOAc, and $KHCO_3$, improved the yield of **15** (Table 1, entries 16-19) beyond that obtained when Na_2CO_3 was employed as the base. The yield decreased slightly when the reaction was run without *n*-Bu$_4$NCl (Table 1, entry 20), and when 1 equiv of *n*-Bu$_4$NCl was employed, the yield remained the same (Table 1, entry 21). Decreasing the amount of Na_2CO_3 to 1 equiv increased the yield of **15** by 15% (Table 1, entry 22).

N-(2-Iodophenyl)methanesulfonamide (**12**) gave a 67% yield of **16** using Jia's conditions (Table 1, entry 23). Lower yields were obtained by using DMA (Table 1, entry 24), demonstrating that DMF was still the preferred solvent. Various inorganic bases were employed. As observed before, NaOAc gave yields similar to those obtained with Na_2CO_3 (Table 1, entry 25), which suggests that both Na_2CO_3 and NaOAc are appropriate bases. Although $NaHCO_3$ gave a very poor yield of 7% (Table 1, entry 26), the bases K_2CO_3, KOAc, and $KHCO_3$ all gave moderate yields of 57%, 40%, and 63% of **16** respectively (Table 1, entries 27-29). Decreasing the amount of Na_2CO_3 moderately increased the yield of **16** (Table 1, entries 30 and 31). Again, running the reaction without n-Bu$_4$NCl decreased the yield (Table 1, entry 32), while employing 1 equiv of n-Bu$_4$NCl did not increase the yield beyond that obtained using 15 mol % (Table 1, entry 33).

The mechanism proposed for these reactions is shown in Scheme 4. We hypothesize that the reaction mechanism involves (1) oxidative addition of the palladium catalyst to the carbon-iodide bond of the aryl iodide, (2) arylpalladation of the olefin carbon-carbon double bond, (3) possible coordination of the internal nucleophile to the palladium, (4) loss of hydrogen iodide with formation of a six-membered palladacycle, and (5) reductive elimination of the palladium intermediate to produce the heteroannulation product and regenerate the Pd(0) catalyst.

During the course of this reaction, a negative charge may build up on the nitrogen atom. 2-Iodoaniline, which has no electron-withdrawing group (EWG) on the nitrogen atom, failed to give any heteroannulation product. Furthermore, *o*-aminoaryl iodides with strong EWGs gave higher yields than those with weak EWGs. An EWG would help to stabilize the negative charge on the nitrogen atom.

Scheme 4

R = H, Ac, Ts, Ms
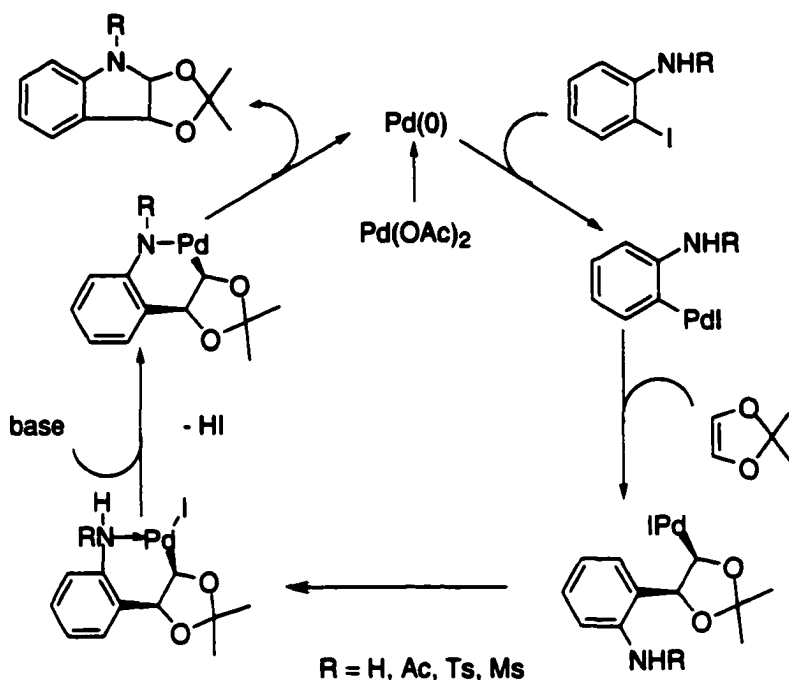
The effect n-Bu$_4$NCl has on the mechanism is unclear; however, Jeffrey long ago demonstrated its importance in Pd(0)-catalyzed Heck reactions.[16] We believe that the chloride atom of n-Bu$_4$NCl coordinates strongly to the Pd(0) catalyst making it more nucleophilic and thus more reactive towards oxidative addition. Therefore, the activated Pd(0) catalyst may insert into the carbon-iodide bond of the electron-rich o-aminoaryl iodide more readily.

After reacting the o-aminoaryl iodides with 4, Jia's conditions were applied to the reaction of o-hydroxyaryl iodides and 4 (eq 5). We have employed in these reactions 2-iodophenol (17), 4-hydroxy-3-iodoacetophenone (18) with an EWG *para* to the internal nucleophile, and 2-iodo-3,5,6-trimethylhydroquinone (19) with an electron-donating group (EDG) *para* to the internal nucleophile.

$$\text{17 X = O, R = H, R' = H}$$
$$\text{18 X = O, R = Ac, R' = H}$$
$$\text{19 X = O, R = OH, R' = CH}_3$$

$$\text{20 X = O, R = H, R' = H}$$
$$\text{21 X = O, R = Ac, R' = H}$$
$$\text{22 X = O, R = OH, R' = CH}_3$$
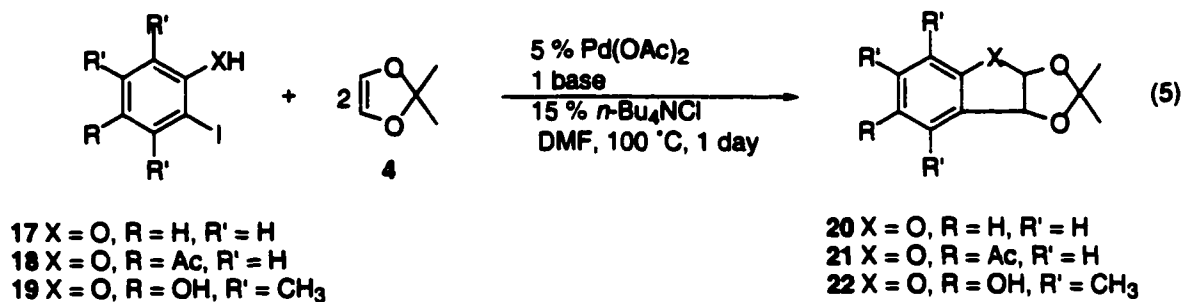
2-Iodophenol (**17**) gave a low 37% yield of heteroannulation product **20** (Table 2, entry 1). This reaction was also run with only 1 mL of DMF, but the same yield was observed. We hypothesized that a more concentrated reaction mixture would improve the yields throughout the rest of the optimization work, so 1 mL instead of 8 mL of solvent was employed in the rest of these reactions.

In an attempt to further optimize the yield, we employed the solvents DMA and dimethyl sulfoxide (DMSO), both of which gave lower yields (Table 2, entries 2 and 3). However, when only 1 equiv of Na_2CO_3 was used, DMF and DMA gave higher yields of 61% and 59% of heteroannulation product **20** respectively (Table 2, entries 4 and 5). On the other hand, DMSO produced a much lower yield of 19% (Table 2, entry 6).

Because 1 equiv of Na_2CO_3 improved the yields of product **20** in DMF and DMA, 1 equiv of various bases were next employed with these solvents. The base $NaHCO_3$ gave a very low yield of **20** in DMA (Table 2, entry 7), but the bases K_2CO_3 and $KHCO_3$ (Table 2, entries 8 and 9) gave results similar to those of Na_2CO_3. Two other inorganic bases were employed in DMF to determine if a better yield could be obtained. The base Li_2CO_3 gave a low yield of 5% in DMF (Table 2, entry 10), and the base $Zn(OAc)_2$ gave a 23% yield (Table 2, entry 11). $n\text{-Bu}_4NCl$ has again proven to be an important additive, because when the

Table 2. Effect of Base on the Reaction of 2-Iodophenol or 4-Hydroxy-3-iodoacetophenone with 2,2-Dimethyl-1,3-dioxole (eq 5).[a]

entry	iodophenol	base	% ^{1}H NMR yield of 20 or 21
1[b, c]	17	Na_2CO_3	37
2[b, d]	17	Na_2CO_3	22
3[b, e]	17	Na_2CO_3	31
4	17	Na_2CO_3	61
5[d]	17	Na_2CO_3	59
6[e]	17	Na_2CO_3	19
7[d]	17	$NaHCO_3$	6
8[d]	17	K_2CO_3	57
9[d]	17	$KHCO_3$	60
10	17	Li_2CO_3	5
11	17	$Zn(OAc)_2$	23
12[f]	17	Na_2CO_3	15
13	18	Na_2CO_3	64
14[d]	18	Na_2CO_3	49
15[e]	18	Na_2CO_3	19
16	18	$NaHCO_3$	12
17	18	K_2CO_3	46
18	18	Li_2CO_3	46
19	18	$KHCO_3$	54
20[f]	18	Na_2CO_3	5

Table 2. (continued)

^{a}The substituted aryl iodide (0.45 mmol), 2,2-dimethyl-1,3-dioxole (90.0 mg, 0.90 mmol), 5 mol % of Pd(OAc)$_2$ (5.0 mg, 0.023 mmol), the base (48.0 mg, 0.45 mmol), and 15 mol % of n-Bu$_4$NCl (19.0 mg, 0.068 mmol) were reacted in 1 mL of DMF at 100 °C for 1 day.
^{b}0.90 Mmol of base was used instead of 0.45 mmol.
^{c}% isolated yield instead of % ^{1}H NMR yield.
^{d}DMA was used as the solvent instead of DMF.
^{e}DMSO was used as the solvent instead of DMF.
^{f}No n-Bu$_4$NCl was used, but all other conditions were the same as in footnote a.

reaction was run without it, a lower yield was obtained (Table 2, entry 12). Based on these results, these altered conditions using 1 equiv of Na$_2$CO$_3$ and 1 mL of solvent, hereafter referred to as "the optimal phenol procedure" (Table 2, footnote a), were employed instead of Jia's conditions in subsequent reactions.

When 4-hydroxy-3-iodoacetophenone (18) was allowed to react with 4 using the optimal phenol procedure, heteroannulation product 21 was obtained in a yield of 64% (Table 2, entry 13). When DMA and DMSO were employed as solvents, lower yields of 21 were obtained (Table 2, entries 14 and 15). To further optimize the yield, a series of inorganic bases were employed. The base NaHCO$_3$ gave a low yield of 12% (Table 2, entry 16). The bases K$_2$CO$_3$ and Li$_2$CO$_3$ both gave yields of 46% (Table 2, entries 17 and 18), and the base KHCO$_3$ gave a yield of 54% (Table 2, entry 19). Running the reaction without n-Bu$_4$NCl again gave a poor yield (Table 2, entry 20).

2-Iodo-3,5,6-trimethylhydroquinone (19) was allowed to react with 4 using the optimal phenol procedure (eq 5). A moderate 46% yield of heteroannulation product 22 was obtained. Because our supply of 4 was depleted, we were unable to pursue optimization work on this reaction.

A couple of conclusions may be drawn from these results. Having an EWG or an EDG *para* to the internal nucleophile of the aryl iodide did not greatly affect the yield. The slightly lower yield from **19** may be due to the electron-rich nature of this arene, and thus oxidative addition of **19** to the palladium species is impaired. The bases Na_2CO_3 and K_2CO_3 consistently gave the best yields in these reactions, although other bases, such as Li_2CO_3 and $KHCO_3$, were just as effective in some cases.

We next employed 1,4-dioxene (**5**) as the alkene in these reactions. The *o*-aminoaryl iodides **10-12** failed to generate any heteroannulation product under Jia's or the optimal phenol procedure; however, the *o*-hydroxyaryl iodides gave the desired products (eq 6). 2-Iodophenol (**17**) gave a 40% yield of heteroannulation product **27** when allowed to react using the optimal phenol procedure (Table 3, entry 1). We attempted to optimize the yield of the product by varying the reaction conditions, but running the reaction in DMA gave a lower yield (Table 3, entry 2). Employing 2 equivs of Na_2CO_3 or 1 equiv of n-Bu$_4$NCl did not substantially improve the yield either (Table 3, entries 3 and 4).

$$\text{(6)}$$

17 R, R' = H
18 R = Ac, R' = H
19 R = OH, R' = CH₃
23 R = Cl, R' = H
24 R = CO₂H, R' = H
25 R = CO₂Et, R' = H
26 R = *t*-butyl, R' = H

27 R, R' = H
28 R = Ac, R' = H
29 R = OH, R' = CH₃
30 R = Cl, R' = H
31 R = CO₂H, R' = H
32 R = CO₂Et, R' = H
33 R = *t*-butyl, R' = H
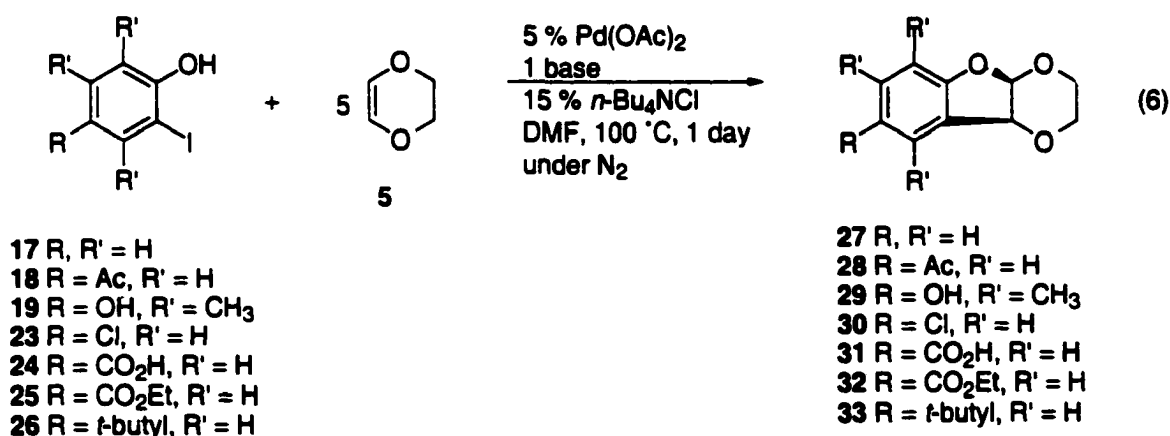
Table 3. Effect of Base on the Reaction of 2-Iodophenol and 1,4-Dioxene (eq 6).[a]

entry	base	time (d)	mmol of 1,4-dioxene	% ^{1}H NMR yield of 27
1[b]	Na_2CO_3	1	0.9	40
2[c]	Na_2CO_3	1	0.9	30
3[d]	Na_2CO_3	1	0.9	42
4[e]	Na_2CO_3	1	0.9	37
5	NaOAc	1	0.9	34
6	K_2CO_3	1	0.9	<5
7	$KHCO_3$	1	0.9	<5
8	LiOAc	1	0.9	5
9	KOAc	1	0.9	25
10	$NaHCO_3$	1	0.9	18
11[f]	Na_2CO_3	1	0.9	13
12	Na_2CO_3	1	2.25	20
13[g]	Na_2CO_3	1	2.25	24
14[b,h]	Na_2CO_3	1	2.25	64
15[b,h]	Na_2CO_3	1	3.6	61
16[h]	Na_2CO_3	1	4.5	62
17[h]	Na_2CO_3	3	0.9	47
18[h]	Na_2CO_3	3	1.35	56
19[b,h]	Na_2CO_3	3	2.25	61

[a]The 2-iodophenol (0.45 mmol), 1,4-dioxene (79.4 mg, 0.90 mmol), 5 mol % of $Pd(OAc)_2$ (5.0 mg, 0.023 mmol), the base (48.0 mg, 0.45 mmol), and 15 mol % of n-Bu_4NCl (19.0 mg, 0.068 mmol) were reacted in 1 mL of DMF at 100 °C for 1 day.

[b]% isolated yield instead of % ^{1}H NMR yield which were obtained using 1,4-dimethoxybenzene as the internal standard.

Table 3. (continued)

*DMA was used as the solvent instead of DMF.
*0.90 Mmol of the base Na_2CO_3 was employed instead of 0.45 mmol.
*1 Equiv of n-Bu_4NCl was employed instead of 15 mol %.
*No n-Bu_4NCl was used, but all other conditions were the same as in footnote a.
*The reaction was run at 80 °C, but all other conditions were the same as in footnote a.
*The reaction was run under N_2, but all other conditions were the same as in footnote a.

We also attempted to optimize the yield by employing the inorganic bases NaOAc, K_2CO_3, $KHCO_3$, LiOAc, KOAc, and $NaHCO_3$ (Table 3, entries 5-10), all of which produced lower yields. We conclude that Na_2CO_3 is the best base for this reaction system. When we excluded n-Bu_4NCl, the yield of 27 decreased considerably (Table 3, entry 11).

To further optimize the yield, the amount of alkene employed was increased. Adding 5 equivs of 1,4-dioxene decreased the yield by one half (Table 3, entry 12), which made us question the thermal stability of 1,4-dioxene in an oxygen atmosphere. We decreased the temperature to 80 °C, hoping to reduce the alkene's decomposition. A 24% yield resulted (Table 3, entry 13). The low yield at 80 °C may result from the inability of the Pd(0) catalyst to undergo oxidative addition at a lower temperature.

Unable to achieve higher yields at a lower temperature, we next considered running the reaction under an N_2 atmosphere at 100 °C. Table 3, entries 14-16, show the results of employing 5, 8, and 10 equivs of 1,4-dioxene respectively; the yields did not increase above that reached with 5 equivs. Running the reaction under N_2 allowed us to employ elevated temperatures while apparently preventing alkene degradation.

Next we increased the length of the reaction to three days and varied the amount of alkene employed. With 2 equivs of 1,4-dioxene, the reaction yielded 47% of 27 (Table 3, entry 17). With 5 equivs, the reaction yielded 56%, and with 8 equivs, 61% (Table 3, entries

18 and 19). These results imply that longer reaction times alone do not improve the yield. The most significant improvement in the yield occurred when an N_2 atmosphere was employed along with Na_2CO_3 as the base. n-Bu_4NCl was again shown to be an important additive.

Next we reacted 2-iodophenol derivatives with 1,4-dioxene. These derivatives had either an EWG or an EDG *para* to the hydroxy group. When 4-hydroxy-3-iodoacetophenone (18) was employed as the *o*-hydroxyaryl iodide, the optimal phenol procedure gave a 32% yield of heteroannulation product 28 (Table 4, entry 1). Running the reaction longer did not improve the yield (Table 4, entries 2 and 3), nor did running the reaction for only 7 hours (Table 4, entry 4).

Running the reaction in DMSO or employing the inorganic bases NaOAc, $NaHCO_3$, K_2CO_3, $KHCO_3$, or KOAc gave only a very low yield of 28 (Table 4, entries 5-10). Surprisingly, running the reaction under an N_2 atmosphere did not improve the yield (Table 4, entry 11).

Two other 2-iodophenol derivatives, one with a carboxylic acid group *para* to the hydroxy group and one with an ester group *para* to the hydroxy group, produced no heteroannulation product (Table 4, entries 12 and 13). The derivative with a chloride group *para* to the hydroxy group gave a very low yield of 30 (Table 4, entry 14).

2-Iodophenol derivatives with an EDG *para* to the hydroxy group were next examined. The derivative with a *t*-butyl group gave a 43% yield of 33 (Table 4, entry 15). However, when hydroquinone 19 was reacted with 1,4-dioxene, the yield of 29 was sharply diminished (Table 4, entry 16). These results imply that neither an electron-rich nor an electron-poor, internal nucleophile greatly affect the formation of heteroannulation product.

Table 4. Effect of Base on the Reaction of 2-Iodophenol Derivatives and 1,4-Dioxene (eq 6).[a]

entry	R	R'	base	% ^{1}H NMR yield of 27-33
1[b]	Ac	H	Na_2CO_3	32
2[c]	Ac	H	Na_2CO_3	33
3[d]	Ac	H	Na_2CO_3	31
4[e]	Ac	H	Na_2CO_3	14
5[f]	Ac	H	Na_2CO_3	0
6	Ac	H	NaOAc	4
7	Ac	H	$NaHCO_3$	4
8	Ac	H	K_2CO_3	<5
9	Ac	H	$KHCO_3$	4
10	Ac	H	KOAc	10
11[b,g]	Ac	H	Na_2CO_3	30
12[g]	CO_2H	H	Na_2CO_3	0
13[g]	CO_2Et	H	Na_2CO_3	0
14[g]	Cl	H	Na_2CO_3	2
15[b,g]	t-butyl	H	Na_2CO_3	43
16[g]	OH	CH_3	Na_2CO_3	<5

[a]The 2-iodophenol (0.45 mmol), 1,4-dioxene (79.4 mg, 0.90 mmol), 5 mol % of $Pd(OAc)_2$ (5.0 mg, 0.023 mmol), the base (48.0 mg, 0.45 mmol), and 15 mol % of n-Bu_4NCl (19.0 mg, 0.068 mmol) were reacted in 1 mL of DMF at 100 °C for 1 day.
[b]% isolated yield instead of % ^{1}H NMR yield.
[c]The reaction was run for 2 days.
[d]The reaction was run for 3 days.
[e]The reaction was run for 7 hours.
[f]DMSO was used as the solvent.
[g]The reaction was run under N_2.

Rather, the success of the process is highly dependent on the specific functional groups

present in the phenol. The low yield from hydroquinone **19** may result from its inability to

undergo oxidative addition to Pd(0).

We attempted to extend the optimal phenol procedure to another alkene, vinylene

carbonate. When *N*-(2-iodophenyl)acetamide was reacted with vinylene carbonate, an

unexpected product, 1-acetylindole, was observed (Scheme 5). This indole product had been

observed previously by another group in a similar palladium-catalyzed process.[17] The

proposed mechanism for formation of this product is shown in Scheme 5. Because this

alkene did not produce any heteroannulation product, further reactions were not conducted.

Other cyclic alkenes, such as 4*H*-pyran-4-one, 4,4-dimethyl-2-cyclohexen-1-one,

maleic anhydride, maleimide, *N*-phenylmaleimide, and *N*-benzylmaleimide, as well as

Scheme 5
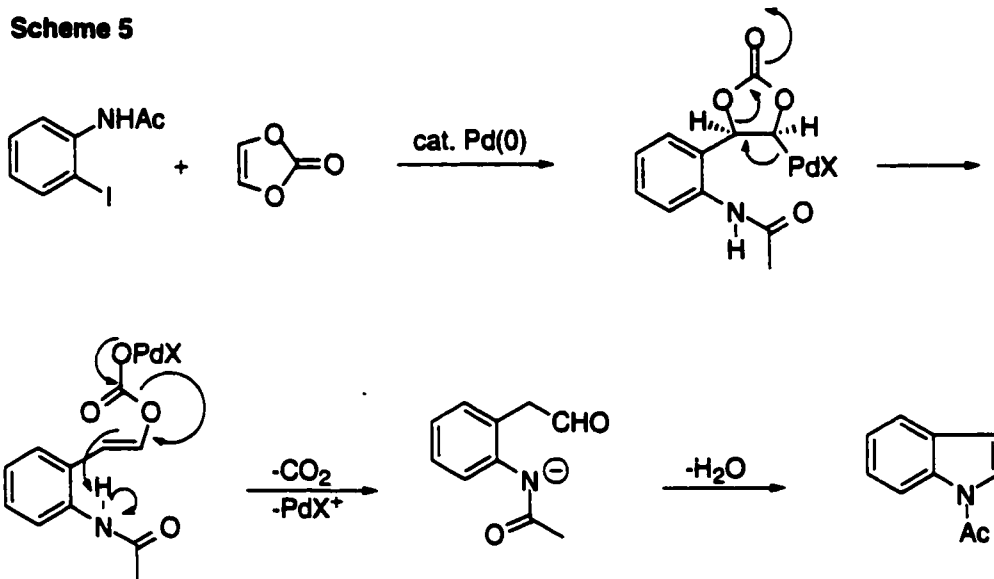
tetraphenylethylene, were allowed to react under the optimal phenol procedure with o-hydroxyaryl and o-aminoaryl iodides; however, no heteroannulation products were observed.

Other o-substituted aryl and vinylic iodides, such as 2-iodobenzoic acid, methyl 2-iodobenzoate, diethyl 2-iodophenylmalonate, 2-iodo-2-cyclohexen-1-ol, 2-iodo-4,4-dimethyl-2-cyclohexen-1-ol, 2-iodo-3-methyl-2-buten-1-ol, (E)-2-iodo-3-phenyl-2-butenoic acid, N-(2-cyclohexylidene-2-iodoethyl)-p-toluenesulfonamide, 1-iodo-2-naphthol, 8-iodonaphthalen-1-yl amine, N-(8-iodonaphthalen-1-yl)methanesulfonamide, and N-(8-iodonaphthalen-1-yl)acetamide, were reacted with 1,4-dioxene under the optimal phenol procedure, but no heteroannulation products were observed.

We next desired to extend the optimal phenol procedure to bicyclic alkenes. First, we will discuss the reactions of o-aminoaryl iodides with the bicyclic alkenes indene, 1,2-dihydronaphthalene, and acenaphthalene; then the reactions of o-hydroxyaryl iodides with these same alkenes will be discussed.

2-Iodoaniline (9) and the o-aminoaryl iodide derivatives with N-mesyl, N-tosyl, and N-acetyl groups were reacted with indene under the optimal phenol procedure, but no heteroannulation products were observed. Although several solvents and inorganic bases were employed, only unreacted starting materials were recovered from the reaction mixtures. Heteroannulation product 35 was observed in a 15% yield when N-(2-iodophenyl)methanesulfonamide was allowed to react with indene using ethylene glycol as the solvent and Na_2CO_3 as the base (Table 5, entry 1) (eq 7).

Table 5. **Effect of Base on the Reaction of _N_-(2-Iodophenyl)methanesulfonamide, _N_-(2-Iodophenyl)-_p_-toluenesulfonamide, or _N_-(2-Iodophenyl)acetamide and Indene (eq 7).[a]**

entry	R	base	% ^{1}H NMR yield of 35-37
1[b]	Ms	Na_2CO_3	15
2	Ms	Na_2CO_3	32
3	Ms	$NaHCO_3$	33
4	Ms	K_2CO_3	43
5	Ms	KOAc	53
6	Ms	CuOAc	49
7	Ms	NaOAc	68
8[c]	Ms	Na_2CO_3	8
9[d]	Ms	Na_2CO_3	40
10[e]	Ms	Na_2CO_3	50
11[b]	Ts	Na_2CO_3	25
12[b]	Ts	NaOAc	30
13[b]	Ts	CuOAc	44
14	Ts	NaOAc	29
15	Ac	NaOAc	20
16	Ac	CuOAc	7

[a]The _N_-mesyl, _N_-tosyl, and _N_-acetyl derivatives of _o_-iodoaniline (0.45 mmol), indene (104.0 mg, 0.90 mmol), 5 mol % of $Pd(OAc)_2$ (5.0 mg, 0.023 mmol), the base (0.45 mmol for the bivalent bases and 0.90 mmol for the monovalent bases), _n_-Bu$_4$NCl (125.0 mg, 0.45 mmol), DMG (43.7 mg, 0.45 mmol), and 1 mL of ethylene glycol were reacted in a 4 dram vial at 100 °C for 1 day.
[b]No DMG was used.
[c]The reaction was run for 1 hour.
[d]The reaction was run for 8 hours.
[e]The reaction was run for 12 hours.

$$
\underset{\substack{9\ R = H \\ 10\ R = Ms \\ 11\ R = Ts \\ 12\ R = Ac}}{\text{NHR, I}} + 2\ \underset{6}{\text{indene}} \xrightarrow[\substack{\text{1 DMG} \\ \text{ethylene glycol} \\ 100\ ^{\circ}C,\ 1\ day}]{\substack{5\ \%\ Pd(OAc)_2 \\ base \\ 1\ n\text{-}Bu_4NCl}} \underset{\substack{34\ R = H \\ 35\ R = Ms \\ 36\ R = Ts \\ 37\ R = Ac}}{\text{product}} \quad (7)
$$
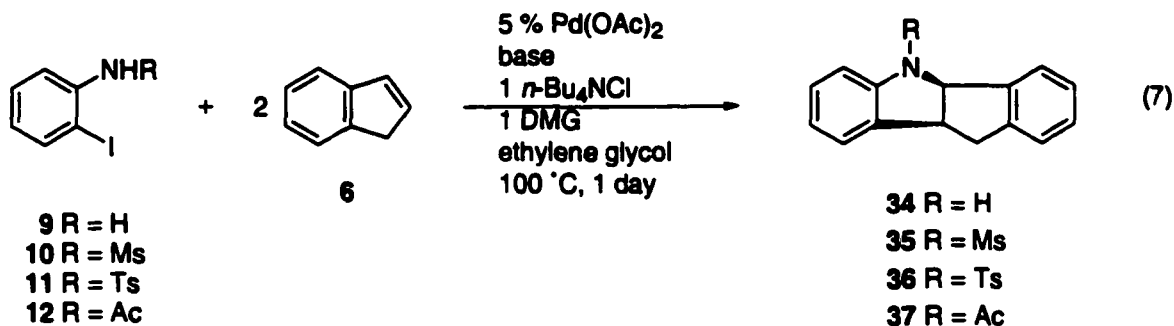
By varying the optimal phenol procedure, the first reasonably successful conditions

were the following: 1 equiv (0.45 mmol) of N-(2-iodophenyl)methanesulfonamide, 2 equivs

(0.90 mmol) of indene, 1 equiv (0.45 mmol) of Na_2CO_3, 1 equiv (0.45 mmol) of n-Bu_4NCl, 1

equiv (0.45 mmol) of N,N-dimethylglycine (DMG), 5 mol % of $Pd(OAc)_2$, and 1 mL of

ethylene glycol at 100 °C for 1 day (eq 7). Hereafter, these conditions will be referred to as

"the optimal amino procedure."

Under these conditions, the yield was increased to 32% (Table 5, entry 2). The role

of DMG in these conditions is uncertain; however, Reetz has observed DMG to be an

excellent additive in the Heck reaction of aryl bromides.[18] He hypothesizes that DMG may

stabilize colloidal palladium, which may be the catalytically active species in his reactions.

Perhaps DMG is performing the same function in the reactions between the o-aminoaryl

iodides and indene.

This reaction was further optimized by employing various inorganic bases. $NaHCO_3$

gave a nearly identical yield (Table 5, entry 3) to that obtained using Na_2CO_3. The yield of

heteroannulation product 35 was increased by employing K_2CO_3 (Table 5, entry 4), and

further increased using KOAc (Table 5, entry 5). The base CuOAc yielded 49% of

compound **35** (Table 5, entry 6). The highest yield, 68% of product **35**, was obtained using
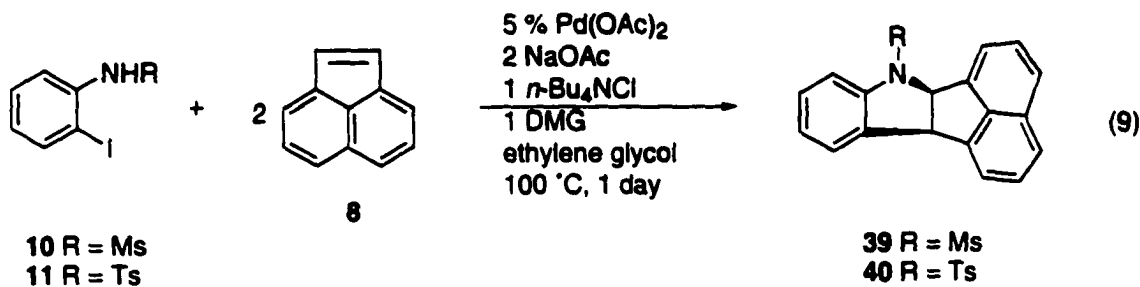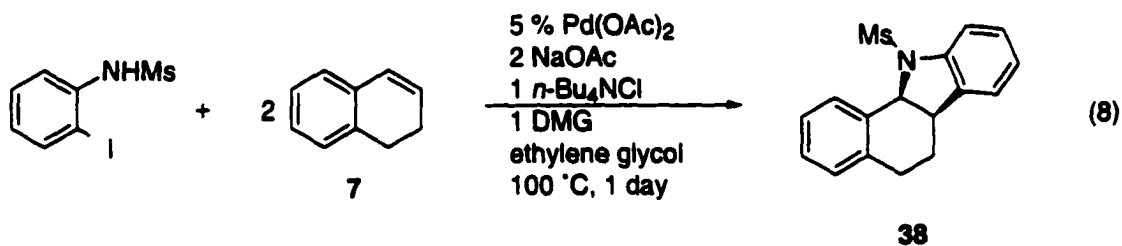
NaOAc (Table 5, entry 7).

We next investigated the effect of reaction time. As shown in Table 5, entry 8, using

Na$_2$CO$_3$ the yield after only 1 hour was 8%. However, the yield increased steadily as the

reaction time lengthened to 8 and 12 hours (Table 5, entries 9 and 10). No further increase in

the yield was observed by employing longer reaction times.

N-(2-Iodophenyl)-*p*-toluenesulfonamide was next allowed to react with indene under

the optimal amino procedure, giving a lower yield of **36**. As shown in Table 5, entries 11-13,

Na$_2$CO$_3$, NaOAc, and CuOAc gave moderate yields when employed as the base. DMG did

not improve the yield (Table 5, entry 14) as it had before with *N*-(2-

iodophenyl)methanesulfonamide.

N-(2-Iodophenyl)acetamide was then allowed to react with indene under the optimal

amino procedure, giving a modest yield of **37** (Table 5, entry 15). The base CuOAc gave a

poor yield of the desired product (Table 5, entry 16).

The amount the optimal amino procedure had to be varied from Jia's or the optimal

phenol procedure to produce heteroannulation product surprised us. For instance, the solvent

ethylene glycol was preferred over DMF, DMG was added, the amount of *n*-Bu$_4$NCl

increased to 1 equiv, and the base NaOAc was preferred over Na$_2$CO$_3$. The role of ethylene

glycol in these reactions remains uncertain. Under Jia's and the optimal phenol procedure,

perhaps palladium formed a stable intermediate, which did not go on to produce product.

Ethylene glycol may be breaking up this intermediate, causing it to react under the optimal

amino procedure.

Next we extended the optimal amino procedure to the aromatic alkenes 1,2-dihydronaphthalene (eq 8) and acenaphthene (eq 9). 1,2-Dihydronaphthalene produced an 86% yield of heteroannulation product **38**, while acenaphthene produced an 80% yield of **39**, but only a 10% yield of **40**. The low yield of **40** may be due to the bulkiness of the R group. As a side note, the alkenes 4H-pyran-4-one, 4,4-dimethyl-2-cyclohexen-1-one, maleic anhydride, tetraphenylethylene, coumarin, maleimide, N-phenylmaleimide, and N-benzylmaleimide gave no heteroannulation product when reacted under these conditions.

$$5\% \ Pd(OAc)_2$$
$$2 \ NaOAc$$
$$1 \ n\text{-}Bu_4NCl$$
$$1 \ DMG$$
ethylene glycol
100 °C, 1 day

(8)

7

38

$$5\% \ Pd(OAc)_2$$
$$2 \ NaOAc$$
$$1 \ n\text{-}Bu_4NCl$$
$$1 \ DMG$$
ethylene glycol
100 °C, 1 day

(9)

10 R = Ms
11 R = Ts

8

39 R = Ms
40 R = Ts

The optimal amino procedure did not produce heteroannulation product when o-hydroxyaryl iodides were employed; however, when they were reacted under the optimal phenol procedure with the same aromatic alkenes (indene, 1,2-dihydronaphthalene, and acenaphthene), heteroannulation products were observed. When 2-iodophenol and indene were allowed to react under the optimal phenol procedure (eq 10), the reaction yielded 26%
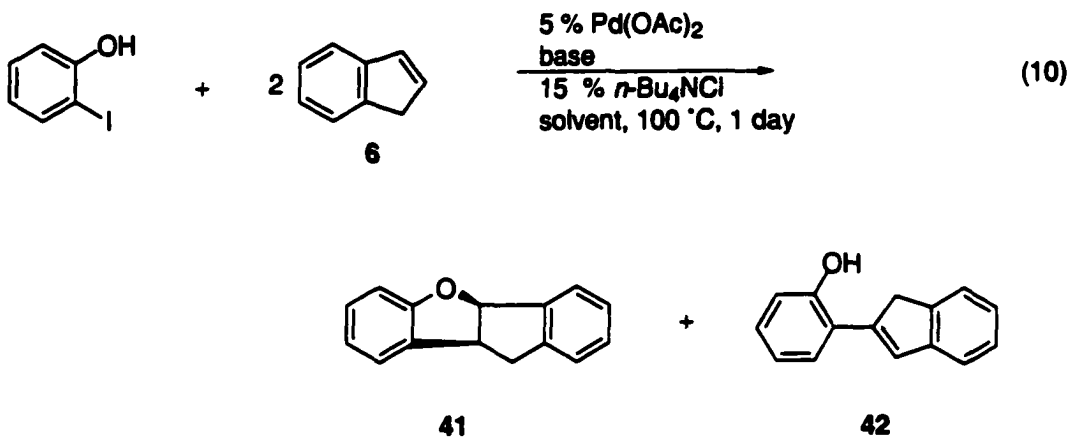
of heteroannulation product **41** and 68% of phenol **42**, an undesired Heck product (Table 6, entry 1).

The optimal phenol procedure, which had proved so successful with cyclic alkenes, now failed to produce the same results with aromatic alkenes. They had to be optimized in an attempt to favor formation of the heteroannulation product over the Heck product. Employing various solvents, including DMA, DMSO, ethylene glycol, 1-methyl-2-pyrrolidinone (NMP), toluene, ethylene glycol dimethyl ether (DME), tetrahydrofuran (THF), and dioxane, gave lower yields of heteroannulation product than had been obtained using DMF (Table 6, entries 2-9).

We were curious to see how additives other than n-Bu$_4$NCl would affect the yield of heteroannulation product **41**. Chloride sources, such as LiCl, CuCl$_2$•2H$_2$O, CuCl, and ZnCl$_2$, and quarternary ammonium salts, such as n-Bu$_4$NOAc, n-Bu$_4$NI, and n-Bu$_4$NBr, when employed in the amount of 15 mol % did not favor formation of **41** and actually gave lower yields than n-Bu$_4$NCl. When 10 mol % of the additive PPh$_3$ was employed under the optimal phenol procedure, only unreacted starting materials were recovered.

Table 6. Effect of Solvent on the Reaction of 2-Iodophenol and Indene (eq 10).[a]

entry	solvent	% ^{1}H NMR yields of 41, 42
1[b]	DMF	26, 68
2[b]	DMA	11, 22
3	DMSO	10, 15
4	ethylene glycol	0, 0
5	NMP	12, 18
6	toluene	12, 30
7	DME	9, 24
8	THF	11, 37
9	dioxane	14, 22

[a] The 2-iodophenol (99.0 mg, 0.45 mmol), indene (104.0 mg, 0.90 mmol), 5 mol % of Pd(OAc)$_2$ (5.0 mg, 0.023 mmol), Na$_2$CO$_3$ (48.0 mg, 0.45 mmol), and 15 mol % of n-Bu$_4$NCl (19.0 mg, 0.068 mmol) were reacted in 1 mL of DMF at 100 °C for 1 day.
[b] % isolated yield instead of % ^{1}H NMR yield.

A series of different bases were next employed in an attempt to improve the yield of 41. The three bases K$_2$CO$_3$, KOAc, and KHCO$_3$ gave low yields of 41 and moderate yields of 42 as compared to Na$_2$CO$_3$ (Table 7, entries 1-3). Li$_2$CO$_3$ and LiOAc gave slightly lower yields of 41 and 42 (Table 7, entries 4 and 5), while Ag$_2$CO$_3$ and i-Pr$_2$NEt gave much lower yields (Table 7, entries 6 and 7). Thus, the optimal phenol procedure produced low yields of heteroannulation product 41, while displaying a preference for formation of the Heck product 42.

Table 7. Effect of Base on the Reaction of 2-Iodophenol and Indene (eq 10).[a]

entry	base	% ^{1}H NMR yields of **41, 42**
1	K_2CO_3	8, 22
2	KOAc	10, 39
3	$KHCO_3$	15, 28
4	Li_2CO_3	20, 48
5	LiOAc	21, 45
6	Ag_2CO_3	10, 9
7	i-Pr_2NEt	11, 23

[a]The 2-iodophenol (99.0 mg, 0.45 mmol), indene (104.0 mg, 0.90 mmol), 5 mol % of $Pd(OAc)_2$ (5.0 mg, 0.023 mmol), the base (48.0 mg, 0.45 mmol), and 15 mol % of n-Bu_4NCl (19.0 mg, 0.068 mmol) were reacted in 1 mL of DMF at 100 °C for 1 day.

Because ethylene glycol produced a high yield of heteroannulation product in the reaction of o-aminoaryl iodides and aromatic alkenes, we employed other alcoholic solvents to optimize this yield. The solvents t-amyl alcohol and t-butanol both gave yields consistent with those obtained previously in DMF (Table 8, entries 1 and 2). When β-phenethyl alcohol, cyclohexanol, n-amyl alcohol, and 1,5-pentanediol were employed as solvents, only unreacted starting materials were recovered (Table 8, entries 3-6). However, 1-propanol and glycerol both gave low yields of only **41**, and no Heck products were apparent in these reactions (Table 8, entries 7 and 8). Higher yields of **41** were obtained when 1-hexanol and ethanol were employed (Table 8, entries 9 and 10). Both solvents favored formation of **41** over **42** as did 1-propanol and glycerol.

Table 8. Effect of Alcohol Solvents on the Reaction of 2-Iodophenol and Indene (eq 10).[a]

entry	solvent	% ^{1}H NMR yields of **41, 42**
1	*t*-amyl alcohol	25, 27
2	*t*-butanol	10, 15
3	β-phenethyl alcohol	0, 0
4	cyclohexanol	trace, 0
5	*n*-amyl alcohol	trace, 0
6	1,5-pentanediol	0, 0
7	1-propanol	10, 0
8	glycerol	10, 0
9	1-hexanol	26, trace
10	ethanol	35, 18

[a]The 2-iodophenol (99.0 mg, 0.45 mmol), indene (104.0 mg, 0.90 mmol), 5 mol % of Pd(OAc)$_2$ (5.0 mg, 0.023 mmol), Na$_2$CO$_3$ (48.0 mg, 0.45 mmol), 15 mol % of *n*-Bu$_4$NCl (19.0 mg, 0.068 mmol), and 1 mL of the solvent were reacted in a 4 dram vial at 100 °C for 1 day.

The solvent 2-(2-ethoxyethoxy)ethanol was also employed (eq 11). A new product, the saturated product **43**, was obtained in a 30% yield (Table 9, entry 1). The source of the hydrogens in this new product remains uncertain. The additive DMG greatly increased the yield of **43** (Table 9, entry 2). We employed several different bases in an attempt to favor product **41**. The bases K$_2$CO$_3$, KOAc, KHCO$_3$, NaHCO$_3$, NaOAc, CuOAc, Cu(OAc)$_2$, and NEt$_3$ all gave the reduced product exclusively in good yields (Table 9, entries 3-10).

Another solvent, triethanolamine, was also employed. This reaction without the DMG gave a mixture of both reduced product and, surprisingly, **41** as well (Table 9, entry
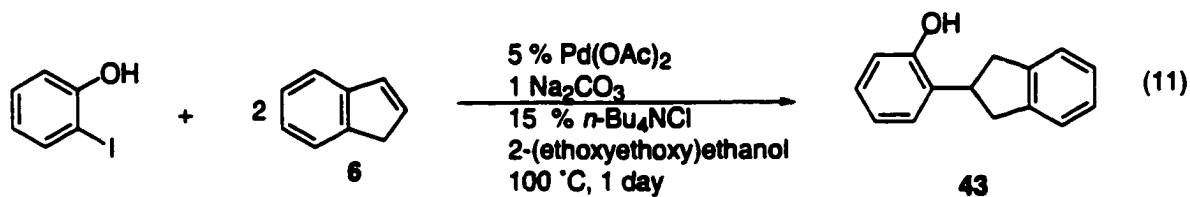
11). The addition of DMG to the reaction mixture resulted in a low yield of only 41 (Table 9, entry 12); however, the base NaOAc doubled this yield (Table 9, entry 13), and CuOAc doubled the NaOAc yield (Table 9, entry 14).

Despite optimization of the optimal phenol procedure with regards to solvents, additives, and bases in the reaction of 2-iodophenol and indene, formation of the heteroannulation product was not favored over Heck or saturated Heck products. The reason for this poor selectivity remains unclear, but perhaps the poor nucleophilicity of oxygen plays a role or the strained geometry of the two fused five-membered rings in the product. Even drastic changes in the optimal phenol procedure failed to improve the selectivity or yields in these reactions, except in the case of the solvent triethanolamine. This improved the selectivity, although the yields of 41 remained low.

Triethanolamine's role may involve its ability to coordinate to the palladium catalyst, thus possibly favoring formation of the heteroannulation product. The new, reduced product 43 may also result from 2-(2-ethoxyethoxy)ethanol's ability to coordinate to the palladium catalyst. DMG again showed some beneficial effects on these yields.[18]

A possible mechanism for the formation of the Heck product and the heteroannulation product is shown in Scheme 6. After oxidative addition of the o-hydroxyaryl iodide to Pd(0), carbopalladation across the double bond of indene gives intermediate 45. The

Table 9. Effect of Various Bases on the Reaction of 2-Iodophenol and Indene
Employing DMG and 2-(2-Ethoxyethoxy)ethanol as the Solvent (eq 11).[a]

entry	base	% isolated yields of 41, 43
1[b]	Na_2CO_3	0, 30
2	Na_2CO_3	0, 76
3	K_2CO_3	0, 81
4	KOAc	0, 67
5	$KHCO_3$	0, 64
6	$NaHCO_3$	0, 62
7	NaOAc	0, 65
8	CuOAc	0, 70
9	$Cu(OAc)_2$	0, 64
10	NEt_3	0, 62
11[b, c]	Na_2CO_3	16, 16
12[c]	Na_2CO_3	7, 0
13[c]	NaOAc	14, 0
14[c]	CuOAc	26, 0

[a]The 2-iodophenol (99.0 mg, 0.45 mmol), indene (104.0 mg, 0.90 mmol), 5 mol % of $Pd(OAc)_2$ (5.0 mg, 0.023 mmol), the base (0.45 mmol for the divalent bases and 0.90 mmol for the monovalent bases), 15 mol % of n-Bu_4NCl (19.0 mg, 0.068 mmol), DMG (45.0 mg, 0.45 mmol), and 1 mL of 2-(2-ethoxyethoxy)ethanol were reacted in a 4 dram vial at 100 °C for 1 day.
[b]No DMG was used.
[c]1 Ml of the solvent triethanolamine was used instead of 2-(2-ethoxyethoxy)ethanol.

Scheme 6
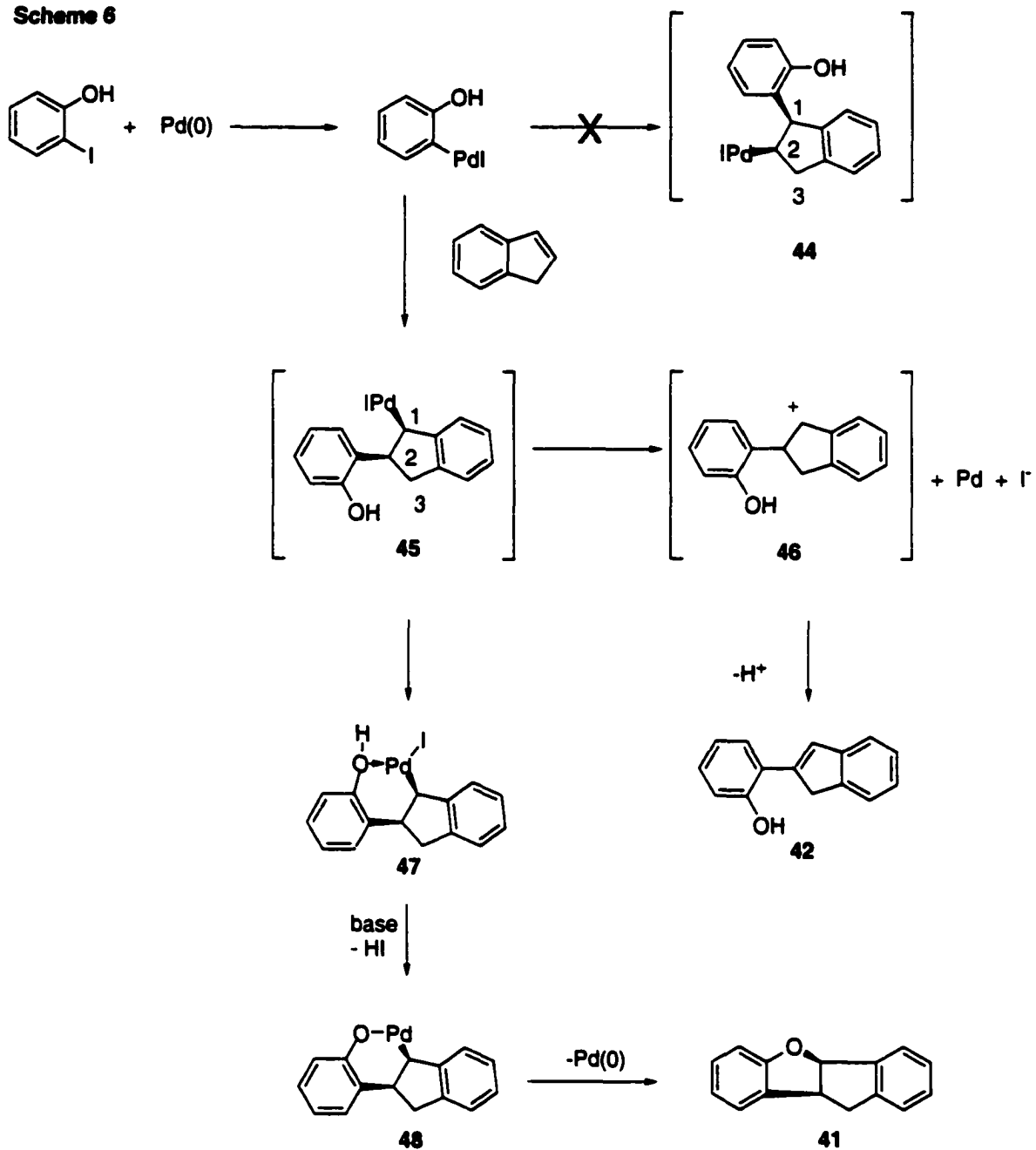
indenylpalladium species **45** can solvolyze in an S_N1 fashion to regenerate Pd(0) and the

stabilized benzylic cation **46**, which loses a proton to form Heck product **42**. If the internal

OH group coordinates to the palladium, then intermediate **47** is formed. Loss of HI from **47**

generates the palladacycle **48**, which upon reductive elimination generates the
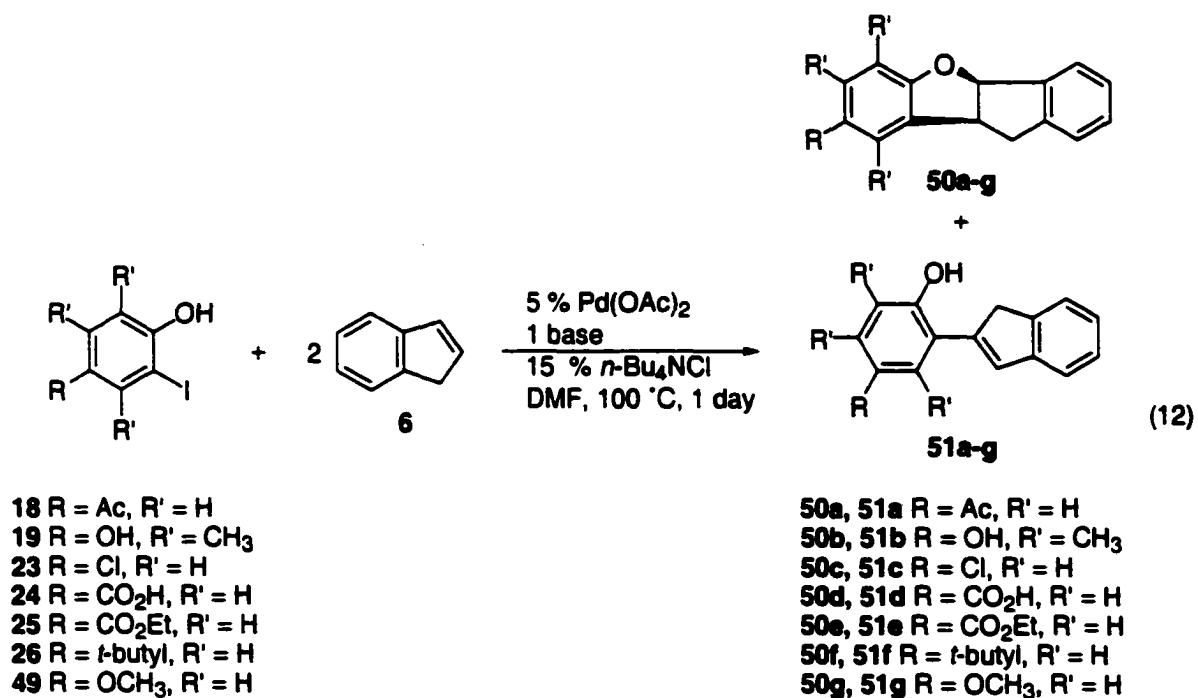
heteroannulation product **41**.

One reason for the poor yields of the heteroannulation product may be failure of the

phenol to ionize to form intermediate **48**. An EWG *para* to the hydroxy group would

facilitate ionization by lowering the pKa of the phenol. *o*-Hydroxyaryl iodides with an

acetyl, chloro, carboxylic acid, and an ester EWG *para* to the hydroxy group were reacted

with indene using the optimal phenol procedure. As shown in Table 10, entries 1-4, the Heck

product remains the favored isomer in each of these examples (eq 12).

$$5\% \text{ Pd(OAc)}_2$$
$$1 \text{ base}$$
$$\overline{15\% \text{ } n\text{-Bu}_4\text{NCl}}$$
$$\text{DMF, 100 °C, 1 day}$$

(12)

18 R = Ac, R' = H
19 R = OH, R' = CH₃
23 R = Cl, R' = H
24 R = CO₂H, R' = H
25 R = CO₂Et, R' = H
26 R = *t*-butyl, R' = H
49 R = OCH₃, R' = H

50a, 51a R = Ac, R' = H
50b, 51b R = OH, R' = CH₃
50c, 51c R = Cl, R' = H
50d, 51d R = CO₂H, R' = H
50e, 51e R = CO₂Et, R' = H
50f, 51f R = *t*-butyl, R' = H
50g, 51g R = OCH₃, R' = H

Because these derivatives failed to improve the yield of heteroannulation product, we employed o-hydroxyaryl iodides with an EDG *para* to the hydroxy group. An EDG in the *para* position should increase electron density on the internal nucleophile. A more nucleophilic oxygen atom should favor coordination to the palladium, and thus facilitate ring-closure to form the heteroannulation product. The o-hydroxyaryl iodide derivative with the *t*-butyl group *para* to the hydroxy group did not increase the yield of heteroannulation product (Table 10, entry 5). The Heck product was again isolated as the major isomer.

The o-hydroxyaryl iodide with a methoxy group *para* to the internal nucleophile gave a 17% yield of only the heteroannulation product (Table 10, entry 6). Hydroquinone 19,

Table 10. Effect of the Substituents on the Reaction of 2-Iodophenol Derivatives and Indene (eq 12).[a]

| entry	R	R'	% isolated yields of 50a-g, 51a-g
1	Ac	H	15, 44
2	Cl	H	17, 37
3	CO_2H	H	14, 20
4	CO_2Et	H	11, 22
5	*t*-butyl	H	15, 51
6	OCH_3	H	17, 0
7	OH	CH_3	30, 0
8[b]	OH	CH_3	61, 0

[a]The substituted 2-iodophenol (99.0 mg, 0.45 mmol), indene (104.0 mg, 0.90 mmol), 5 mol % of $Pd(OAc)_2$ (5.0 mg, 0.023 mmol), Na_2CO_3 (48.0 mg, 0.45 mmol), 15 mol % of n-Bu_4NCl (19.0 mg, 0.068 mmol), and 1 mL of DMF were reacted in a 4 dram vial at 100 °C for 1 day.
[b]The reaction was run under N_2.

which has an hydroxy group *para* to the internal nucleophile, gave a yield of 30% of only the heteroannulation product (Table 10, entry 7). Running the latter reaction under an N_2 atmosphere gave a substantially higher yield of 61% (Table 10, entry 8); however, running the reaction summarized in entry 1 under an N_2 atmosphere produced little to no annulation product.

Because derivatives with EDGs *para* to the hydroxy group gave better yields of heteroannulation product than those with EWGs, it can be concluded that an electron-rich internal nucleophile favors formation of the heteroannulation product. Furthermore, stronger EDGs produce better selectivity for the heteroannulation product than weaker EDGs. The *o*-hydroxyaryl iodides, which are themselves electron-rich, undergo oxidative addition to the Pd(0) catalyst slowly. The lower yields may result because this rate-determining step of the mechanism is slower. Running the hydroquinone 19 under N_2 possibly prevented its decomposition, thus increasing the yield.

Next, the optimal phenol procedure was applied to the reaction of 2-iodophenol and the alkene 1,2-dihydronaphthalene (eq 13). A low yield of heteroannulation product 52 was observed, as well as two Heck regioisomers 53 and 54 in equal amounts (Table 11, entry 2). Lack of regioselectivity may be due to conformational issues brought about by the larger six-membered ring of 1,2-dihydronaphthalene. Increasing and decreasing the amount of 1,2-dihydronaphthalene employed neither improved the yield of 52 nor improved the regioselectivity (Table 11, entries 1 and 3).

$$5\% \; Pd(OAc)_2$$

1 base

$$15\% \; n\text{-}Bu_4NCl$$

DMF, 100 °C, 1 day

(13)

7

52

53

54
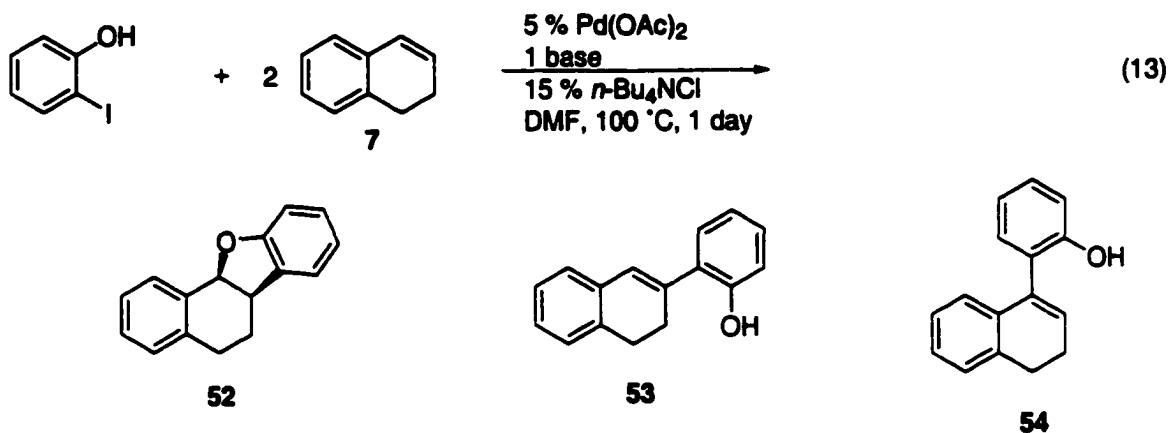
The optimal phenol procedure was next applied to the reaction of 2-iodophenol and acenaphthene (eq 14), but no heteroannulation product was observed. Increasing the reaction time to 3 days gave a very low yield (Table 12, entry 1). We sought to vary the reaction conditions to obtain a higher yield of 55. Increasing the reaction temperature to 130 °C produced a slight improvement in the yield (Table 12, entry 2). Varying the amount of n-Bu$_4$NCl employed did not substantially improve the yield either (Table 12, entries 3 and 4).

Table 11. Effect of Alkene Stoichiometry on the Reaction of 2-Iodophenol and 1,2-Dihydronaphthalene (eq 13).[a]

entry	equivs of alkene	% yields of 52, 53, 54
1	1	8, 24, 24
2	2	13, 24, 24
3	3	9, 25, 25

[a] The 2-iodophenol (99.0 mg, 0.45 mmol), 1,2-dihydronaphthalene (0.90 mmol), 5 mol % of Pd(OAc)$_2$ (5.0 mg, 0.023 mmol), Na$_2$CO$_3$ (48.0 mg, 0.45 mmol), and 15 mol % of n-Bu$_4$NCl (19.0 mg, 0.068 mmol) were reacted in 1 mL of DMF at 100 °C for 1 day.

$$5\ \%\ Pd(OAc)_2$$
$$1\ Na_2CO_3$$
$$\overline{15\ \%\ n\text{-}Bu_4NCl}$$
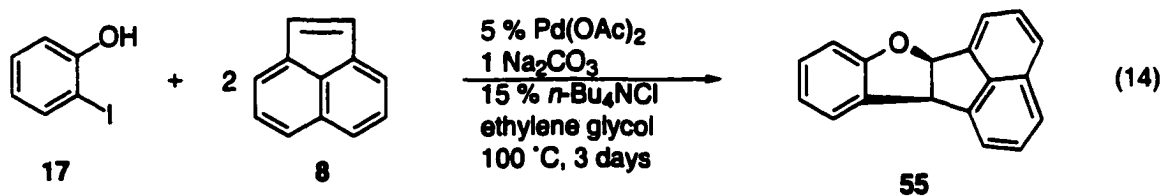ethylene glycol
$$100\ ^\circ C,\ 3\ days$$

(14)

Table 12. Effect of Solvent on the Reaction of 2-Iodophenol and Acenaphthene (eq 14).[a]

entry	base	solvent	temp. (°C)	% isolated yield of 55
1	Na_2CO_3	DMF	100	2
2	Na_2CO_3	DMF	130	9
3[b]	Na_2CO_3	DMF	130	12
4[c]	Na_2CO_3	DMF	130	13
5	Na_2CO_3	DMA	130	0
6	Na_2CO_3	DMSO	130	0
7	Na_2CO_3	2-(2-ethoxy-ethoxy)ethanol	100	0
8	Na_2CO_3	ethylene glycol	130	47
9[d,e]	Na_2CO_3	ethylene glycol	100	8
10[e,f]	CuOAc	ethylene glycol	100	45

[a]The 2-iodophenol (99.0 mg, 0.45 mmol), acenaphthene (0.90 mmol), 5 mol % of Pd(OAc)$_2$ (5.0 mg, 0.023 mmol), the base (0.45 mmol for Na$_2$CO$_3$ or 0.90 mmol for CuOAc), 15 mol % of n-Bu$_4$NCl (19.0 mg, 0.068 mmol), and 1 mL of the solvent were reacted in a 4 dram vial for 3 days.
[b]No n-Bu$_4$NCl was used.
[c]15 Mol % of n-Bu$_4$NCl was used.
[d]0.45 Mmol of DMG was added.
[e]The reaction was run for 1 day.

Employing the solvents DMA, DMSO, and 2-(2-ethoxyethoxy)ethanol gave no

observed yield of **55** (Table 12, entries 5-7), but the solvent ethylene glycol gave a yield of

47% (Table 12, entry 8). The additive DMG decreased the yield (Table 12, entry 9). CuOAc

gave similar yields to those observed with Na_2CO_3 (Table 12, entry 10). Typically, the

reaction only had to be run for 1 day, instead of the 3 days required with Na_2CO_3. It is

unclear why ethylene glycol substantially improves the yield in this reaction. It may simply

be improving the solubility of the base in the reaction mixture.

The success of the reaction described in Table 12, entry 8 encouraged us to apply

those reaction conditions to 1,2-dihydronaphthalene. A 26 % yield of **52** resulted, and no

Heck product resulted.

The optimal phenol procedure was then applied to other alkenes. 1,4-Dioxa-

spiro[4,5]dec-6-ene, 2,2-dimethyl-4a,8a-dihydro-2*H*-chromene, 2,3-dihydrobenzo[*b*]oxepine,

coumarin, and 4a,8a-dihydro-1*H*-isochromene failed to give any heteroannulation product

when reacted with 2-iodophenol. 7-Methoxy-4a,8a-dihydro-2*H*-chromene (**56**) and 2-

phenyl-4a,8a-dihydro-2*H*-chromene (**58**) both gave good 73% and 60% yields of their

respective heteroannulation products when allowed to react with 2-iodophenol (eqs 15 and

16). A NOSEY experiment confirmed the *cis* ring juncture shown in equation 15. Lulin

Wei had annulated 2-iodophenol onto the same alkenes, albeit in lower yields (40% of **57** and

36% of **59**) using the following conditions: 1.50 mmol of the 2-iodophenol, 0.50 mmol of

the 2*H*-benzopyran, 1.75 mmol of $NaHCO_3$, and 0.50 mmol of n-Bu_4NCl in DMF for 3 days

at 100 °C under an N_2 atmosphere.[19]

(15)

(16)
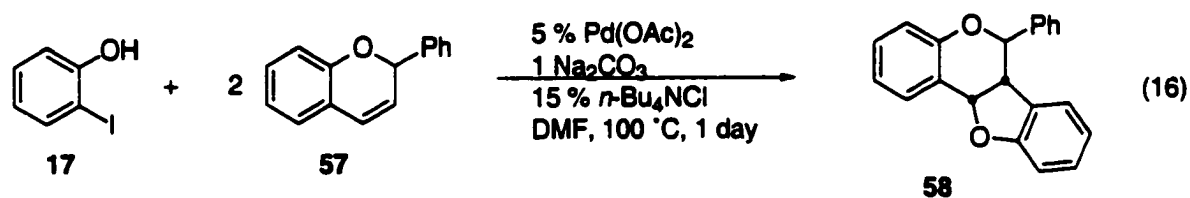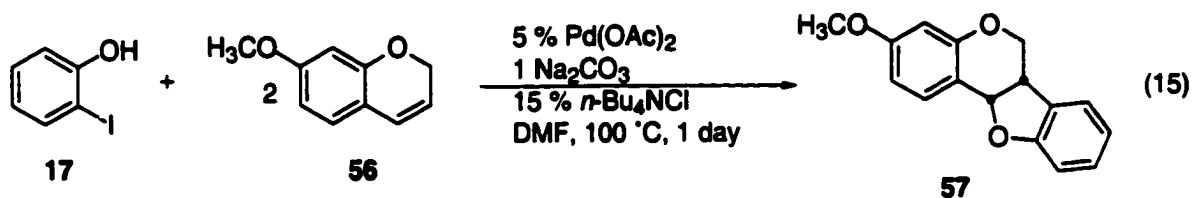
Several other *o*-substituted aryl iodides were allowed to react with norbornene using the optimal phenol procedure in an attempt to obtain additional heteroannulation products. The *o*-substituted aryl iodides 2-iodobenzaldehyde, 2-iodobenzoic acid, methyl 2-iodobenzoate, 1-iodo-2-naphthol, and diethyl (2-iodophenyl)malonate failed to produce any heteroannulation products. Vinylic iodides, such as 2-iodo-2-cyclohexen-1-ol, 2-iodo-4,4-dimethyl-2-cyclohexen-1-ol, 2-iodo-3-methyl-2-buten-1-ol, (*E*)-2-iodo-3-phenyl-2-butenoic acid, and *N*-(2-cyclohexylidene-2-iodoethyl)-*p*-toluenesulfonamide, were also allowed to react with norbornene using the optimal phenol procedure, but they also failed to give any heteroannulation products.

Conclusion

A reasonably efficient, palladium(0)-catalyzed synthesis of benzofuran, carbazole, and indoline derivatives has been developed. The key to the success of these heteroannulation processes lies in the correct choice of the cyclic or bicyclic alkene, such that β-hydride elimination is prevented in the initial organopalladium adduct. The o-hydroxyaryl iodides give good yields of heteroannulation product when reacted with the alkenes 2,2-dimethyl-1,3-dioxole, 1,4-dioxene, acenaphthene, 53, and 55. Reactions of the o-hydroxyaryl iodides with indene and 1,2-dihydronaphthalene afford only low yields of heteroannulation products due to competing reaction pathways, which lead to Heck products. An EWG *para* to the hydroxy group of the o-hydroxyaryl iodides has been shown to favor formation of the heteroannulation product over the Heck product. However, low yields of heteroannulation products are still observed. These low yields may be due to the low reactivity of these electron-rich aromatic iodides towards oxidative addition. The heteroannulation of o-aminoaryl iodides onto alkenes was greatly facilitated by employing ethylene glycol as the solvent and DMG as an additive. Good yields of heteroannulation products from o-aminoaryl iodides have been obtained using 2,2-dimethyl-1,3-dioxole, indene, 1,2-dihydronaphthalene, and acenaphthene.

Experimental

General Procedures. All ^{1}H and ^{13}C spectra were obtained at 300 or 400 MHz. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh

silica gel plates (Whatman K6F) and visualization was accomplished with short wavelength

UV light (254 nm) or with a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL

of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. High-resolution mass

spectra were recorded on a Kratos MS50TL double focusing magnetic sector mass

spectrometer using EI at 70eV. Elemental analyses were performed at Iowa State University

on a Perkin Elmer 2400 CHNS/O series 11 analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise

stated. $KMnO_4$, HOAc, NaOAc, KOAc, LiOAc, $NaHCO_3$, $KHCO_3$, $NaCO_3$, LiCl, $KHSO_4$, n-

Bu_4NCl, DMF, DMSO, NaCl, NH_4Cl, NaOH, HCl, hexane, ethyl acetate,

phenanthrenequinone, diethylene glycol, dioxane, dimethyl sulfoxide, methanol, ethyl ether,

2,2-dimethoxypropane, methyl 2-iodobenzoate, maleic anhydride, methyl 2-iodobenzoate,

DMF, and DMA were obtained from Fisher Scientific. 2-Iodophenol, 2-iodoaniline,

acenaphthene, indene, 1,2-dihydronaphthalene, 4-hydroxyacetophenone, copper chromite,

2,6-dimethyl-2-cyclohexen-1-ol, tetraphenylethylene, vinylene carbonate, maleimide, phenyl

maleimide, benzyl maleimide, and coumarin were obtained from Aldrich Chemical Co.

Palladium acetate was obtained from Kawaken Fine Chemical Co., Ltd. The cyclic alkenes

2,2-dimethyl-1,3-dioxole,[20] 1,4-dioxene,[21] and 1,4-dioxa-spiro[4,5]dec-6-ene,[22] as well as the

aryl iodides N-(2-iodophenyl)methanesulfonamide,[23] N-(2-iodophenyl)-p-

toluenesulfonamide,[24] N-(2-iodophenyl)acetamide,[24] 4-hydroxy-3-iodoacetophenone,[24] 4-

chloro-2-iodophenol,[25] 4-hydroxy-3-iodobenzoic acid,[25] 4-tert-butyl-2-iodophenol,[25] and 1-

iodo-2-naphthol[25] were prepared by their respective literature procedures. 2-Iodo-3,5,6-

trimethyl-p-benzoquinone was provided by Dr. Norman G. Berrios-Peña. 2,2-Dimethyl-

4a,8a-dihydro-2H-chromene, 1,4-dioxa-spiro[4,5]dec-6-ene, 7-methoxy-4a,8a-dihydro-2H-

chromene, 2-phenyl-4a,8a-dihydro-2*H*-chromene, 2,3-dihydrobenzo[*b*]oxepine, and 4a,8a-

dihydro-1*H*-isochromene were provided by Lulin Wei. 2-Iodo-2-cyclohexen-1-ol, diethyl (2-

iodophenyl)malonate, 2-iodo-4,4-dimethyl-2-cyclohexen-1-ol, *N*-(2-iodo-2-propenyl)-*p*-

toluenesulfonamide, 8-iodonaphthalen-1-ylamine, (*E*) 2-iodo-3-phenyl-2-butenoic acid, 2-

iodo-3-methyl-2-buten-1-ol, *N*-(2-cyclohexylidene-2-iodoethyl)-*p*-toluenesulfonamide,

methyl (*Z*)-3-trifluoromethanesulfonyloxy-2,3-diphenyl-2-propenoate, and 2-

iodobenzaldehyde were provided by Dr. Xiaojun Han.

General procedure for the palladium(0)-catalyzed heteroannulation.

Jia's Conditions: The aryl iodide (0.45 mmol), the olefin (0.90 mmol), Na_2CO_3 (96.0 mg,

0.90 mmol), 15 mol % of *n*-Bu$_4$NCl (19.0 mg, 0.068 mmol), and 5 mol % of Pd(OAc)$_2$ (5.0

mg, 0.023 mmol) were added to a 4 dram vial equipped with a stirring bar and Teflon-lined

screw cap. 8 Ml of DMF were added by plastic syringe. The vial was placed in a mineral

oil bath set at 100 °C for 1 day. The reaction mixture was cooled to room temperature then

pipetted into 30 mL of ethyl ether. The ethyl ether was washed sequentially with aq NH$_4$Cl

and brine. The drying agent MgSO$_4$ was then added to the organic layer and filtered.

Evaporation of the ethyl ether under reduced pressure produced the crude product, which was

further purified by silica gel chromatography using a 91:9 hexane/ethyl acetate solution as

the eluent.

The optimal phenol procedure: The aryl iodide (0.45 mmol), the olefin (0.90 mmol),

Na$_2$CO$_3$ (0.45 mmol), 15 mol % of *n*-Bu$_4$NCl, and 5 mol % of Pd(OAc)$_2$ (5.0 mg, 0.023

mmol) were added to a 4 dram vial equipped with a stirring bar and Teflon-lined screw cap.

1 Ml of DMF were added by plastic syringe. The vial was placed in a mineral oil bath set at

100 °C for 1 day. The reaction mixture was cooled to room temperature then pipetted into 30

mL of ethyl ether. The ethyl ether was washed sequentially with aq NH₄Cl and brine. The

drying agent MgSO₄ was then added to the organic layer and filtered. Evaporation of the

ethyl ether under reduced pressure produced the crude product, which was further purified by

silica gel chromatography using a 91:9 hexane/ethyl acetate solution as the eluent.

The optimal amino procedure: The aryl iodide (0.45 mmol), the olefin (0.90 mmol),

NaOAc (0.90 mmol), n-Bu₄NCl (125.0 mg, 0.45 mmol), DMG (43.7 mg, 0.45 mmol), and 5

mol % of Pd(OAc)₂ were added to a 4 dram vial equipped with a stirbar and Teflon-lined

screw cap. 1 Ml of ethylene glycol was added at 100 °C for 1 day. The reaction mixture was

then cooled to room temperature and pippetted into 30 mL of ethyl ether. The ethyl ether

was washed sequentially with aq NaOH and brine. The drying agent MgSO₄ was then added

to the organic layer and filtered. Evaporation of the ethyl ether under reduced pressure

produced the crude product, which was further purified by silica gel using a 91:9

hexane/ethyl acetate solution as the eluent.

N-**Acetyl-2,2-dimethylindole[1,3-*b*]dioxole (14).** *N*-(2-Iodophenyl)acetamide was reacted

with the cyclic alkene 2,2-dimethyl-1,3-dioxole using the optimal phenol procedure. Further

purification was achieved using preparative TLC. This compound was isolated as a white

solid (38% yield): mp = 83-88 °C; R_f = 0.24 (silica, 80:20 Hex/EtOAc); IR (neat) 3010,

2995, 2934, 1602, 1115 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.13 (s, 3 H), 1.48 (s, 3 H), 2.41

(s, 3 H), 5.66 (d, J = 6.1 Hz, 1 H), 6.07 (d, J = 6.1 Hz, 1 H), 7.08 (dd, J = 8.0, 8.0 Hz, 1 H),

7.31 (dd, J = 8.0, 8.0 Hz, 1 H), 7.44 (m, 1 H), 8.18 (m, 1 H); ¹³C NMR (300 MHz, CDCl₃) δ

23.98, 27.43, 27.63, 79.67, 90.99, 112.33, 117.01, 124.41, 125.55, 128.99, 130.61, 142.37,

170.06; HRMS calcd for $C_{13}H_{15}NO_3$: 233.10519. Found: 233.10453.

N-Tosyl-2,2-dimethylindole[2,3-*b*]dioxole (15). *N*-(2-Iodophenyl)-*p*-toluenesulfonamide

and the cyclic alkene 2,2-dimethyl-1,3-dioxole (7) were allowed to react using the optimal

phenol procedure. Compound 15 was obtained and recrystallized out of chloroform. This

compound was isolated as a clear, colorless, crystalline solid (64% yield): mp = 113-118 °C;

R_f = 0.30 (silica, 80:20 Hex/EtOAc); IR (neat) 3010, 2929, 2849, 1599, 1161, 1113 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 0.95 (s, 3 H), 1.46 (s, 3 H), 2.37 (s, 3 H), 5.57 (d, *J* = 6.0 Hz, 1

H), 6.20 (d, *J* = 6.0 Hz, 1 H), 7.01 (m, 1 H), 7.06 (m, 5 H), 7.87 (d, *J* = 1.4 Hz, 2 H); ^{13}C

NMR (300 MHz, CDCl$_3$) δ 21.63, 27.24, 27.41, 79.41, 92.46, 112.33, 113.67, 123.94,

126.27, 127.53, 129.38, 129.67, 129.73, 130.70, 140.94, 144.37; HRMS calcd for

$C_{18}H_{19}NO_4S$: 345.10348. Found: 345.10328. Anal. calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H,

5.54; N, 4.06; S, 9.28. Found: C, 62.43; H, 5.84; N, 4.33; S, 9.12.

N-Mesyl-2,2-dimethylindole[2,3-*b*]dioxole (16). *N*-(2-Iodophenyl)methanesulfonamide

was allowed to react with 2,2-dimethyl-1,3-dioxole using the optimal phenol procedure to

form compound 16. Compound 16 was recrystallized out of chloroform. This compound

was isolated as a clear, colorless, crystalline solid (74% yield): mp = 160-161 °C; R_f = 0.20

(silica 80:20 Hex/EtOAc); IR (neat) 3008, 3001, 2980, 1600, 1150, 1040 cm^{-1}; ^{1}H NMR (300

MHz, CDCl$_3$) δ 1.16 (s, 3 H), 1.49 (s, 3 H), 3.11 (s, 3 H), 5.71 (d, *J* = 5.9 Hz, 1 H), 6.15 (d, *J*

= 5.9 Hz, 1 H), 7.10 (m, 1 H), 7.34 (m, 3 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 27.44, 27.62,

40.43, 79.54, 92.16, 112.40, 112.82, 123.98, 126.56, 129.08, 130.92, 140.94; HRMS calcd

for $C_{12}H_{15}NO_4S$: 269.07218. Found: 269.07169. Anal. calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H,

5.61; N, 5.20; S, 1.91. Found: C, 53.53; H, 5.89; N, 5.45; S, 1.91.

2,2-Dimethylbenzofurano[2,3-*b*]dioxole (20). 2-Iodophenol was allowed to react with the

cyclic alkene 2,2-dimethyl-1,3-dioxole using the optimal phenol procedure to form

compound **20**. Further purification was achieved using preparative TLC. Compound **20** was

isolated as a clear, colorless oil (61% yield): R_f = 0.41 (silica, 80:20 Hex/EtOAc); IR (neat)

3020, 2938, 1612, 1478, 1317, 1213, 1102 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.21 (s, 3 H),

1.49 (s, 3 H), 5.66 (d, J = 4.9 Hz, 1 H), 6.27 (d, J = 4.9 Hz, 1 H), 6.84 (d, J = 8.1 Hz, 1 H),

6.94 (m, 1 H), 7.25 (m, 1 H), 7.42 (d, J = 7.4 Hz, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 27.65,

27.80, 81.27, 107.26, 110.48, 113.16, 121.60, 125.85, 125.92, 131.17, 159.01; HRMS calcd

for C$_{11}$H$_{12}$O$_3$: 192.07864. Found: 192.07858.

5-Acetyl-2,2-dimethyl-benzofurano[2,3-*b*]dioxole (21). 2-Iodophenol was allowed to react

with the cyclic alkene 2,2-dimethyl-1,3-dioxole using the optimal phenol procedure to form

compound **21**. Further purification was achieved using preparative TLC. Compound **21** was

isolated as an off-white solid (64% yield): mp = 71-75 °C; R_f = 0.18 (silica, 80:20

Hex/EtOAc); IR (neat) 3013, 3004, 2938, 2849, 1678, 1153 cm^{-1}; ^{1}H NMR (300 MHz,

CDCl$_3$) δ 1.22 (s, 3 H), 1.5 (s, 3 H), 2.57 (s, 3 H), 5.67 (d, J = 4.8 Hz, 1 H), 6.36 (d, J = 4.8

Hz, 1 H), 6.89 (d, J = 8.5 Hz, 1 H), 7.96 (d, J = 8.5 Hz, 1 H), 8.06 (s, 1 H); ^{13}C NMR (300

MHz, CDCl$_3$) δ 26.51, 27.65, 27.87, 80.56, 108.51, 110.47, 113.99, 126.61, 127.03, 131.78,

132.85, 162.85, 196.32; HRMS calcd for C$_{13}$H$_{14}$O$_4$: 234.08921. Found: 234.08886. Anal.

calcd for C$_{13}$H$_{14}$O$_4$: C, 66.66; H, 6.02. Found: C, 66.47; H, 6.12.

2,2-Dimethyl-5-hydroxy-4,6,7-trimethylbenzofurano[2,3-*b*]dioxole (22). 2-Iodo-3,5,6-

trimethylhydroquinone was allowed to react with 2,2-dimethyl-1,3-dioxole using the optimal

phenol procedure to form compound **22**. Compound **22** was isolated as a clear, yellow oil

(46% yield): R_f = 0.22 (silica, 91:9 Hex/EtOAc); IR (neat) 3499, 2995, 2932, 1682, 1604,

1417, 1214, 1151, 3318 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.21 (s, 3 H), 1.49 (s, 3 H), 2.13

(s, 3 H), 2.16 (s, 3 H), 2.28 (s, 3 H), 4.24 (s, 1 H), 5.67 (d, *J* = 5.0 Hz, 1 H), 6.20 (d, *J* = 5.0

Hz, 1 H); ¹³C NMR (300 MHz, CDCl₃) δ 12.10, 12.20, 12.38, 27.81, 27.92, 81.77, 106.60,

112.72, 116.93, 118.30, 121.89, 125.29, 146.44, 151.04; HRMS calcd for C₁₄H₁₈O₄:

250.12051. Found: 250.12065.

2,3-Dihydroethanobenzofuran[1,4]dioxine (27). 2-Iodophenol was allowed to react with

the cyclic alkene 1,4-dioxene using the optimal phenol procedure with a 5-fold excess of the

alkene under N₂ to form compound **27**. Further purification was achieved using preparative

TLC. Compound **27** was isolated as a light yellow solid (64% yield): mp = 89-92 °C; *R_f* =

0.54 (silica, 80:20 Hex/EtOAc); IR (neat) 3013, 3008, 2994, 2890, 1166, 1080, 1042 cm⁻¹; ¹H

NMR (300 MHz, CDCl₃) δ 3.70 (m, 3 H), 4.06 (m, 1 H), 4.73 (d, *J* = 3.9 Hz, 1 H), 5.57 (d, *J*

= 3.9 Hz, 1 H), 6.90 (m, 2 H), 7.25 (m, 1 H), 7.40 (d, *J* = 0.9 Hz, 1 H); ¹³C NMR (300 MHz,

CDCl₃) δ 60.97, 62.17, 71.19, 101.14, 110.90, 121.55, 125.97, 126.36, 131.26, 158.29;

HRMS calcd for C₁₀H₁₀O₃: 178.06299. Found: 178.06328. Anal. calcd for C₁₀H₁₀O₃: C,

67.41; H, 5.66. Found: C, 67.06; H, 5.66; N, 0.09.

5-Acetyl-2,3-dihydroethanobenzofuran[1,4]dioxine (28). 4-Hydroxy-3-iodoacetophenone

was allowed to react with the cyclic alkene 1,4-dioxene using the optimal phenol procedure

with a 5-fold excess of the alkene under N₂ to form compound **28**. Further purification was

achieved using preparative TLC. Compound **28** was isolated as a clear, light yellow oil (32%

yield): *R_f* = 0.34 (silica, 80:20 Hex/EtOAc); IR (neat) 3015, 2919, 1671, 1616, 1358, 1261,

117 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.55 (s, 3 H), 3.76 (m, 3 H), 4.05 (m, 1 H), 4.78 (d,

J = 3.9 Hz, 1 H), 5.66 (d, *J* = 3.9 Hz, 1 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 1

H), 8.04 (s, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 26.42, 60.99, 62.11, 70.33, 102.17, 110.70,

126.90, 126.92, 131.49, 132.72, 162.21, 196.24; HRMS calcd for C$_{12}$H$_{12}$O$_4$: 220.07356.

Found: 220.07334.

Compound 33. 4-t-Butyl-2-iodophenol was allowed to react with the cyclic alkene 1,4-

dioxene using the optimal phenol procedure with a 5-fold excess of the alkene under N$_2$ to

form compound **33**. Compound **33** was isolated as a yellow oil (43% yield): R_f = 0.30

(silica, 83:17 Hex/EtOAc); IR (neat) 3012, 2969, 1489 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ

1.32 (s, 9 H), 3.74 (m, 3 H), 3.83 (m, 1 H), 4.71 (d, J = 3.8 Hz, 1 H), 5.56 (d, J = 3.8 Hz, 1

H), 6.84 (d, J = 8.5 Hz, 1 H), 7.32 (m, 2 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 16.61, 31.85,

35.02, 61.16, 62.49, 71.87, 101.47, 110.41, 122.80, 126.64, 128.51, 144.90; HRMS calcd for

C$_{13}$H$_{18}$O$_3$: 234.12559. Found: 234.12595.

Compound 35. N-(2-Iodophenyl)methanesulfonamide was allowed to react with indene

using the optimal amino procedure to form compound **35**. Compound **35** was isolated as an

off-white solid (64% yield): mp 176-180 °C; R_f = 0.10 (silica, 91:9 Hex/EtOAc); IR (neat)

3068, 3025, 2931, 2854, 1488 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.91 (s, 3 H), 3.23 (m, 1

H), 3.52 (m, 1 H), 4.33 (m, 1 H), 5.81 (d, J = 8.0 Hz, 1 H), 7.10 (m, 2 H), 7.25 (m, 4 H), 7.40

(d, J = 7.5 Hz, 1 H), 7.77 (m, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 36.35, 38.69, 44.21,

71.72, 116.50, 124.82, 125.09, 125.19, 126.55, 127.62, 128.64, 129.04, 136.18, 140.69,

140.89, 181.05; HRMS calcd for C$_{16}$H$_{15}$NSO$_2$: 285.08235. Found: 285.08277.

Compound 36. N-(2-Iodophenyl)-p-toluenesulfonamide was allowed to react with indene

using the optimal amino procedure to form compound **36**. Compound **36** was isolated as an

off-white solid (44% yield): mp 186-189 °C; R_f = 0.26 (silica, 91:9 Hex/EtOAc); IR (neat)

3050, 2924, 1476 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.37 (s, 3 H), 3.08 (m, 1 H), 3.33 (m, 1

H), 3.65 (m, 1 H), 5.68 (d, J = 8.0 Hz, 1 H), 7.05 (m, 8 H), 7.61 (m, 3 H), 7.80 (d, J = 7.0 Hz,

1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 21.62, 38.07, 43.86, 71.48, 118.15, 124.66, 124.71,

125.40, 126.50, 127.21, 127.53, 128.30, 128.89, 129.68, 135.30, 137.23, 140.67, 140.72,

141.08, 143.94; HRMS calcd for C$_{22}$H$_{19}$NSO$_2$: 361.11358. Found: 361.11310.

Compound 37. N-(2-Iodophenyl)acetamide was allowed to react with indene using the

optimal amino procedure to form compound **37**. Compound **37** was an apparent 50:50

mixture of two regioisomers (20% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.50 (s, 3 H), 2.61

(s, 3 H), 3.21 (dd, J = 16.2, 21.6 Hz, 2 H), 3.53 (m, 2 H), 4.14 (m, 1 H), 4.25 (m, 1 H), 5.79

(d, J = 7.4 Hz, 1 H), 6.32 (d, J = 7.7 Hz, 1 H), 7.32 (m, 16 H); ^{13}C NMR (300 M Hz) δ 24.44,

24.62, 37.11, 38.36, 42.68, 45.05, 69.21, 69.88, 155.36, 118.63, 124.05, 124.17, 124.58,

124.79, 125.62, 125.68, 127.09 127.53, 127.99, 128.28, 128.57, 129.22, 135.27, 137.73,

140.84, 141.10, 141.62, 142.05, 142.12, 142.49; HRMS calcd for C$_{17}$H$_{15}$NO: 249.11536.

Found: 249.11566.

Compound 38. N-(2-Iodophenyl)methanesulfonamide was allowed to react with 1,2-

dihydronaphthalene using the optimal amino procedure to form compound **38**. Compound

38 was isolated as a clear, crystalline solid (80% yield): mp 174-177 °C; R_f = 0.10 (silica,

91:9 Hex/EtOAc); IR (neat) 3050, 2924, 1476 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.31 (m, 2

H), 2.57 (m, 2 H), 2.83 (s, 3 H), 4.05 (m, 1 H), 5.55 (d, J = 8.9 Hz, 1 H), 6.97 (d, J = 7.4 Hz,

1 H), 7.15 (m, 5 H), 7.40 (d, J = 7.2 Hz, 1 H), 7.84 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (300 MHz,

CDCl$_3$) δ 24.68, 25.18, 37.21, 40.35, 64.41, 118.34, 124.05, 125.61, 126.99, 127.53, 128.16,

128.38, 130.60, 134.42, 135.11, 138.05, 141.98; HRMS calcd for C$_{17}$H$_{17}$NSO$_2$: 299.09800.

Found: 299.09838. Anal calcd. for : C$_{17}$H$_{17}$NSO$_2$ C, 68.20; H, 5.72; N, 4.68. Found: C,

68.03; H, 6.05; N, 4.58.

Compound 39. *N*-(2-Iodophenyl)methanesulfonamide was allowed to react with

acenaphthene using the optimal amino procedure to form compound **39**. Compound **39** was

isolated as a yellow oil (80% yield): R_f = 0.40 (silica, 80:20 Hex/EtOAc); IR (neat) 3018 cm⁻

¹; ¹H NMR (300 MHz, CDCl₃) δ 2.97 (s, 3 H), 5.42 (d, *J* = 8.3 Hz, 1 H), 6.20 (d, *J* = 8.3 Hz,

1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.18 (m, 1 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.49 (m, 4 H), 7.72

(m, 2 H), 7.92 (d, *J* = 6.5 Hz, 1 H); ¹³C NMR (300 MHz, CDCl₃) δ 36.88, 51.04, 69.60,

115.43, 119.22, 123.03, 123.96, 124.62, 125.04, 125.27, 128.25, 128.78, 128.83, 131.56,

132.87, 137.13, 141.21, 142.05, 143.73; HRMS calcd for C₁₉H₁₅NSO₂: 321.08351. Found:

321.08354.

Compound 40. *N*-(2-Iodophenyl)-*p*-toluenesulfonamide was allowed to react with

acenaphthene using the optimal amino procedure to form compound **40**. Compound **40** was

isolated as an off-white solid (10% yield): mp = 189-194 °C; R_f = 0.15 (silica, 91:9

Hex/EtOAc); IR (neat) 3050, 2996, 2922, 2852, 1344, 1152 cm⁻¹; ¹H NMR (300 MHz,

CDCl₃) δ 2.37 (s, 3 H), 4.97 (d, *J* = 6.0 Hz, 1 H), 6.09 (d, *J* = 6.0 Hz, 1 H), 7.00 (m, 1 H),

7.21 (m, 3 H), 7.60 (d, *J* = 3.1 Hz, 1 H), 7.64 (m, 2 H), 7.69 (m, 6 H), 7.90 (d, *J* = 5.0 Hz, 1

H); ¹³C NMR (300 MHz, CDCl₃) δ 21.66, 50.71, 69.42, 117.49, 119.03, 123.03, 123.86,

124.68, 124.99, 125.05, 127.43, 128.08, 128.49, 128.87, 129.81, 131.42, 134.04, 134.90,

137.10, 141.42, 142.21, 143.74, 144.23; HRMS calcd for C₂₅H₁₉NSO₂: 397.113651. Found:

397.114358.

5,9b,10-Trihydro-4b-oxabenzofuro[2,1-*a*]indene (41) and 2-(2'-hydroxyphenyl)indene

(42). 2-Iodophenol was allowed to react with indene using the optimal phenol procedure to

form compounds **41** and **42**. Using a stepwise elution of 97:3, 90:10, and 50:50 hexane/ethyl

acetate solutions, the isomers were separated on a silica gel column. Compound **41** was

isolated as a yellow oil (26% yield): R_f = 0.50 (silica, 91:9 Hex/EtOAc); IR (neat) 3067,

3024, 2920, 2848, 1608, 1476, 1016 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.18 (dd, J = 8.0,

16.0 Hz, 1 H), 3.05 (dd, J = 8.0, 16.0 Hz, 1 H), 4.28 (dd, J = 8.0, 8.0 Hz, 1 H), 6.19 (d, J =

8.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.84 (dd, J = 6.0, 13.0 Hz, 1 H), 7.06 (dd, J = 6.0,

13.0 Hz, 1 H), 7.24 (m, 4 H), 7.55 (m, 1 H); ¹³C NMR (300 MHz, CDCl₃) δ 39.28, 44.83,

90.65, 110.02, 120.77, 124.83, 125.23, 126.05, 127.34, 128.55, 129.34, 131.03, 140. 86,

142.42, 159.01; HRMS calcd for $C_{15}H_{12}O$: 208.08882. Found: 208.08909.

2-(2'-Hydroxyphenyl)indene (42). Compound **42** was isolated as a yellow oil (68% yield):

R_f = 0.26 (silica, 91:9 Hex/EtOAc); IR (neat) 3050, 3300, 2904, 1694, 1598, 1459 cm⁻¹; ¹H

NMR (300 MHz, CDCl₃) δ 3.83 (s, 2 H), 5.47 (s, 1 H), 6.73 (d, J = 6.0 Hz, 1 H), 6.90 (m, 1

H), 7.27 (m, 6 H); ¹³C NMR (300 MHz, CDCl₃) δ 38.79, 115.76, 120.49, 120.72, 121.74,

124.23, 125.67, 126.59, 129.44, 129.63, 132.94, 140.67, 143.93, 144.47, 153.26; HRMS

calcd for $C_{15}H_{12}O$: 208.08882. Found: 208.08889.

2-Acetyl-5,9b,10-trihydro-4b-oxabenzofuro[2,1-a]indene (50a) and 2-(5'-acetyl-2'-
hydroxyphenyl)indene (51a). 4-Hydroxy-3-iodoacetophenone was allowed to react with

indene under the optimal phenol procedure to form compounds **50a** and **51a**. Further

purification was achieved using preparative TLC. Compound **50a** was isolated as a clear,

yellow oil (15% yield): R_f = 0.12 (silica, 91:9 Hex/EtOAc); IR (neat) 3270, 3192, 3017,

2928 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.58 (s, 3 H), 3.21 (d, J = 16.3 Hz, 1 H), 3.53 (dd, J

= 8.4, 16.3 Hz, 1 H), 4.29 (t, J = 8.4 Hz, 1 H), 6.29 (d, J = 8.3 Hz, 1 H), 6.75 (d, J = 8.3 Hz, 1

H), 7.24 (m, 3 H), 7.55 (m, 1 H), 7.91 (m, 1 H), 7.92 (s, 1 H); ¹³C NMR (300 MHz, CDCl₃) δ

26.66, 39.40, 44.34, 92.41, 109.78, 125.48, 125.70, 126.19, 127.65, 129.85, 131.07, 131.24,

132.22, 140.16, 142.42, 163.54, 196.87; HRMS calcd for $C_{17}H_{14}O_2$: 250.09938. Found: 250.09952.

2-(5'-Acetyl-2'-hydroxyphenyl)indene (51a). Compound **51a** was purified using preparative TLC and was isolated as a dark yellow oil (44% yield): $R_f = 0.20$ (silica, 91:9 Hex/EtOAc); IR (neat) 3270, 3192, 3017, 2928, 1698, 1653, 1578, 1436 cm⁻¹; ¹H NMR (300 MHz, d^6-acetone) δ 2.57 (s, 3 H), 3.97 (s, 2 H), 7.06 (d, J = 8.0 Hz, 1 H), 7.17 (dd, J = 7.0, 8.0 Hz, 1 H), 7.20 (dd, J = 7.0, 8.0 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.81 (s, 1 H), 8.22 (d, J = 8.0 Hz, 1 H), 8.23 (s, 1 H); ¹³C NMR (300 MHz, d^6-acetone) δ 25.60, 40.42, 116.02, 121.05, 123.09, 123.45, 124.78, 126.47, 128.91, 129.39, 129.97, 131.04, 142.67, 142.87, 145.91, 159.51, 206.38; HRMS calcd for $C_{17}H_{14}O_2$: 250.09938. Found: 250.09880.

5,9b,10-Trihydro-2-hydroxy-1,3,4-trimethyl-4b-oxabenzofuro[2,1-a]indene (50b). 2-Iodo-3,5,6-trimethylhydroquinone was allowed to react with indene using the optimal phenol procedure to form compound **50b**. Further purification was achieved by using a stepwise elution of 97:3, 90:10, and 50:50 Hex/EtOAc solutions on a silica gel column. Compound **50b** was isolated as a yellow oil (30% yield): $R_f = 0.12$ (silica, 91:9 Hex/EtOAc); IR (neat) 3570, 2958, 2867, 1436 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.08 (s, 6 H), 2.24 (s, 3 H), 3.13 (m, 1 H), 3.48 (m, 1 H), 4.16 (s, 1 H), 4.39 (m, 1 H), 6.14 (d, J = 6.0 Hz, 1 H), 7.21 (m, 3 H), 7.56 (m, 1 H); ¹³C NMR (300 MHz, CDCl₃) δ 12.09, 12.32, 12.82, 39.08, 45.14, 90.02, 116.16, 117.19, 122.12, 125.14, 126.09, 126.65, 127.18, 129.21, 141.44, 142.66, 145.91, 151.34; HRMS calcd for $C_{18}H_{18}O_2$: 266.13076. Found: 266.13119.

2-Chloro-5,9b,10-trihydro-4b-oxabenzofuro[2,1-a]indene (50c) and 2-(5'-chloro-2'-hydroxyphenyl)indene (51c). 4-Chloro-2-iodophenol was allowed to react with indene

under the optimal phenol procedure to form compounds **50c** and **51c**. Using a stepwise

elution of 97:3, 90:10, and 50:50 Hex/EtOAc solutions, the two isomers were separated on a

silica gel column. Compound **50c** was isolated as a yellow oil (17% yield): R_f = 0.39 (silica,

91:9 Hex/EtOAc); IR (neat) 3067, 2956, 2924, 1436 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ

3.16 (m, 1 H), 3.51 (m, 1 H), 4.28 (m, 1 H), 6.21 (d, J = 9.0 Hz, 1 H), 6.64 (d, J = 9.0 Hz, 1

H), 7.06 (m, 5 H), 7.53 (m, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 39.06, 44.88, 91.37, 110.95,

124.92, 125.21, 125.33, 125.99, 127.46, 128.43, 129.54, 132.97, 140.39, 142.09, 157.69;

HRMS calcd for C$_{27}$H$_{14}$ClO: 242.04984. Found: 242.04983.

2-(5'-Chloro-2'-hydroxyphenyl)indene (51c). Compound **51c** was purified using

preparative TLC and was isolated as a light yellow oil (37% yield): R_f = 0.14 (silica, 91:9

Hex/EtOAc); IR (neat) 3270, 2925, 1590, 1461 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.81 (s,

2 H), 5.6 (br s, 1 H), 6.75 (m, 2 H), 7.12 (m, 5 H), 7.48 (m, 1 H); ^{13}C NMR (300 MHz,

CDCl$_3$) δ 41.29, 116.73, 117.54, 121.63, 123.65, 125.37, 125.75, 126.81, 128.12, 128.34,

129.57, 131.17, 141.75, 142.79, 145.11; HRMS calcd for C$_{17}$H$_{14}$O$_2$: 242.04984. Found:

242.04952.

2-*t*-Butyl-5,9b,10-trihydro-4b-oxabenzofuro[2,1-*a*]indene (50f) and 2-(5'-*t*-butyl-2'-
hydroxyphenyl)indene (51f). 4-*t*-Butyl-2-iodophenol was allowed to react with indene

using the optimal phenol procedure to form compounds **50f** and **51f**. Using a stepwise

elution of 97:3, 90:10, and 50:50 Hex/EtOAc solutions, the two isomers were separated on a

silica gel column. Compound **50f** was isolated as a yellow oil (15% yield): R_f = 0.40 (silica,

91:9 Hex/EtOAc); IR (neat) 3070, 2958, 2867, 1436 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ

1.28 (s, 9 H), 3.20 (m, 1 H), 3.49 (m, 1 H), 4.30 (m, 1 H), 6.18 (d, J = 6.0 Hz, 1 H), 6.66 (d, J

= 6.0 Hz, 1 H), 7.10 (m, 1 H), 7.24 (m, 4 H), 7.55 (m, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ

31.83, 34.41, 39.28, 45.01, 90.77, 109.13, 121.64, 125.20, 125.44, 126.02, 127.26, 129.25,

130.51, 141.00, 142.44, 143.93, 156.80; HRMS calcd for $C_{19}H_{20}O$: 264.15142. Found

264.15152.

2-(5'-t-Butyl-2'-hydroxyphenyl)indene (51f). Compound **51f** was purified using

preparative TLC and was isolated as a light yellow oil (51% yield): R_f = 0.25 (silica, 91:9

Hex/EtOAc); IR (neat) 3526, 2867, 1607, 1505 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.31 (s,

9 H), 3.88 (s, 2 H), 5.45 (br s, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 7.25 (m, 7 H); ^{13}C NMR (300

MHz, CDCl$_3$) δ 31.62, 34.25, 41.47, 115.88, 121.18, 122.70, 123.59, 124.90, 125.57, 125.75,

126.70, 129.79, 142.97, 143.57, 143.80, 145.46, 151.11; HRMS calcd for $C_{19}H_{20}O$:

264.15142. Found: 264.15146.

5,9b,10-Trihydro-2-methoxy-4b-oxabenzofuro[2,1-a]indene (50g). 4-Methoxy-2-

iodophenol was allowed to react with indene using the optimal phenol procedure to form

compound **50g**. Further purification was achieved using preparative TLC. Compound **50g**

was isolated as a yellow oil (17% yield): R_f = 0.45 (silica, 70:30 Hex/EtOAc); IR (neat) 3020

cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.17 (m, 1 H), 3.47 (m, 1 H), 3.74 (s, 3 H), 4.28 (m, 1

H), 6.16 (d, J = 6.0 Hz, 1 H), 6.63 (s, 2 H), 6.68 (s, 1H), 7.22 (m, 3 H), 7.53 (m, 1 H); ^{13}C

NMR (300 MHz, CDCl$_3$) δ 39.03, 45.33, 56.11, 90.79, 109.87, 110.97, 113.58, 125.14,

125.96, 127.31, 129.28, 131.88, 140.99, 142.30, 153.09, 154.45; HRMS calcd for $C_{16}H_{14}O_2$:

238.0998. Found: 238.0994.

2-(2'-Hydroxyphenyl)indane (43). 2-Iodophenol was reacted with indene using the optimal

phenol procedure to form **43** with the exception that one mL of 2-(2-ethoxy)ethoxyethanol

was used as the solvent and 1 equiv of DMG (45.0 mg, 0.45 mmol) was employed. Further

purification was achieved by using a stepwise elution of 97:3, 90:10, and 50:10 Hex/EtOAc

solutions on a silica gel column. Compound **43** was isolated as a yellow oil (81% yield): R_f

= 0.45 (silica, 70:30 Hex/EtOAc); IR (neat) 3500, 3020, 2935, 1455 cm^{-1}; ^{1}H NMR (300

MHz, CDCl$_3$) δ 3.09 (dd, J = 8.2, 8.2 Hz, 2 H), 3.30 (dd, J = 8.2, 8.2 Hz, 2 H), 3.93 (m, 1 H),

6.75 (d, J = 1.0 Hz, 1 H), 6.77 (t, J = 1.0 Hz, 1 H), 7.18 (m, 6 H); ^{13}C NMR (300 MHz,

CDCl$_3$) δ 39.32, 39.40, 115.38, 115.52, 120.87, 120.99, 124.48, 126.47, 127.24, 127.86,

131.32, 143.16, 153.52, 155.51 (one peak is missing, because two peaks overlap at 39.40);

HRMS calcd for C$_{15}$H$_{14}$O: 210.10466. Found 210.10447.

Compound 52, 4-(2'Hydroxyphenyl)-1,2-dihydronaphthalene (53), and 3-

(2'Hydroxyphenyl)-1,2-dihydronaphthalene (54). 2-Iodophenol was allowed to react with

1,2-dihydronaphthalene using the optimal phenol procedure to form isomers **52**, **53**, and **54**.

Compounds **52**, **53**, and **54** were separated on a silica gel column by using 91:9 Hex/EtOAc

as the eluent. Further purification was achieved using preparative TLC. Compound **52** was

isolated as a clear, yellow oil (13% yield): R_f = 0.39 (silica, 91:9 Hex/EtOAc); IR (neat)

3020, 2926, 2857, 1595, 1458, 1359 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.79 (m, 1 H), 2.05

(m, 1 H), 2.63 (m, 2 H), 3.66 (m, 1 H), 5.65 (d, J = 8.0 Hz, 1 H), 6.76 (d, J = 8.0 Hz, 1 H),

6.86 (m, 1 H), 7.12 (m, 2 H), 7.22 (m, 3 H), 7.50 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (300 MHz,

CDCl$_3$) δ 27.67, 28.15, 41.18, 81.89, 109.66, 120.67, 124.46, 126.77, 128.36, 128.38, 128.53,

130.29, 131.43, 133.52, 138.99, 159.48; HRMS calcd for C$_{16}$H$_{14}$O: 222.10447. Found:

222.10434.

4-(2'Hydroxyphenyl)-1,2-dihydronaphthalene (53). Compound **53** was obtained as a light

yellow oil (24% yield): R_f = 0.25 (silica 91:9 Hex/EtOAc); IR (neat) 3305, 2965 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 2.61 (t, J = 8.6 Hz, 2 H), 2.96 (t, J = 8.6 Hz, 2 H), 5.53 (s, 1 H),

6.71 (s, 1 H), 6.92 (d, J = 6.6 Hz, 2 H), 7.11 (m, 5 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 28.22,

28.53, 115.82, 120.67, 126.58, 126.81, 127.15, 127.56, 127.63, 128.03, 128.61, 128.74,

133.79, 134.67, 136.64, 159.34; HRMS calcd for $C_{16}H_{14}O$: 222.10447. Found: 222.10434.

3-(2'Hydroxyphenyl)-1,2-dihydronaphthalene (54). Compound **54** was obtained as a light

yellow oil (24% yield): $R_f = 0.25$ (silica 91:9 Hex/EtOAc); IR (neat) 3305, 2965 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 2.54 (m, 2 H), 4.43 (m, 1 H), 4.73 (s, 1 H), 5.99 (m, 1 H), 6.53 (d,

$J = 8.5$ Hz, 1 H), 6.81 (m, 3 H), 7.02 (m, 5 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 28.36, 28.67,

115.97, 120.81, 126.73, 126.96, 127.29, 127.70, 127.78, 128.19, 128.75, 128.89, 133.94,

134.81, 136.79, 152.49; HRMS calcd for $C_{16}H_{14}O$: 222.10447. Found: 222.10686.

Compound 55. 2-Iodophenol was allowed to react with acenaphthalene using the optimal

phenol procedure with the exception that ethylene glycol was used as the solvent.

Compound **55** was purified on a silica gel column using 91:9 Hex/EtOAc as the eluent.

Further purification was achieved using preparative TLC. Compound **55** was isolated as a

red oil (47% yield): $R_f = 0.51$ (silica, 91:9 Hex/EtOAc); IR (neat) 3045, 2953, 2922, 2850,

1461, 1215 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.40 (d, $J = 6.0$ Hz, 1 H), 6.63 (d, $J = 6.0$ Hz,

1 H), 6.77 (m, 1 H), 6.87 (m, 1 H), 7.09 (m, 1 H), 7.47 (m, 4 H), 7.70 (m, 2 H), 7.79 (m, 1

H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 52.15, 88.58, 110.40, 119.12, 120.87, 122.07, 123.67,

124.63, 125.71, 128.14, 128.42, 128.45, 128.80, 131.65, 137.42, 141.85, 144.50, 159.71;

HRMS calcd for $C_{18}H_{12}O$: 244.08882. Found: 244.08837.

3-Methoxy-6a,11a-*cis*-dihydro-6*H*-benzofuro[3,2-*c*]benzopyran (57). 2-Iodophenol was

allowed to react with **56** using the optimal phenol procedure to form compound **57**.

Compound **57** was obtained as a white solid (73% yield): mp = 89-91 °C; IR (CDCl$_3$) 2980,

2894, 2252, 2360, 1620 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.69 (m, 2 H), 3.78 (s, 3 H),

4.27 (m, 1 H), 5.49 (d, $J = 6.6$ Hz, 1 H), 6.46 (d, $J = 2.4$ Hz, 1 H), 6.64 (dd, $J = 8.4, 2.4$ Hz, 1

H), 6.87 (m, 2 H), 7.18 (m, 2 H), 7.43 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ

40.11, 55.33, 66.32, 77.65, 101.59, 109.16, 110.14, 112.20, 120.78, 124.66, 127.08, 129.13,

131.84, 156.50, 159.29, 160.97; HRMS calcd for C$_{16}$H$_{14}$O$_3$: 254.09400. Found: 254.09430.

6-Phenyl-6a,11a-*cis*-dihydro-6H-benzofuro[3,2-*c*]benzopyran (59). 2-Iodophenol was

allowed to react with **58** under the optimal phenol procedure to form compound **59**.

Compound **59** was obtained as a white solid (60% yield): mp = 198-199 °C; IR (CDCl$_3$)

2980, 2894, 2360, 1239 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.63 (dd, J = 10.8, 6.9 Hz, 1 H),

4.43 (d, J = 11.1 Hz, 1 H), 5.70 (d, J = 6.9 Hz, 1 H), 6.83-7.75 (m, 10 H), 7.63 (dd, J = 7.8,

1.5 Hz, 1 H), 7.86 (dd, J = 8.4, 1.8 Hz, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 26.22, 46.53,

80.02, 109.79, 117.78, 118.95, 122.02, 127.10, 127.46, 128.11, 128.52, 129.14, 130.41,

130.50, 130.63, 130.96, 137.14, 155.51, 163.41. HRMS calcd for C$_{21}$H$_{16}$O$_2$: 300.11503.

Found: 300.11557.

References

1. (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*,

1081. (c) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567. (d) Trost, B. *Science*

1991, *234*, 1471. (e) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.; Liu, F. *Chem. Rev.* **1996**,

96, 365. (f) Ojima, I.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (g) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111.

2. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

3. (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (c) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.

4. Larock, R. C.; Doty, M. J.; Cacchi, S. J. *J. Org. Chem.* **1993**, *58*, 4579.

5. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

6. (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.

7. Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551.

8. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

9. (a) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds; Pergamon Press: New York, 1984; Vol. 3, pp 657-712. (b) Nakanishi, K. In *Natural Products Chemistry*; Kodansha, Ltd.: Tokyo, 1974.

10. (a) Gribble, G. W. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1990; Vol. 39, p 1. (b) Auclair, C. *Arch. Biochem. Biophys.* **1987**, *259*, 1. (c) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389. (d) Suffness, M.; Cordell, G. A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. XXV, p 1. (e) Marsais, F.; Pineau, P.; Wivollios, F.; Mallat, M.; Turck A.; Godard, A.; Quequiner, G. *J. Org. Chem.* **1992**, *57*, 565.

11. (a) Obaza-Nutaitis, J. A.; Gribble, G. W. *Nat. Prod.* **1986**, *49*, 449. (b) Gribble, G. W.;

Saulinor, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem.* **1992**, *57*, 5891.

12. (a) Hughes, R. P.; Powell, J. *J. Organomet. Chem.* **1971**, *30*, C45. (b) Gallazzi, M. C.;

Hanlon, T. L.; Vitulli, G.; Porri, L. *J. Organomet. Chem.* **1971**, *33*, C45. (c) Horino, H.;

Arai, M.; Inouc, N. *Tetrahedron Lett.* **1974**, 647. (d) Li, C.-S.; Jou, D.-C.; Cheng, C.-H.

J. Chem. Soc., Chem. Commun. **1991**, 710.

13. (a) Markies, B. A.; Verkerk, K. A. N.; Rietveld, M. H. P.; Boersma, J.; Kooijman, H.;

Spek, A. L.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1993**, 1317. (b) van Asselt,

R.; Gielens, E. E. C. G.; Rülke, R. E.; Elsevier, C. J. *J. Chem. Soc., Chem. Commun.*

1993, 1203. (c) Dalcanale, E.; An, Z.; Battaglia, L. P.; Catellani, M.; Chiusoli, G. P. *J.*

Organomet. Chem. **1992**, *437*, 375. (d) Roberto, D.; Catellani, M.; Chiusoli, G. P.

Tetrahedron Lett. **1988**, *29*, 2115. (e) Larock, R. C.; Hershberger, S. S.; Takagi, K.;

Mitchell, M. A. *J. Org. Chem.* **1986**, *51*, 2450. (f) Catellani, M.; Chiusoli, G. P.; Peloso,

C. *Tetrahedron Lett.* **1983**, *24*, 813. (g) Torri, S.; Okumoto, H.; Ozaki, H.; Nakayasu,

S.; Tadokoro, T.; Kotani, T. *Tetrahedron Lett.* **1992**, *33*, 3499. (h) Tori, S.; Okumoto, H.;

Ozaki, H.; Nakayasu, S.; Kotani, T. *Tetrahedron Lett.* **1990**, *31*, 5319. (i) Oda, H.; Ito,

K.; Kosugi, M.; Migita, T. *Chem. Lett.* **1994**, 1443. (j) Kosugi, M.; Kimura, T.; Oda, H.;

Migita, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3522. (k) Kosugi, M.; Tamura, H.; Sano, H.;

Migita, T. *Tetrahedron* **1989**, *45*, 961. (l) Larock, R. C.; Srinivasan, B. *Tetrahedron*

1987, *43*, 2013. (m) Larock, R. C.; Srinivasan, B. *Tetrahedron Lett.* **1985**, *26*, 2763. (n)

Larock, R. C.; Burkhart, J. P.; Oertle K. *Tetrahedron Lett.* **1982**, *23*, 1071. (o) Catellani,

M. *Izv. Akad. Nauk., Ser. Khim.* **1995**, 412 [*Russ. Chem. Bull.* **1995**, *44*, 397 (Engl.

Transl.)].

14. Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769.

15. Catellani, M.; Del Rio, A. *Izv. Akad. Nauk., Ser. Khim.* **1998**, 957 [*Russ. Chem. Bull.* **1998**, *47*, 928 (Engl. Transl.)].

16. Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

17. Ogasawara, K.; Samizu, K. *Heterocycles* **1995**, *41*, 1627.

18. (a) Reetz, M. T.; Westermann, E. *Angew, Chem., Int. Ed. Engl.* **2000**, *39*, 165. (b) Reetz, M. T.; Breinbauer,; Wanniger, K. *Tetrahedron Lett.* **1996**, *37*, 4499. (c) Beller, M.; Fischer, H.; Kühlein, K.; Reisinger, C.-P.; Hermann, W. A. *J. Organomet. Chem.* **1996**, *520*, 257.

19. Wei, L., unpublished results.

20. Posner, G.; Nelson, T. *Tetrahedron* **1990**, *46*, 4573.

21. Moss, R. D.; Paige, J. *J. Chem. Eng. Data* **1967**, *12*, 4573.

22. (a) Viesweswariah, S.; Prakash, G.; Bhushan, V.; Chandrasekaran, S. *Synthesis* **1982**, 309. (b) Chandrasekaran, S.; Bhushan, V. *Synth. Commun.* **1984**, *14*, 339.

23. Sakamonto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305.

24. (a) Berrios-Peña, N. Ph.D Thesis, *Iowa State University*, **1989**, 60. (b) Schreiber, F. G.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 90.

25. Kometani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, *26*, 2043.

CHAPTER 2. SYNTHESIS OF TETRASUBSTITUTED ALKENES BY THE PALLADIUM-CATALYZED TERNARY COUPLING OF ARYL IODIDES, ALKYNES, AND ORGANOMETALLICS

A paper to be submitted to the *Journal of Organic Chemistry*

Daniel E. Emrich and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Abstract

Tetrasubstituted alkenes can be prepared by a palladium(0)-catalyzed procedure which involves the coupling of an aryl iodide, an internal alkyne, and an organometallic. This process presumably proceeds by (1) oxidative addition of the aryl iodide to the palladium(0), (2) carbopalladation of the alkyne, (3) transmetallation between palladium and the organometallic (e.g. a boron, tin, or silicon organometallic), and (4) reductive elimination of the tetrasubstituted alkene with simultaneous regeneration of the Pd(0) catalyst. Other reagents, such as various bases, additives, and phosphine ligands, and reactions conditions, such as time and temperature, have been varied to optimize the yield.

Introduction

Palladium-catalyzed reactions are important for the formation of carbon-carbon bonds.[1] In our laboratories, it has been shown that the palladium(0)-catalyzed annulation of 1,2-, 1,3-, and 1,4-dienes, as well as alkynes, can be employed for the synthesis of indoles,[2] benzofurans,[3] benzopyrans,[3] isocoumarins,[3] α-pyrones,[3] indenones,[4] polycyclic aromatic hydrocarbons,[5] isoquinolines,[6] and isoindoloindoles.[7]

Herein we have employed a palladium(0)-catalyzed reaction to make tetrasubstituted alkenes, a typically difficult functionality to make both regio- and stereoselectively.[8] Our method intermolecularly couples an aryl iodide, an alkyne, and an organometallic to form the tetrasubstituted products. Other researchers have utilized palladium to intramolecularly couple organic halides, alkenes or alkynes, and an organometallic or nucleophile to form hetero- or carbocyclic products.[9] Other researchers have also utilized palladium to intermolecularly couple organic halides, alkenes or alkynes, and an organometallic or nucleophile to form disubstituted products.[10]

Before presenting our results, a brief review of related work will be discussed in the following order: (1) the palladium-catalyzed reactions which intramolecularly couple organic halides, alkenes, and an external organometallic or nucleophile, (2) the palladium-catalyzed reactions which intramolecularly couple organic halides, alkynes, and an external organometallic or nucleophile, (3) the palladium-catalyzed reactions which intermolecularly couple organic halides, alkenes (such as norbornene), and an external organometallic or nucleophile, and, (4) a few palladium-catalyzed reactions which intermolecularly couple organic halides with alkynes.

Firstly, Grigg has employed a palladium catalyst to react a variety of organic halides

tethered to an alkene to form various hetero- or carbocyclic products.[11] The general process

is outlined in Scheme 1. First, oxidative addition of the organic halide or starter species to

palladium(0) gives the organopalladium species, which then adds across the adjacent alkene

or relay species. The organopalladium intermediate formed by this process then

transmetallates with an external organometallic. This is followed by reductive elimination of

the palladium to produce the hetero- or carbocyclic product. Alternatively, instead of

reacting with an external organometallic, an external nucleophile can displace the palladium

to form a substitution product.

Many of Grigg's palladium-catalyzed reactions undergo tandem cyclizations to form

polycyclic products. Suitably constructed organic halides tethered to two or three alkenes

Scheme 1

starter species

X = NSO$_2$Ph, O, CH$_2$ -transmetallation or nucleophilic displacement
R = relay moiety   -reductive elimination
T = terminating moiety   Y = organometallic or nucleophile
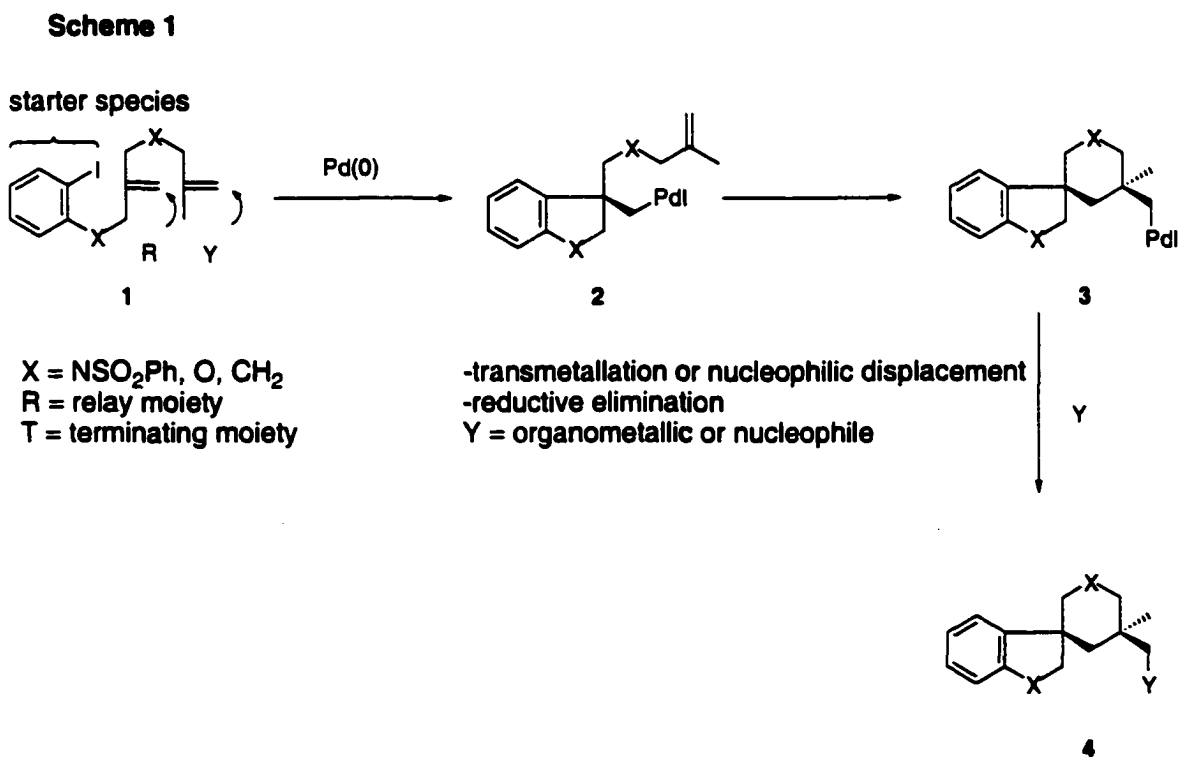
undergo multiple carbopalladation steps before the palladium reacts with an external

organometallic or nucleophile. To be successful, aryl iodides tethered to alkenes, like 1,

must be constructed so that after the carbopalladation step there is no hydrogen *syn* and *beta*

to the palladium (Scheme 1). Intermediate palladium species, like 2, are stable enough to

further react with nearby alkenes.

The second carbopalladation step can be performed with other unsaturated functional

groups, such as alkynes, 1,2-dienes, and 1,3-dienes, for the formation of polycyclic

products.[11] Grigg refers to these functional groups, which undergo the second (or third)

carbopalladation step, as terminating species.[11a] After this step, the palladium reacts with the

external organometallic or nucleophile, which Grigg refers to as the anion transfer reagent.

Aryl iodides tethered to multifunctional alkenes undergo palladium-catalyzed

reactions with external anion transfer reagents, such as metal hydrides;[11a] organotin,[11b-d]

-zinc,[11e] or -borates;[11f] or with a nucleophile.[11g-j] During this palladium-catalyzed process,

carbon monoxide can be inserted into the palladium-carbon bond to form ketones (eq 1) and

esters.[11k,l] In addition to aryl iodides, other starter species, such as aryl triflates,[11m] vinylic

iodides,[11n,o] vinylic triflates,[11p] and propargylic carbonates,[11q,r] can be used in these reactions.

Similarly, Grigg has also used a palladium catalyst to intramolecularly react aryl

iodides tethered to alkynes with an external organometallic or nucleophile.[12] These reactions

$$\text{5} \quad + \quad CO \quad + \quad \text{6} \quad \xrightarrow{\text{cat. Pd(0)}} \quad \text{7} \quad (1)$$
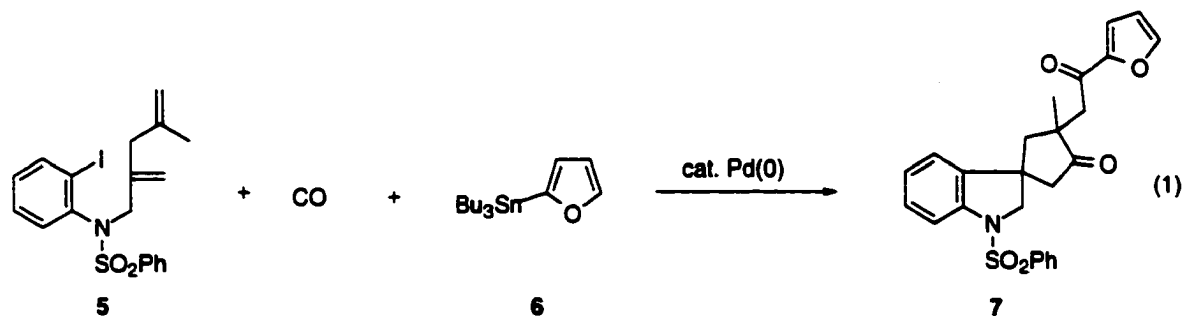
are identical to the ones discussed above, only the generated organopalladium reacts first

with an alkyne rather than an alkene (Scheme 2). In this case, aryl iodides tethered to

multiple alkynes or one alkyne and additional alkenes can undergo multiple 5-exo or 6-exo

carbopalladations in cascade fashion to form polycyclic products such as 11.

Scheme 2
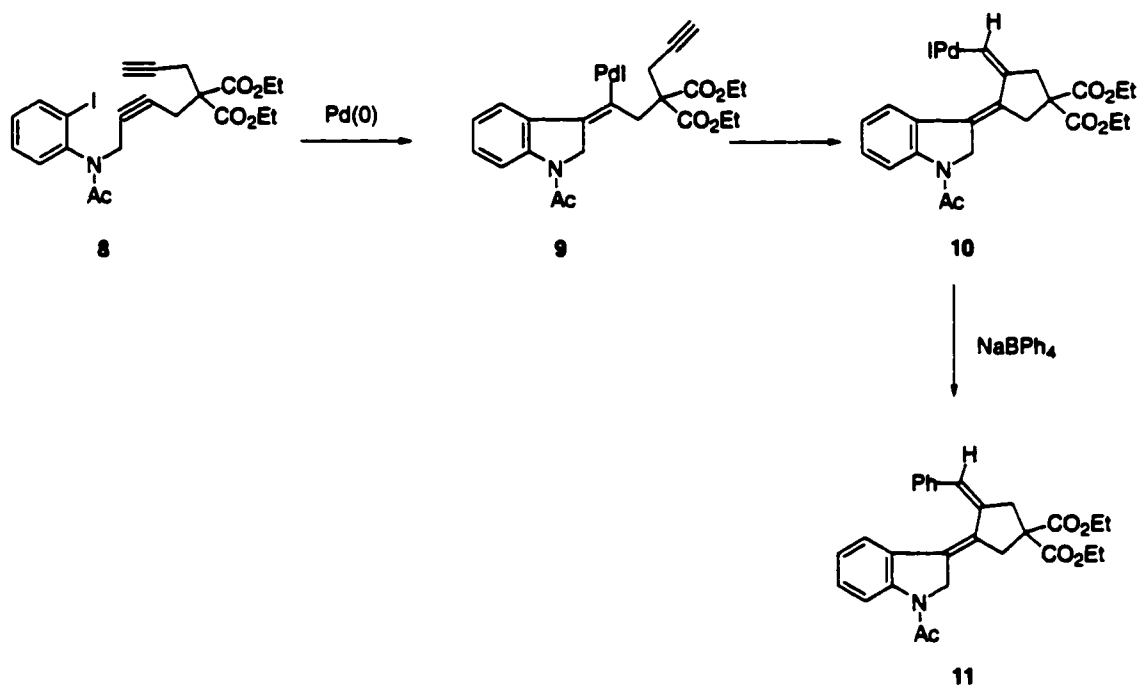
For these reactions, Grigg has also employed metal hydrides;[12a-c] tin,[12d-f] zinc,[12g-k] or

boron[12l-n] organometallics; or various nucleophiles[12o-r] as the anion transfer reagent to form a

variety of functionalized hetero- or carbocyclic products. Further functionalization can be

accomplished by the insertion of carbon monoxide into the palladium-carbon bond.[12s-u] Aryl

triflates,[12f] vinylic iodides,[12m] and benzylic halides[12v] have been used as the starter species in

these intramolecular reactions.

Other researchers have used a palladium catalyst to intermolecularly couple organic halides, alkenes and organometallics or nucleophiles.[13] This ternary coupling process has predominately been performed on norbornene. The reason for choosing norbornene is that after carbopalladation, a stable palladium intermediate is formed which does not undergo facile β-hydride elimination.

In this process, aryl or vinylic iodides undergo oxidative addition to the palladium catalyst, followed by carbopalladation onto norbornene. The palladium intermediate thus formed can transmetallate with a tin[13a-g] or boron[13h] organometallic or can be displaced by a nucleophile (eq 2).[13i-n] In addition, the palladium intermediate can intermolecularly carbopalladate alkynes[13o-s] or alkenes[13t] or insert carbon monoxide[14] to form a variety of functionalized products, including prostaglandins.[13o-s] In the case of aryl iodides, the palladium intermediate has been observed to undergo electrophilic aromatic substitution back onto the initial aryl group to form carbocycles[15] as well.

$$
\text{12} \quad + \quad \text{RI} \quad + \quad \text{MY} \quad \xrightarrow{\text{cat. Pd(0)}} \quad \text{16} \qquad (2)
$$

12   R = aryl, vinylic   13 M = Bu$_3$Sn, Y = Ph,   16
14 M = NaBPh$_3$, Y = Ph,
15 M = K, Y = CN
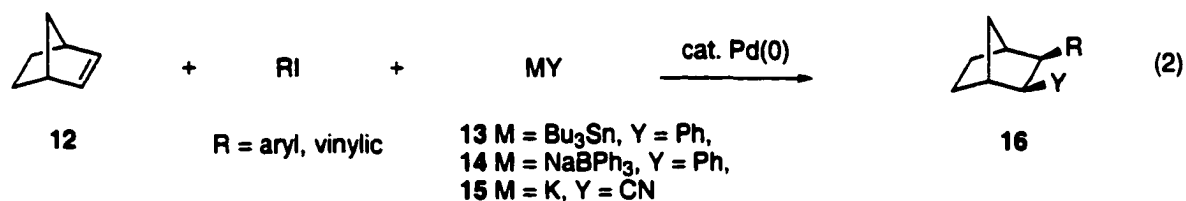
A few other alkenes[16] and allenes[17] have been used in place of norbornene in these intermolecular, palladium-catalyzed, ternary couplings. After carbopalladation, acetals, such as 18-21, have been coupled together with organostannanes (eq 3). Allenes, such as 24, have undergone carbon monoxide insertion, followed by nucleophilic displacement of the palladium (eq 4).

$$
\mathbf{17} + \mathbf{18\text{-}21} + Bu_3SnPh \xrightarrow{\text{cat. Pd(0)}} \mathbf{22} \tag{3}
$$
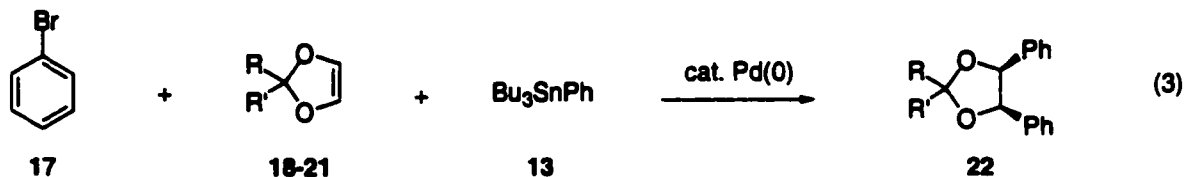
18 R = H, R' = H
19 R = H, R' = Me
20 R = H, R' = t-Bu
21 R = Me, R' = Me

$$
\mathbf{23} + \mathbf{24} + CO \xrightarrow[\text{NaSO}_2\text{Ph}]{\text{cat. Pd(0)}} \mathbf{25} \tag{4}
$$
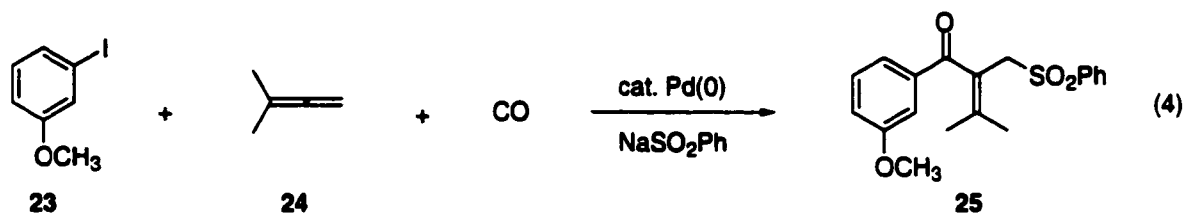
Finally, a palladium catalyst has been employed to intermolecularly couple organic halides and alkynes.[18] Grigg has reacted organic halides with enynes,[18a-c] where carbopalladation occurs first across the more reactive alkyne and then across the alkene. In some cases, the palladium intermediate undergoes electrophilic aromatic substitution (Scheme 3) or β-hydride elimination to form carbocyclic products (eq 5).

Cacchi has reacted vinylic and aryl iodides in these palladium-catalyzed ternary couplings. Vinylic iodides have been used to make dienes,[18d] and aryl iodides have been used to make trisubstituted alkenes.[18e,f] In either case, the palladium intermediate formed after carbopalladation of the alkyne is reduced by formic acid. In these reactions, Cacchi noted regioselective addition of the organopalladium to unsymmetrical alkynes. The carbopalladation occurred, placing the palladium on the more sterically hindered end of the alkyne (Scheme 4).

Scheme 3

(5)

Scheme 4

RI   +

R = aryl, vinylic

34   Pd(0)   **35**

HCO_2H

36
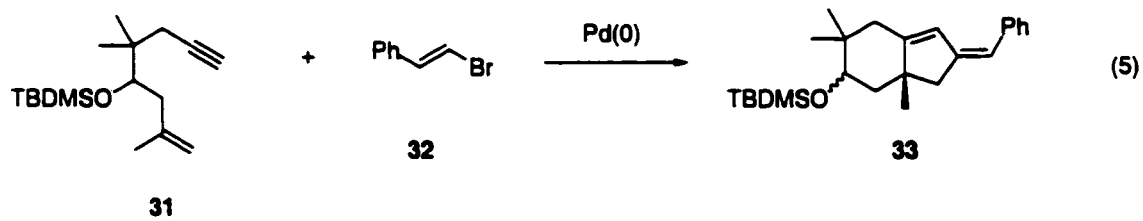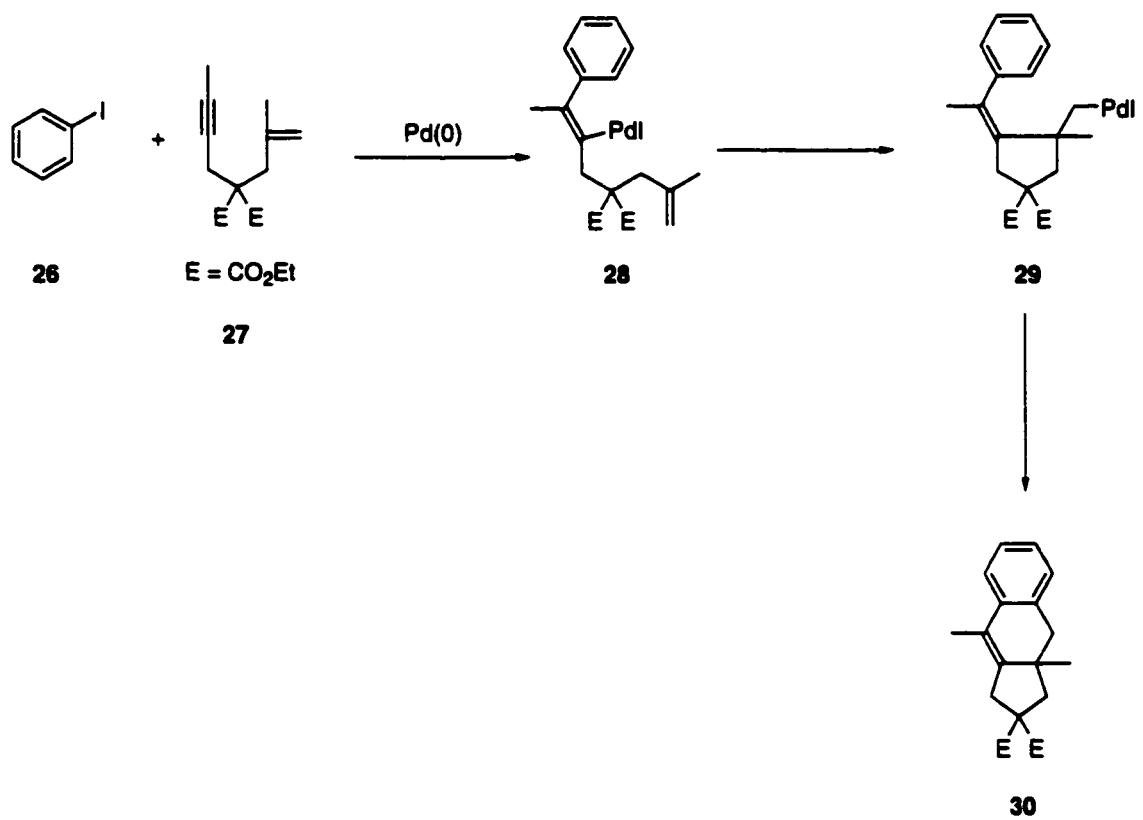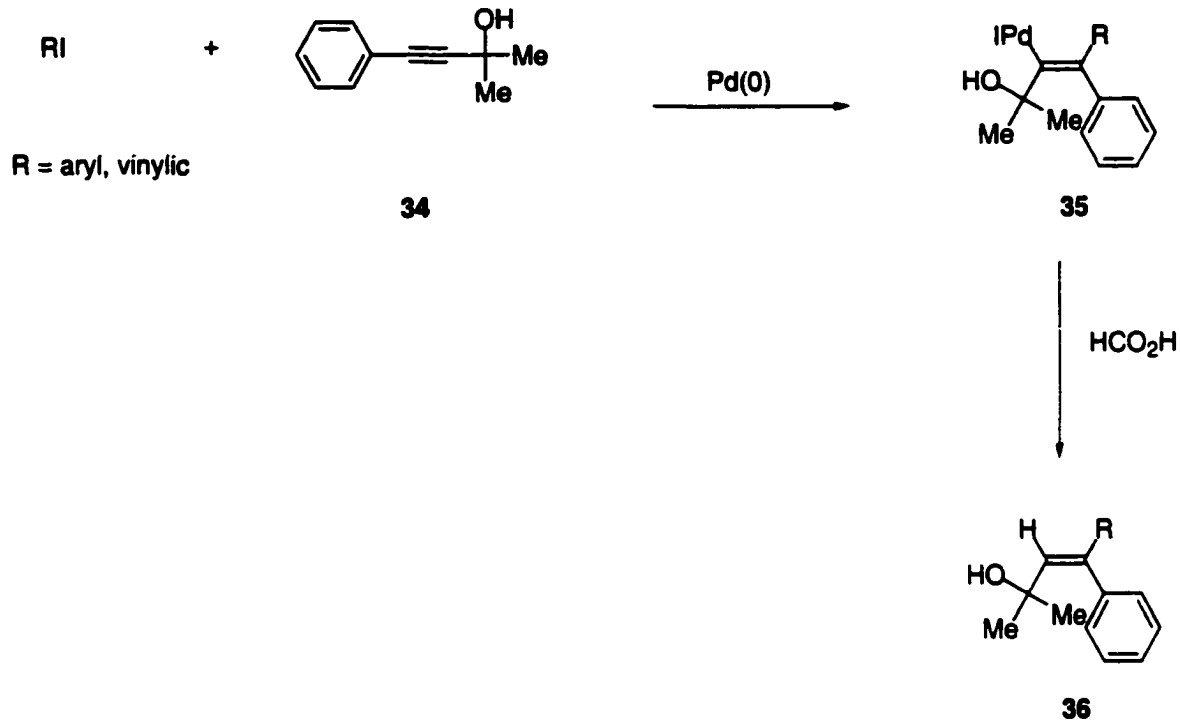
We have sought to extend Cacchi's reactions to form tetrasubstituted alkenes. Instead of reducing the palladium intermediate, we have sought to further react the palladium with an organometallic. This regioselective reaction may prove useful for the synthesis of a variety of tetrasubstituted alkenes, such as tamoxifen derivatives (eq 6).

PhI + Ph—≡—CH₂CH₃ + (HO)₂B—⟨benzene⟩—OR $\xrightarrow{\text{cat. Pd(0)}}$ (6)

R = CH₂CH₂N(CH₃)₂

26   **37**   **38**

OR

Ph

CH₃CH₂   Ph

tamoxifen

39
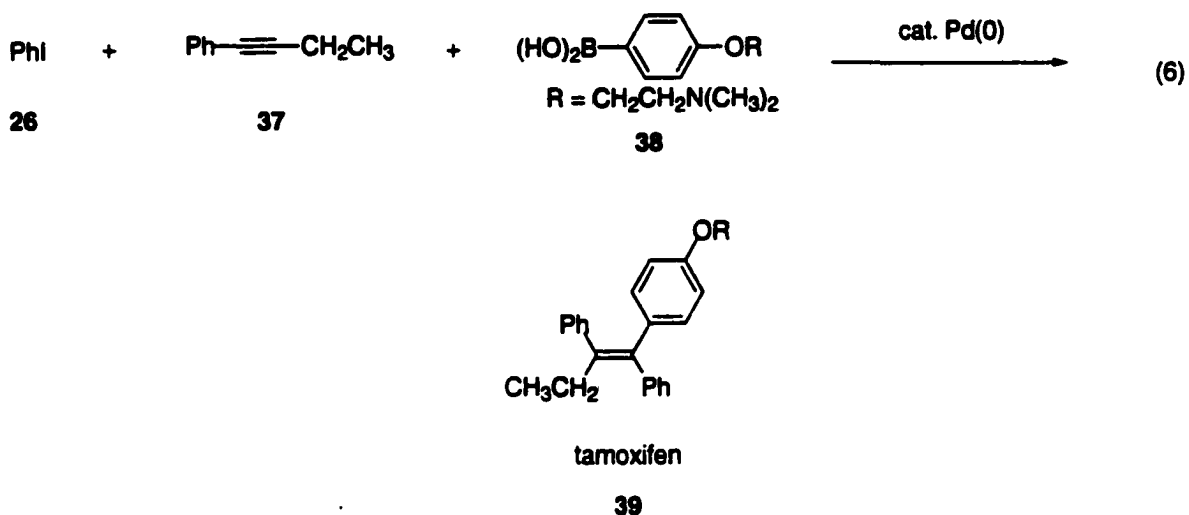
Results and Discussion

In order to develop an intermolecular methodology for the synthesis of

tetrasubstituted alkenes, we chose a simple model system and sought to optimize reaction

conditions. Iodobenzene, diphenylacetylene, and sodium tetraphenylborate (NaBPh₄) were

chosen as the aryl iodide, alkyne, and organometallic respectively.

The mechanism for the desired reaction is shown in Scheme 5. After oxidative

addition of the aryl iodide to Pd(0), carbopalladation across the alkyne gives a vinylic

palladium intermediate **41**. Transmetallation with NaBPh₄ gives intermediate **42**. Reductive

elimination of **42** by palladium gives the desired product tetraphenylethene (**43**) and

regenerates palladium(0). Alternatively, after oxidative addition of the aryl iodide to

palladium(0), transmetallation with NaBPh₄, **14**, generates intermediate **44**. Reductive

elimination of **44** by palladium gives the side product biphenyl (**45**) and regenerates Pd(0).

Scheme 5
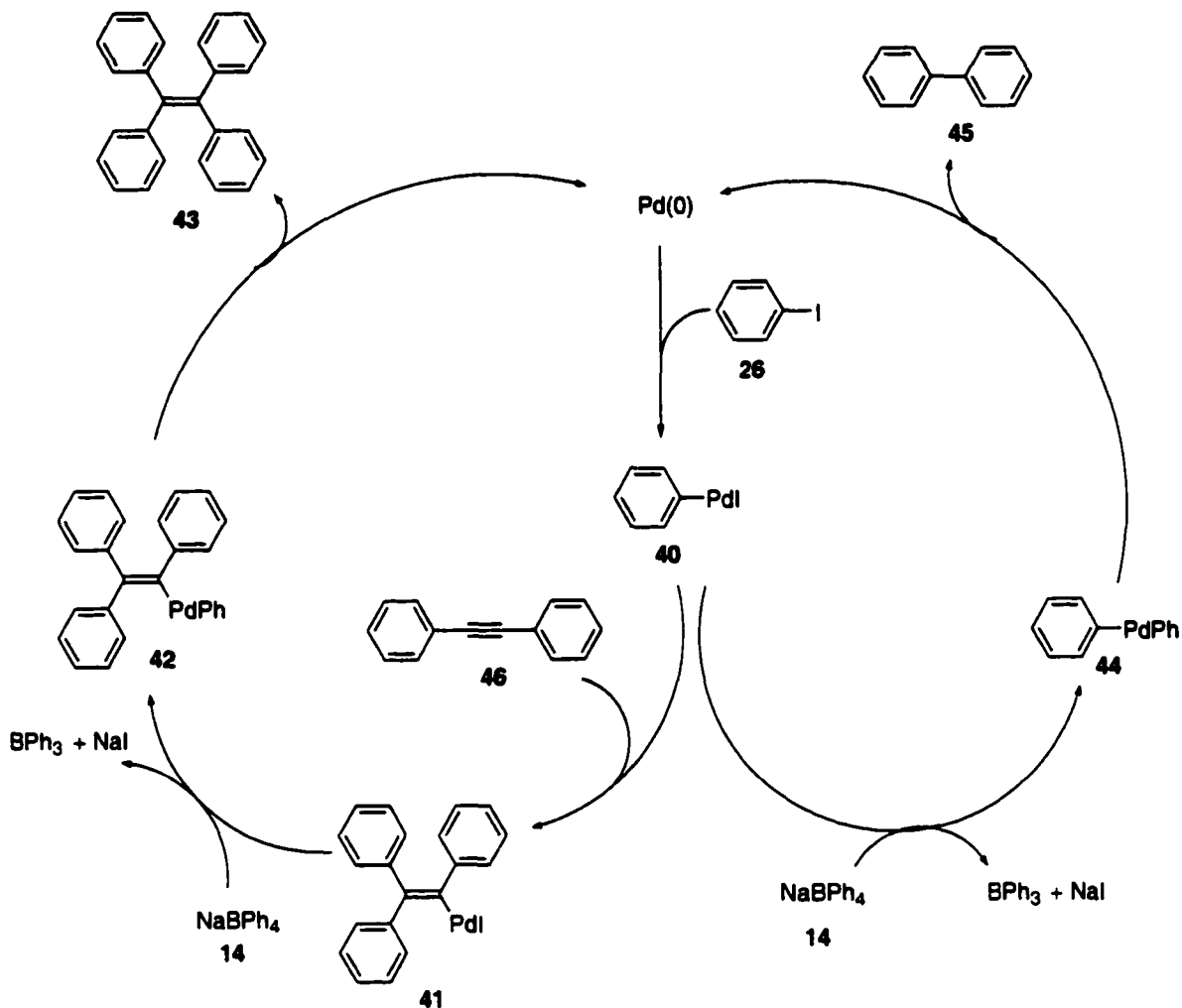
As hoped, iodobenzene, diphenylacetylene, and NaBPh$_4$ underwent ternary coupling when reacted with Pd(OAc)$_2$ as the catalyst for 1 day at 100 °C (eq 7) (Table 1, entry 1). A 60% yield of the desired alkene **43** and 0.39 mmol of **45** were found. Because NaBPh$_4$ contains four phenyl rings, the yields of **43** plus **45** can exceed 100%. Therefore, the number of mmol of biphenyl will be reported instead of the % yield.

$$\text{26} \quad + \quad \text{46} \quad + \quad \text{NaBPh}_4 \quad \xrightarrow[\substack{\text{5-10 mol \% ligand} \\ \text{1 equiv base} \\ \text{DMF, 100 °C, 1 day}}]{\substack{\text{5 mol \% Pd(OAc)}_2 \\ \text{1 equiv additive}}} \quad \text{43} \quad + \quad \text{45}$$

(7)
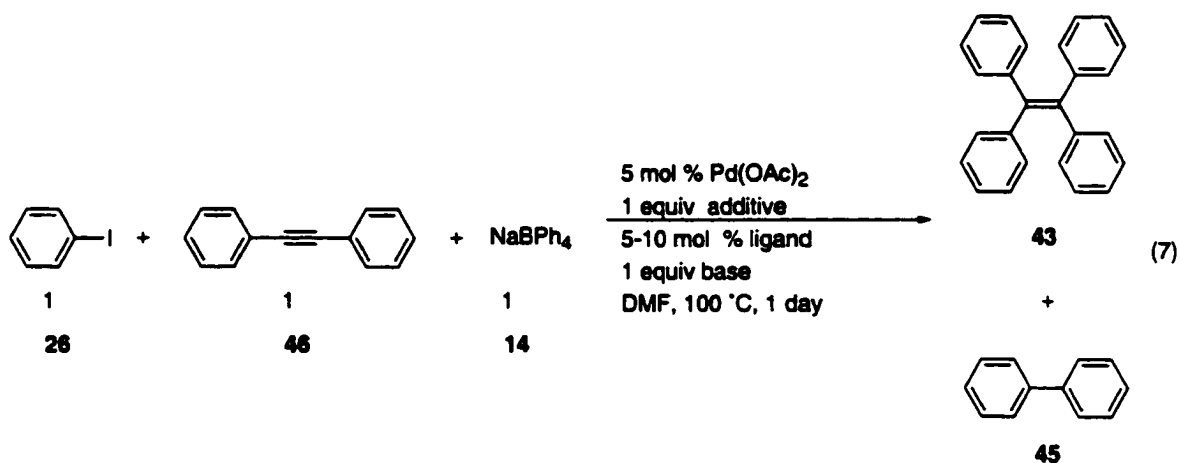
We first used various ligands to optimize the reaction illustrated in equation 7. Di-*tert*-butylphosphinoferrocene (D'BPF) and 2-(dicyclohexylphosphino)biphenyl gave improved yields of **43** and decreased yields of **45** (Table 1, entries 2 and 3). Other phosphine ligands, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), tri-2-furylphosphine, tri-*o*-tolylphosphine, and triphenylphosphine (PPh$_3$), gave decreased yields of **43** and varied yields of **45** (Table 1, entries 4-7).

Bulky phosphine ligands, such as D'BPF and 2-(dicyclohexylphosphino)biphenyl, may be giving slightly improved yields of **43**, because they prevent the boron organometallic from directly coupling with **40**, which leads to the undesired side product **45**. However, the bulky ligand tri-*o*-tolylphosphine gave a decreased yield of **43**, which seems to suggest the situation is more complicated.

Table 1. Effect of Ligand on the Reaction of Sodium Tetraphenylborate with Diphenylacetylene and Iodobenzene (eq 7).[a]

entry	ligand	% GC yield of 43, mmol of 45
1	-	60, 0.39
2	D'BPF	64, 0.31
3	2-(dicyclohexylphosphino)-biphenyl	67, 0.15
4	BINAP	46, 0.77
5	tri-2-furylphosphine	28, 0.10
6	tri-o-tolylphosphine	11, 0.19
7	PPh$_3$	36, 0.31
8	dppm	64, 0.19
9	dppe	35, 0.25
10	dppp	18, 0.33
11	dppb	61, 0.28
12	AsPh$_3$	40, 0.18
13[b]	AsPh$_3$	72, 0.13
14[c]	AsPh$_3$	52, 0.15

[a]Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), Na$_2$CO$_3$ (25.8 mg, 0.25 mmol), and the ligand (0.012 mmol for bidentate and 0.025 mmol for monodentate ligands) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b]0.25 Mmol of LiCl was employed.
[c]0.25 Mmol of n-Bu$_4$NCl was employed.

Four bidentate ligands, bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), and 1,4-bis(diphenylphosphino)butane (dppb), were next allowed to react in the system. Dppm and dppb gave 64% and 61% yields of **43** and 0.19 and 0.28 mmol of **45** respectively (Table 1, entries 8 and 11). Conversely, dppe and dppp gave markedly lower yields of **43**, but increased yields of **45** (Table 1, entries 9 and 10).

From the results of Table 1, entries 7-11, there seems to be no obvious correlation between increased yields of **43** and the denticity of the phosphine ligand. The bidentate ligand dppe gave a yield of **43** similar to the monodentate ligand PPh_3, but dppp gave the lowest yield of all of the bidentate ligands. One might expect the bidentate ligands to enhance the yield of **43**, because the coordination site on palladium is blocked from directly coupling with $NaBPh_4$.

When triphenylarsine ($AsPh_3$) was allowed to react, a 40% yield of **43** and only 0.18 mmol of **45** were obtained (Table 1, entry 12). When 1 equiv of lithium chloride (LiCl) was added to the reaction, the yield increased to 72% (Table 1, entry 13). The addition of 1 equiv of tetra-n-butylammonium chloride (n-Bu_4NCl) gave only a 52% yield (Table 1, entry 14).

Thus, a chloride source increased the yield of **43** when $AsPh_3$ was employed as the ligand. Employing a chloride source has been beneficial in much previous organopalladium chemistry.[19] The increased yields in entries 13 and 14 may result from the chloride's ability to coordinate to the palladium, thus facilitating oxidative addition of the aryl iodide.

Because the addition of LiCl gave the highest yield in Table 1, all of the reactions were run again with the same additives, plus 1 equiv of LiCl. First, we were curious to see what the effect of LiCl alone was on the reaction. Surprisingly, this produced a 98% yield of

43 and only 0.13 mmol of 45 (Table 2, entry 1). When the phosphine ligands were added to the reaction mixture approximately half as much of 43 and approximately 0.10 mmol of 45 were observed (Table 2; entries 2-7 and 9). Dppp yielded only 20% of 43 and 0.06 mmol of 45 (Table 2, entry 8). The phosphine ligands seem to be lowering the yield of 43, while LiCl alone substantially increases it.

Next we explored the effect of base on these reactions. Table 3, entry 1 (which is identical to Table 2, entry 1 and will be referred to hereafter as "the general procedure for borates") shows that running the reaction without base produced the highest yield of 43 and a

Table 2. Effect of Ligand on the Reaction of Sodium Tetraphenylborate with Diphenylacetylene and Iodobenzene (eq 7).[a]

entry	ligand	% GC yield of 43, mmol of 45
1	-	98, 0.13
2	BINAP	50, 0.08
3	2-(dicyclohexylphosphino)-biphenyl	50, 0.08
4	tri-2-furylphosphine	47, 0.08
5	PPh$_3$	47, 0.08
6	dppm	51, 0.13
7	dppe	48, 0.10
8	dppp	20, 0.06
9	dppb	56, 0.09

[a]Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) and the ligand (0.012 mmol for bidendate ligands and 0.025 for mondendate ligands) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

Table 3. Effect of Base on the Reaction of Sodium Tetraphenylborate with Diphenylacetylene and Iodobenzene (eq 7).[a]

entry	base	% GC yield of **43**, mmol of **45**
1	-	98, 0.13
2	NaOAc	91, 0.16
3	KOAc	90, 0.15
4	CsOAc	62, 0.14
5	$NaHCO_3$	80, 0.20
6	$KHCO_3$	60, 0.34
7	Na_2CO_3	72, 0.14
8	K_2CO_3	80, 0.20
9	Cs_2CO_3	84, 0.60
10	Et_3N	88, 0.10
11	i-Pr_2NEt	67, 0.32
12	pyridine	35, 0.18
13	aniline	20, 0.17
14	AgOAc	14, 0.03
15	AgOTf	21, 0.05
16	Ag_2CO_3	28, 0.10
17	Ag_3PO_4	34, 0.16
18	TlOAc	40, 0.23
19	Tl_2CO_3	44, 0.23

[a] Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) and the base (0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

modest yield of **45**. We employed other bases to explore their effect on the yields of **43** and

45. Although some bases decreased the yield of **45**, their yield of **43** was also substantially

lower (Table 3, entries 14-19).

NaOAc and KOAc gave 91% and 90% yields of **43**, but CsOAc, with its larger

cation, afforded only a 62% yield (Table 3, entries 2-4). All three bases gave approximately

the same yield of **45** . Two bicarbonate bases, $NaHCO_3$ and $KHCO_3$, gave 80% and 60%

yields of **43** respectively, but both gave more of **45** than the acetate bases (Table 3, entries 5

and 6). Na_2CO_3, K_2CO_3, and Cs_2CO_3 gave 72%, 80%, and 84% yields of **43** respectively, but

Cs_2CO_3 gave a great deal more of **45** than the other two (Table 3, entries 7-9). Four organic

bases [(triethylamine (Et_3N), diisopropylethylamine (i-Pr_2NEt), pyridine, and aniline] were

employed with the first two giving good yields of **43** and the last two giving lower yields

(Table 3, entries 10-13).

Grigg has reported that silver and thallium salts prevent the direct coupling of

arylpalladium species with organometallics.[9b,c] Thus, several silver salts and a couple of

thallium salts were employed in this reaction. All of the silver salts gave greatly reduced

yields of **43**, and AgOAc and AgOTf also gave reduced yields of **45** (Table 3, entries 14-17).

The thallium salts TlOAc and Tl_2CO_3 gave 40% and 44% yields of **43** and both gave 0.23

mmol of **45** (Table 3, entries 18 and 19). From these results, we conclude that silver and

thallium salts decrease the yield of **45** at the expense of **43**.

We next varied the palladium catalyst to optimize the reaction. Other palladium

catalysts, such as $PdCl_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd(dba)_2$, all gave substantially lower

yields of the desired product and small amounts of the side product **45**. Because $Pd(OAc)_2$

gave much higher yields (Table 2, entry 1), it was chosen as the best catalyst and used in the rest of the optimization reactions.

The effect of time and temperature on the reaction yield was next studied. After a reaction time of 1 hour at 100 °C, a 62% yield of **43** was observed (Table 4, entry 1). Increasing the time to 12 hours gave a 96% yield (Table 4, entry 2). These results imply that the reaction is finished within 12 hours; however, we have run all of our optimization reactions for 1 day to be consistent. Running the reaction at room temperature gave substantially lower yields (Table 4, entries 3 and 4). Decreasing the temperature to 60 °C or 80 °C gave moderate yields of 61% and 72% of **43** respectively (Table 4, entries 5 and 6). We thus conclude that lower reaction times and temperatures lower the yield.

We next investigated the effect of varying the amount of NaBPh$_4$ on the yield of the reaction. We have hypothesized that NaBPh$_4$ decomposes in the presence of palladium to

Table 4. Effect of Time and Temperature on the Reaction of Sodium Tetraphenylborate with Diphenylacetylene and Iodobenzene (eq 7).[a]

entry	time (hours)	temperature (°C)	% GC yield of **43**, mmol of **45**
1	1	100	62, 0.12
2	12	100	96, 0.10
3	24	room temp.	0, 0.05
4	96	room temp.	30, 0.08
5	24	60	61, 0.12
6	24	80	72, 0.32

[a] Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF.

form biphenyl (45) in this reaction. Thus, decreasing the amount of NaBPh$_4$ employed

should decrease the amount of 45. However, when only 0.19 mmol of NaBPh$_4$ was

employed, the yield of 43 decreased by one half to 50%, and the yield of 45 remained the

same (Table 5, entry 1). When 0.125 mmol of NaBPh$_4$ was employed, the yields of 43 and

45 were halved to 25% and 0.05 mmol respectively (Table 5, entry 2). The same trend

applied when only 0.06 mmol of NaBPh$_4$ was used (Table 5, entry 3).

Table 5. Effect of Varying the Amount of Sodium Tetraphenylborate on the Reaction (eq 7).[a]

entry	NaBPh$_4$ (mmol)	% GC yield of 43, mmol of 45
1	0.19	50, 0.13
2	0.125	25, 0.05
3	0.06	13, 0.02
4[b]	0.25	58, 0.20
5[c]	0.25	95, 0.09

[a] Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), sodium tetraphenylborate, Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b] 0.5 Mmol of iodobenzene were employed instead of 0.25 mmol and all other conditions were the same as in footnote a.
[c] 0.5 Mmol of diphenylacetylene were employed instead of 0.25 mmol and all other conditions were the same as in footnote a.

We also varied the amount of iodobenzene and diphenylacetylene employed in the

reaction. We observed a decrease in the yield of 43 when 2 equivs of iodobenzene were

employed instead of 1 equiv (Table 5, entry 4). When 2 equivs of diphenylacetylene were

employed instead of 1 equiv, a yield of 95% was found (Table 5, entry 5), which is similar to

the yield obtained when only 1 equiv was used. Apparently, the use of excess aryl iodide is harmful to the yield, but the use of excess diphenylacetylene is not.

We have also employed CO in our reaction mixture in an attempt to form the unsaturated ketone **47** (eq 8). Unfortunately, the only product we found in the reaction mixture was benzophenone **48**. After CO insertion into the Pd-aryl bond, the NaBPh₄ apparently cross-coupled with this species to form **48** rather than insert the alkyne. Apparently cross-coupling with NaBPh₄ is more facile than carbopalladation of the diphenylacetylene.
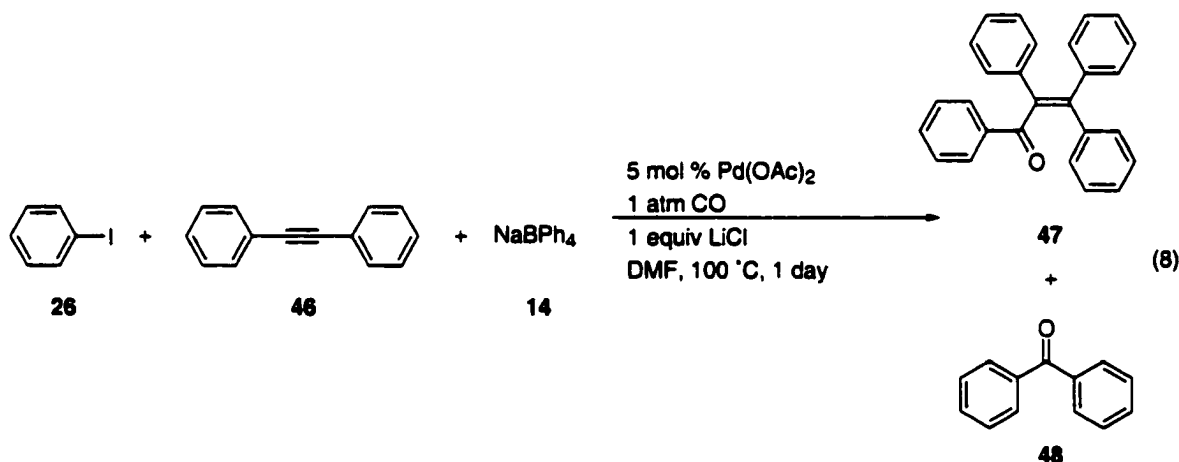
We next extended the general procedure for borates to other organometallics. A few commercially available tin reagents were used in place of NaBPh₄. Ph₄Sn was first allowed to react with iodobenzene and diphenylacetylene. This reaction gave a 68% yield of **43**. However, it also gave 0.52 mmol of **45**, which is substantially higher than that obtained with NaBPh₄ (Table 6, entry 1). Ph₃SnCl produced basically the same yield as Ph₄Sn (Table 6, entry 2), and Ph₃SnOAc gave a modest decrease in the yield of **43**, but a slightly increased yield of **45** (Table 6, entry 3). When Ph₃SnOH was allowed to react, it gave a high 90%

yield of **43**, but also a high yield of **45** (Table 6, entry 4). Conversely, PhSnMe₃ didn't

produce any yield of **43** or **45** (Table 6, entry 5). Adding 4 equivs of PhSnMe₃, instead of 1

equiv, also failed to produce **43**, but 0.30 mmol of **45** were produced (Table 6, entry 6).

Because there are not many commercially available tin reagents, we sought to extend this

reaction to other organometallics.

Table 6. Effect of the Tin Reagent on the Reaction with Diphenylacetylene and Iodobenzene.*

entry	tin reagent	% GC yield of 43, mmol of 45
1	Ph₄Sn	68, 0.52
2	Ph₃SnCl	63, 0.54
3	Ph₃SnOAc	51, 0.56
4	Ph₃SnOH	90, 0.71
5	PhSnMe₃	0, 0
6ᵇ	PhSnMe₃	0, 0.30

*Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), the tin reagent (0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
ᵇ1.0 Mmol of PhSnMe₃ was employed instead of 0.25 mmol.

Silicon reagents were next used in place of NaBPh₄. As shown in Table 7, many

silicon reagents were unreactive in this process (Table 7; entries 1-10, 15, and 18). Marginal

yields of **43** could be obtained by employing a fluoride additive in some instances (Table 7;

entries 11-14, 16, and 17). Tetra-*n*-butylammonium triphenyldifluorosilane [*n*-

Bu₄N(Ph₃SiF₂)] and diphenyldifluorosilane (Ph₂SiF₂) were the only silicon reagents to

produce the desired product (Table 7, entries 11-14 and 17).

Table 7. Effect of Silicon Reagents on the Reaction.[a]

entry	reagent	additive	% GC yield of 43, mmol of 45
1	PhSi(OCH₂CH₃)₃	-	0, 0
2	PhSi(CH₃)₃	-	0, 0
3	Ph₄Si	-	0, 0.09
4	Ph₄Si	CsF	0, 0
5	Ph₄Si	KF	0, 0
6	Ph₄Si	n-Bu₄NF	0, 0
7	PhSi(CH₃)Cl₂	-	0, 0
8	PhSi(CH₂CH₃)₃	-	0, 0
9	Ph₃SiCl	-	0, 0.08
10	PhSi(CH₃)₂OH	-	0, 0
11	Ph₂SiF₂	CsF	23, 0.03
12	Ph₂SiF₂	KF	23, 0.04
13	Ph₂SiF₂	n-Bu₄NF	28, 0.02
14[b]	Ph₂SiF₂	n-Bu₄NF	24, 0.04
15	n-Bu₄N(Ph₃SiF₂)	-	0, 0
16	n-Bu₄N(Ph₃SiF₂)	CsF	6, 0.02
17	n-Bu₄N(Ph₃SiF₂)	KF	28, 0.16
18	n-Bu₄N(Ph₃SiF₂)	n-Bu₄NF	0, 0

[a]Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), the silicon reagent (0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b]10 Mol % PPh₃ (9.1 mg, 0.025 mmol) was added to the reaction mixture.

The failure of these reactions to produce high yields may be due to the nonpolar

nature of the C-Si bond, which does not exhibit substantial reactivity towards electrophiles.

Since the Si-F bond energy is very strong, an added fluoride ion bonds with the silicon to

form a pentacoordinated silicate. This silicate could induce transmetallation of the silicon's

phenyl group with palladium.[20] Although there are many known palladium-catalyzed cross-

coupling reactions of organosilicon compounds that are mediated by a fluoride ion,[20,21] the

arylsilanes generally seem less reactive in this reaction.

Sodium tetrakis(*p*-tolyl)borate, **49**, and potassium tetrakis(2-thienyl)borate, **52**, have

also been employed in place of NaBPh$_4$. The borate **49** gave a high 80% yield of the desired

product **50** and 0.36 mmol of the unsymmetrical biaryl **51** (eq 9). No biphenyl (**45**) was

observed. The borate **52** gave only a trace of the desired product and the corresponding

unsymmetrical biaryl product under these conditions. A much better result was obtained

when 10 mol % of PPh$_3$ was added to the reaction mixture, and when 2 equiv of iodobenzene
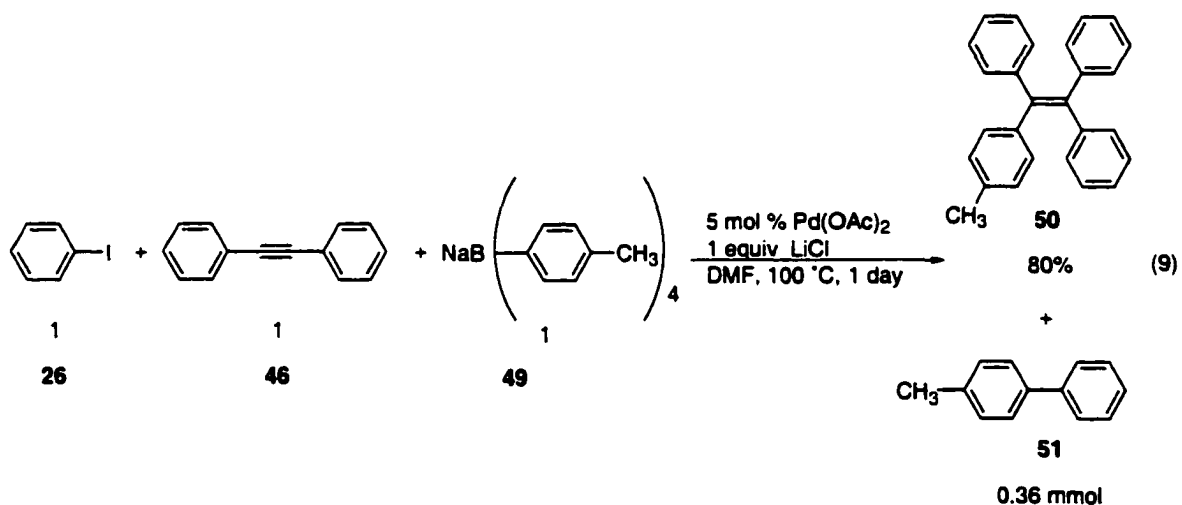
were employed instead of 1 equiv. A low 32% yield of the desired product was obtained

along with 0.13 mmol of the corresponding unsymmetrical biaryl product (eq 10).

Since many arylboronic acids are now commercially available, we next used

phenylboronic acid [PhB(OH)₂] in place of NaBPh₄. Unfortunately, the previously optimized

conditions gave no **43** or **45** (Table 8, entry 1). Thus, we sought to explore the use of various

$$
\begin{array}{c}
\text{2} + \text{1} + \text{KB} \left(\text{S} \right)_4 \quad \xrightarrow[\substack{10 \text{ mol \% PPh}_3 \\ 1 \text{ equiv LiCl} \\ \text{DMF, 100 }^\circ\text{C, 1 day}}]{5 \text{ mol \% Pd(OAc)}_2} \quad \substack{\textbf{53} \\ 32\%} \quad + \quad \substack{\textbf{54} \\ 0.13 \text{ mmol}}
\end{array}
\tag{10}
$$

26   46   52

Table 8. Effect of Base on the Reaction of Phenylboronic Acid with Diphenylacetylene and Iodobenzene.[a]

entry	base	% GC yield of **43**, mmol of **45**
1[b]	-	0, 0
2	NaOAc	18, 0.12
3	KOAc	24, 0.17
4	CsOAc	30, 0.11
5	Tl(OAc)₃	3, 0.01
6	NaHCO₃	14, 0.14

Table 8. (continued)

7	$KHCO_3$	16, 0.14
8	Cs_2CO_3	22, 0.39
9	Na_2CO_3	13, 0.08
10	K_2CO_3	34, 0.10
11[c]	K_2CO_3	31, 0.09
12	AgOAc	5, trace
13	AgOTf	0, 0
14	Ag_2CO_3	17, 0.02
15	Ag_3PO_4	7, trace
16	TlOAc	17, 0.06
17	Tl_2CO_3	24, 0.20
18[d]	TlOAc	19, 0.14
19[d]	Tl_2CO_3	32, 0.30
20	aniline	0, 0
21	Et_3N	24, 0.08

[a] Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), phenylboronic acid (30.0 mg, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) and the base (0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b] ~5% Triphenylethylene was observed by GC-MS.
[c] 1 Equiv of n-Bu$_4$NCl was employed instead of LiCl.
[d] Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), phenylboronic acid (60.0 mg, 0.5 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol), PPh$_3$ (0.025 mmol), and the base (0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

bases in this reaction. As shown in Table 8, entries 2-5, the use of acetate bases produced

low yields of **43** and moderate yields of **45**. Various bicarbonate and carbonate bases were

next employed in an attempt to increase the yield of **43** (Table 8, entries 6-10). The use of

K_2CO_3 gave 34%, the highest yield of any base employed. We then changed the chloride

source from LiCl to n-Bu_4NCl, and a slightly lower yield of **43** resulted (Table 8, entry 11).

Silver, thallium, and organic bases gave much lower to nearly identical yields of **43**

compared to K_2CO_3 (Table 8, entries 12-21). Triphenylphosphine (10 mol %) and 2 equivs

of $PhB(OH)_2$ were added in entries 18 and 19, but did not increase the yield over that

obtained in entry 10.

Because K_2CO_3 appeared to be the best base for this system, we next explored the

effect of ligands on the reaction using this base. Using Table 8, entry 10 as a reference, one

can see that ligands improved the yield of **43** (Table 9). In general, most ligands increased

the yield to around 50% (Table 9, entries 2-6 and 8-10), with the exception of dppe, which

gave a low yield of 15% (Table 9, entry 7). Triphenylphosphine was chosen as the best

ligand, not because it gave vastly better yields than the other ligands, but because of its

availability and affordability.

We next sought to increase the yield of **43** by varying the stoichiometry of the

reaction. The amount of $PhB(OH)_2$ was increased incrementally from 0.25 mmol as shown

in Table 10. Table 10, entry 1 shows a 92% yield of **43** when 0.5 mmol of $PhB(OH)_2$ was

employed. Increasing the amount of $PhB(OH)_2$ beyond 0.5 mmol lowered the yields (Table
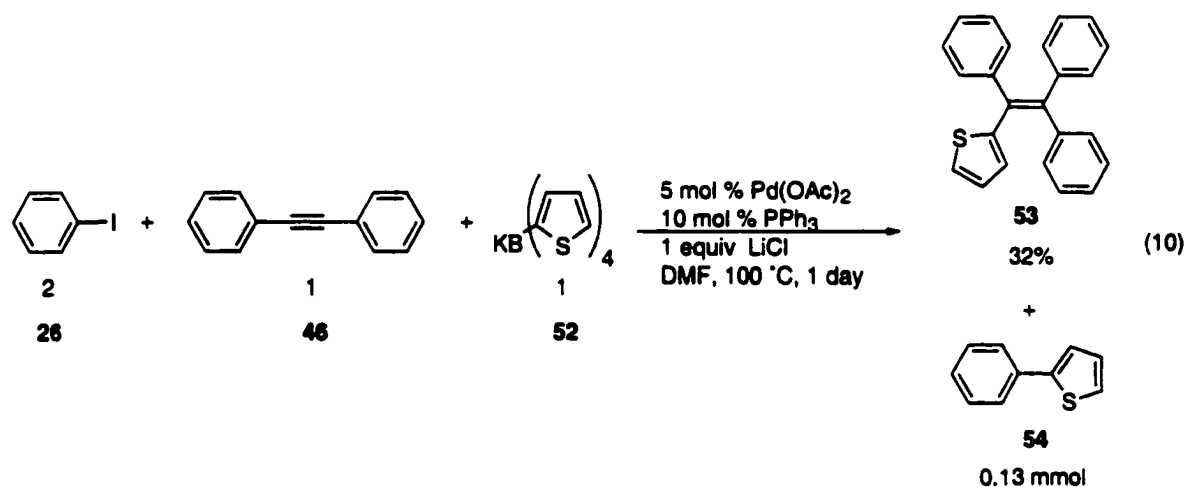
10, entries 2 and 3).

Table 9. Effect of Ligand on the Reaction of Phenylboronic Acid with Diphenylacetylene and Iodobenzene.[a]

entry	ligand	% GC yield of 43, mmol of 45
1	-	34, 0.10
2	BINAP	49, 0.05
3	2-(dicyclohexylphosphino)-biphenyl	41, 0.12
4	tri-2-furylphosphine	49, 0.05
5	PPh₃	50, 0.12
6	dppm	43, 0.04
7	dppe	15, 0.06
8	dppp	50, 0.16
9	dppb	46, 0.06
10	AsPh₃	48, 0.18

[a]Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), phenylboronic acid (30.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) K₂CO₃ (34.0 mg, 0.25 mmol), and the ligand (0.012 mmol for bidendate ligands and 0.025 for mondendate ligands) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

Table 10. Effect of Varying the Amount of Phenylboronic Acid on the Reaction.[a]

entry	PhB(OH)₂ (mmol)	% GC yield of 43, mmol of 45
1	0.5	92, 0.12
2	0.75	80, 0.20
3	1.0	62, 0.24

[a]Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), phenylboronic acid, Pd(OAc)₂ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol), K₂CO₃ (34.0 mg, 0.25 mmol), and PPh₃ (6.0 mg, 0.025 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

The amount of diphenylacetylene was next varied incrementally from 0.25 mmol.

The yield did increase from 50% in Table 9, entry 5, to 79% when 0.5 mmol of

diphenylacetylene was employed. Only 0.06 mmol of **45** was observed, substantially less

than that obtained in Table 10 or Table 9, entry 5 (Table 11, entry 1). Increasing the amount

of diphenylacetylene beyond 0.5 mmol lowered the yields and gave more **45** (Table 11,

entries 2 and 3).

Table 11. Effect of Varying the Amount of Diphenylacetylene on the Reaction.[a]

entry	diphenylacetylene (mmol)	% GC yield of **43**, mmol of **45**
1	0.5	79, 0.06
2	0.75	60, 0.07
3	1.0	47, 0.44

[a] Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene, phenylboronic acid (30.0 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) K$_2$CO$_3$ (34.0 mg, 0.25 mmol), and PPh$_3$ (6.0 mg, 0.025 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

The previous yield of 50% did increase when the amount of iodobenzene was

increased to 0.5 mmol (Table 12, entry 1). However, increasing the amount of iodobenzene

further did not improve the yield (Table 12, entries 2 and 3). There was also always a

substantial amount of **45** in these reactions.

From Tables 10-12, where the stoichiometry of the reaction has been varied, we

surmise that employing 1 equiv of iodobenzene, 2 equivs of diphenylacetylene, and 2 equivs

of phenylboronic acid is most beneficial in increasing the yield of **43**. In subsequent

reactions, the following will be referred to as "the general procedure for boronic acids:" aryl

Table 12. Effect of Varying the Amount of Iodobenzene on the Reaction.[a]

entry	PhI (mmol)	% GC yield of **43**, mmol of **45**
1	0.5	68, 0.38
2	0.75	41, 0.26
3	1.0	64, 0.22

[a]Iodobenzene, diphenylacetylene (44.5 mg, 0.25 mmol), phenylboronic acid (30.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) K₂CO₃ (34.0 mg, 0.25 mmol), and PPh₃ (6.0 mg, 0.025 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

iodide (0.25 mmol), diphenylacetylene (89.0 mg, 0.50 mmol), phenylboronic acid (61.0 mg, 0.50 mmol), tetracosane (3.1 mg, 0.01 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol), K₂CO₃ (34.0 mg, 0.25 mmol), and PPh₃ (6.0 mg, 0.025 mmol) in 1 mL of DMF for 1 day at 100 °C.

Next, phenylboronic acid derivatives were employed in the reaction (eq 11). p-Chlorophenylboronic acid, **55**, and p-methoxyphenylboronic acid, **56**, gave 78% and 72% of the desired products **62** and **63** (Table 13, entries 1 and 2). The respective biaryl derivatives were also formed (**69** and **70**). 3-Thiopheneboronic acid, **57**, gave a lower 50% yield of the heterocyclic product **64** (Table 13, entry 3) and 0.10 mmol of the biaryl derivative **71**. 3-Nitrophenylboronic acid, **58**, and 3-aminophenylboronic acid, **59**, both gave good yields of the expected products **65** and **66** (Table 13, entries 4 and 5). Of course, the biaryl derivatives **72** and **73** were also present in these reactions. p-Tolylboronic acid and o-tolylboronic acid gave 74% and 87% yields of the tetrasubstituted products (Table 13, entries 6 and 7).

$$
\begin{array}{ccccc}
\text{PhI} & + & \text{PhC≡CPh} & + & \text{ArB(OH)}_2 \\
\mathbf{1} & & \mathbf{2} & & \mathbf{2} \\
\mathbf{26} & & \mathbf{46} & &
\end{array}
\xrightarrow[\substack{\text{10 mol \% PPh}_3 \\ \text{1 equiv LiCl} \\ \text{DMF, 100 °C, 1 day}}]{\substack{\text{5 mol \% Pd(OAc)}_2 \\ \text{1 equiv K}_2\text{CO}_3}}
$$

(11)

55 Ar = p-ClC₆H₄
56 Ar = p-CH₃OC₆H₄
57 Ar = 3-thiophenyl
58 Ar = m-NO₂C₆H₄
59 Ar = m-NH₂C₆H₄
60 Ar = p-CH₃C₆H₄
61 Ar = o-CH₃C₆H₄

62 Ar = p-ClC₆H₄
63 Ar = p-CH₃OC₆H₄
64 Ar = 3-thiophenyl
65 Ar = m-NO₂C₆H₄
66 Ar = m-NH₂C₆H₄
67 Ar = p-CH₃C₆H₄
68 Ar = o-CH₃C₆H₄

+

69 Ar = p-ClC₆H₄
70 Ar = p-CH₃OC₆H₄
71 Ar = 3-thiophenyl
72 Ar = m-NO₂C₆H₄
73 Ar = m-NH₂C₆H₄
74 Ar = p-CH₃C₆H₄
75 Ar = o-CH₃C₆H₄

Table 13. Effect of Various Phenylboronic Acids on the Reaction (eq 11).[a]

entry	Ar	% isolated yields of 62-68, mmol of 69-75
1	p-ClC$_6$H$_4$-	78, 0.05
2	p-CH$_3$OC$_6$H$_4$-	72, 0.05
3	3-thienyl	50, 0.10
4	m-NO$_2$C$_6$H$_4$-	70, 0.07
5	m-NH$_2$OC$_6$H$_4$-	71, 0.08
6[b]	p-CH$_3$PhB(OH)$_2$	74, 0.09
7[b]	o-CH$_3$PhB(OH)$_2$	87, 0.02

[a]Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (89.0 mg, 0.5 mmol), the arylboronic acid (61.0 mg, 0.50 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) K₂CO₃ (34.0 mg, 0.25 mmol), and PPh₃ (6.0 mg, 0.025 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b]Yield was obtained by ¹H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard.

We next tried a few reactions in this system where the aryl iodide and the boronic

acid were varied (eq 12). 4-Chloroiodobenzene (76) and 4-iodoanisole (77) were used

instead of iodobenzene. The corresponding arylboronic acids were also employed. The

resulting disubstituted products 78 and 79 were isolated in 67% and 68% yields respectively.

Because electron poor aryl iodides, such as 76, will be shown later in this chapter to give

poor yields of tetrasubstituted alkenes, we suspect that both of the 4-chloroaryl groups of 78

may have come from the boronic acid instead of the aryl iodide.

$$X\text{—}\langle\rangle\text{—}I \quad + \quad \langle\rangle\text{==}\langle\rangle \quad + \quad ArB(OH)_2 \quad \xrightarrow[\substack{10\ mol\ \%\ PPh_3 \\ 1\ equiv\ LiCl \\ DMF,\ 100\ °C,\ 1\ day}]{\substack{5\ mol\ \%\ Pd(OAc)_2 \\ 1\ equiv\ K_2CO_3}} \quad (12)$$

1   2   2

76 X = Cl   46   55 Ar = p-ClC$_6$H$_4$
77 X = CH$_3$O   56 Ar = p-CH$_3$OC$_6$H$_4$

78 Ar = p-ClC$_6$H$_4$ 80 Ar = p-ClC$_6$H$_4$
79 Ar = p-CH$_3$OC$_6$H$_4$ 81 Ar = p-CH$_3$OC$_6$H$_4$
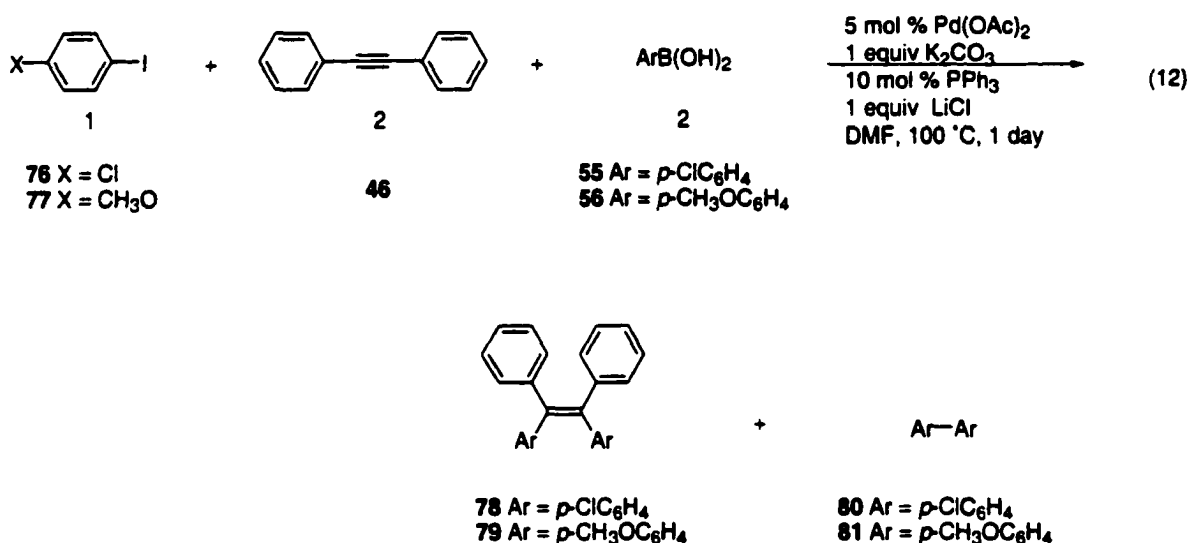
Next, potassium phenyltrifluoroborate (KPhBF$_3$) was used as the organometallic.

When the general procedure for borates was employed without the NaBPh$_4$, but with 1 equiv

of KPhBF$_3$, only unreacted starting materials were found. Increasing the amount of KPhBF$_3$

sequentially to 2, 3, and 4 equivs did not improve the yield.

When the general procedure for boronic acids was employed without the PhB(OH)$_2$,

but with 1 equiv of KPhBF$_3$, a 35% yield of 43 was observed, as well as 0.15 mmol of 45.

Increasing the amount of KPhBF$_3$ employed to 4 equivs improved the yield of **43** to 53%,

and lowered the yield of **45** to only 0.08 mmol.

We next turned our attention to determining which aryl iodides could be used in the

general procedure for borates using NaBPh$_4$ as the organometallic (eq 13). First we

employed electron-deficient aryl iodides with an electron-withdrawing group (EWG) on the

benzene ring to obtain the corresponding tetrasubstituted alkenes. The strength of the EWG

is indicated by the Hammett parameter shown in Table 14.[22] First, 1-iodo-4-nitrobenzene

(**82**) was employed as the aryl iodide using the general procedure for borates (Table 14, entry

1). None of the desired tetrasubstituted alkene **100** was found. Only the biaryl derivative

115 was recovered.

Other electron deficient aryl iodides, such as 1-iodo-3-nitrobenzene (**83**), 4-

iodobenzotrifluoride (**84**), 4-iodoacetophenone (**85**), and 4-iodobenzoic acid (**86**) gave

similar results (Table 14, entries 2-5). These electron deficient aryl iodides are expected to

be particularly reactive towards oxidative addition. Apparently the resulting arylpalladium

intermediate more rapidly cross-couples with NaBPh$_4$ than with the acetylene, thus

generating the biaryl side product exclusively. Apparently electron deficient aryl iodides

cannot be employed in this new olefin synthesis.

Next, we employed aryl iodides with weaker EWGs on the benzene rings: ethyl-4-

iodobenzoate (**87**), 3-iodobenzotrifluoride (**88**), ethyl-3-iodobenzoate (**89**), 4-bromo-1-

iodobenzene (**90**), 4-chloro-1-iodobenzene (**76**), and 2-iodobenzotrifluoride (**91**). The aryl

iodides **87**, **89**, and **76** gave low yields of the desired tetrasubstituted products and moderate

yields of their respective biaryl derivatives (Table 14, entries 6, 8, and 10). Aryl iodide **88**

gave only the biaryl derivative (Table 14, entry 7), and aryl iodide **90** gave a messy reaction
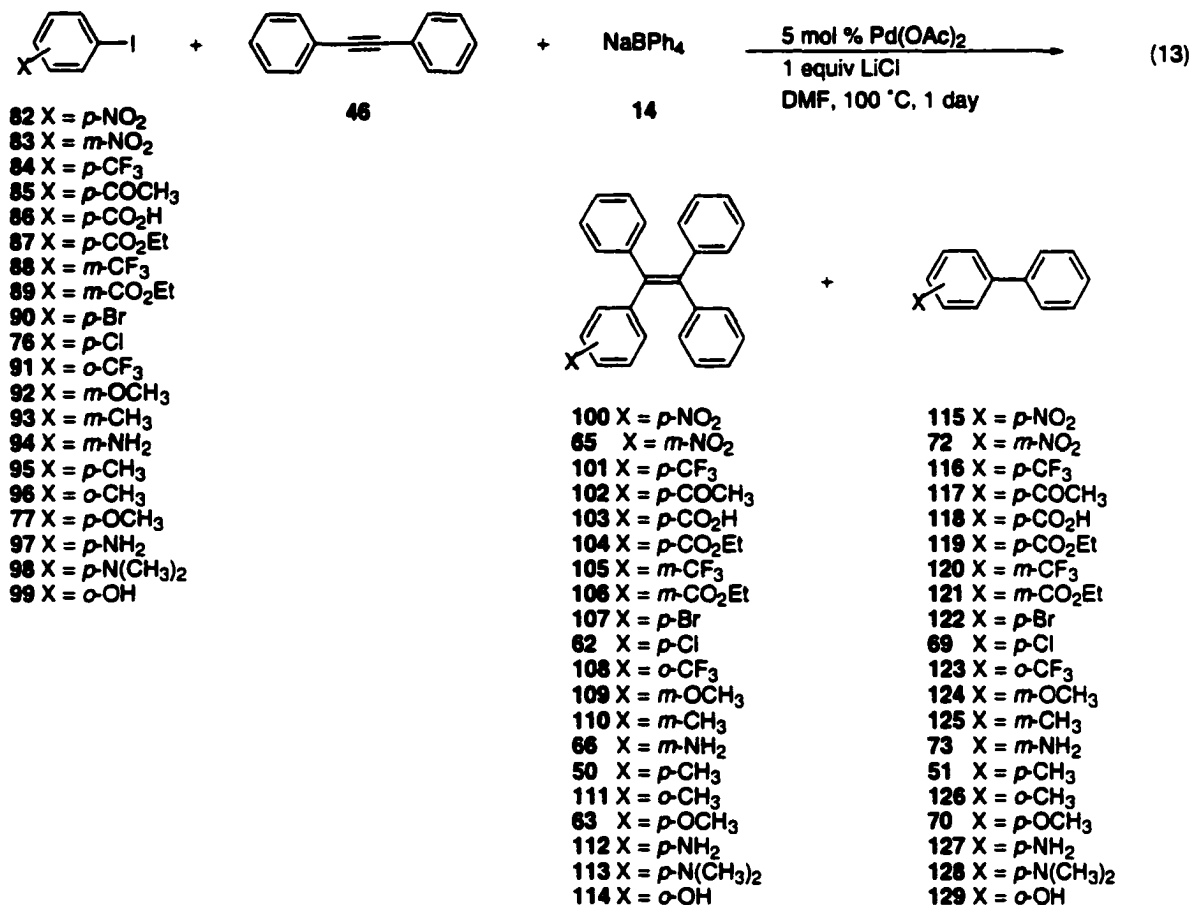
$$\text{X} \overset{}{\underset{}{\bigcirc}}\text{-I} \quad + \quad \bigcirc\!-\!\!\equiv\!\!-\!\bigcirc \quad + \quad \text{NaBPh}_4 \quad \xrightarrow[\substack{\text{1 equiv LiCl} \\ \text{DMF, 100 °C, 1 day}}]{\text{5 mol \% Pd(OAc)}_2} \quad (13)$$

46   **14**

82 X = p-NO₂
83 X = m-NO₂
84 X = p-CF₃
85 X = p-COCH₃
86 X = p-CO₂H
87 X = p-CO₂Et
88 X = m-CF₃
89 X = m-CO₂Et
90 X = p-Br
76 X = p-Cl
91 X = o-CF₃
92 X = m-OCH₃
93 X = m-CH₃
94 X = m-NH₂
95 X = p-CH₃
96 X = o-CH₃
77 X = p-OCH₃
97 X = p-NH₂
98 X = p-N(CH₃)₂
99 X = o-OH

100 X = p-NO₂
65   X = m-NO₂
101 X = p-CF₃
102 X = p-COCH₃
103 X = p-CO₂H
104 X = p-CO₂Et
105 X = m-CF₃
106 X = m-CO₂Et
107 X = p-Br
62   X = p-Cl
108 X = o-CF₃
109 X = m-OCH₃
110 X = m-CH₃
66   X = m-NH₂
50   X = p-CH₃
111 X = o-CH₃
63   X = p-OCH₃
112 X = p-NH₂
113 X = p-N(CH₃)₂
114 X = o-OH

115 X = p-NO₂
72   X = m-NO₂
116 X = p-CF₃
117 X = p-COCH₃
118 X = p-CO₂H
119 X = p-CO₂Et
120 X = m-CF₃
121 X = m-CO₂Et
122 X = p-Br
69   X = p-Cl
123 X = o-CF₃
124 X = m-OCH₃
125 X = m-CH₃
73   X = m-NH₂
51   X = p-CH₃
126 X = o-CH₃
70   X = p-OCH₃
127 X = p-NH₂
128 X = p-N(CH₃)₂
129 X = o-OH

Table 14. Effect of Various Aryl Iodides on the Reaction of Diphenylacetylene and NaBPh₄ (eq 13).[a]

entry	X	Hammett parameter σ	% isolated yields of alkene, mmol of biaryl
1	p-NO₂	0.78	0, 0.24
2	m-NO₂	0.71	0, 0.24
3	p-CF₃	0.54	0, 0.23
4	p-COCH₃	0.50	0, 0.20
5	p-CO₂H	0.45	0, 0.21
6	p-CO₂Et	0.45	15, 0.17

Table 14. (continued)

7	m-CF$_3$	0.43	0, 0.17
8	m-CO$_2$Et	0.37	10, 0.16
9	p-Br	0.23	trace, trace[b]
10	p-Cl	0.23	12, 0.17
11	o-CF$_3$	-	0, 0.17
12	m-OCH$_3$	0.12	40, 0.10
13	m-CH$_3$	- 0.07	40, 0.10
14	m-NH$_2$	- 0.16	< 5, trace
15	p-CH$_3$	- 0.17	88, 0.11
16	o-CH$_3$	-	86, 0.12
17[c]	p-OCH$_3$	- 0.27	68, 0.04
18	p-NH$_2$	- 0.66	0, 0
19	p-N(CH$_3$)$_2$	-	0, 0
20	o-OH	-	trace, trace

[a] The aryl iodide (0.25 mmol), diphenylacetylene (44.5 mg, 0.25 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b] The reaction mixture was messy with biphenyl, tetraphenylethene, terphenyl, bromobenzene, and 4-bromobiphenyl evident in the GC-MS trace.
[c] The reaction was run for 3 days instead of 1 day.

mixture with only a trace of the desired product 107 and biaryl derivative 122 as indicated by gas chromatographic analysis (Table 14, entry 9).

The aryl iodides with the weaker EWGs seemed to be less reactive towards direct coupling with the organometallic, and thus they at least produced some product, though the

yields remained low. 4-Bromo-1-iodobenzene gave a messy reaction mixture, presumably because the aryl bromide also underwent oxidative addition to the palladium catalyst.
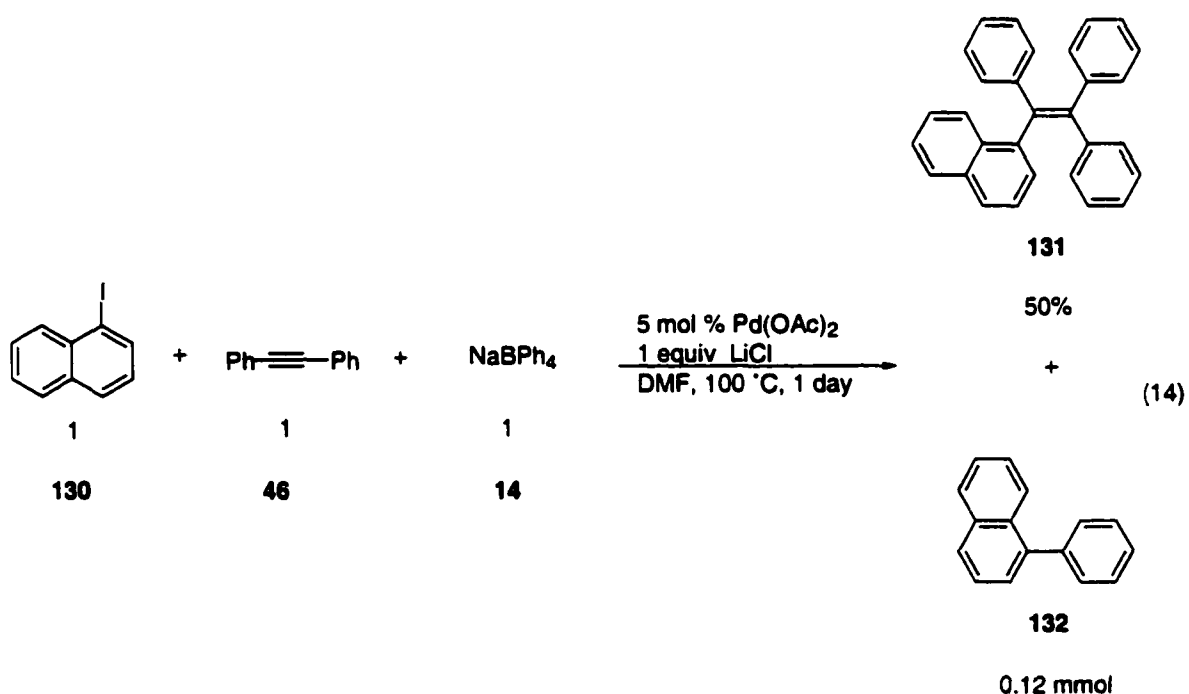
Because the electron-deficient aryl iodides failed to give decent yields of product, we turned our attention to electron-rich aryl iodides. Aryl iodides with weak electron-donating groups (EDG) were first employed. 3-Iodoanisole (92) and 3-iodotoluene (93) gave modest 40% yields of the desired products 109 and 110 and approximately 0.10 mmol of their respective biaryl derivatives 124 and 125 (Table 14, entries 12 and 13). 3-Iodoaniline (94) gave only a very small amount of product 66 and a trace amount of the biaryl derivative 73. The lone pair of electrons on the nitrogen may be coordinating to the palladium and interfering with the reaction (Table 14, entry 14).

4-Iodotoluene (95) and 2-iodotoluene (96) with their stronger EDGs gave good yields of the desired products 50 and 111, but also gave the biaryl derivatives 51 and 126 (Table 14, entries 15 and 16). We were pleased that 2-iodotoluene gave the desired product, indicating that even hindered aryl iodides work in this reaction.
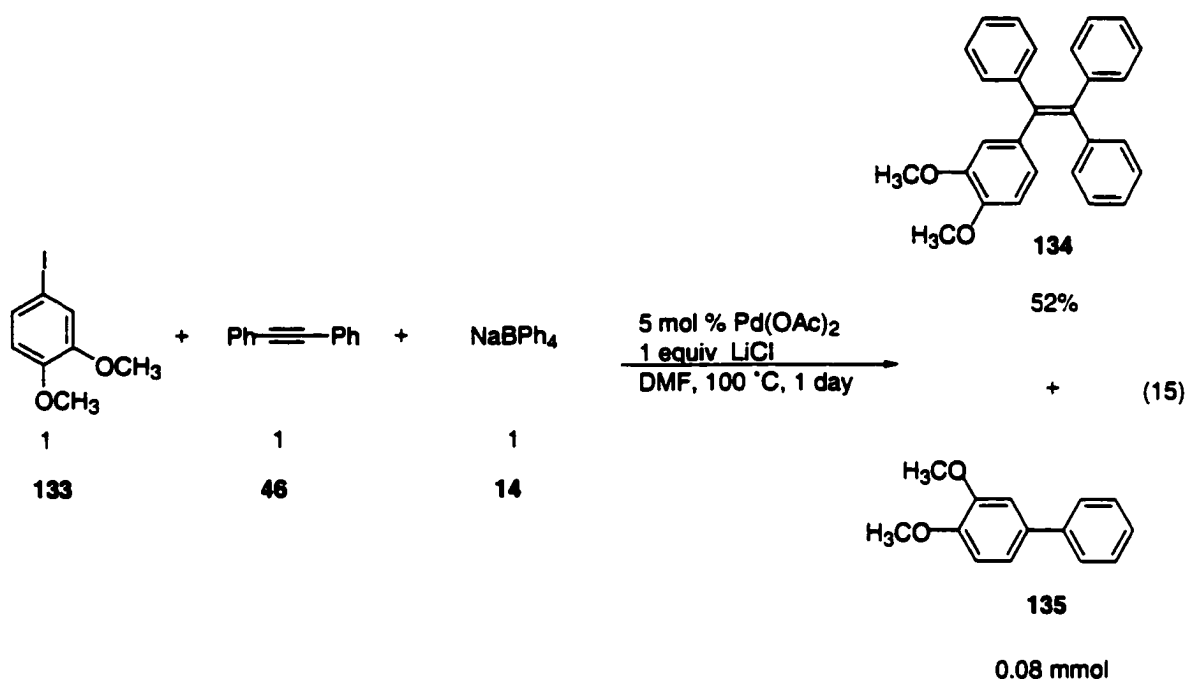
4-Iodoanisole (77) with its very strong EDG gave a 68% yield of product 63, but the reaction had to be run for 3 days instead of 1 day (Table 14, entry 17). The longer reaction time was necessary, because the electron-rich aryl iodide is unreactive towards oxidative addition to the palladium catalyst. 0.04 Mmol of the biaryl derivative 70 was also recovered.

4-Iodoaniline (97), 4-iodo-N,N-dimethylaniline (98), and 2-iodophenol (99) gave none of the desired products (Table 14, entries 18-20). Perhaps the electron lone pairs on the nitrogen and oxygen of 97 and 99 coordinate to the palladium and interfere with the reaction. Surprisingly, even 98 with its two methyl groups hindering coordination to the palladium did not work in the reaction.

Two other aryl iodides, 1-iodonaphthalene (130) (eq 14) and 4-iodo-1,2-

dimethoxybenzene (133) (eq 15), gave reasonable yields in this reaction. 1-Iodonaphthalene

(130) gave a 50% yield of 131 and 0.12 mmol of side product 132, while 4-iodo-1,2-

dimethoxybenzene (133) gave a 52% yield of 134 and 0.08 mmol of side product 135.

Bromobenzene has also been employed as the aryl halide. Because aryl bromides undergo

oxidative addition at a slower rate than aryl iodides, we thought the desired product could be

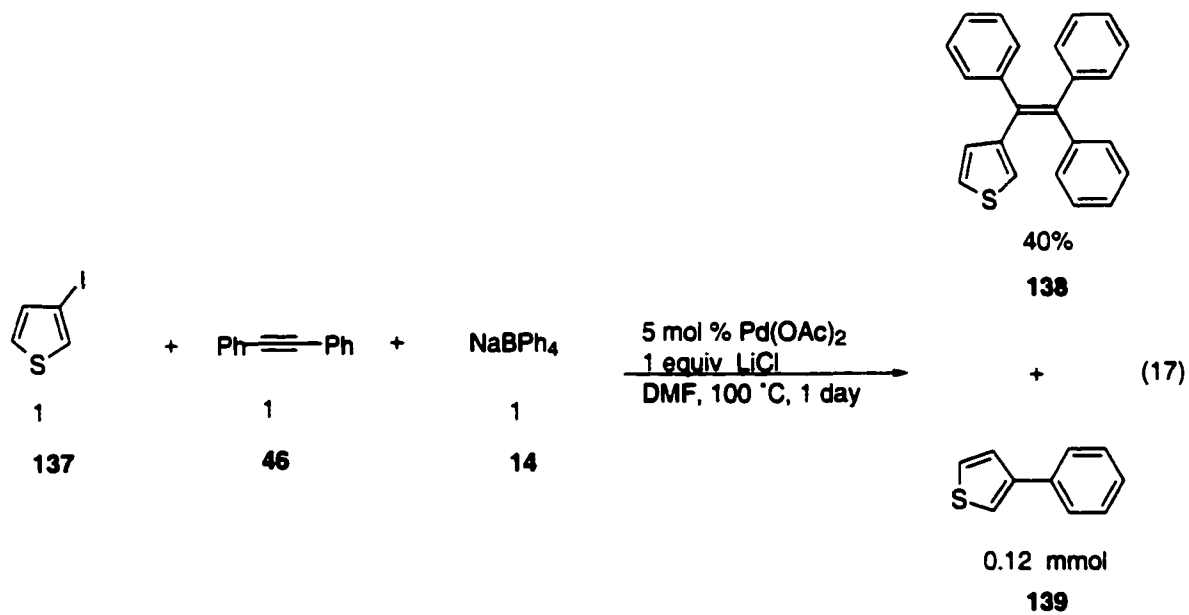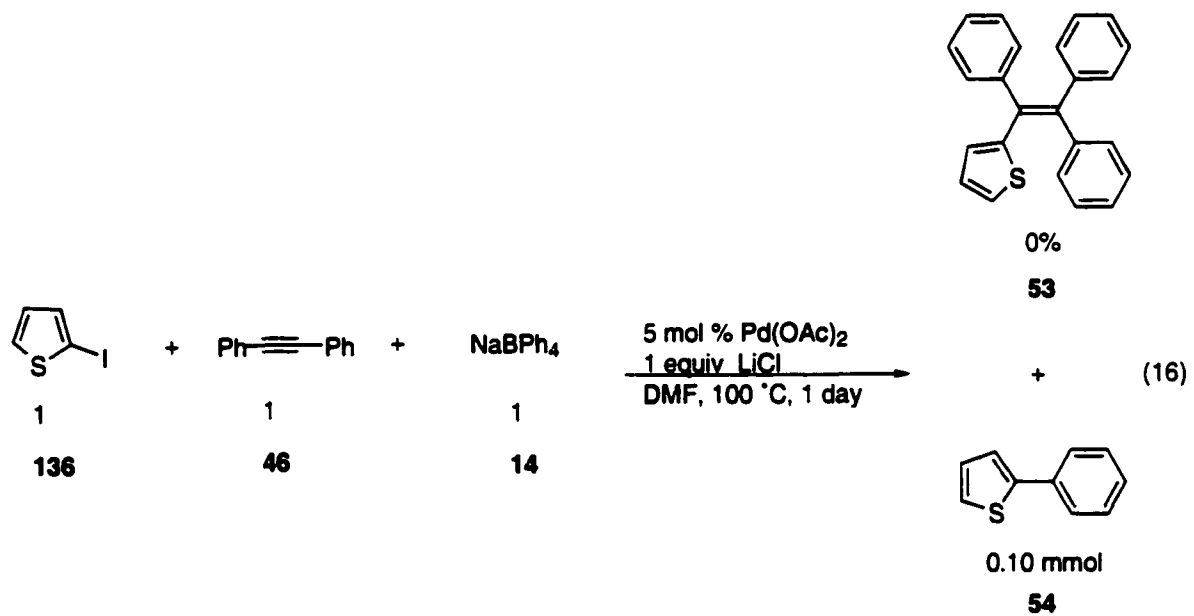favored over the undesired biphenyl, but it was not.

$$\text{130} \quad + \quad \text{Ph}\!\!=\!\!\!=\!\!\!\text{Ph} \quad + \quad \text{NaBPh}_4 \quad \xrightarrow[\text{DMF, 100 °C, 1 day}]{\substack{\text{5 mol \% Pd(OAc)}_2 \\ \text{1 equiv LiCl}}}$$

131

50%

+

(14)

132

0.12 mmol

2-Iodothiophene (136) was next employed as the aryl iodide, but none of the desired

tetrasubstituted product 53 was observed (eq 16). 0.10 Mmol of the biaryl product 54 was

observed as the only product. 3-Iodothiophene (137) gave a 40% yield of the desired product

138 as determined by gas chromatography. 0.12 Mmol of biaryl derivative 139 was also

$$133 + Ph\!\!-\!\!\equiv\!\!-\!\!Ph + NaBPh_4 \xrightarrow[\text{DMF, 100 °C, 1 day}]{\substack{\text{5 mol \% Pd(OAc)}_2 \\ \text{1 equiv LiCl}}} 134 + 135 \quad (15)$$
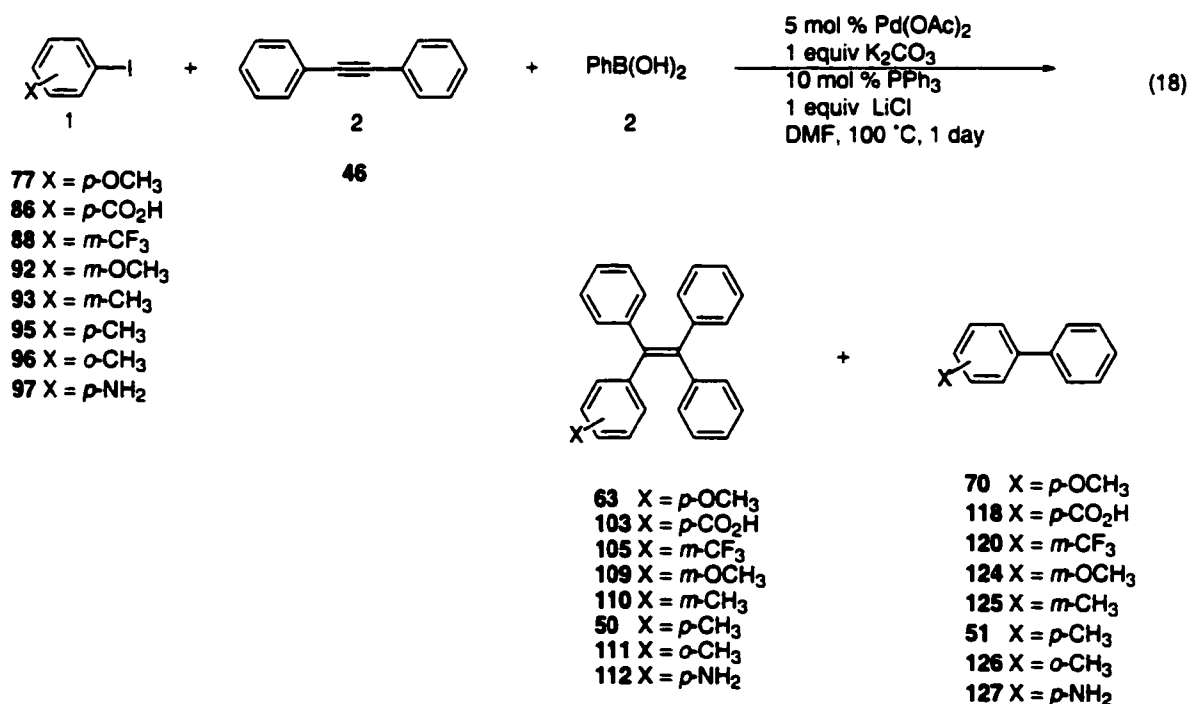
recovered (eq 17). We hypothesize that 2-iodothiophene did not work in this reaction, because the adjacent heteroatom may be coordinating to the palladium in the vinylic palladium intermediate, which is formed after carbopalladation of the alkyne. This stable intermediate may prevent the reaction from reaching completion. In the reaction of 3-iodothiophene the heteroatom cannot easily coordinate to the palladium of the vinylic palladium intermediate during the reaction, thus allowing product formation, albeit in a low yield.

3-Iodopyridine was also employed as the aryl iodide in this reaction, but gave none of the desired tetrasubstituted product. This is probably not too surprising since electron-deficient aryl halides failed earlier.

0%

53

+ (16)

0.10 mmol

54

1	1	1	
136	**46**	**14**	

5 mol % Pd(OAc)$_2$
1 equiv LiCl
DMF, 100 °C, 1 day

40%

138

+ (17)

0.12 mmol

139

1	1	1	
137	**46**	**14**	

5 mol % Pd(OAc)$_2$
1 equiv LiCl
DMF, 100 °C, 1 day

A few of the aryl iodides, including 4-iodoanisole (**77**), 4-iodobenzoic acid (**86**), 3-iodobenzotrifluoride (**88**), 3-iodoanisole (**92**), 3-iodotoluene (**93**), 4-iodotoluene (**95**), 2-iodotoluene (**96**), and 4-iodoaniline (**97**), were allowed to react using the general procedure for boronic acids (eq 18). Overall, the reaction gave much lower yields than the general procedure for borates had given earlier. The aryl iodides with EWGs again gave none of the desired products (Table 15, entries 1 and 2), and the aryl iodides with EDGs failed to give good yields of their respective products (Table 15, entries 3-9). Surprisingly, even those aryl iodides which had given good yields when NaBPh₄ was employed as the organometallic failed to give good yields when PhB(OH)₂ was employed. Perhaps these reactions are proceeding by a slightly different mechanism than when NaBPh₄ is employed. If this is true, more optimization work may be required to achieve the same good yields for other aryl iodides, as was observed with NaBPh₄.

77 X = *p*-OCH₃
86 X = *p*-CO₂H
88 X = *m*-CF₃
92 X = *m*-OCH₃
93 X = *m*-CH₃
95 X = *p*-CH₃
96 X = *o*-CH₃
97 X = *p*-NH₂

63 X = *p*-OCH₃
103 X = *p*-CO₂H
105 X = *m*-CF₃
109 X = *m*-OCH₃
110 X = *m*-CH₃
50 X = *p*-CH₃
111 X = *o*-CH₃
112 X = *p*-NH₂

70 X = *p*-OCH₃
118 X = *p*-CO₂H
120 X = *m*-CF₃
124 X = *m*-OCH₃
125 X = *m*-CH₃
51 X = *p*-CH₃
126 X = *o*-CH₃
127 X = *p*-NH₂

In general, aryl iodides with strong EWGs unfortunately give none of the
tetrasubstituted product when employing NaBPh$_4$, and only biaryl side products are observed.
Aryl iodides with weaker EWGs, when allowed to react with NaBPh$_4$, give only low yields of
the tetrasubstituted products and modest yields of the biaryl side products. When aryl
iodides with weaker EWGs were allowed to react with PhB(OH)$_2$, they gave none of the
desired products and modest yields of the biaryl side products. Only aryl iodides with EDGs
give good yields of the desired products when reacted with NaBPh$_4$. However, longer

Table 15. Effect of Various Aryl Iodides on the Reaction of Diphenylacetylene and Phenylboronic Acid (eq 18).[a]

entry	X	Hammett parameter σ	% isolated yield of alkene, mmol of biaryl derivative
1	p-CO$_2$H	0.45	0, 0.19
2	m-CF$_3$	0.43	0, 0.19
3	m-OCH$_3$	0.12	20, 0.10
4	m-CH$_3$	- 0.07	25, 0.06
5[b]	p-CH$_3$	- 0.17	40, 0.01
6[b]	o-CH$_3$	-	16, 0.06
7	p-OCH$_3$	- 0.27	trace, trace
8[b,c]	p-OCH$_3$	- 0.27	10, 0.04
9	p-NH$_2$	- 0.66	0, 0

[a]The aryl iodide (0.25 mmol), diphenylacetylene (89.0 mg, 0.5 mmol), phenylboronic acid (61.0 mg, 0.50 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol) K$_2$CO$_3$ (34.0 mg, 0.25 mmol) and PPh$_3$ (6.0 mg, 0.025 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b]The yield was determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard.
[c]The reaction was allowed to run for 3 days.

reaction times have to be employed. When aryl iodides with EDGs are allowed to react with

PhB(OH)$_2$, poor yields of the desired products are obtained (Tables 14 and 15).

We next sought to increase the yields by varying the stoichiometry of the reaction.

Because 4-iodoanisole (77) gave a reasonable yield in a previous reaction (Table 16, entry 1),

we chose it as the aryl iodide for this study and varied the amounts of aryl iodide, alkyne, and

NaBPh$_4$ employed (eq 19) (Table 16, entries 2-4). As shown in Table 16, the highest yields

of the desired product could be achieved by employing 2 equivs of the alkyne (Table 16,

entry 3).

Table 16. Effect of Varying the Amount of p-Iodoanisole, Diphenylacetylene, and NaBPh$_4$ in the Reaction (eq 19).[a]

entry[b]	aryl iodide 77 (equiv)	alkyne 46 (equiv)	NaBPh$_4$ (equiv)	% isolated yield of 63, mmol of 70
1	1	1	1	68, 0.04
2	2	1	1	80, 0.10
3	1	2	1	85, 0.09
4	1	1	2	70, 0.11

[a]p-Iodoanisole (0.25 or 0.50 mmol), diphenylacetylene (0.25 or 0.50 mmol), sodium tetraphenylborate (0.25 or 0.50 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 3 days at 100 °C.
[b]Trace amounts of biphenyl (45) were present in all of these reactions.

Because ethyl 2-iodobenzoate (87) produced a better yield of the desired product than

the other aryl iodides bearing an EWG (Table 17, entry 1), the stoichiometry of its reaction

was next varied (eq 20). As shown in Table 17, the amount of aryl iodide, alkyne, and

organometallic were sequentially used in excess. Only low yields of 104 were obtained,

showing again that aryl iodides with EWGs do not work well in these reactions (Table 17,

entries 2-4).

Next, we employed different alkynes in the reaction using iodobenzene as the aryl

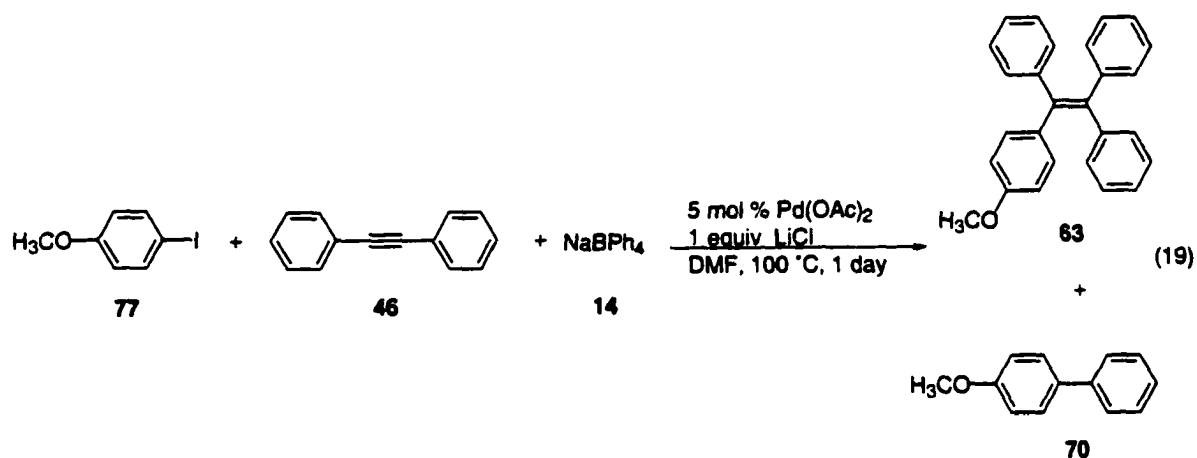iodide and NaBPh₄ as the organometallic. The first alkyne we employed wa; ethyl

Table 17. Effect of Varying the Amount of Ethyl p-Iodobenzoate, Diphenylacetylene, and NaBPh₄ in the Reaction (eq 20).[a]

entry[b]	aryl iodide 87 (equiv)	alkyne 46 (equiv)	NaBPh₄ (equiv)	% isolated yield of 104, mmol of 119
1	1	1	1	15, 0.17
2	2	1	1	trace, 0.24
3	1	2	1	~8, 0.23
4	1	1	2	0, 0.23

[a]Ethyl p-iodobenzoate (0.25 or 0.50 mmol), diphenylacetylene (0.25 or 0.50 mmol), sodium tetraphenylborate (0.25 or 0.50 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
[b]Trace amounts of biphenyl (45) were present in all of these reactions.
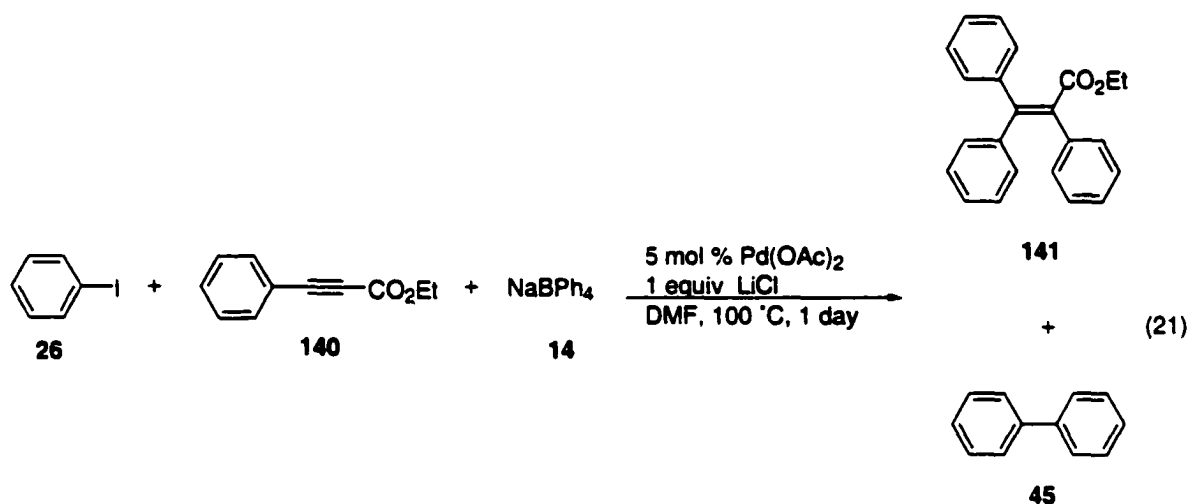
$$\text{(20)}$$
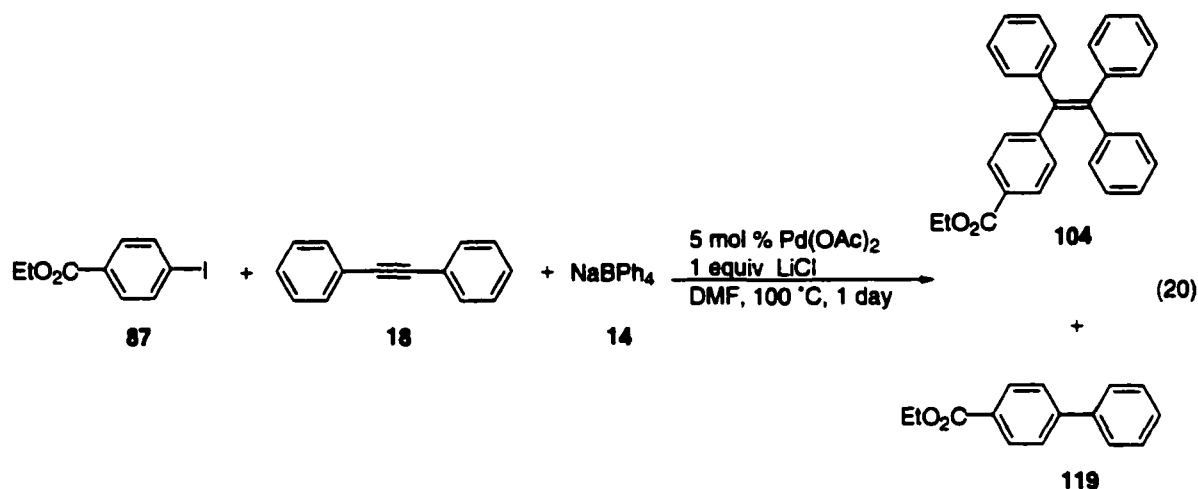
phenylpropiolate (**140**) (Table 18 and eq 21). The general procedure for borates gave a low

yield of the desired product **141** (Table 18, entry 1). Varying the stoichiometry of the

reaction gave vastly improved yields as shown in Table 18, entries 2-4. Using an excess of

the aryl iodide or alkyne gave an increased yield of **141**. The highest yield that was obtained

was 64% (Table 18, entry 4). This was achieved using 2 equivs of aryl iodide and alkyne.

We also noted that employing an excess of **140** reduced the amount of the side product **45**

(Table 18, entry 3).

Next we moved on to other alkynes using equivalent amounts of the aryl iodide,

alkyne, and arylborate (eq 22). Four alkynes with EWGs were next allowed to react. 4-

Phenyl-3-butyn-2-one (**142**) gave a modest yield of the desired tetrasubstituted product **170**

(Table 19, entry 1), but the alkynes ethyl 2-butynoate (**143**), phenyl phenylethynyl sulfone

(**144**) and 2-butynoic acid (**145**) did not give any of the desired tetrasubstituted products **171-**

173 respectively (Table 19, entries 2 and 4). However, when **143** was allowed to react using

Table 18. Effect of Varying the Amount of Iodobenzene and Ethyl Phenylpropiolate in the Reaction (eq 21).[a]
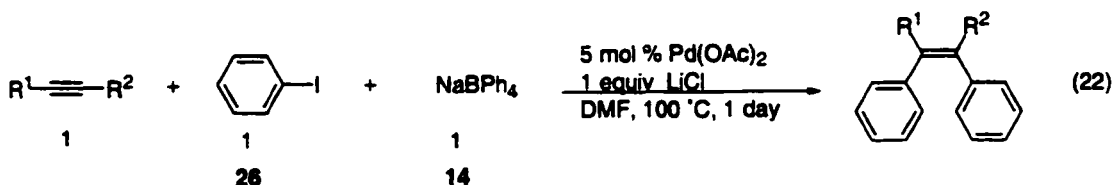
entry	aryl iodide 26 (equiv)	alkyne 140 (equiv)	NaBPh₄ (equiv)	% isolated yield of 141, mmol of 45
1	1	1	1	10, 0.11
2	2	1	1	61, 0.28
3	1	2	1	57, 0.05
4	2	2	1	64, 0.16

[a]Iodobenzene, the alkyne, sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

$$\text{26} \quad + \quad \text{140 (CO}_2\text{Et)} \quad + \quad \text{NaBPh}_4 \text{ 14} \quad \xrightarrow[\text{DMF, 100 °C, 1 day}]{\begin{array}{c}\text{5 mol % Pd(OAc)}_2\\ \text{1 equiv LiCl}\end{array}} \quad \text{141} \quad + \quad \text{45} \qquad (21)$$

the general procedure for boronic acids, a 57% yield of the desired tetrasubstituted product

171 was obtained (Table 19, entry 5).

The alkynes 1-(3-methoxyphenyl)-2-phenylacetylene (146), ethyl 3-

(phenylethynyl)benzoate (147), 1-(3-trifluoromethylphenyl)-2-phenylacetylene (148), 1-(m-

tolyl)-2-phenylacetylene (149), 1-(3-aminophenyl)-2-phenylacetylene (150), 1-(3-

nitrophenyl)-2-phenylacetylene (151), 1-(3,4-dimethoxyphenyl)-2-phenylacetylene (152),

$$R^1\!\!-\!\!\equiv\!\!-R^2 + \underset{\substack{\textbf{26}}}{\overset{\textbf{1}}{\bigcirc\!\!-\!\!I}} + \underset{\textbf{14}}{\overset{\textbf{1}}{NaBPh_4}} \xrightarrow[\text{DMF, 100 °C, 1 day}]{\substack{\text{5 mol \% Pd(OAc)}_2 \\ \text{1 equiv LiCl}}} \underset{\textbf{1}}{} \qquad (22)$$

142 R^1 = Ph, R^2 = COCH$_3$

143 R^1 = CH$_3$, R^2 = CO$_2$Et

144 R^1 = Ph, R^2 = SO$_2$Ph

145 R^1 = Ph, R^2 = CO$_2$H

146 R^1 = m-CH$_3$OC$_6$H$_4$, R^2 = Ph

147 R^1 = m-EtO$_2$CC$_6$H$_4$, R^2 = Ph

148 R^1 = m-CF$_3$C$_6$H$_4$, R^2 = Ph

149 R^1 = m-CH$_3$C$_6$H$_4$, R^2 = Ph

150 R^1 = m-NH$_2$C$_6$H$_4$, R^2 = Ph

151 R^1 = m-NO$_2$C$_6$H$_4$, R^2 = Ph

152 R^1 = 3,4-(CH$_3$O)$_2$C$_6$H$_4$, R^2 = Ph

153 R^1 = p-EtO$_2$CC$_6$H$_4$, R^2 = Ph

154 R^1 = Ph, R^2 = CH$_3$

155 R^1 = Ph, R^2 = CH$_2$CH$_3$

156 R^1 = Ph, R^2 = (CH$_2$)$_3$CH$_3$

157 R^1 = Ph, R^2 = C(CH$_3$)$_3$

158 R^1 = Ph, R^2 = C(CH$_3$)$_2$OH

159 R^1 = 5-pyrimidinyl, R^2 = (CH$_2$)$_3$CH$_3$

160 R^1 = m-CH$_3$C$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

161 R^1 = m-EtO$_2$CC$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

162 R^1 = m-CF$_3$C$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

163 R^1 = m-CH$_3$OC$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

164 R^1 = Ph, R^2 = Si(CH$_3$)$_3$

165 R^1 = 2-thienyl, R^2 = (CH$_2$)$_3$CH$_3$

166 R^1 = (CH$_2$)$_2$CH$_3$, R^2 = (CH$_2$)$_2$CH$_3$

167 R^1 = (CH$_2$)$_2$CH$_2$OH, R^2 = (CH$_2$)$_2$CH$_2$OH

168 R^1 = CO$_2$CH$_3$, R^2 = CO$_2$CH$_3$

169 R^1 = 2-pyridinyl, R^2 = 2-pyridinyl

170 R^1 = Ph, R^2 = COCH$_3$

171 R^1 = CH$_3$, R^2 = CO$_2$Et

172 R^1 = Ph, R^2 = SO$_2$Ph

173 R^1 = Ph, R^2 = CO$_2$H

109 R^1 = m-CH$_3$OC$_6$H$_4$, R^2 = Ph

106 R^1 = m-EtO$_2$CC$_6$H$_4$, R^2 = Ph

105 R^1 = m-CF$_3$C$_6$H$_4$, R^2 = Ph

110 R^1 = m-CH$_3$C$_6$H$_4$, R^2 = Ph

66 R^1 = m-NH$_2$C$_6$H$_4$, R^2 = Ph

65 R^1 = m-NO$_2$C$_6$H$_4$, R^2 = Ph

134 R^1 = 3,4-(CH$_3$O)$_2$C$_6$H$_4$, R^2 = Ph

104 R^1 = p-EtO$_2$CC$_6$H$_4$, R^2 = Ph

174 R^1 = Ph, R^2 = CH$_3$

175 R^1 = Ph, R^2 = CH$_2$CH$_3$

176 R^1 = Ph, R^2 = (CH$_2$)$_3$CH$_3$

177 R^1 = Ph, R^2 = C(CH$_3$)$_3$

178 R^1 = Ph, R^2 = C(CH$_3$)$_2$OH

179 R^1 = 5-pyrimidinyl, R^2 = (CH$_2$)$_3$CH$_3$

180 R^1 = m-CH$_3$C$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

181 R^1 = m-EtO$_2$CC$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

182 R^1 = m-CF$_3$C$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

183 R^1 = m-CH$_3$OC$_6$H$_4$, R^2 = (CH$_2$)$_3$CH$_3$

184 R^1 = Ph, R^2 = Si(CH$_3$)$_3$

185 R^1 = 2-thienyl, R^2 = (CH$_2$)$_3$CH$_3$

186 R^1 = (CH$_2$)$_2$CH$_3$, R^2 = (CH$_2$)$_2$CH$_3$

187 R^1 = (CH$_2$)$_2$CH$_2$OH, R^2 = (CH$_2$)$_2$CH$_2$OH

188 R^1 = CO$_2$CH$_3$, R^2 = CO$_2$CH$_3$

189 R^1 = 2-pyridinyl, R^2 = 2-pyridinyl

+
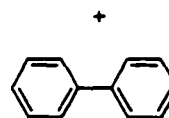
45

Table 19. Effect of Various Alkynes in the Reaction of Iodobenzene and NaBPh$_4$ (eq 22).[a]

entry	R^1	R^2	% isolated yield of alkene, mmol of 45
1	Ph	COCH$_3$	52, 0.20
2	CH$_3$	CO$_2$Et	trace, 0.14
3	Ph	SO$_2$Ph	0, 0
4	Ph	CO$_2$H	0, 0.23
5[b]	CH$_3$	CO$_2$Et	57, 0.04
6	m-CH$_3$OC$_6$H$_4$	Ph	75, 0.19
7	m-EtO$_2$CC$_6$H$_4$	Ph	66, 0.09
8	m-CF$_3$C$_6$H$_4$	Ph	54, 0.11
9	m-CH$_3$C$_6$H$_4$	Ph	20, 0.09
10	m-NH$_2$C$_6$H$_4$	Ph	0, 0.13
11	m-NO$_2$C$_6$H$_4$	Ph	50, 0.20
12	3,4-(CH$_3$O)$_2$C$_6$H$_3$	Ph	55, 0.20
13	p-EtO$_2$CC$_6$H$_4$	Ph	44, 0.14
14	Ph	CH$_3$	trace, 0.05
15[b]	Ph	CH$_3$	23, 0.03
16	Ph	CH$_2$CH$_3$	trace, 0.07
17[b]	Ph	CH$_2$CH$_3$	15, 0.03
18	Ph	(CH$_2$)$_3$CH$_3$	20, 0.08
19[b]	Ph	(CH$_2$)$_3$CH$_3$	30, 0.06
20	Ph	C(CH$_3$)$_2$OH	0, 0.19

Table 19. (continued)

21	Ph	C(CH₃)₃	53, 0.12
22	5-pyrimidinyl	$(CH_2)_3CH_3$	59, 0.04
23	m-$CH_3C_6H_4$	$(CH_2)_3CH_3$	trace, 0.22
24	m-$EtO_2CC_6H_4$	$(CH_2)_3CH_3$	trace, 0.28
25	m-$CF_3C_6H_4$	$(CH_2)_3CH_3$	trace, 0.27
26	m-$CH_3OC_6H_4$	$(CH_2)_3CH_3$	trace, 0.29
27	m-$CF_3C_6H_4$	$(CH_2)_3CH_3$	53[b], 0.10
28	Ph	$Si(CH_3)_3$	0, 0.23
29	2-thienyl	$(CH_2)_3CH_3$	0, 0.22
30	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	0, 0.22
31	$(CH_2)_2CH_2OH$	$(CH_2)_2CH_2OH$	0, 0.22
32	CO_2CH_3	CO_2CH_3	0, 0.20
33	2-pyridinyl	2-pyridinyl	0, 0.22
34[c]	2-thienyl	$(CH_2)_3CH_3$	0, 0.23
35[c]	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	0, 0.23
36[c]	$(CH_2)_2CH_2OH$	$(CH_2)_2CH_2OH$	0, 0.23
37[c]	CO_2CH_3	CO_2CH_3	0, 0.22
38[c]	2-pyridinyl	2-pyridinyl	0, 0.19

[a]Iodobenzene (51.0 mg, 0.25 mmol), the alkyne (0.25 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

[b]Iodobenzene (51.0 mg, 0.25 mmol), diphenylacetylene (89.0 mg, 0.50 mmol), phenylboronic acid, Pd(OAc)₂ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol), K₂CO₃ (34.0 mg, 0.25 mmol), and PPh₃ (6.0 mg, 0.025 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

[c]2 Equivs of ZnCl₂ were added to the reaction.

and ethyl 4-(phenylethynyl)benzoate (**153**) all gave good to moderate yields of the respective

tetrasubstituted products (Table 19, entries 6-13).

The alkynes 1-phenylpropyne (**154**), 1-phenylbutyne (**155**), and 1-phenylhexyne

(**156**) gave only trace to low amounts of **174-176** respectively (Table 19; entries 14, 16, and

18). When they were allowed to react using the general procedure for boronic acids, slightly

higher yields were obtained (Table 19; entries 15, 17, and 19). These results indicate that

having an alkyl group on one end of the alkyne, rather than an aryl group, has a deleterious

effect on the reaction.

The bulky alkynes **157** and **158** were next employed. Alkyne **158** gave none of the

expected product, but **157** gave a modest yield of the expected product **177** (Table 19, entries

20 and 21). Although both alkynes have one bulky end, one gave a modest yield while the

other failed to give any product. The hydroxy group of **158** may be hindering the reaction

due to the lone pair of electrons which can coordinate to the intermediate palladium.

5-(1-Hexynyl)pyrimidine (**159**) afforded a moderate yield of alkene **179** (Table 19,

entry 22). However, when other alkynes bearing an alkyl group were allowed to react, such

as 1-(*m*-tolyl)-1-hexyne (**160**), ethyl 3-(1-hexynyl)benzoate (**161**), 1-(*m*-

trifluoromethylphenyl)-1-hexyne (**162**), and 3-(1-hexynyl)anisole (**163**), they gave only trace

amounts of the desired products **180-183** (Table 19, entries 23-26). When alkyne **162** was

allowed to react using the general procedure for boronic acids, a 53% yield of **182** was

obtained (Table 19, entry 27).

1-Phenyl-2-(trimethylsilyl)acetylene (**164**), 2-(1-hexynyl)thiophene (**165**), 4-octyne

(**166**), 2-butyne-1,4-diol (**167**), dimethyl acetylenedicarboxylate (**168**), and di-(2-

pyridinyl)acetylene (**169**) gave none of the expected tetrasubstituted products **184-189** (Table

19, entries 28-33). The lack of product formation with some of these alkynes could result from the heteroatom in these alkynes coordinating to the palladium, thus forming a stable palladium intermediate, which cannot go on to form product. We hypothesized that the addition of a Lewis acid, such as $ZnCl_2$, could coordinate to these heteroatoms and thus promote product formation. However, when 2 equivs of $ZnCl_2$ were added to these reactions, none of the desired products were observed (Table 19, entries 34-38).

A few of the alkynes, which gave a very low or no yield of the desired tetrasubstituted product, were employed in a series of optimization reactions to determine if the yield could be increased. The stoichiometry of the reaction employing 26 and the alkyne was systematically varied. In the reactions where the amount of either 4-octyne or ethyl 2-butynoate were varied, the yields did not improve (Table 20 and Table 21 respectively). When the stoichiometry was varied in the reactions where 1-phenyl-1-hexyne and 1-(m-tolyl)-1-hexyne were employed as alkynes, the yields actually decreased (Table 22 and Table 23 respectively).

Table 20. Effect of Varying 4-Octyne and Iodobenzene in the Reaction with NaBPh₄.[a]

entry	aryl iodide 26 (equiv)	alkyne 166 (equiv)	NaBPh₄	% isolated yield of 186, mmol of 45
1	1	1	1	0, 0.22
2	2	1	1	0, 0.25
3	1	2	1	0, 0.11
4	2	2	1	0, 0.26

[a] Iodobenzene (0.25 or 0.50 mmol), 4-octyne (0.25 or 0.50 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

Table 21. Effect of Varying Ethyl 2-Butynoate and Iodobenzene in the Reaction with NaBPh₄.[a]

entry	aryl iodide 26 (equiv)	alkyne 143 (equiv)	NaBPh₄	% isolated yield of 171, mmol of 45
1	1	1	1	trace, 0.14
2	2	1	1	0, 0.11
3	1	2	1	0, 0.09
4	2	2	1	0, 0.13

[a]Iodobenzene (0.25 or 0.50 mmol), ethyl 2-butynoate (0.25 or 0.50 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

Table 22. Effect of Varying 1-Phenyl-1-hexyne and Iodobenzene in the Reaction with NaBPh₄.[a]

| entry	aryl iodide 26 (equiv)	alkyne 156 (equiv)	NaBPh₄	% isolated yield of 176, mmol of 45
1	1	1	1	20, 0.08
2	2	1	1	16, 0.08
3	1	2	1	13, 0.04
4	2	2	1	12, 0.09

[a]Iodobenzene (0.25 or 0.50 mmol), 1-phenyl-1-hexyne (0.25 or 0.50 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

When 1-(*m*-trifluoromethylphenyl)-1-hexyne (162) was employed as the alkyne, the

yields of the olefin did improve. Although the yields were low, the best improvement was

observed when 2 equivs of the alkyne were employed (Table 24, entries 3 and 4). A slight

improvement in the yield was observed when the aryl iodide was used in excess (Table 24,

Table 23. Effect of Varying 1-(m-Tolyl)-1-hexyne and Iodobenzene in the Reaction with NaBPh₄.ᵃ

entry	aryl iodide 26 (equiv)	alkyne 149 (equiv)	NaBPh₄	% isolated yield of 110, mmol of 45
1	1	1	1	20, 0.09
2	2	1	1	trace, 0.10
3	1	2	1	trace, 0.19
4	2	2	1	trace, 0.13

ᵃIodobenzene (0.25 or 0.50 mmol), 1-(m-tolyl)-1-hexyne (0.25 or 0.50 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

Table 24. Effect of Varying 1-(m-Trifluoromethylphenyl)-1-hexyne and Iodobenzene in the Reaction with NaBPh₄.ᵃ

entry	aryl iodide 26 (equiv)	alkyne 162 (equiv)	NaBPh₄	% isolated yield of 182, mmol of 45
1	1	1	1	trace, 0.27
2	2	1	1	20, 0.03
3	1	2	1	30, 0.04
4	2	2	1	34, 0.03

ᵃIodobenzene (0.25 or 0.50 mmol), 1-(m-trifluoromethylphenyl)-1-hexyne (0.25 or 0.50 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

entry 2). Of the four alkynes optimized, only the reaction employing 1-(m-trifluoromethylphenyl)-1-hexyne improved the yield.

We next investigated the regioselectivity of this reaction. o-Iodotoluene, ethyl phenylpropiolate, and sodium tetraphenylborate were allowed to react using the general

procedure for borates. Of the two possible regioisomers, one isomer was formed

predominantly and a trace amount of the other isomer was observed only by GC-MS analysis

(eq 23). Unfortunately, we were unable to definitively determine whether the predominate

isomer was **190** or **191**.

In order to determine the regiochemistry of this reaction, iodobenzene, ethyl

phenylpropiolate, and *o*-tolylboronic acid were allowed to react under the reaction conditions

shown in equation 22. However, GC-MS and ^{1}H NMR analyses showed appromixately a

50:50 mixture of both regioisomers.

$$ \text{(23)} $$
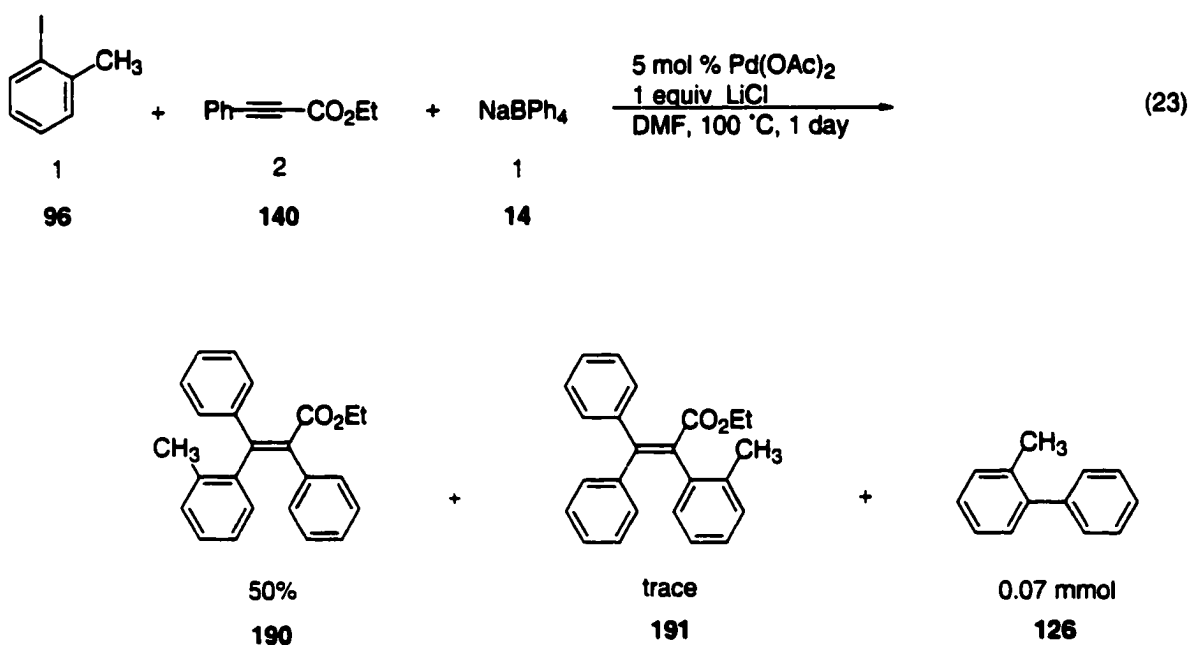
What appears to be complete regioselectivity was observed in the reactions

employing iodobenzene, 5-(1-hexynyl)pyrimidine (**159**), and *p*-chlorophenylboronic acid

(**55**) or *p*-methoxyphenylboronic acid (**56**) (eq 24). Products **192** and **193** resulted from these

reactions respectively. The regiochemistry of product **193** was also determined by NOESY

^{1}H NMR spectroscopic analysis, wherein the protons on the 4-methoxyphenyl moiety

interacted with the protons on the pyrimidyl moiety. Based on the results from product **193**,

the regiochemistry of **192** is assumed to be the same.

Apparently, the bulkiness of the alkyne is not the only factor in determining

regioselectivity in these reactions. The electronics of the alkyne or other reaction parameters

may also be factors. More research is required in this area to determine the regioselectivity

of these reactions.

$$
\text{(24)}
$$

26   159   55 Ar = p-ClC$_6$H$_4$

56 Ar = p-CH$_3$OC$_6$H$_4$

192 Ar = p-ClC$_6$H$_4$, 68%

193 Ar = p-CH$_3$OC$_6$H$_4$, 70%

69 Ar = p-ClC$_6$H$_4$, 0.05 mmol

70 Ar = p-CH$_3$OC$_6$H$_4$, 0.04 mmol
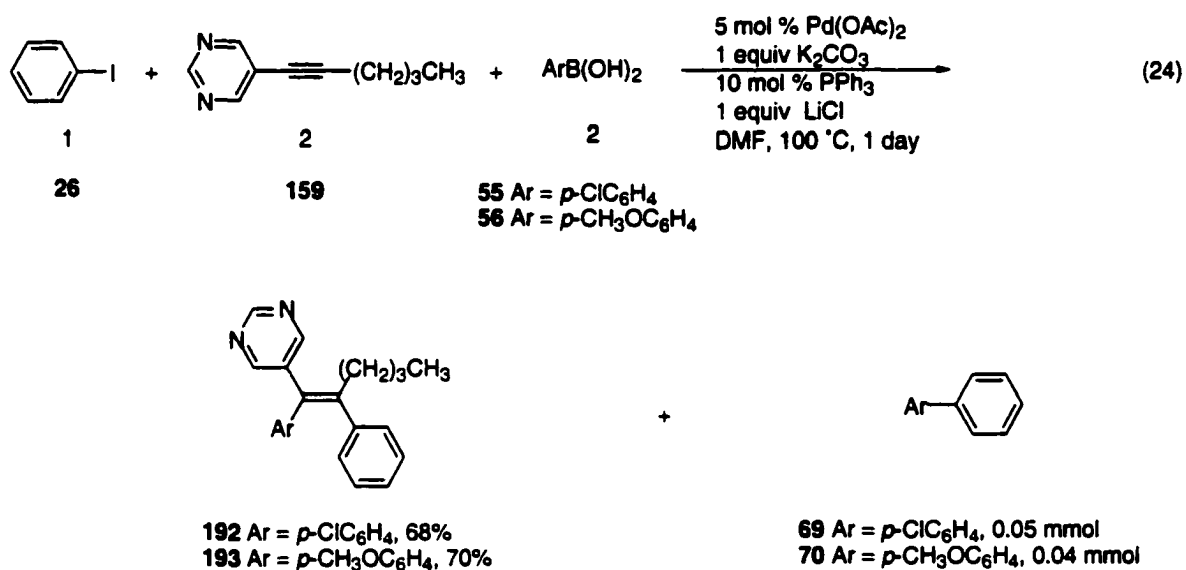
Also, we have employed an aryl triflate, instead of an aryl iodide, in the reaction of

diphenylacetylene and NaBPh$_4$ or phenylboronic acid. At first we employed the general

procedure for borates, where NaBPh$_4$ was employed as the organometallic. As shown in

Table 25, entry 1, a very low yield of the desired product **43** was observed. We next

employed phenylboronic acid as the organometallic, using the general procedure for boronic

acids. As shown in Table 25, entries 2-6, the yields of **43** did not improve until NEt$_3$ was

employed as the base. A 23% yield of the desired tetrasubstituted alkene was then observed

(Table 25, entry 6). The base pyridine failed to give either product **43** or **45** (Table 25, entry

7), and the base diisopropylamine gave a low yield of **43** (Table 25, entry 8). Apparently,

more optimization work is needed to successfully employ aryl triflates in this reaction.

Table 25. Effect of Base on the Reaction of Phenyl Trifluoromethanesulfonate, Diphenylacetylene, and Arylboron Compounds.

entry	arylboron compound	base	% GC yield of **43**, mmol of **45**
1	NaBPh$_4$^{a}	-	~2, 0
2	PhB(OH)$_2$^{b}	K$_2$CO$_3$	0, 0
3	PhB(OH)$_2$	Tl$_2$(CO$_3$)$_3$	trace, trace
4	PhB(OH)$_2$	Ag$_2$CO$_3$	0, 0.09
5	PhB(OH)$_2$	Cs$_2$CO$_3$	0, 0.14
6	PhB(OH)$_2$	NEt$_3$	23, 0.04
7	PhB(OH)$_2$	pyridine	0, 0
8	PhB(OH)$_2$	i-Pr$_2$NH	17, 0.04

^{a}Phenyl trifluoromethanesulfonate (56.5 mg, 0.25 mmol), the diphenylacetylene (44.0 mg, 0.25 mmol), sodium tetraphenylborate (85.0 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.
^{b}Phenyl trifluoromethanesulfonate (56.5 mg, 0.25 mmol), diphenylacetylene (89.0 mg, 0.50 mmol), phenylboronic acid (61.0 mg, 0.5 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), K$_2$CO$_3$ (34.0 mg, 0.25 mmol), PPh$_3$ (6.0 mg, 0.025 mmol), and LiCl (10.5 mg, 0.25 mmol) were allowed to react in 1 mL of DMF for 1 day at 100 °C.

Conclusion

Our preliminary results indicate the feasibility of employing our palladium(0)-catalyzed, intermolecular methodology for the regio- and stereoselective synthesis of tetrasubstituted alkenes. After optimization of our model system, good yields of the desired alkene have been produced. The electronics of the aryl iodide are important for the success of the reaction. Various alkynes (other than diphenylacetylene) can be employed in the reaction as well. When the organometallic reagent was varied, aryl tin and aryl boronic acid reagents gave high yields, and aryl silicon reagents gave lower yields. More optimization work is needed to successfully employ aryl triflates in the reaction.

Experimental

General Procedures. All ^1H and ^{13}C NMR spectra were obtained at 300 or 400 MHz. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F) and visualization was accomplished with short wavelength UV light (254 nm) or with a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. High-resolution mass spectra were recorded on a Kratos MS50TL double focusing magnetic sector mass spectrometer using EI at 70eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O series 11 analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise stated. $KMnO_4$, HOAc, NaOAc, KOAc, LiOAc, $NaHCO_3$, K_2CO_3, $KHCO_3$, $NaCO_3$, LiCl,

KHSO$_4$, n-Bu$_4$NCl, DMF, DMSO, NaCl, NH$_4$Cl, NaOH, HCl, hexane, ethyl acetate,

dimethyl sulfoxide, methanol, ethyl ether, DMF, and DMA were obtained from Fisher

Scientific. 2-Iodophenol, diphenylacetylene, sodium tetraphenylborate, 1-iodo-3-

nitrobenzene, 4-iodobenzotrifluoride, 4-iodoacetophenone, 4-iodobenzoic acid, ethyl 4-

iodobenzoate, 4-iodoanisole, 3-iodobenzotrifluoride, ethyl 3-iodobenzoate, 3-iodoaniline, 4-

bromoiodobenzene, 4-chloroiodobenzene, 4-iodotoluene, 2-iodotoluene, 4-iodoaniline, 2-

iodobenzotrifluoride, 3-iodoanisole, 3-iodotoluene, 3-iodothiophene, phenylpropiolic acid,

ethyl propiolate, 2-iodoaniline, NaBPh$_4$, phenylboronic acid, sodium tetrakis(p-tolyl)borate,

tetra-n-butylammonium triphenyldifluorosilane, diphenyldifluorosilane, tetraphenyltin,

triphenyltin chloride, triphenyltin acetate, triphenyltin hydroxide, phenyltrimethyltin,

potassium tetrakis(2-thienyl)borate, tri-2-furylphosphine, 2-

(dicyclohexylphosphino)biphenyl, BINAP, dppm, dppe, dppp, dppb, AsPh$_3$, 4-

chlorophenylboronic acid, and 4-methoxyphenylboronic acid were obtained from Aldrich

Chemical Co. Potassium phenyltrifluoroborate, 3-nitrophenylboronic acid, 3-

aminophenylboronic acid, and 3-thiopheneboronic acid were obtained from Lancaster

Synthesis Inc. Pd(OAc)$_2$ and PPh$_3$ were obtained from Kawaken Fine Chemical Co., Ltd. 1-

(m-Tolyl)-1-hexyne, 1-(m-methoxyphenyl)-1-hexyne, 1-(m-trifluoromethylphenyl)-1-hexyne,

ethyl 2-(1-hexynyl)benzoate, 5-(1-hexynyl)pyrimidine, and 2-(1-hexynyl)thiophene were

donated by Kevin Roesch. The phenyl phenylethynyl sulfone was donated by Hao Yin. 2-

Butynoic acid was obtained from ACRO. 3-Iodopyridine was donated by Guangxiu Dai.

PdCl$_2$(PPh$_3$)$_2$ was prepared by a literature procedure.[23]

General Procedure for the Synthesis of Alkynes.[24] To a solution of $PdCl_2(PPh_3)_2$ (196 mg,

0.28 mmol) and CuI (107 mg, 0.98 mmol) in 60 mL of NEt_3 was added the aryl iodide (14.0

mmol) and the alkyne (16.8 mmol). The mixture was then stirred under a N_2 atmosphere at

room temperature. The reaction was monitored by TLC to establish completion. If the

reaction was not completed after 6 h, then the reaction was warmed to 60 °C until

completion. The reaction mixture was cooled to room temperature and the ammonium salt

was removed by filtration. The filtrate was dissolved into ethyl ether and washed several

times with 10% HCl solution until the smell of ammonia was no longer present. The ether

layer was then washed with water and dried with Mg_2SO_4. The solvent was removed under

reduced pressure and the resulting solid was recrystallized from methanol.

Alkynes Prepared

1-(3-Methoxyphenyl)-2-phenylacetylene (146). This acetylene was prepared in 78% yield

by employing 3-iodoanisole (2.81g, 14.0 mmol) and phenylacetylene (1.71 g, 16.8 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 6.89 (m, 1 H), 7.08 (s, 1 H), 7.16 (m, 1 H), 7.25

(m, 1 H), 7.36 (m, 3 H), 7.56 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 55.53, 89.45, 89.56,

115.20, 116.57, 123.43, 124.43, 124.51, 128.56, 128.61, 129.66, 131.87, 159.57. The

spectral properties of this compound are identical to those in the literature.[25]

Ethyl 3-(phenylethynyl)benzoate (147). This acetylene was prepared in 90% yield by

employing ethyl 3-iodobenzoate (3.86g, 14.0 mmol) and phenylacetylene (1.71 g, 16.8

mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3 H), 4.35 (q, J = 7.0 Hz, 2 H),

7.33 (m, 4 H), 7.54 (m, 2 H), 7.70 (m, 1 H), 8.02 (m, 1 H), 8.23 (s, 1 H); ^{13}C NMR (300

MHz, CDCl₃) δ 14.58, 61.44, 88.70, 90.56, 123.14, 123.93, 128.66, 128.71, 128.80, 129.45,

131.05, 131.92, 132.91, 135.82, 166.08. The spectral properties of this compound are

identical to those in the literature.[26]

1-(3-Trifluoromethylphenyl)-2-phenylacetylene (148). This acetylene was prepared in

80% yield by employing 3-(trifluoromethyl)iodobenzene (3.26 g, 14.0 mmol) and

phenylacetylene (1.71 g, 16.8 mmol). ^{1}H NMR (300 MHz, CDCl₃) δ 7.26 (m, 3 H), 7.50 (m,

1 H), 7.58 (m, 3 H), 7.60 (m, 1 H), 7.82 (s, 1 H); ^{13}C NMR (300 MHz, CDCl₃) δ 88.04,

91.15, 122.85, 124.50, 124.96, 128.60, 128.65, 128.69, 128.99, 129.10, 131.95, 134.87,

134.89. The spectral properties of this compound are identical to those in the literature.[24]

1-(3-Methylphenyl)-2-phenylacetylene (149). This acetylene was prepared in 69% yield by

employing 3-iodotoluene (3.05 g, 14.0 mmol) and phenylacetylene (1.71 g, 16.8 mmol). ^{1}H

NMR (300 MHz, CDCl₃) δ 2.34 (s, 3 H), 7.12 (m, 1 H), 7.24 (m, 1 H), 7.50 (m, 5 H), 7.53

(m, 2 H); ^{13}C NMR (300 MHz, CDCl₃) δ 21.22, 89.04, 89.58, 123.06, 123.37, 128.16,

128.24, 128.33, 128.69, 129.16, 131.59, 132.49, 137.99. The spectral properties of this

compound are identical to those in the literature.[26]

1-(3-Aminophenyl)-2-phenylacetylene (150). This acetylene was prepared in 80% yield by

employing 3-iodoaniline (3.07 g, 14.0 mmol) and diphenylacetylene (1.71 g, 16.8 mmol). ^{1}H

NMR (300 MHz, CDCl₃) δ 7.34 (m, 5 H), 7.53 (m, 4 H); ^{13}C NMR (300 MHz, CDCl₃) δ

81.81, 122.02, 126.64, 128.57, 128.70, 128.86, 129.47, 131.86, 132.28, 132.40, 132.75.

1-(3-Nitrophenyl)-2-phenylacetylene (151). This acetylene was prepared in 90% yield by

employing 3-iodonitrobenzene (2.98 g, 14.0 mmol) and phenylacetylene (1.71 g, 16.8 mmol).

IR (neat) 3080 cm⁻¹; ^{1}H NMR (300 MHz, CDCl₃) δ 7.26 (m, 3 H), 7.55 (m, 3 H), 7.80 (m, 1

H), 8.19 (m, 1 H), 8.37 (s, 1 H); ^{13}C NMR (300 MHz, CDCl₃) δ 87.11, 92.23, 122.42, 123.11,

125.41, 126.63, 128.74, 129.30, 129.59, 132.02, 132.74, 137.45; HRMS calcd for $C_{14}H_9NO_2$: 223.06333. Found: 223.06367. Anal. calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 74.84; H, 4.41; N, 5.75.

1-(3,4-Dimethoxyphenyl)-2-phenylacetylene (152). This acetylene was prepared in 88% yield by employing 4-iodo-1,2-dimethoxybenzene (3.17 g, 14.0 mmol) and phenylacetylene (1.71 g, 16.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 3.90 (s, 3 H), 6.82 (m, 1 H), 7.13 (s, 1 H), 7.32 (m, 1 H), 7.53 (m, 3 H), 8.36 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 56.21, 56.23, 88.30, 90.22, 111.35, 114.58, 115.98, 125.24, 128.36, 128.67, 131.79, 132.83, 148.97, 149.83. The spectral properties of this compound are identical to those in the literature.[26]

Ethyl 4-(phenylethynyl)benzoate (153). This acetylene was prepared in 75% yield by employing ethyl 4-iodobenzoate (3.80 g, 14.0 mmol) and phenylacetylene (1.71 g, 16.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, $J = 7.1$ Hz, 3 H), 4.35 (q, $J = 7.1$ Hz, 2 H), 7.35 (m, 3 H), 7.53 (m, 4 H), 8.01 (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 61.35, 88.94, 92.52, 122.97, 128.11, 128.67, 128.97, 129.72, 130.07, 131.69, 131.97, 166.28. The spectral properties of this compound are identical to those in the literature.[27]

3,3-Dimethyl-1-phenyl-1-butyne (157). This acetylene was prepared in 67% yield by employing iodobenzene (2.86 g, 14.0 mmol) and t-butylacetylene (1.36 g, 16.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9 H), 7.26 (m, 3 H), 7.39 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.17, 31.31, 124.32, 127.63, 128.35, 131.80.

General Procedure for the Synthesis of Phenyl Trifluoromethanesulfonate. An ether solution of the phenol (0.1 mmol) was added to an ether suspension of sodium hydride

(prewashed with ether, 0.1 mmol) at 0 °C. The trifluoromethanesulfonic anhydride was added slowly to the phenoxide and the mixture was refluxed for 4 h. Water was added to the solution and the ether layer was separated. After washing with a 5% aqueous NaOH solution and water, the ether layer was dried with Mg_2SO_4. The solvent was evaporated and the residue was purifed by column chromatography on silica gel using hexanes as the eluent.

General procedure for the palladium(0)-catalyzed ternary coupling.

General procedure for borates: The aryl iodide (0.25 mmol), the alkyne (0.25 mmol), the borate (0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), and LiCl (10.5 mg, 0.25 mmol) were added to a 4 dram vial equipped with a stirring bar and Teflon-lined screw cap. One mL of DMF was added. The vial was placed in a mineral oil bath at 100 °C for 1 day, and the reaction mixture was stirred. The reaction mixture was cooled to room temperature and then quenched with 30 mL of aq NaCl. The aqueous layer was extracted three times with 30 mL of ethyl ether. The organic layer was dried using MgSO$_4$. Filtration and evaporation of the ethyl ether under reduced pressure produced the crude product, which was further purified by silica gel chromatography. When GC analysis was used to determine the yields, tetracosane (3.1 mg, 0.01 mmol) was added to the reaction mixture, serving as an internal standard.

General procedure for boronic acids: The aryl iodide (0.25 mmol), the alkyne (0.5 mmol), the boronic acid (0.5 mmol), Pd(OAc)$_2$ (2.8 mg, 0.012 mmol), LiCl (10.5 mg, 0.25 mmol), K$_2$CO$_3$ (34.0 mg, 0.25 mmol), and PPh$_3$ (6.0 mg, 0.25 mmol) were added to a 4 dram vial equipped with a stirring bar and Teflon-lined screw cap. One mL of DMF was added. The vial was placed in a mineral oil bath at 100 °C for 1 day, and the reaction mixture was stirred.

The reaction mixture was cooled to room temperature and then quenched with 30 mL of aq

NaCl. The aqueous layer was extracted three times with 30 mL of ethyl ether. The organic

layer was dried using $MgSO_4$. Filtration and evaporation of the ethyl ether under reduced

pressure produced the crude product, which was further purified by silica gel

chromatography.

1,2,2-Triphenyl-1-(p-tolyl)ethene (50). Iodobenzene, diphenylacetylene, and sodium

tetrakis(p-tolyl)borate were allowed to react using the general procedure for borates to

produce **50** as a light yellow oil (80% yield): IR (neat) 3073, 2921cm^{-1}; ^{1}H NMR (300 MHz,

CDCl$_3$) δ 2.28 (s, 3 H), 6.89 (m, 5 H), 7.07 (m, 14 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 16.61,

126.41, 126.49, 126.53, 127.81, 127.87, 128.59, 128.61, 131.43, 131.53, 131.57, 136.14,

136.29, 140.67, 140.94, 141.11, 141.14, 144.23, 144.39; HRMS calcd for C$_{27}$H$_{22}$: 346.17215.

Found: 346.17267.

2-(1,2,2-Triphenylethenyl)thiophene (53). Iodobenzene, diphenylacetylene, and potasium

tetrakis(2-thienyl)borate were allowed to react using the general procedure for borates to

produce **53** as a yellow oil (32% yield): IR (neat) 3022, 1598 cm^{-1}; ^{1}H NMR (300 MHz,

CDCl$_3$) δ 6.55 (m, 1 H), 6.75 (m, 1 H), 7.04 (m, 16 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ

126.29, 126.35, 126.61, 127.16, 127.33, 127.80, 127.92, 128.46, 129.79, 131.09, 131.20,

131.50, 134.18, 141.32, 143.39, 143.84, 145.36, 146.68; HRMS calcd for C$_{24}$H$_{18}$S:

338.11292. Found: 338.11341.

1,2,2-Triphenyl-1-(4-chlorophenyl)ethene (62). Iodobenzene, diphenylacetylene, and p-

chlorophenylboronic acid were allowed to react using the general procedure for boronic acids

to produce **62** as a yellow oil (78% yield): IR (neat) 3075, 3022 cm^{-1}; ^{1}H NMR (300 MHz,

CDCl$_3$) δ 6.89 (s, 1 H), 7.05 (m, 18 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 126.84, 126.85,

126.90, 126.95, 127.95, 128.05, 128.14, 128.18, 131.51, 131.53, 131.56, 132.92, 139.90,

141.84, 142.49, 143.56, 143.63, 143.69; HRMS calcd for C$_{26}$H$_{19}$Cl: 366.11753. Found:

366.11827.

1,2,2-Triphenyl-1-(4-methoxyphenyl)ethene (63). Iodobenzene, diphenylacetylene, and *p*-

methoxyphenylboronic acid were allowed to react using the general procedure for boronic

acids to produce **63** as a yellow oil (72% yield): IR (neat) 3050, 2954, 1604, 1442 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 3.74 (s, 3 H), 6.91 (m, 2 H), 7.08 (m, 18 H); ^{13}C NMR (300 MHz,

CDCl$_3$) δ 55.06, 112.97, 126.17, 126.18, 126.29, 127.54, 127.55, 127.66, 131.28, 131.31,

131.33, 132.01, 132.47, 136.06, 140.01, 140.42, 144.05, 150.87, 158.36; HRMS calcd for

C$_{27}$H$_{21}$O: 362.16707. Found: 362.16759.

1-(3-Nitrophenyl)-1,2,2-triphenylethene (65). Iodobenzene, 1-(3-nitrophenyl)-2-

phenylacetylene, and NaBPh$_4$ were allowed to react using the general procedure for borates

to produce **65** as an orange oil (70% yield): IR (neat) 3076, 3019, 1348 cm^{-1}; ^{1}H NMR (300

MHz, CDCl$_3$) δ 7.00 (m, 6 H), 7.11 (m, 9 H), 7.34 (m, 1 H), 7.37 (m, 1 H), 7.92 (m, 2 H); ^{13}C

NMR (300 MHz, CDCl$_3$) δ 121.62, 126.29, 127.21, 127.32, 127.40, 128.03, 128.30, 128.32,

128.77, 131.33, 131.43, 131.44, 137.56, 138.69, 142.57, 142.84, 142.99, 143.60, 145.83,

148.24; HRMS calcd for C$_{26}$H$_{19}$NO$_2$: 377.14158. Found: 377.14229.

1-(3-Aminophenyl)-1,2,2-triphenylethene (66). Iodobenzene, diphenylacetylene, and *m*-

nitrophenylboronic acid were allowed to react using the general procedure for boronic acids

to produce **66** as a dark yellow oil (71% yield): IR (neat) 3478, 3384, 3072, 1488 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 3.36 (m, 3 H), 6.84 (m, 1 H), 7.00 (m, 15 H); ^{13}C NMR (300

MHz, CDCl$_3$) δ 113.73, 118.39, 122.43, 126.55, 126.56, 126.64, 127.82, 127.85, 128.70,

128.88, 131.40, 131.51, 131.60, 140.88, 141.33, 143.95, 144.04, 144.06, 144.98, 144.94;

HRMS calcd for $C_{26}H_{21}N$: 347.16740. Found: 347.16781.

(Z)-1,2-Diphenyl-1,2-di-(4-chlorophenyl)ethene (78). p-Chloroiodobenzene,

diphenylacetylene, and p-chlorophenylboronic acid were allowed to react using the general

procedure for boronic acids to produce **78** as a yellow solid (67% yield): mp = 150-153 °C;

IR (neat) 3075, 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.94 (m, 8 H), 7.13 (m, 10 H); ¹³C

NMR (300 MHz, CDCl₃) δ 127.04, 128.04, 128.36, 131.43, 132.74, 132.80, 140.48, 142.08,

143.22; HRMS calcd for $C_{26}H_{18}Cl_2$: 400.07856. Found: 400.07903.

(Z)-1,2-Diphenyl-1,2-di-(4-methoxyphenyl)ethene (79). p-Iodoanisole, diphenylacetylene,

and p-methoxyphenylboronic acid were allowed to react using the general procedure for

boronic acids to produce **79** as a yellow oil (68% yield): IR (neat) 3072, 2882, 2833, 1290,

1033 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.73 (s, 3 H), 3.75 (s, 3 H), 6.62 (m, 4 H), 6.92 (m,

14 H); ¹³C NMR (300 MHz, CDCl₃) δ 55.31, 86.55, 113.20, 113.29, 126.43, 127.79, 127.86,

131.63, 132.78, 144.43; HRMS calcd for $C_{28}H_{24}O_2$: 392.17763. Found: 392.17807.

Ethyl 4-(1,2,2-triphenylethenyl)benzoate (104). Iodobenzene, ethyl 4-

(phenylethynyl)benzoate, and NaBPh₄ were allowed to react using the general procedure for

borates to produce **104** as a yellow oil (44% yield): IR (neat) 3075, 2979, 2870 cm⁻¹; ¹H

NMR (300 MHz, CDCl₃) δ 1.31 (t, J = 5.3 Hz, 3 H), 4.28 (q, J = 5.3 Hz, 2 H), 6.99 (m, 17

H), 7.75 (d, J = 6.1 Hz, 2 H); ¹³C NMR (300 MHz, CDCl₃) δ 14.55, 61.06, 126.93, 126.95,

127.07, 127.93, 128.04, 128.08, 128.47, 129.18, 131.48, 131.51, 140.22, 142.59, 143.35,

143.39, 143.49, 148.92, 166.79 (two peaks are missing, because three peaks overlap at

131.51); HRMS calcd for $C_{29}H_{24}O_2$: 404.17763. Found: 404.17823.

1,2,2-Triphenyl-1-(3-trifluoromethylphenyl)ethene (105). Iodobenzene, 1-(3-

trifluoromethyl)-2-phenylacetylene, and NaBPh$_4$ were allowed to react using the general

procedure for borates to produce **105** as an orange oil (54% yield): IR (neat) 3056, 3023,

1443 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.00 (m, 6 H), 7.10 (m, 9 H), 7.19 (m, 2 H), 7.27

(m, 2 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 122.58, 123.31, 123.36, 126.05, 127.00, 127.08,

127.11, 127.99, 128.15, 128.32, 128.38, 130.09, 131.53, 131.59, 134.79, 139.66, 142.78,

143.05, 143.27, 143.38, 144.72; HRMS calcd for C$_{27}$H$_{19}$F$_3$: 400.14389. Found: 400.14462

Ethyl 3-(1,2,2-triphenylethenyl)benzoate (106). Iodobenzene, ethyl 3-

(phenylethynyl)benzoate, and NaBPh$_4$ were allowed to react using the general procedure for

borates to produce **106** as a light yellow oil (66% yield): IR (neat) 3076, 2980, 1718, 1491,

1282 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.26 (t, J = 7.0 Hz, 3 H), 2.24 (q, J = 7.0 Hz, 2 H),

7.00 (m, 17 H), 7.76 (m, 1 H), 7.78 (m, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 16.61, 60.78,

126.84, 126.88, 126.90, 127.79, 127.94, 127.96, 127.97, 128.04, 128.65, 130.27, 131.46,

131.51, 132.65, 135.93, 139.89, 142.18, 143.27, 143.50, 143.58, 144.26, 166.76; HRMS

calcd for C$_{29}$H$_{24}$O$_2$: 404.17763. Found: 404.17823.

1,2,2-Triphenyl-1-(3-methoxyphenyl)ethene (109). Iodobenzene, 1-(3-methoxyphenyl)-2-

phenylacetylene, and NaBPh$_4$ were allowed to react using the general procedure for borates

to produce **109** as a yellow oil (75% yield): IR (neat) 3076, 3022, 2953, 1443, 1284 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 3.55 (s, 3 H), 6.59 (m, 3 H), 7.03 (m, 16 H); ^{13}C NMR (300 MHz,

CDCl$_3$) δ 55.27, 112.86, 116.89, 124.21, 126.66, 126.68, 126.69, 127.46, 127.83, 127.95,

128.79, 128.88, 131.38, 131.52, 131.55, 141.26, 143.73, 143.87, 144.05, 145.22, 159.13;

HRMS calcd for C$_{27}$H$_{22}$O: 362.16707. Found 362.16753.

1-(3-Tolyl)-1,2,2-triphenylethene (110). Iodobenzene, 1-(3-tolyl)-2-phenylacetylene, and

NaBPh$_4$ were allowed to react using the general procedure for borates to produce **110** as a

yellow oil (20% yield): IR (neat) 3076, 3021, 2918, 2849, 1491 cm^{-1}; ^{1}H NMR (300 MHz,

CDCl$_3$) δ 2.14 (s, 3 H), 6.81 (m, 5 H), 7.00 (m, 14 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 21.51,

126.13, 126.54, 127.39, 127.64, 127.79, 127.81, 127.83, 128.68, 130.41, 131.47, 131.53,

131.55, 132.18, 134.38, 137.28, 140.99, 141.27, 141.50, 143.77, 144.02; HRMS calcd for

C$_{27}$H$_{22}$: 346.17215. Found: 346.17267.

1,2,2-Triphenyl-1-(o-tolyl)ethene (111). o-Iodotoluene, diphenylacetylene, and NaBPh$_4$

were allowed to react using the general procedure for borates to produce **111** as a yellow oil

(86% yield): IR (neat) 3073, 3018, 2921, 2853, 1490 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ

2.09 (s, 3 H), 6.95 (m, 19 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 16.61, 126.45, 126.69, 126.77,

127.06, 127.58, 127.78, 127.86, 127.98, 130.74, 130.88, 131.55, 131.67, 131.91, 136.75,

141.79, 142.92, 143.16, 143.79, 143.95, 150.60; HRMS calcd for C$_{27}$H$_{22}$: 346.17215. Found

396.17267.

1-(1-Naphthyl)-1,2,2-triphenylethene (131). 1-Iodonaphthalene, diphenylacetylene, and

NaBPh$_4$ were allowed to react using the general procedure for borates to produce **131** as a

clear, colorless oil (50% yield): IR (neat) 3076 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.89 (m,

5 H), 7.04 (m, 5 H), 7.32 (m, 5 H), 7.36 (m, 2 H), 7.64 (m, 2 H), 7.67 (m, 1 H), 7.75 (m, 1

H), 8.00 (m, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 125.48, 125.59, 126.09, 126.58, 126.62,

126.88, 127.53, 127.88, 128.04, 128.46, 129.62, 130.24, 130.63, 131.67, 132.56, 134.00,

141.34, 143.23, 143.28, 143.45, 143.52, 143.89, 145.33, 145.77; HRMS calcd for C$_{30}$H$_{22}$:

382.17215. Found: 382.17261.

1-(3,4-Dimethoxyphenyl)-1,2,2-triphenylethene (134). Iodobenzene, 1-(3,4-dimethoxyphenyl)-2-phenylacetylene, and NaBPh$_4$ were allowed to react using the general procedure for borates to produce **134** as a yellow oil (55% yield): IR (neat) 3075, 2955, 1269, 1140, 1027 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.44 (s, 3 H), 3.79 (s, 3 H), 6.55 (m, 3 H), 7.04 (m, 12 H), 7.46 (m, 2 H), 7.81 (d, J = 6.8, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 55.75, 55.88, 110.41, 115.31, 124.20, 126.50, 126.55, 126.68, 127.84, 128.08, 128.17, 131.40, 131.57, 131.67, 134.95, 136.40, 140.92, 143.94, 144.09, 144.47, 147.80, 148.05; HRMS calcd for C$_{28}$H$_{24}$O$_2$: 392.17763. Found: 392.17821.

Ethyl 2,3,3-triphenylacrylate (141). Iodobenzene, ethyl phenylpropiolate, and NaBPh$_4$ were allowed to react using the general procedure for borates to produce **141** as a clear, colorless oil (64% yield): IR (neat) 3050, 2998, 1716, 1492, 1253 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.96 (t, J = 7.1 Hz, 3 H), 4.03 (q, J = 7.1 Hz, 2 H), 7.10 (m, 2 H), 7.12 (m, 8 H), 7.32 (m, 5 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 13.95, 61.18, 127.64, 127.88, 128.08, 128.28, 128.37, 128.44, 129.40, 130.12, 131.16, 134.04, 137.77, 140.82, 142.73, 146.19, 170.75; HRMS calcd for C$_{23}$H$_{20}$O$_2$: 328.14633. Found: 328.16700.

1,1,2-Triphenyl-1-buten-3-one (170). Iodobenzene, 1-phenyl-1-butyn-3-one, and NaBPh$_4$ were allowed to react using the general procedure for borates to produce **170** as a yellow oil (52% yield): IR (neat) 3077, 2992, 1682, 1491 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.09 (s, 3 H), 6.97 (m, 2 H), 7.00 (m, 2 H), 7.12 (m, 3 H), 7.19 (m, 4 H), 7.33 (m, 4 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 31.44, 127.63, 127.85, 128.00, 128.61, 128.71, 128.78, 130.09, 130.33, 131.22, 138.72, 140.99, 142.21, 142.82, 145.29, 190.87; HRMS calcd for C$_{22}$H$_{18}$O: 298.13577. Found: 298.13629.

(E)-Ethyl 2,3-diphenyl-2-butenoate (171). Iodobenzene, ethyl 2-butynoate, and PhB(OH)$_2$

were allowed to react using the general procedure for boronic acids to produce **171** as an

orange oil (57% yield): IR (neat) 3078, 2978, 2851, 1715, 1490, 1247 cm^{-1}; ^{1}H NMR (300

MHz, CDCl$_3$) δ 1.26 (t, J = 5.0 Hz, 3 H), 2.32 (s, 3 H), 4.23 (q, J = 5.0 Hz, 2 H), 7.00 (m, 10

H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 14.45, 23.30, 61.13, 126.99, 127.24, 127.98, 128.12,

128.74, 130.06, 132.29, 137.35, 142.08, 143.50, 169.93; HRMS calcd for C$_{18}$H$_{18}$O$_2$:

266.13068. Found: 266.13036.

1,1,2-Triphenyl-1-hexene (176). Iodobenzene, 1-phenyl-1-hexyne, and NaBPh$_4$ were

allowed to react using the general procedure for borates to produce **176** was a light yellow oil

(20% yield): IR (neat) 3078, 2958, 2859 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.77 (t, J = 5.3

Hz, 3 H), 1.19 (m, 4 H), 2.41 (m, 2 H), 6.87 (m, 2 H), 6.97 (m, 3 H), 7.00 (m, 4 H), 7.23 (m,

4 H), 7.33 (m, 2 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 14.16, 22.96, 31.11, 36.33, 125.89,

126.35, 126.77, 127.55, 127.56, 127.99, 128.00, 128.31, 129.73, 129.80, 130.95, 141.33,

142.73, 143.28; HRMS calcd for C$_{24}$H$_{24}$: 312.18780. Found: 312.18835.

3,3-Dimethyl-1,1,2-triphenyl-1-butene (177). Iodobenzene, 3,3-dimethyl-1-phenyl-1-

butyne. and NaBPh$_4$ were allowed to react using the general procedure for borates to produce

177 as a colorless oil (53% yield): IR (neat) 3075, 2958, 2865 cm^{-1}; ^{1}H NMR (300 MHz,

CDCl$_3$) δ 0.99 (s, 9 H), 6.93 (m, 9 H), 7.26 (m, 6 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 32.42,

37.14, 125.19, 125.54, 126.39, 126.88, 127.51, 128.09, 129.23, 129.24, 130.99, 141.00,

142.93, 144.67, 145.51, 149.06. HRMS calcd for C$_{24}$H$_{24}$: 312.18780. Found: 312.18875.

(E)-5-(1,2-Diphenyl-1-hexenyl)pyrimidine (179). Iodobenzene, 5-(1-hexynyl)pyrimidine,

and NaBPh$_4$ were allowed to react using the general procedure for borates to produce **179** as

a yellow oil (59% yield): IR (neat) 2995, 2858, 1546 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ

0.77 (t, J = 7.0 Hz, 3 H), 1.30 (m, 4 H), 2.41 (t, J = 7.0 Hz, 2 H), 6.82 (m, 2 H), 7.04 (m, 8

H), 8.71 (s, 2 H), 9.13 (s, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 14.03, 22.99, 31.42, 35.99,

126.80, 127.07, 128.11, 128.26, 129.46, 130.89, 132.20, 137.21, 141.42, 141.46, 145.36,

157.06, 157.33; HRMS calcd for C$_{22}$H$_{22}$N$_2$: 314.17830. Found: 314.17875.

(E)-1-(3-Trifluoromethylphenyl)-1,2-diphenyl-1-hexene (182). Iodobenzene, 3-(1-

hexynyl)-1-trifluoromethylbenzene, and PhB(OH)$_2$ were allowed to react using the general

procedure for boronic acids to produce **182** as a light yellow oil (53% yield): IR (neat) 3077,

2856 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.75 (t, J = 7.0 Hz, 3 H), 1.20 (m, 4 H), 2.37 (m, 2

H), 6.84 (m, 2 H), 7.00 (m, 8 H), 7.14 (m, 4 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 13.99, 16.61,

22.93, 31.26, 35.90, 123.64, 123.69, 126.29, 126.38, 126.44, 126.62, 127.76, 128.12, 128.85,

129.66, 130.93, 133.24, 142.19, 142.41, 142.70, 144.37; HRMS calcd for C$_{25}$H$_{23}$F$_3$:

380.17519. Found: 380.17562.

(E)-Ethyl-2,3-diphenyl-3-(o-tolyl)acrylate (190). o-Iodotoluene, ethyl phenylpropiolate,

and phenylboronic acid were allowed to react using the general procedure for boronic acids

to produce **190** as a clear, light yellow oil (50% yield): IR (neat) 3077, 2977, 1717, 1492,

1036 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.89 (t, J = 7.0 Hz, 3 H), 2.20 (s, 3 H), 3.92 (q, J =

7.0 Hz, 2 H), 6.93 (m, 1 H), 7.09 (m, 7 H), 7.30 (m, 6 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ

16.39, 19.85, 60.70, 125.67, 127.51, 127.65, 127.73, 127.96, 128.07, 129.24, 130.18, 130.39,

130.74, 133.03, 136.73, 137.44, 140.60, 142.33, 147.92, 169.99; HRMS calcd for C$_{24}$H$_{22}$O$_2$:

342.16198. Found: 342.16247.

5-[1-(4'-Chlorophenyl)-2-phenylhexenyl]pyrimidine (192). Iodobenzene, 5-(1-

hexynyl)pyrimidine, and p-chlorophenylboronic acid were allowed to react using the general

procedure for boronic acids to produce **192** as a yellow oil (68% yield): IR (neat) 3050,

2930, 1590, 1162 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.76 (t, J = 7.0 Hz, 3 H), 1.23 (m, 4

H), 2.39 (m, 2 H), 6.75 (m, 2 H), 7.02 (m, 4 H), 7.18 (m, 3 H), 8.61 (s, 2 H), 9.14 (s, 1 H);

^{13}C NMR (300 MHz, CDCl$_3$) δ 14.01, 22.99, 31.37, 36.09, 127.33, 128.38, 128.49, 129.36,

131.05, 132.19, 132.74, 136.80, 139.95, 141.07, 146.16, 157.31, 157.33; HRMS calcd for

C$_{22}$H$_{21}$ClN$_2$: 348.13933. Found: 348.13973.

5-[1-(4'-Methoxyphenyl)-2-phenyl-1-hexenyl]pyrimidine (193). Iodobenzene, 5-(1-

hexynyl)pyrimidine, and p-methoxyphenylboronic acid were allowed to react using the

general procedure for boronic acids to produce **193** as an orange oil (70% yield): IR (neat)

3031, 2955, 1605, 1463, 1247 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.77 (t, J = 5.0 Hz, 3 H),

1.22 (m, 4 H), 2.39 (m, 2 H), 3.69 (s, 3 H), 6.57 (m, 2 H), 6.73 (m, 2 H), 7.10 (m, 5 H), 8.62

(s, 2 H), 9.14 (s, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 14.16, 23.00, 31.47, 36.04, 55.30,

113.51, 126.94, 128.34, 129.47, 131.67, 132.11, 133.88, 137.55, 141.70, 144.54, 156.99,

157.34, 158.38; HRMS calcd for C$_{23}$H$_{24}$ON$_2$: 344.18886. Found: 344.18957.

References

1. (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas*

1990, *109*, 567. (c) Trost, B. *Science* **1991**, *234*, 1471. (d) Negishi, E.; Copéret, C.; Ma,

S.; Liou, S.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (e) Ojima, I.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (f) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111.

2. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

3. (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (c) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.

4. Larock, R. C.; Doty, M. J.; Cacchi, S. J. *J. Org. Chem.* **1993**, *58*, 4579.

5. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

6. (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.

7. Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551.

8. (a) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A. *Eur. J. Org. Chem.* **1999**, 1421. (b) Hardcastle, I. R.; Rowlands, M. G.; Grimshaw, R. M.; Houghton, J.; Jarman, M.; Sharff, A.; Neidle, S. *J. Med. Chem.* **1996**, *39*, 999. (c) McCague, R.; Leclercq, G.; Legros, N.; Goodman, J.; Blackburn, G. M.; Jarman, M.; Foster, A. B. *J. Med. Chem.* **1989**, *32*, 2527. (d) Al-Hassan, M. I. *Syn. Commun.* **1987**, *17*, 1413. (e) Al-Hassan, M. I. *Syn. Commun.* **1987**, *17*, 1247. (f) Al-Hassan, M. I. *Syn. Commun.* **1989**, *19*, 1619. (g) El-Wakil, H. A. *Org. Prep. Proc. Int.* **1991**, *23*, 754. (h) McCague, R.; Potter, G. A.; Jarman, M. *Org. Prep. Proc. Int.* **1994**, *26*, 343. (i) Chen, J.; Li, J.; Yu, M.-H.; Chen, W.-X. *Org. Prep. Proc. Int.* **1997**, *29*, 569. (j) Oda, H.; Morishita, M.; Fugami, K.; Sano, H.; Kosugi, M. *Chem. Lett.* **1996**, 811. (k) Okuma, K.; Koda, G.; Okumura, S.; Ohno, A. *Chem. Lett.*

1996, 609. (l) Okuma, K.; Yamasaki, Y.; Komiya, T.; Kodera, Y.; Ohta, H. *Chem. Lett.*

1987, 357. (m) Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.

(n) Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475. (o) Baran, J.;

Laszlo, P. *Tetrahedron Lett.* **1985**, *26*, 5135. (p) Kamata, M.; Murayama, K.; Miyashi, T.

Tetrahedron Lett. **1989**, *30*, 4129. (q) Shi, D.-Q.; Chen, J.-X.; Chai, W.-Y.; Chen, W.-X.;

Kao, T.-Y. *Tetrahedron Lett.* **1993**, *34*, 2963. (r) Stüdemann, T.; Ibrahim-Ouali, M.;

Knochel, P. *Tetrahedron* **1998**, *54*, 1299. (s) Gauthier, S.; Sancéau, J-Y.; Mailhot, J.;

Caron, B.; Cloutier, J. *Tetrahedron* **2000**, *56*, 703. (t) Miller, R. B.; Al-Hassan, M. I. *J.*

Org. Chem. **1985**, *50*, 2121. (u) Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*,

6184. (v) Katritzky, A. R.; Cheng, D.; Henderson, S. A.; Li, J. *J. Org. Chem.* **1998**, *63*,

6704. (w) Mahato, S. B.; Mandal, N. B.; Pal, A. K.; Maitra, S. K.; Lehmann, C.; Luger,

P. *J. Org. Chem.* **1988**, *53*, 5554. (x) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.*

1988, *53*, 607. (y) Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**,

122, 3228. (z) Ossor, H.; Pfeffer, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1540. (aa)

Suzuki, H.; Tani, H.; Takeuchi, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2421. (bb) Reger, D.

L.; Mintz, E.; Lebioda, L. *J. Am. Chem. Soc.* **1986**, *108*, 1940. (cc) Bower, A.; Miller, M.

W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, 254.

9. (a) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (b) Grigg, R.;

Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (c) Grigg, R.; Sridharan, V. *Pure*

Appl. Chem. **1998**, *70*, 1047. (d) Grigg, R. *J. Heterocyclic Chem.* **1994**, *31*, 631. (e)

Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323.

10. de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

11. (a) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Workakun, T. *Tetrahedron* **1992**, *48*, 7297. (b) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Workakun, T. *Tetrahedron Lett.* **1988**, *29*, 5565. (c) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 4429. (d) Grigg, R.; Sridharan, V.; Zhang, J. *Tetrahedron Lett.* **1999**, *40*, 8277. (e) Grigg, R.; Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 6573. (f) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson D. *Tetrahedron* **1997**, *53*, 11803. (g) Grigg, R.; Major, J. P.; Martin, F. M.; Whittaker M. *Tetrahedron Lett.* **1999**, *40*, 7709. (h) Evans, P.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1999**, *40*, 3021. (i) Grigg, R.; Sridharan, V.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1139. (j) Grigg, R.; Pratt, R. *Tetrahedron Lett.* **1997**, *38*, 4489. (k) Grigg, R.; Kennewell, P.; Teasdale, A. J. *Tetrahedron Lett.* **1992**, *33*, 7789. (l) Grigg, R.; Sridharan, V.; Terrier, C. *Tetrahedron Lett.* **1996**, *37*, 4421. (m) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 7661. (n) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. (o) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4329. (p) Brown, A.; Grigg, R.; Ravishankar, T.; Thornton-Pett, M. *Tetrahedron Lett.* **1994**, *35*, 2753. (q) Grigg, R.; Rasul, R.; Redpath, J.; Wilson, D. *Tetrahedron Lett.* **1996**, *37*, 4609. (r) Böhmer, J.; Grigg, R. *Tetrahedron* **1999**, *55*, 13463.

12. (a) Grigg, R.; Loganathan, V.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1996**, *52*, 11479. (b) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343. (c) Grigg, R.;

Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 6573. (d)

Brown, S.; Clarkson S.; Grigg, R.; Sridharan, V. *J. Chem. Soc., Chem. Commun.* **1995**,

1135. (e) Casasachi, A.; Grigg, R.; Sansono, J. M.; Wilson, D.; Redpath, J. *Tetrahedron*

Lett. **1996**, *37*, 4413. (f) Luo, F.-T.; Wang, R.-T. *Tetrahedron Lett.* **1991**, *32*, 7703. (g)

Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4864. (h) Luo, F-T.;

Wang, R.-T. *Heterocycles* **1990**, *31*, 2181. (i) Luo, F.-T.; Wang, R.-T. *Heterocycles*

1990, *31*, 1543. (j) Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4846.

(k) Grigg, R.; Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1990**,

31, 6573. (l) Grigg, R.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*,

2545. (m) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.;

Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135. (n) Negishi, E.; Noda, Y.; Lamaty, F.;

Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (o) Grigg, R.; Savic, V. *Tetrahedron*

Lett. **1996**, *37*, 6565. (p) Grigg, R.; Santhakumar, V.; Sridharan, V. *Tetrahedron Lett.*

1993, *34*, 3163. (q) Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.*

1992, *114*, 1923. (r) Grigg, R.; Rasul, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 1825.

(s) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem.*

Soc. **1994**, *116*, 7923. (t) Copéret, C.; Sugihara, T.; Negishi, E. *Tetrahedron Lett.* **1995**,

36, 1771. (u) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**,

29, 4325. (v) Wu, G-Z.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507.

13. (a) Fugami, K.; Mishiba, Y.; Hagiwara, S.; Koyama, D.; Kammeyama, M.; Kosugi, M.

Synlett **2000**, 553. (b) Fugami, K.; Hagiwara, S.; Oda, H.; Kosugi, M. *Synlett* **1998**, 447.

(c) Oda, H.; Ito, K.; Kosugi, M.; Migita, T. *Chem. Lett.* **1994**, 1443. (d) Kosugi, M.;

Kimura, T.; Oda, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3522. (e) Bhagwat, S.;

Gude, C.; Cohen, D. S.; Lee, W.; Furness, P.; Clarke, F. H. *J. Med. Chem.* **1991**, *34*,

1790. (f) Kosugi, M.; Tamura, H.; Sano, H.; Migita, T. *Tetrahedron* **1989**, *45*, 961. (g)

Kosugi, M.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1987**, 193. (h) Catellani, M.;

Chiusoli, G. P.; Concari, S. *Tetrahedron* **1989**, *45*, 5263. (i) Torii, S.; Okumoto, H.;

Ozaki, H.; Nakayasu, S.; Tadokoro, T.; Kotani, T. *Tetrahedron Lett.* **1992**, *33*, 3499. (j)

Torii, S.; Okumoto, H.; Ozaki, H.; Nakayasu, S.; Kotani, T. *Tetrahedron Lett.* **1990**, *31*,

5319. (k) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1985**, *26*, 2763. (l) Larock, R. C.;

Hershberger, S. S.; Takagi, K.; Mitchell, M. A. *J. Org. Chem.* **1986**, *51*, 2450. (m)

Larock, R. C.; Burkhart, J. P.; Oertle, K. *Tetrahedron Lett.* **1982**, *23*, 1071. (n) Torii, S.;

Okomoto, H.; Ozaki, H.; Nakayasu, S.; Kotani, T. *Tetrahedron Lett.* **1990**, *31*, 5319. (o)

Torii, S.; Okumoto, H.; Kotani, T.; Nakayasu, S.; Ozaki, H. *Tetrahedron Lett.* **1992**, *33*,

3503. (p) Larock, R. C.; Babu, S. *Tetrahedron* **1987**, *43*, 2013. (q) Larock, R. C.;

Hershberger, S. S.; Takagi, K.; Mitchell, M. A. *J. Org. Chem.* **1986**, *51*, 2450. (r)

Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1982**, *23*, 4517. (s) Catellani, M.;

Chiusoli, G. P., Mari, A. *J. Organomet. Chem.* **1984**, *275*, 129. (t) Larock, R. C.;

Narayanan, K.; Carlson, R. K.; Ward, J. A. *J. Org. Chem.* **1987**, *52*, 1364.

14. (a) van Asselt, R.; Gielens, E. E. C. G.; Rülke, R. E.; Elsevier, C. J. *J. Chem. Soc., Chem.

Commun.* **1993**, 1203. (b) Dalcanale, E.; An, Z.; Battaglia, L. P.; Catellani, M.; Chiusoli,

G. P. *J. Organomet. Chem.* **1992**, *437*, 375. (c) Markies, B. A.; Verkerk, K. A. N.;

Rietveld, M. H. P.; Boersma, J.; Kooijman, H.; Spek, A. L.; van Koten, G. *J. Chem. Soc.,

Chem. Commun.* **1993**, 1317. (d) Roberto, D.; Catellani, M.; Chiusoli, G. P. *Tetrahedron

Lett.* **1988**, *29*, 2115. (e) Catellani, M.; Chiusoli, G. P.; Peloso, C. *Tetrahedron Lett.*

1983, *24*, 813. (f) Larock, R. C.; Hsu, M. H.; Narayanan, K. *Tetrahedron* **1987**, *43*, 2891.

(g) James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810.

15. (a) Catellani, M.; Cugini, F.; Bocelli, G. *J. Organomet. Chem.* **1999**, *584*, 63. (b)

Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769. (c) Bocelli, G.; Catellani, M.; Ghelli, S. *J.*

Organomet. Chem. **1983**, *458*, C12. (d) Catellani, M.; Fagnola, M. C. *Gazz. Chim. Ital.*

1992, *122*, 481. (e) Roberto, D.; Catellani, M.; Chiusoli, G. P.; Mann, B. E. *Gazz. Chim.*

Ital. **1990**, *120*, 251. (f) Catellani, M.; Chiusoli, G. P.; Castagnoli, C. *J. Organomet.*

Chem. **1991**, *407*, C30. (g) Bocelli, G.; Catellani, M.; Chiusoli, G. P. *J. Organomet.*

Chem. **1984**, *279*, 225. (h) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1983**,

247, C59. (i) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *437*, 369.

16. Oda, H.; Hamataka, K.; Fugami, K.; Kosugi, M.; Migita, T. *Synlett* **1995**, 1225.

17. Grigg, R.; Brown, S.; Sridharan, V.; Uttley, M. D. *Tetrahedron Lett.* **1997**, *38*, 5031.

18. (a) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157. (b)

Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19. (c) Grigg, R.; Kennewell, P.;

Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 153. (d) Arcadi, A.; Bernocchi,

E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron Lett.* **1989**, *30*, 3465.

(e) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B.

Tetrahedron **1988**, *44*, 481. (f) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1985**,

41, 5121.

19. (a) Jeffrey, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron*

Lett. **1985**, *26*, 2667.

20. Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.

21. (a) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (b) Homsi, F.; Nozaki, K.; Hiyama, T. *Tetrahedron Lett.* **2000**, *41*, 5869. (c) Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Synlett* **1999**, 199. (d) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266. (e) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (f) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137. (g) Brescia, M.-R.; DeShong, P. *J. Org. Chem.* **1998**, *63*, 3156. (h) Hatanaka, Y.; Goda, K.; Hiyama, T. *J. Organomet. Chem.* **1994**, *465*, 97.

22. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry, 3rd Edition*; Harper Collins: New York, 1987.

23. Itatani, H.; Bailar, J. C. *J. Am. Oil Chem. Soc.* **1967**, *44*, 147.

24. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagaihara, N. *Synthesis* **1980**, 627.

25. (a) Mataka, S.; Liu, G.-B.; Tashiro, M. *Synthesis* **1995**, 133. (b) Yoshida, F. *J. Org. Chem.* **1973**, *38*, 1045.

26. Rudenko, A. P.; Vasil'ev, A. V. *Russ. J. Org. Chem.* **1995**, *31*, 1360.

Shirakawa, E.; Yoshida, H.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 3759.

CHAPTER 3. PALLADIUM MIGRATION FROM AN ARYL GROUP TO AN ACYL GROUP

A paper to be submitted to the *Journal of Organic Chemistry*

Daniel E. Emrich and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Abstract

A palladium(0)-catalyzed reaction wherein the palladium moiety in an arylpalladium intermediate migrates to form an acylpalladium intermediate has been investigated. A mechanism for this new palladium migration chemistry is proposed with supporting evidence from deuterium labeling experiments. The reaction has been optimized by varying the base, the ligand, and the solvent, but the original conditions have proven satisfactory for the migration to occur. These conditions include: 1 equiv of the aryl iodide, 5 mol % of Pd(OAc)$_2$, 5 mol % of bis(diphenylphosphino)methane (dppm), 2 equivs of cesium pivalate (CsPiv), and 10 equivs of n-butanol in DMF at 100 °C for 1 day. Formamides, aldehydes, and formates have also been observed to undergo this new palladium migration chemistry, suggesting that this type of migration chemistry is fairly general.

Introduction

Palladium has been used catalytically in a wide variety of synthetic reactions, because

of its compatibility with many functional groups and because it is nontoxic.[1] The Larock

group has used palladium for the synthesis of long chain compounds[2] and heterocycles.[3] In

these instances, palladium migration chemistry has been employed. This chemistry involves

the migration of palladium down a saturated carbon chain by elimination of a β-hydride and

palladium to form an olefin complex, such as 2 (Scheme 1). The palladium hydride

reversibly readds to the double bond with the opposite regiochemistry to form 3, effectively

moving the palladium down the carbon chain until a stable palladium intermediate is formed,

such as the π-allylpalladium species 4.

Scheme 1
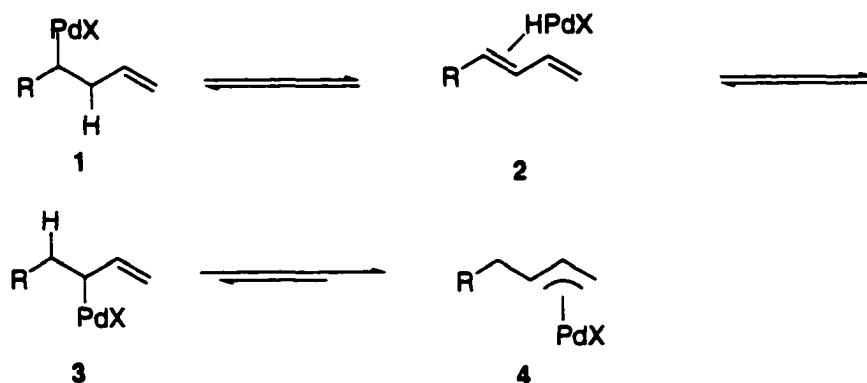
Recently the Larock group has discovered a different kind of migration chemistry,

which involves the migration of palladium from one carbon to another "through space." This

new process was observed during a study of the annulation of unsymmetrical iodobiphenyls

onto unsymmetrical, internal alkynes (eq 1). Regioselectivity due to steric effects was
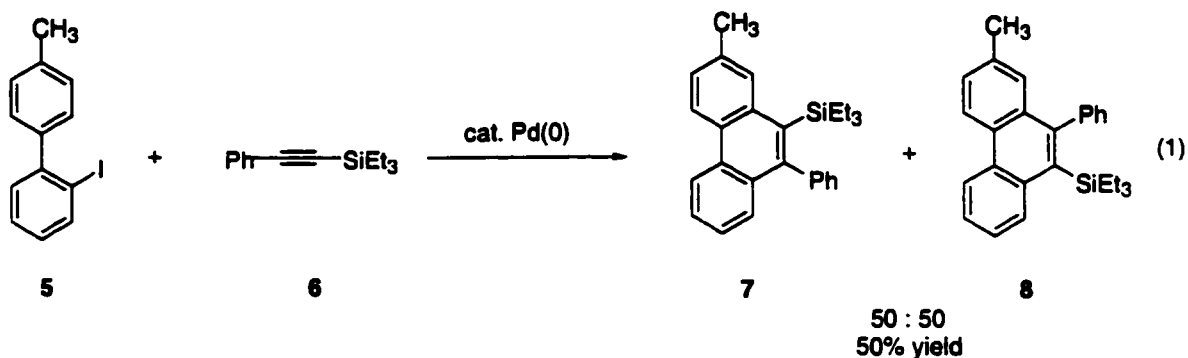
expected in this reaction based on the Larock group's previous annulation chemistry,[4] but this was not observed in the process described in equation 1.

The lack of regioselectivity in equation 1 can be explained by a reversible reaction mechanism where the palladium migrates from one aryl ring to the other (Scheme 2). After oxidative addition of the unsymmetrical iodobiphenyl to the palladium to form 9, the palladium may undergo one of two mechanisms: (A) electrophilic aromatic substitution onto the adjacent aryl ring to form 10, a palladium(II) intermediate; or (B), oxidative addition of an adjacent aryl C-H bond onto the palladium to form 11, a palladium(IV) intermediate. Either mechanism leads to formation of intermediate 12. Organopalladium intermediates 9 or 12 may then undergo regioselective carbopalladation onto the alkyne to give the observed mixture of phenanthrenes 7 and 8.

The Larock group has sought to further prove that palladium is indeed migrating from one aryl ring to the other. The iodobiphenyl 5 has also been shown to undergo a Heck reaction using the reaction conditions in equation 2 that were optimized for the reaction shown in equation 2. The result is a 50:50 mixture of two regioisomers, 14 and 15, in a

Scheme 2

5% Pd(OAc)$_2$
5% dppm
2 CsO$_2$CC(CH$_3$)$_3$
100 °C, 24 h, DMF

50 : 50
88% yield

(2)
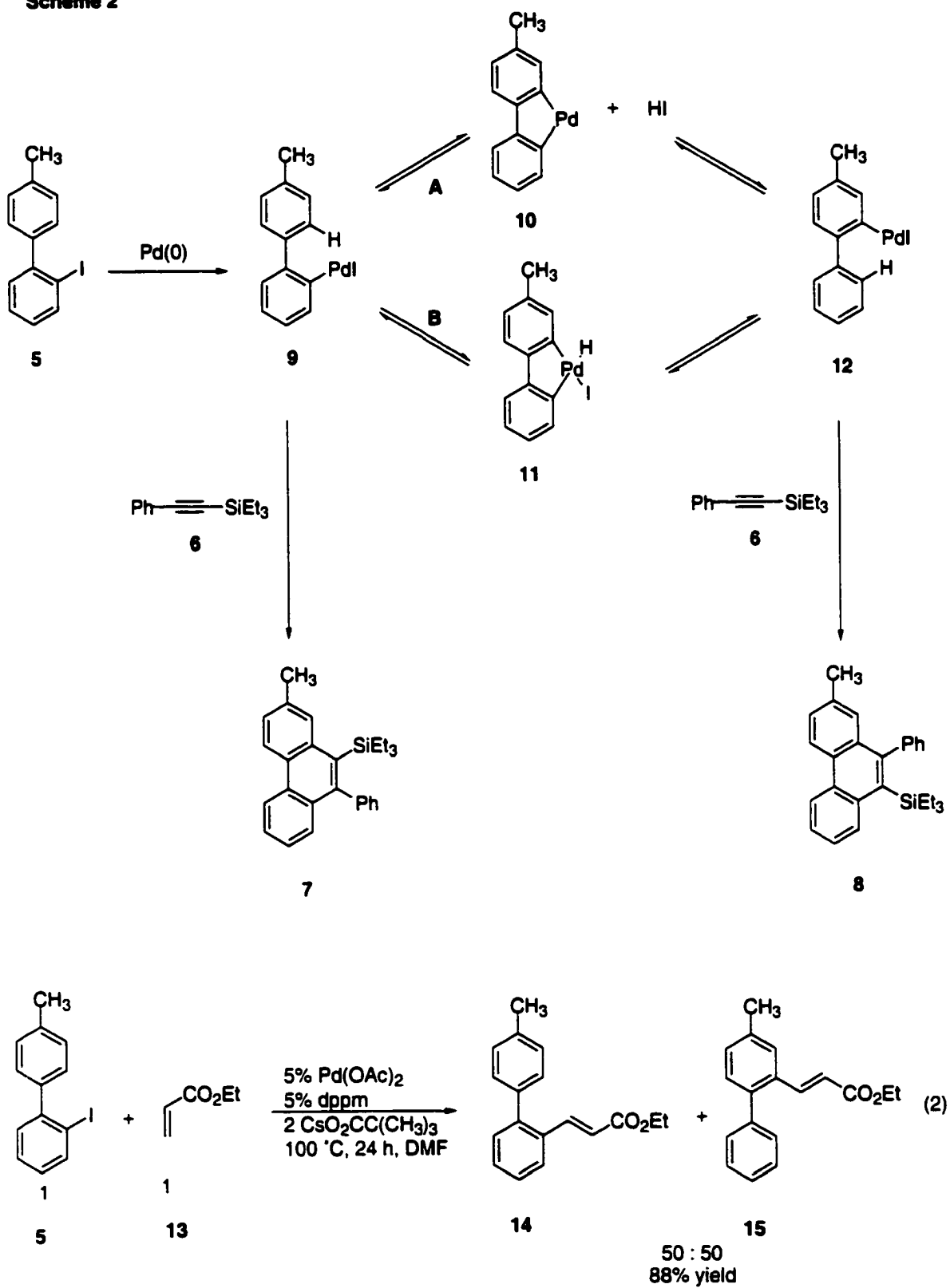
combined 88% yield (eq 2). The fact that there were two regioisomers implies that the

palladium migrated from one aryl ring to the adjacent aryl ring.

The Larock group has also shown that known, naturally occurring ring systems can be

formed by this migration process. The unsymmetrical iodobiphenyl **16** undergoes palladium

migration under our reaction conditions to form compound **17** (eq 3). This example shows

that the palladium intermediate can be trapped by cross-coupling with a neighboring

heterocycle. As shown in Scheme 3, aryl iodide **18** forms the polycyclic, aromatic

hydrocarbon **23**, presumably by the same palladium migration mechanism mentioned earlier.
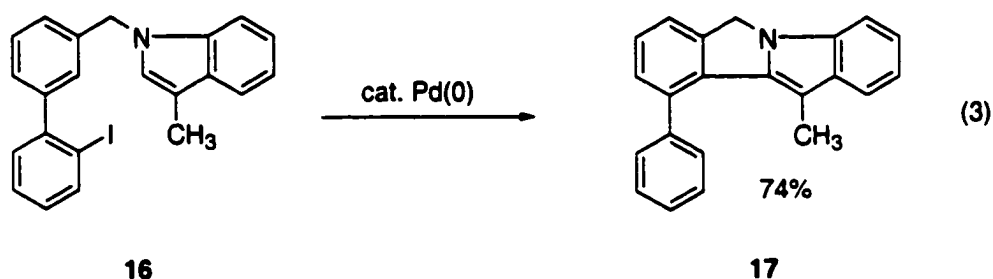
In order to use this palladium migration chemistry synthetically, the Larock group

needed to explore the reaction conditions wherein palladium migrates through space. Herein

we report conditions where palladium migrates from an aryl group to an acyl group

producing a novel new synthesis of carbamates and esters. Although there are currently

more efficient routes to the synthesis of carbamates and esters, this palladium migration

chemistry may provide a unique new route to acylpalladium intermediates of value in organic

synthesis.

Scheme 3
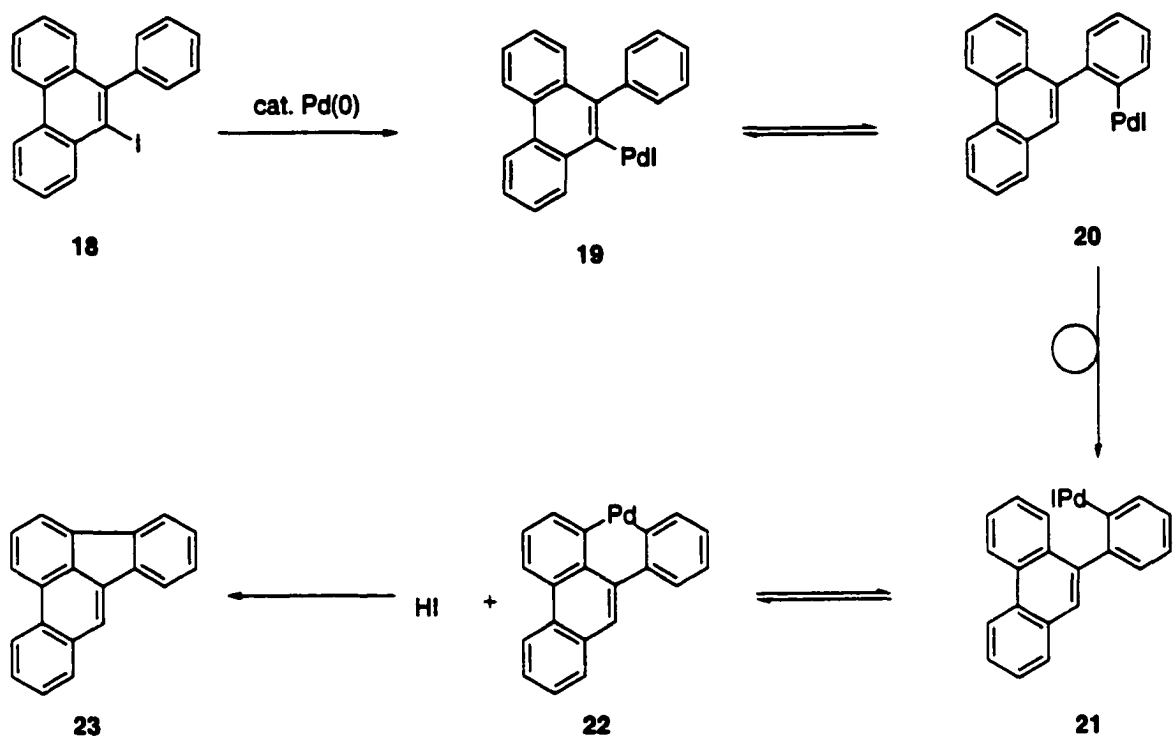
Results and Discussion

Our first example of palladium migrating from an aryl group to an acyl group is

shown in equation 4. One equiv of the aryl iodide N-(2-iodophenyl)formamide (24) (0.25

mmol) was allowed to react with 5 mol % of Pd(OAc)$_2$ (0.012 mmol), 5 mol % of

bis(diphenylphosphino)methane (dppm) (0.012 mmol), 2 equivs of cesium pivalate (CsPiv)

(0.50 mmol), and 4 equivs of n-butanol (1.00 mmol) in DMF at 100 °C for 1 day. n-Butyl-N-

phenylcarbamate (25) and N-phenyl-2,2-dimethylpropanamide (26) were formed in 30% and

15% yields respectively. The dppm serves as a chelating ligand for the palladium catalyst,

presumably making it more nucleophilic. CsPiv serves as a mild base to absorb the hydrogen

NHCO₂(CH₂)₃CH₃ compound

$$\underset{\textbf{24}}{\text{(2-iodophenyl)NHCHO}} \xrightarrow[\substack{2\ \text{CsPiv} \\ 4\ n\text{-butanol} \\ \text{DMF, 100 °C, 1 day}}]{\substack{5\ \text{mol \% Pd(OAc)}_2 \\ 5\ \text{mol \% dppm}}} \underset{\textbf{25}}{\text{Ph-NHCO}_2(\text{CH}_2)_3\text{CH}_3} + \underset{\textbf{26}}{\text{Ph-NHCOC(CH}_3)_3} \tag{4}$$
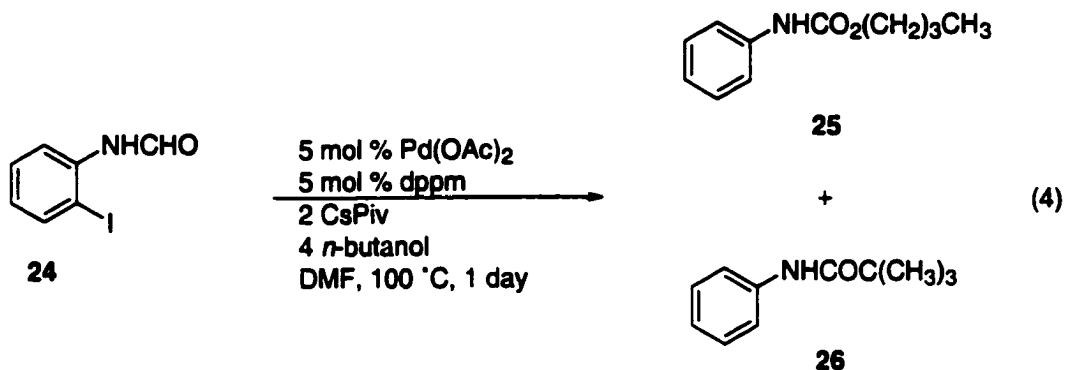
iodide (HI) generated during the reaction. The *n*-butanol serves as a trapping agent for the acylpalladium intermediate.

The mechanism for the proposed migration is shown in Scheme 4. After the aryl iodide oxidatively adds to Pd(0), the palladium may undergo a Pd(IV) process, where the C–H bond of the formyl group oxidatively adds to the palladium, to give **28**. Reductive elimination gives intermediate **30**. The very reactive acylpalladium **30** is trapped by *n*-butanol giving the observed product **25**.

Side product **26** could result from the mechanism shown in Scheme 5. After oxidative addition of **24** to palladium(0), intermediate **27** and then **28** form and a rearrangement gives **30** as shown in Scheme 5. The iodide in intermediate **30** is displaced by the pivalate anion to form **31**, which undergoes reductive elimination regenerating the palladium(0) catalyst and forming **32**. Intermediate **32** loses CO_2 forming side product **26**. The loss of CO_2 from similar types of substrates is known in the literature.[5]

We attempted to eliminate side product **26** from the reaction by employing sodium butyrate [NaO₂C(CH₂)₂CH₃] in place of CsPiv. Because **26** possesses a *t*-butyl group believed to originate from the CsPiv, we expected that sodium butyrate, which does not
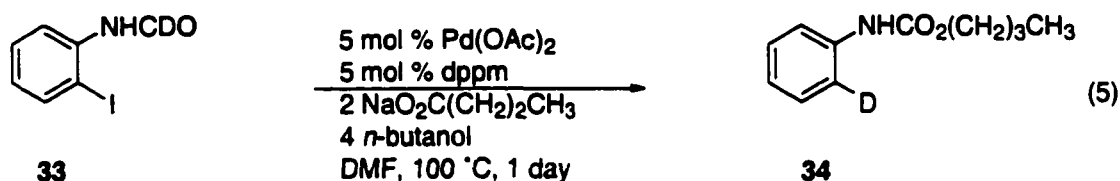
Scheme 4
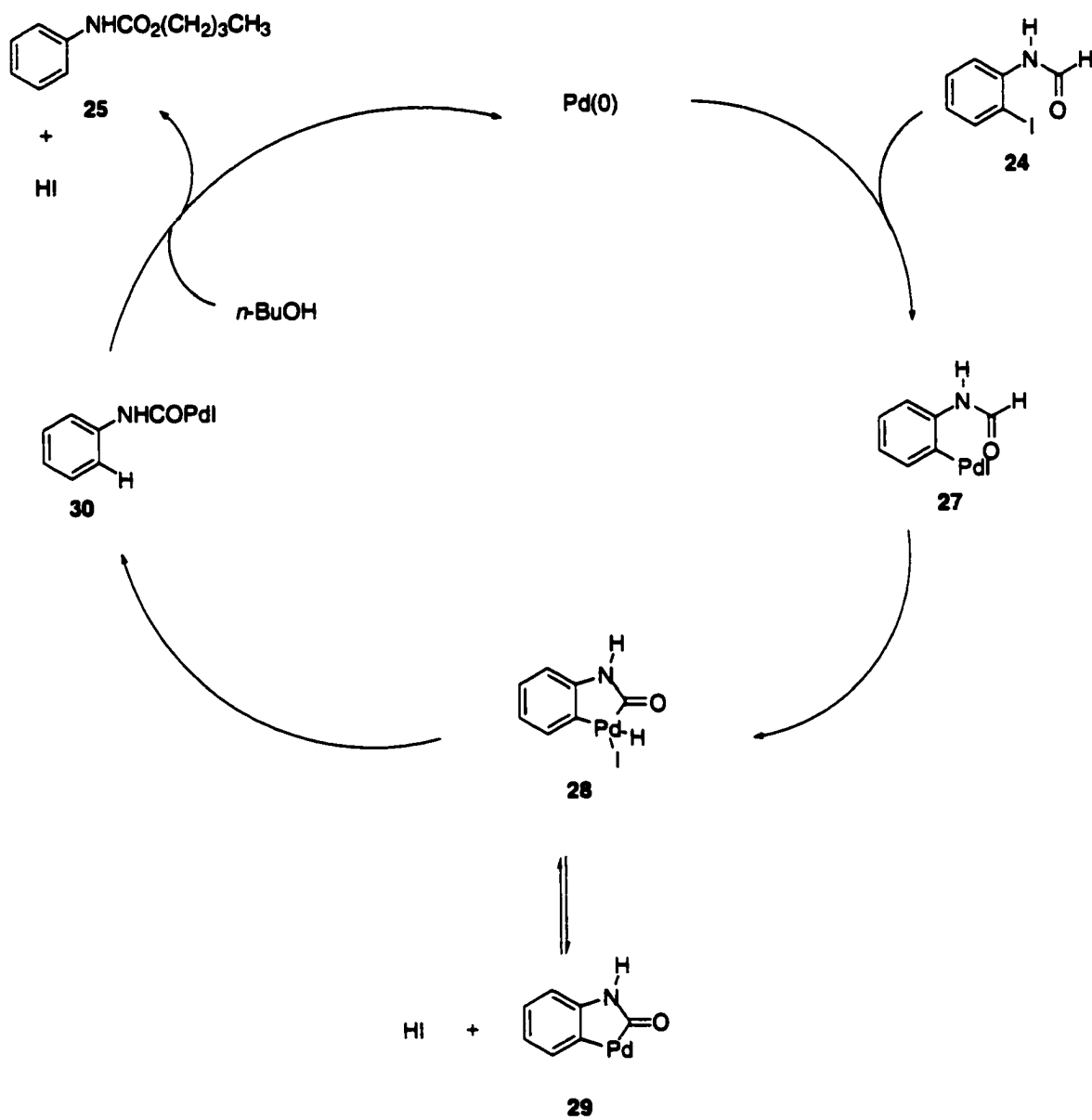
Scheme 5
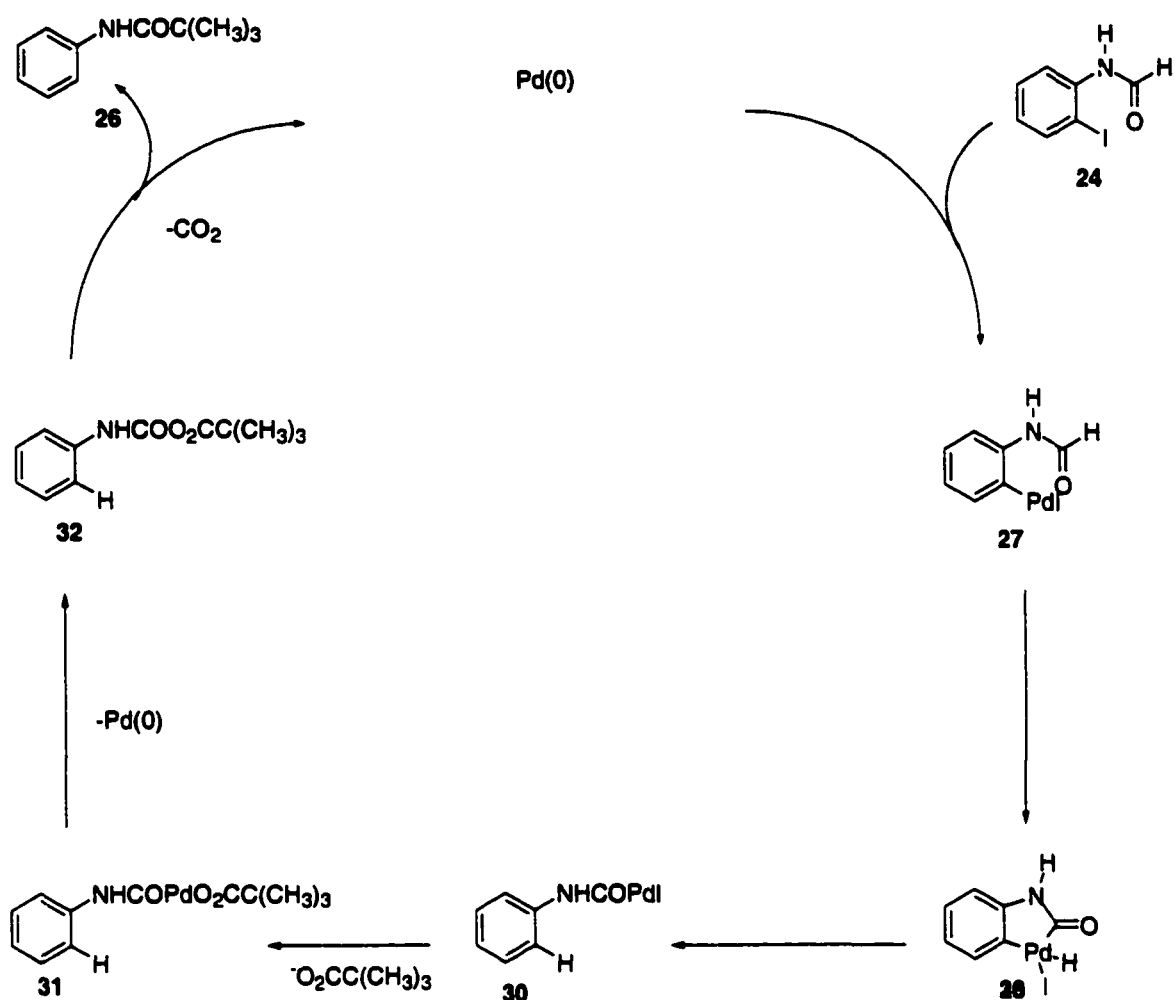
possess a *t*-butyl group, would not produce **26**. As expected, employing sodium butyrate

gave a 42% yield of **25** and no **26**.

Having eliminated **26**, we next ran deuterium labeling experiments to further support

our proposed mechanism shown in Scheme 4. *N*-(2-Iodophenyl)formamide-1-*d* (**33**) was

prepared with greater than 98% deuterium incorporation as determined by gas

chromatography-mass spectrometric (GC-MS) analysis where deuterium incorporation was

determined using a solids probe at 70 eV electron impact ionization. All other deuterium

incorporation measurements were determined using this method. When 33 was allowed to

react using the conditions shown in equation 5, the deuterium labeled product 34 was

obtained in a 33% yield with 60% incorporation of deuterium. It appears that the

palladium(IV) intermediate 28 shown in Scheme 4 actually formed, because the deuterium

atom, which originated in the formamide, was incorporated on the aromatic ring *ortho* to the

nitrogen.

$$
\begin{array}{c}
\underset{\textbf{33}}{\text{NHCDO}} \\
\end{array}
\quad
\begin{array}{c}
\text{5 mol \% Pd(OAc)}_2 \\
\underline{\text{5 mol \% dppm}} \\
\text{2 NaO}_2\text{C(CH}_2)_2\text{CH}_3 \\
\text{4 }n\text{-butanol} \\
\text{DMF, 100 }^\circ\text{C, 1 day}
\end{array}
\longrightarrow
\begin{array}{c}
\underset{\textbf{34}}{\text{NHCO}_2\text{(CH}_2)_3\text{CH}_3} \\
\text{D}
\end{array}
\qquad (5)
$$

In addition, because there was less than 100% deuterium incorporation into the

aromatic ring, there may be an equilibrium between Pd(IV) intermediate 28 and Pd(II)

intermediate 29 (Scheme 4). Reductive elimination of HI (or DI) may allow for the exchange

of protons from the palladium intermediate with protons from the solvent.

A second deuterium experiment was run to try to find out whether the hydrogen

attached to the formamide was being incorporated into the aromatic ring by an intramolecular

process (shown in Scheme 4) or an intermolecular process. We ran this deuterium reaction

using the conditions shown in equation 6 with a 1:1 ratio of 24, which contains no deuterium,

and *N*-phenylformamide-*d* (35), which was prepared with 70% deuterium incorporation, to

see whether deuterium would appear in product 34. Analysis of the product by GC-MS

$$25 \quad \text{or} \quad 34 \quad (6)$$
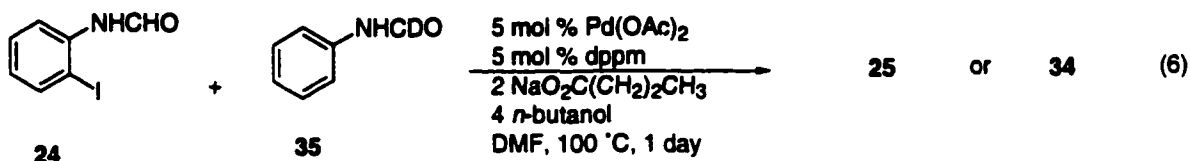
analysis revealed no deuterium incorporation into the carbamate product, indicating that the reaction proceeds intramolecularly. The carbamate product was obtained in 38% yield.

In addition, N-phenylformamide (36) was allowed to react using the conditions shown in equation 7. One equiv of iodobenzene was added to generate the prerequisite aryl palladium intermediate. This reaction was run to see whether the substrate without the iodide would independently form product 25. After GC-MS analysis of the reaction mixture, unreacted 36 and biphenyl were observed. None of the carbamate 25 was observed. The biphenyl most likely forms by homocoupling of iodobenzene.

$$(7)$$
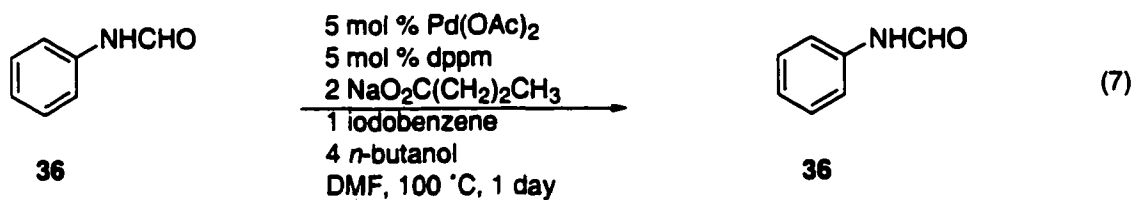
Having explored the reaction mechanism, we next sought to optimize the original reaction conditions in equation 4 due to the low yield of 25. We wanted to know what conditions would give the highest yield of the migration product, so we employed different cesium salts. We were also curious to see whether the presence of the cesium cation itself was important for the migration to occur, although we had already shown that sodium salts

work well in this reaction. Secondly, we wanted to see whether the presence of other cesium

salts would result in migration products.

The first cesium salt employed was CsOAc, which gave a lower yield of the desired

migration product (Table 1, entry 1). N-Phenylformamide and aniline were also recovered in

5% yields. N-Phenylformamide possibly results from simple reduction of aryl iodide 24 by

the palladium catalyst. Aniline most likely results from the hydrolysis of N-

phenylformamide. These two products appeared as minor side products in all reactions

carried out in an attempt to optimize this reaction.

Table 1. Effect of the Cesium Salt on the Reaction.[a]

entry	cesium salt	% isolated yield of 25
1	CsOAc	15
2	CsO_2CH	0
3	Cs_2CO_3	0
4	CsCl	0
5	$CsO_2C(CH_2)_3CH_3$	10
6	-	0

[a]The N-(2-iodophenyl)formamide (0.25 mmol), 5 mol % $Pd(OAc)_2$ (0.012 mmol), 5 mol % dppm (0.012 mmol), the cesium salt (0.50 mmol), and n-butanol (1.00 mmol) were allowed to react in 4 mL of DMF at 100 °C for 1 day.

Cesium formate gave none of the carbamate 25 (Table 1, entry 2) and gave only the

reduced product, N-phenylformamide, in a 63% yield, which was not surprising given that

formates are well-known reducing agents in organopalladium chemistry. One might thus

conclude from this result that the reduction of the arylpalladium intermediate occurs faster

than the migration chemistry. The salts Cs_2CO_3 and $CsCl$ produced no migration product, but did produce a small amount of the reduced product (Table 1, entries 3 and 4), as well as unreacted starting material. The salt $CsO_2C(CH_2)_2CH_3$ gave a low 10% yield of the desired product (Table 1, entry 5), but gave predominately aniline. We also ran the reaction without base, but only unreacted starting material was recovered (Table 1, entry 6).

As seen from the results of Table 1, other cesium salts (or bases) are ineffective in producing the same yield of migration product as CsPiv. It is not known at this time whether it is the bulkiness or the low basicity of CsPiv that promotes the palladium migration chemistry.

Next, we sought to explore the effect of other bases on the palladium migration chemistry. Sodium butyrate gave a slightly higher yield of 25 than CsPiv (Table 2, entry 2). The base sodium pivalate gave a 33% yield of 25 and a 10% yield of side product 26 (Table 2, entry 3). At first we thought sodium butyrate gave a higher yield than CsPiv and NaPiv, because sodium butyrate was a weaker base. However, when two other bases with pK_b values similar to sodium butyrate were employed, no or little migration product was observed (Table 2, entries 4 and 5). Two other sodium salts of carboxylic acids, which are weaker bases than sodium butyrate, gave low yields of 25 (Table 2, entries 6 and 7). Thus, we conclude that the pK_b of the base is not the sole determinant of the amount of 25 formed.

Other sodium bases, such as tartaric acid, disodium salt dihydrate; citric acid, monosodium salt; Na_2CO_3; NaO_2CH; and $NaHSO_4$, gave none or only very low yields of the migration product (Table 2, entries 8-12). Sodium formate gave only the reduced product as expected. When NaOH was employed as the base, a 32% yield of 25 resulted (Table 2, entry 13). When sodium methoxide ($NaOCH_3$) was employed, two carbamates were observed:

Table 2. Effect of Base on the Reaction.[a]

entry	base	% isolated yield of 25
1	CsPiv	30
2	$NaO_2C(CH_2)_2CH_3$	42
3[b]	$NaO_2CC(CH_3)_3$	33
4	NaO_2CPh	0
5	NaOAc	13
6	NaO_2CCCl_3	2
7	NaO_2CCF_3	5
8	tartaric acid, disodium salt dihydrate	0
9	citric acid, monosodium salt	5
10	Na_2CO_3	5
11	NaO_2CH	0
12	$NaHSO_4$	0
13	NaOH	32
14[c]	$NaOCH_3$	25
15	K_2CO_3	0
16	KOAc	5
17	$KOC(CH_3)_3$	13
18	Li_2CO_3	18
19	LiOAc	22
20[d]	$LiO_2CC(CH_3)_3$	20

Table 2. (continued)

21	LiO₂C(CH₂)₂CH₃	0
22	Ca(OAc)₂	12
23	pyridine	0
24	aniline	3
25	NEt₃	40
26	diisopropylamine	21

"The N-(2-iodophenyl)fomamide (0.25 mmol), 5 mol % Pd(OAc)₂ (0.012 mmol), 5 mol % dppm (0.012 mmol), the base (0.50 mmol), and n-butanol (1.00 mmol) were allowed to react in 4 mL of DMF at 100 °C for 1 day.
^{b}A 10% yield of 2,2-dimethyl-N-phenylpronanamide was also obtained.
^{c}A 38% yield of methyl N-phenylcarbamate was also obtained.
^{d}A 5% yield of 2,2-dimethyl-N-phenylpropanamide was also obtained.

$$\begin{array}{c}\text{24} \xrightarrow[\substack{\text{2 NaOMe} \\ \text{4 } n\text{-butanol} \\ \text{DMF, 100 °C, 1 day}}]{\substack{\text{5 mol \% Pd(OAc)}_2 \\ \text{5 mol \% dppm}}} \text{25} + \text{37}\end{array}$$

NHCO₂(CH₂)₃CH₃

25

25%

+

(8)

NHCO₂CH₃

37

38%
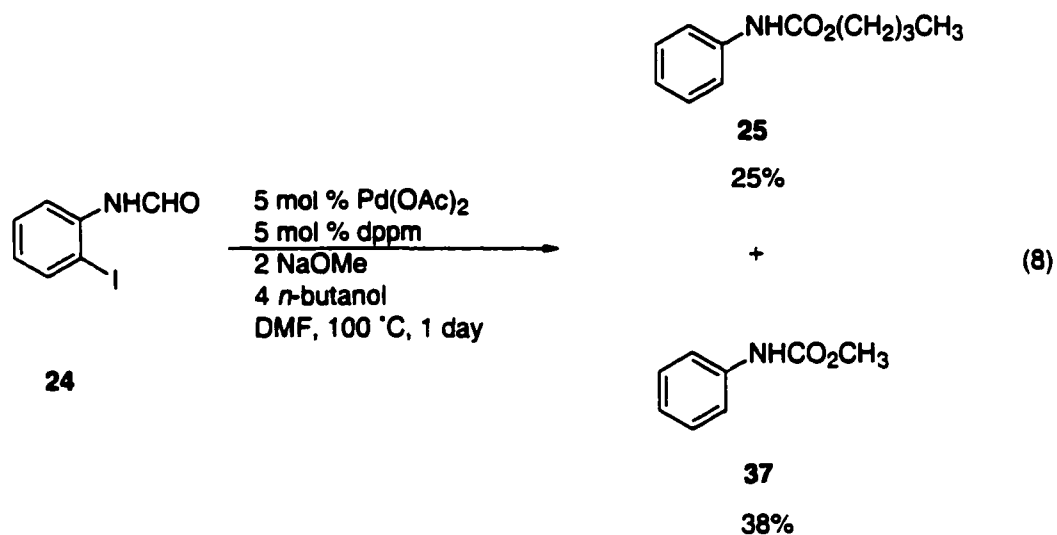
products **25** and **37** (Table 2, entry 14) (eq 8). Product **37** most certainly resulted, because the base acted as a trapping agent along with n-butanol.

Two potassium bases, K₂CO₃ and KOAc, were employed, but only trace amounts or none of the desired product was obtained (Table 2, entries 15 and 16). However, the base

potassium *tert*-butoxide [KOC(CH₃)₃] gave a 13% yield of **25** (Table 2, entry 17). The

lithium bases we employed gave substantially higher yields of **25** (Table 2, entries 18 and

19), although the yields were still lower than those obtained using CsPiv or sodium butyrate.

The bases lithium pivalate and lithium butyrate were next employed. Lithium pivalate gave a

20% yield of **25** and a 5% yield of side product **26** (Table 2, entry 20). Lithium butyrate

gave none of the desired product **25** (Table 2, entry 21). Only *N*-phenylformamide was

formed.

Calcium acetate (CaOAc) gave a 12% yield of the desired product (Table 2, entry 22),

and the organic bases pyridine and aniline gave none or only very low amounts of **25** (Table

2, entries 23 and 24). However, the organic base triethylamine (NEt₃) gave a 40% yield of

25 (Table 2, entry 25), and diisopropylamine gave a moderate yield of 21% (Table 2, entry

26).

All of the acetate bases produced migration product in moderate to low yields.

Because the acetate base with the smallest counter ion (lithium) gave the highest yield, we

believe the counter ions may be influencing these results. Larger counter ions, such as

sodium, calcium, potassium, and cesium, gave lower yields.

Sodium hydroxide and sodium methoxide, which have nearly identical pK_b values,

both gave similar yields of migration product. We thought that the pK_b values might

correlate with the amount of migration product formed. However, other bases with very

different pK_b values gave better yields (Table 2, entries 1 and 21). The organic bases,

especially NEt₃, gave good yields of **25**. Because sodium butyrate gave a slightly higher

yield though, it was used in subsequent optimization reactions.

Next we optimized the reaction with respect to the phosphine ligand. As shown in

Table 3, entry 1, when the reaction was run without any phosphine ligand, a 30% yield of 25

resulted. This result implies that a phosphine ligand may not be too important in this

migration reaction.

Table 3. Effect of Phosphine Ligand on the Reaction.[a]

entry	phosphine ligand	% isolated yield of 25
1	-	30
2	dppm	42
3	dppe	18
4	dppp	26
5	dppb	9
6	1,5-bis(diphenylphosphino)-pentane	14
7	dppf	18
8	PPh_3	15
9	$(o\text{-tolyl})_3P$	15
10	$(p\text{-tolyl})_3P$	18
11	$(Cy)_3P$	19
12	$Ph_2PCH_2CO_2H$	0
13	3,3',3''-phosphinidynetrisbenzenesulfonic acid sodium salt	8

[a]The N-(2-iodophenyl)fomamide (0.25 mmol), 5 mol % $Pd(OAc)_2$ (0.012 mmol), the phosphine ligand (0.012 mmol), sodium butyrate (0.50 mmol), and n-butanol (1.00 mmol) were allowed to react in 4 mL of DMF at 100 °C for 1 day.

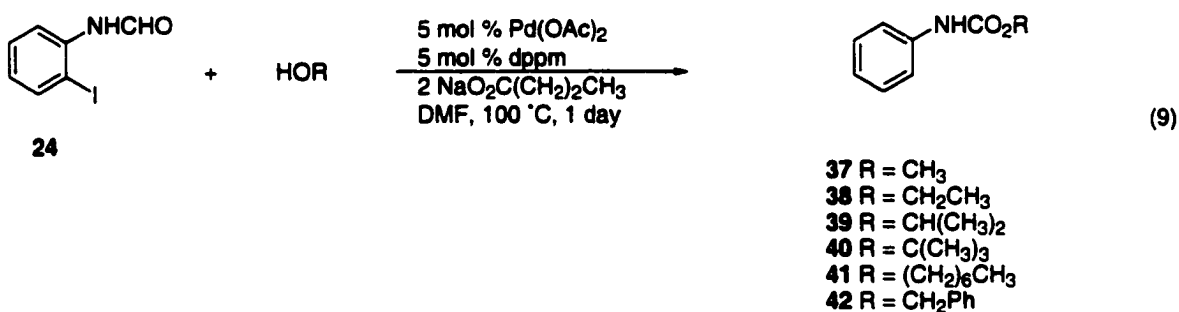The effect of bidentate ligands other than dppm (Table 3, entry 2) was next explored.

The ligands 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane

(dppp), 1,4-bis(diphenylphosphino)butane (dppb), 1,5-bis(diphenylphosphino)pentane, and

1,1'-bis(diphenylphosphino)ferrocene (dppf) all gave lower yields of 25 than did dppm

(Table 3, entries 3-7).

Monodentate ligands were next investigated. Triphenylphosphine (PPh_3), tri-o-

tolylphosphine [(o-tolyl)$_3$P], and tri-p-tolylphosphine [(p-tolyl)$_3$P] all gave nearly identical,

low yields of migration product (Table 3, entries 8-10). Tricyclohexylphosphine [(Cy)$_3$P]

gave a yield of 25 similar to those of the other monodentate ligands above (Table 3, entry

11). Two other phosphine ligands, diphenylphosphinoacetic acid ($Ph_2PCH_2CO_2H$) and

3,3',3''-phosphinidynetrisbenzenesulfonic acid sodium salt, gave no to little migration

product (Table 3, entries 12 and 13).

The bidentate ligands gave decreased yields of 25 with respect to dppm. Apparently,

bidentate ligands evoke a greater chelating effect, which may tie up reactive sites on the

palladium, thus lowering the yields. However, the monodentate ligands (sterically and non-

sterically hindered) also gave lower yields of 25 than dppm. Considering the fact that a

similar yield of 25 was obtained when no phosphine ligand was used, the actual utility of

dppm in this reaction is questionable.

Next we sought to optimize the solvent. We first investigated a few nonpolar, aprotic

solvents. Benzene and methylene chloride both gave yields comparable to DMF (Table 4,

entries 1 and 2). Tetrahydrofuran (THF) gave a lower yield of 18% (Table 4, entry 3). All of

the dipolar aprotic solvents employed, such as acetone, acetonitrile, N,N-dimethylacetamide

(DMA), and dimethyl sulfoxide (DMSO) gave lower yields of 25 than those obtained using

Table 4. Effect of Solvent on the Reaction.[a]

entry	solvent	% isolated yield of 25
1	benzene	30
2	CH_2Cl_2	36
3	THF	18
4	acetone	16
5	CH_3CN	14
6	DMA	14
7	DMSO	11
8	DMF	42
9[b]	DMF	25

[a] The N-(2-iodophenyl)fomamide (0.25 mmol), 5 mol % Pd(OAc)$_2$ (0.012 mmol), 5 mol % dppm (0.012 mmol), sodium butyrate (0.50 mmol), and n-butanol (1.00 mmol) were allowed to react in 4 mL of solvent at 100 °C for 1 day.
[b] 1 Ml of DMF was employed instead of 4 mL.

DMF (Table 4, entries 4-7). When the reaction was run in only 1 mL of DMF, a more concentrated reaction mixture resulted (Table 4, entry 9). This change produced a lower yield of 25.

From the results in Table 4, nonpolar aprotic solvents, in addition to DMF, seem to be appropriate for this reaction. Dipolar aprotic solvents other than DMF provided lower yields, which seems inconsistent, since DMF itself is a dipolar aprotic solvent. Also, a concentrated reaction mixture seems to have a deleterious effect upon the yield.

We next sought to employ various alcohols as trapping agents in the reaction (eq 9). When methanol was employed, a 14% yield of product 37 was obtained (Table 5, entry 1).

When 10 or 50 equivs of methanol were employed, the same result was found. The trapping

agent ethanol gave an 18% yield of **38**, but isopropanol produced none of the desired product

39 (Table 5, entries 2 and 3). Curiously, when *t*-butanol, heptanol, and benzyl alcohol were

employed as trapping agents, none of their respective desired migration products **40-42** were

obtained (Table 5, entries 4-6). *t*-Butanol may not be producing any migration product,

because it is either too bulky to react as a good trapping agent or because its boiling point is

too low to remain in solution. When 10 equivs of *n*-butanol were employed instead of 4

equivs, an increased yield of **25** was obtained (Table 5, entry 8).

$$
\begin{array}{c}
\underset{\mathbf{24}}{\underset{\text{I}}{\text{C}_6\text{H}_4}\text{NHCHO}} \quad + \quad \text{HOR} \quad \xrightarrow[\substack{2\ \text{NaO}_2\text{C}(\text{CH}_2)_2\text{CH}_3 \\ \text{DMF, 100 °C, 1 day}}]{\substack{5\ \text{mol}\ \%\ \text{Pd(OAc)}_2 \\ 5\ \text{mol}\ \%\ \text{dppm}}} \quad \text{C}_6\text{H}_4\text{NHCO}_2\text{R}
\end{array}
\tag{9}
$$

37 R = CH$_3$
38 R = CH$_2$CH$_3$
39 R = CH(CH$_3$)$_2$
40 R = C(CH$_3$)$_3$
41 R = (CH$_2$)$_6$CH$_3$
42 R = CH$_2$Ph

Upon consideration of the optimization data, we have observed that the largest

improvement in the yield of migration product was obtained when both the base NaOCH$_3$

and the alcohol *n*-butanol acted as trapping agents giving a combined yield of **25** and **37** of

63% (eq 8). We expected that a higher yield of a single migration product could be obtained

if the base and trapping agent were both derived from the same alcohol. This encouraged us

to develop the reaction conditions shown in equation 10, where the desired migration product

was obtained in a 57% yield when either 10 or 50 equivs of the trapping agent CH$_3$OH was

used.

Table 5. Effect of Trapping Agent on the Reaction.[a]

entry	alcohol	% isolated yields of 37-42
1	methanol	14
2	ethanol	18
3	i-propanol	0
4	t-butyl alcohol	0
5	heptanol	0
6	benzyl alcohol	0
7	n-butanol	42
8[b]	n-butanol	54

[a]The N-(2-iodophenyl)formamide (0.25 mmol), 5 mol % Pd(OAc)$_2$ (0.012 mmol), 5 mol % dppm (0.012 mmol), sodium butyrate (0.50 mmol), and the trapping agent (1.00 mmol) were allowed to react in 4 mL of DMF at 100 °C for 1 day.

[b]10 Equivs of the trapping agent n-butanol were employed instead of 4 equivs.

24

5 mol % Pd(OAc)$_2$
5 mol % dppm
2 NaOMe
10 or 50 MeOH
DMF, 100 °C, 1 day

37

57%

(10)
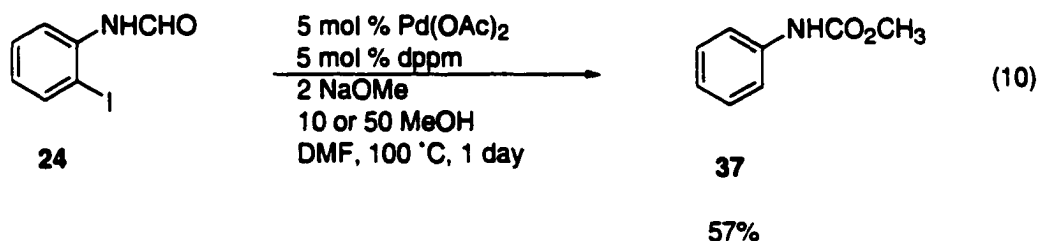
The reaction conditions shown in equation 10 that we have developed produce a good yield of migration product. However, these conditions are similar to those of the Cannizzaro reaction. The Cannizzaro reaction is a well-known, oxidation-reduction reaction where an aldehyde in the presence of a strong base disproportionates to an acid and an alcohol.[6] Fear that the reactants shown in equation 10 might undergo a Cannizzaro reaction and give similar

products caused us to abandon the conditions shown in equation 10. Evidence that this occurs was provided when o-iodobenzaldehyde was employed as the substrate, using the reaction conditions shown in equation 10. GC-MS analysis showed that all of the starting material had been converted to benzyl alcohol. Thus, we employed the original conditions of equation 4 as we studied other amides and aldehydes, but 10 equivs of the trapping agent were employed instead of 4 equivs.

Another formamide that appears to undergo palladium migration chemistry is N-formyl-2,3-dihydro-7-iodoindole (43) (eq 11). Amide 43 was allowed to react using reaction conditions similar to those employed in the reaction of 24. Although we were expecting carbamate 44 as the palladium migration product, the ester 45 was obtained in 44% yield. We believe that 45 is formed by a slightly different palladium migration pathway than before (Scheme 6).

5% Pd(OAc)$_2$
5% dppm
2 CsPiv
10 n-butanol
DMF, 100 °C, 1 day

(11)

43

44
0%

45
44%
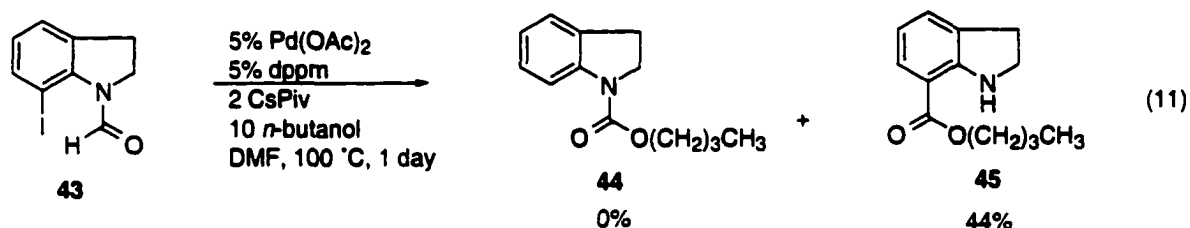
As shown in Scheme 6, ester 45 most likely forms by oxidative addition of the carbon-iodide bond of 43 to the palladium(0) to form 46. Oxidative addition of the formamide C-H bond to the palladium generates the palladium(IV) intermediate 47. Elimination of HI gives 48. Palladacycle 48 undergoes attack of n-butanol upon the carbonyl group to form 49, which isomerizes to 50. Elimination of the amino group forms 51, which

Scheme 6
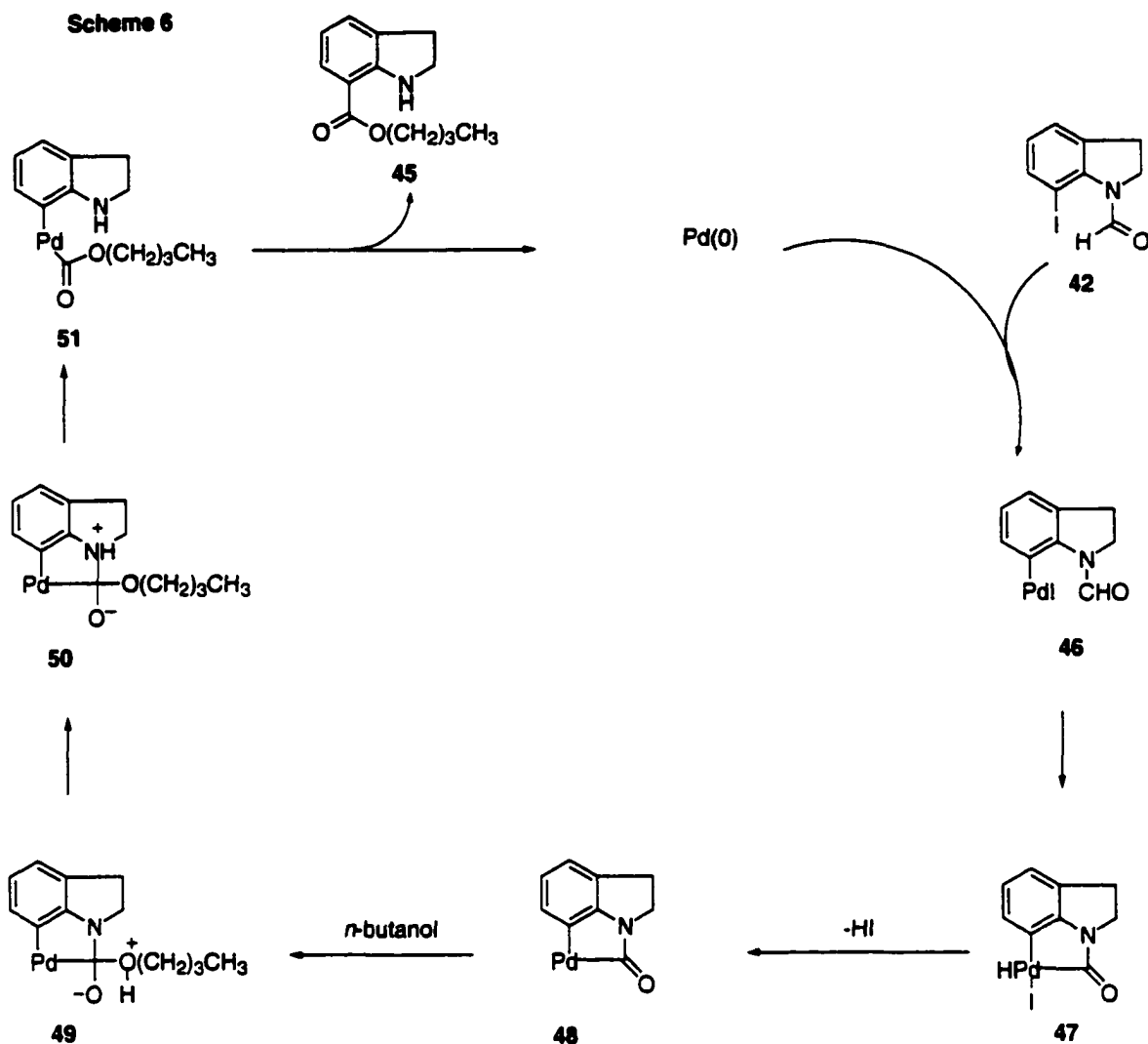
undergoes reductive elimination to regenerate the palladium(0) catalyst and form the

observed product **45**. Because **45** was formed instead of the expected carbamate **44**, it

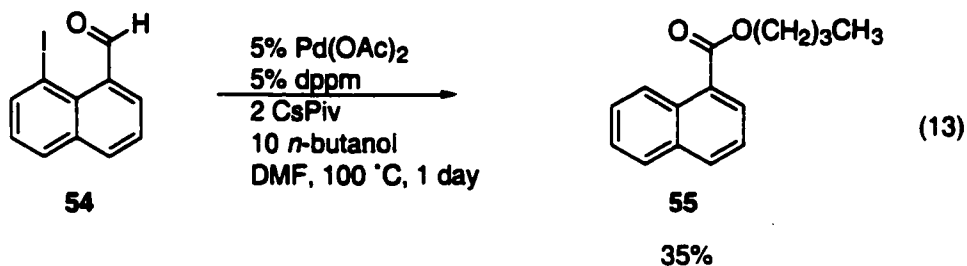appears that the amino group is a better leaving group than the palladium.

We also ran a deuterium labeling experiment to find out if the hydrogen on the

formamide would migrate onto the nitrogen atom. *N*-Formyl-2,3-dihydro-7-iodoindole-*d*

(**52**), which was prepared with 66% deuterium incorporation (determined by GC-MS

analysis), was allowed to react using the conditions shown in equation 12. After completion

of the reaction, analysis of **45** by GC-MS determined that no deuterium had been

incorporated into the product, which was obtained in 40% yield. Thus, the hydrogen on the

formamide appears to be lost to the solvent, instead of directly migrating onto the aryl ring of

the product as seen before in Scheme 4.

$$
\text{52} \quad \xrightarrow[\substack{\text{2 CsPiv} \\ \text{10 }n\text{-butanol} \\ \text{DMF, 100 °C, 1 day}}]{\substack{\text{5\% Pd(OAc)}_2 \\ \text{5\% dppm}}} \quad \text{45} \tag{12}
$$
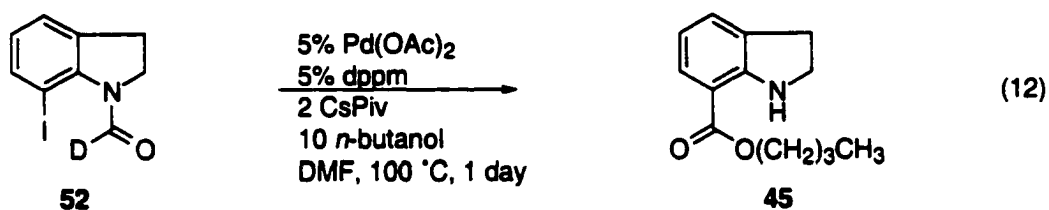
Also, N-formyl-2,3-dihydroindole (**54**) was allowed to react under the reaction

conditions shown in equation 12. One equiv of iodobenzene was added, as was done

previously in the reaction of N-phenylformamide in equation 7. We were curious to see

whether carbamate **44** or the rearranged migration product **45** would form without the iodide

being present in the amide starting material. As before, we observed only unreacted starting

material and biphenyl in the GC-MS analysis. None of **44** or **45** was observed.

We then moved on to look at other functionalities to determine the generality of this

palladium migration chemistry. 8-Iodo-1-naphthaldehyde (**54**) was first studied. When **54**

was allowed to react under the conditions of equation 13, a 35% yield of the ester product **55**

was obtained. As shown in Scheme 7, product **55** may result from our proposed mechanism,

where the aryl iodide **55** oxidatively adds to palladium forming **56**, followed by oxidative

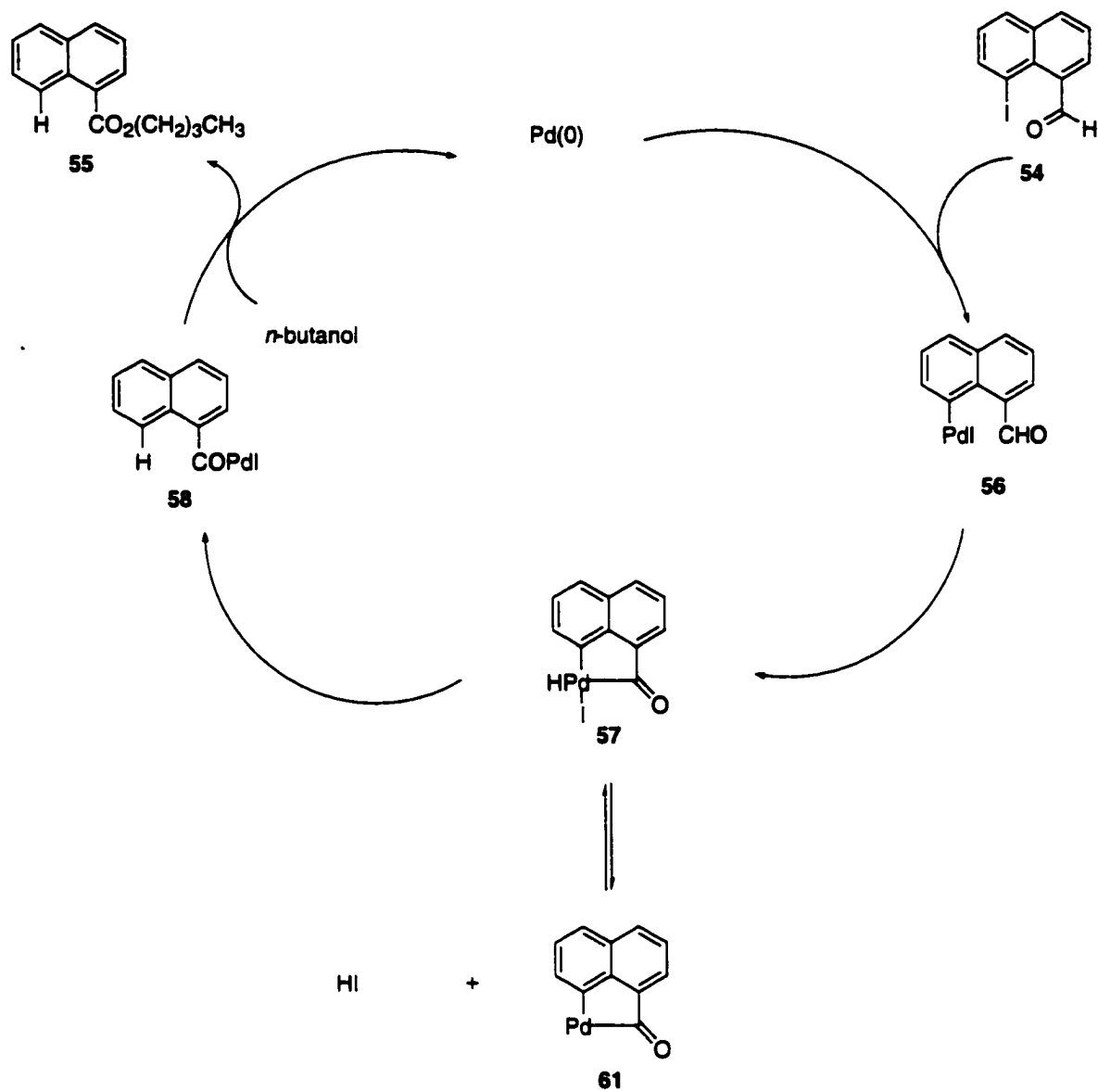addition of the carbon-hydrogen bond of the aldehyde to the palladium to form **57**.

$$5\% \text{ Pd(OAc)}_2$$
$$5\% \text{ dppm}$$
$$2 \text{ CsPiv}$$
$$10 \text{ n-butanol}$$
$$\text{DMF, 100 °C, 1 day}$$

(13)

54

55

35%

Reductive elimination of 57 then gives an acylpalladium(II) intermediate 58, which is trapped with n-butanol giving the observed ester 55.

A deuterium labeled substrate was next employed in this reaction. 1-Deutero-8-iodo-1-naphthaldehyde (59), which was prepared with 47% deuterium incorporation (determined by GC-MS analysis), was allowed to react using the reaction conditions shown in equation 14. The deuterated product 60 was found in 32% yield with 53% deuterium incorporation. This result seems to suggest that the hydrogen on the aldehyde has migrated to the aryl position as shown in equation 14. Because the product did not have 100% deuterium incorporation, there may be an equilibrium between intermediates 57 and 61 as shown in Scheme 7. The equilibrium would allow for the exchange of protons from the substrate with protons from the solvent.

Additionally, 1-naphthaldehyde (62), which has no iodide, was allowed to react using the reaction conditions shown in equation 14 (with the addition of 1 equiv of iodobenzene) to determine if any migration product 55 results. After analysis of the reaction mixture, only unreacted starting material and biphenyl were observed by GC-MS analysis. There was no migration product present. Again, this migration product did not form without an iodide being present in 63, thus supporting our mechanism.

Scheme 7

Pd(0)

54

56

57

HI + 61

58

55

n-butanol

$$\text{59} \xrightarrow[\substack{\text{5\% Pd(OAc)}_2 \\ \text{5\% dppm} \\ \text{2 CsPiv} \\ \text{10 } n\text{-butanol} \\ \text{DMF, 100 }^\circ\text{C, 1 day}}]{} \text{60}$$

(14)

32%
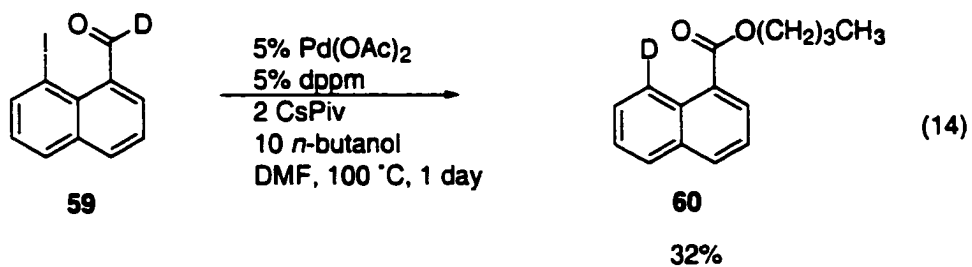
We next employed 2-iodophenyl formate (63) as the starting material for our

migration reaction (eq 15). We were expecting to obtain n-butyl phenyl carbonate (64) as the

migration product, but we observed phenol 65 instead.

As shown in Scheme 8, we propose the formation of ester 65 by the following

mechanism. After oxidative addition of the aryl iodide to the palladium to form 66 and

oxidative addition of the formate C-H bond to the palladium to form 67, the palladium loses

HI to form intermediate 68. Palladacycle 68 is readily attacked by n-butanol and hydrolyzed

to phenol 69, because the phenoxide anion is such a good leaving group. Reductive

elimination of 69 gives the observed phenol 65.
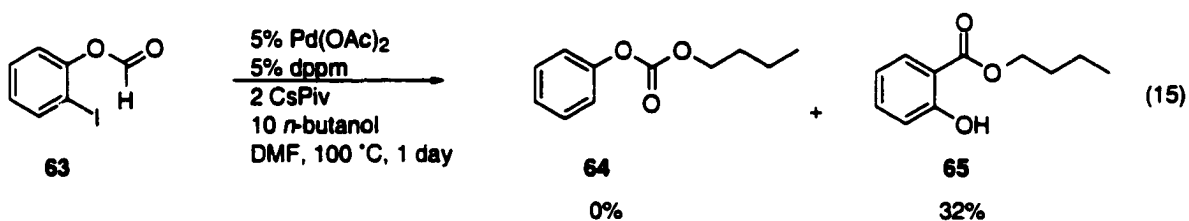
Scheme 8
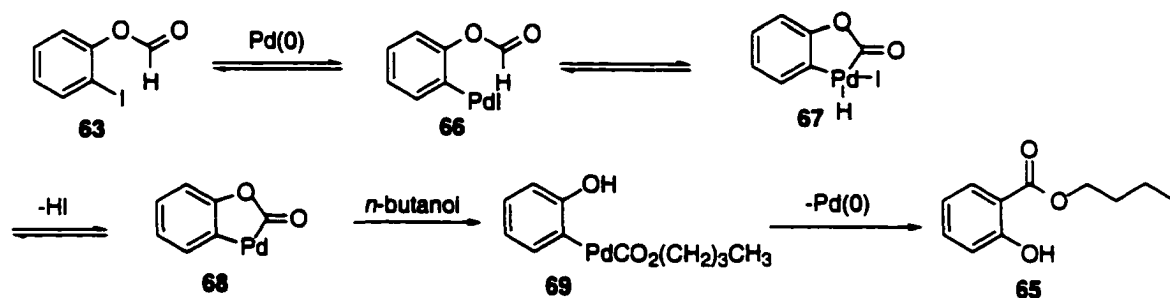
We wanted to know whether the carbonate **64** was being formed and then

decomposing. To find out, we employed *t*-butanol and 2-butanol as the trapping reagents in

an attempt to isolate products like **70** (eq 16). A more hindered carbonate, such as **70**, should

be less prone to decomposition. When *t*-butanol was used, we only found unreacted starting

materials, but 2-butanol gave the rearranged product **71** in 33% yield. In these reactions a

trace amount of phenol was visible upon gas chromatographic analysis. The phenol may

result from decomposition of **64** or **70**, but neither of these could be isolated.
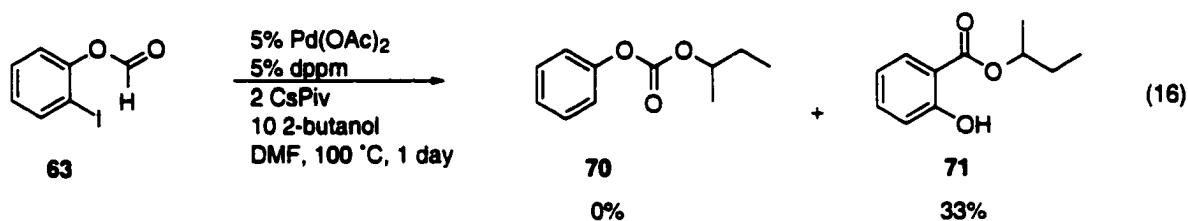
Next, we sought to observe palladium migration from an alkylpalladium intermediate

to form an acylpalladium species. The reaction of 2-chloromercurioacetaldehyde with

lithium tetrachloropalladate and norbornene has been investigated by Jeff Ward as a synthetic

approach to prostaglandin derivatives.[7] We sought to evoke similar reaction conditions to

observe palladium migrating from an alkyl carbon to an acyl carbon. This was done by using

Jeff Ward's conditions: a stoichiometric, instead of a catalytic, amount of palladium

dichloride with 1 equiv of norbornene, 1 equiv of chloromecurioacetaldehyde, 1 equiv of

LiCl, and 10 equivs of 2-phenylethanol (Scheme 9). We were expecting to see palladium

migration product **72**, but only unidentifiable reaction products and unreacted 2-

phenylethanol were recovered. At this point, we have no evidence for the migration of

palladium in an alkylpalladium intermediate to an acylpalladium intermediate in this system,

although Jeff Ward has provided such evidence.

Scheme 9

R = (CH₂)₂Ph

72
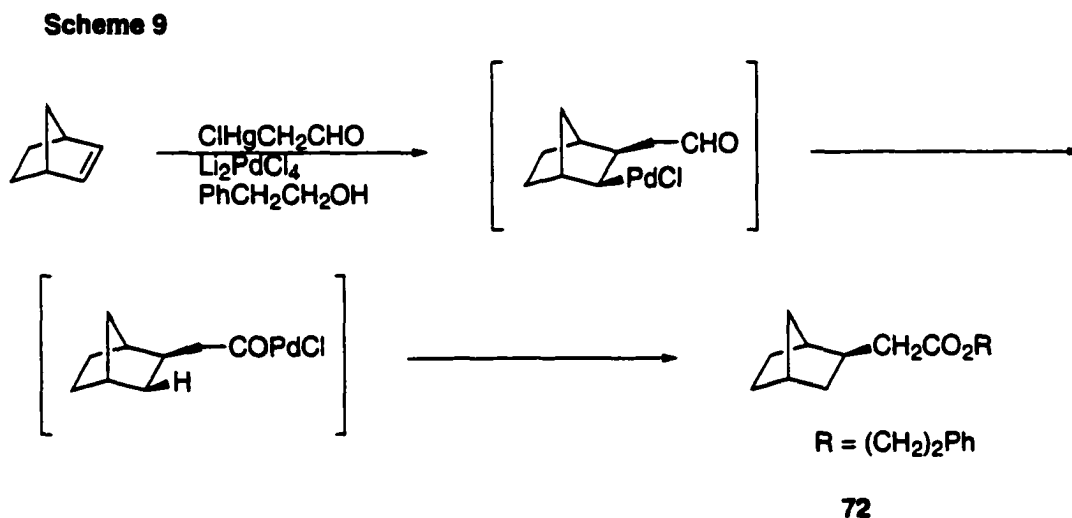
Conclusion

The reaction conditions under which palladium will undergo intramolecular migration

from an aryl group to an acyl group have been investigated using the reaction of *N*-(2-

iodophenyl)fomamide with *n*-butanol as a model system. We have optimized the reaction

conditions by varying the phosphine ligand, the base, and the solvent, but have found that the

original reaction conditions gave the highest yields of migration product **25**. Substrates *N*-(2-

iodophenyl)formamide and 8-iodo-1-naphthaldehyde gave their respective palladium

migration products, *n*-butyl *N*-phenylcarbamate and *n*-butyl naphthalene-1-carboxylate, in

moderate yields. Formation of these products and subsequent deuterium labeling experiments indicate that the palladium may have migrated from an aryl group to an acyl group via a palladium(IV) intermediate.

We have noted during our studies of this palladium migration process that other interesting rearrangements can occur. Instead of the expected migration product, only rearranged products n-butyl salicylate and n-butyl 2,3-dihydo-1H-indolo-7-carboxylate were observed in the reactions of o-iodophenyl formate and N-formyl-7-iodo-2,3-dihydroindole. These rearrangements most likely occur because the phenoxide anion and amino group respectively are better leaving groups than palladium. All of these results together suggest that palladium migration from an aryl group to an acyl group can and does occur.

Experimental

General Procedures. All ^{1}H and ^{13}C spectra were obtained at 300 or 400 MHz. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F) and visualization was accomplished with short wavelength UV light (254 nm) or with a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. High-resolution mass spectra were recorded on a Kratos MS50TL double focusing magnetic sector mass spectrometer using EI at 70 eV. The deuterium incorporation was determined on a Kratos MS50TL double focusing magnetic sector mass spectrometer using a solids probe at 70 eV electron impact ionization. The probe was heated to 150 °C at a rate of 50 °C per min. The % deuterium was obtained by simple comparison of the intensities of the molecular ion

peaks. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O series 11 analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise stated. $KMnO_4$, HOAc, NaOAc, KOAc, LiOAc, $NaHCO_3$, $KHCO_3$, Na_2CO_3, LiCl, $KHSO_4$, n-Bu$_4$NCl, DMF, DMSO, NaCl, NH_4Cl, NaOH, HCl, hexane, ethyl acetate, iodine, acetyl chloride, diethylene glycol, dimethyl sulfoxide, methanol, ethanol, ethyl ether, DMF, and DMA were obtained from Fisher Scientific. 2-Iodoaniline, 2-iodophenol, indoline, sodium formate, and formic-d-acid, sodium salt (NaO_2CD) were obtained from Aldrich Chemical Co. Palladium acetate and PPh_3 were obtained from Kawaken Fine Chemical Co., Ltd. 1-Hydroxymethyl-8-iodonaphthalene was obtained from Maybridge Chemical Company. N-Formyl-2,3-dihydroindole was obtained from Lancaster Synthesis Inc.

Preparation of chloromercurioacetaldehyde.[8] While stirring the reaction mixture, 10 g (0.1 mole) of n-butyl vinyl ether was gradually added to a filtered solution of 32 g (0.1 mole) of mercuric acetate in 150 mL of water. The addition was carried out rapidly with only slight evolution of heat. The resulting solution (freed of traces of mercury) was treated with a solution of 7.5 g (0.1 mole) of KCl in the least possible amount of water. White crystals appeared at once. The crystals were filtered and recrystallized from hot water. Yield: 85%; mp 130-131 °C.

Preparation of N-(2-iodophenyl)formamide (24). To a 50 mL round bottom flask was added NaO_2CH (1.36 g, 20.0 mmol), 8 mL of anhydrous ethyl ether, a magnetic stirring bar, and 0.02 g of n-Bu$_4$NCl. The mixture was stirred at room temperature, and 1 g (12.7 mmol) of acetyl chloride was added. The resulting mixture was stirred at room temperature for 4 h. The mixture was cooled to 0 °C, and a solution of 2-iodoaniline (1.0 g, 5.0 mmol) in 1.4 mL

of ethyl ether was added. The reaction was allowed to proceed at 0 °C for 20 min and then

quenched with 3 mL of methanol. Acetone (20 mL) was added, and the resulting solution

was filtered. The ethyl ether was removed under reduced pressure, and the resulting solid

was recrystallized from 2:3 methanol/water. Yield: 73%; mp 110-111 °C. ^{1}H NMR (300

MHz, CDCl$_3$) δ 6.85 (m, 2 H), 7.19 (m, 1 H), 7.78 (m, 1 H), 8.28 (d, J = 8.3 Hz, 1 H), 8.49

(s, 1 H), 8.64 (d, J = 11.0 Hz, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 89.53, 91.04, 119.67,

122.57, 126.66, 127.31, 129.57, 129.87, 137.62, 138.09, 139.22, 140.54, 159.24, 162.47.

The spectral properties of this compound were identical to those in the literature.[9]

Preparation of N-(2-iodophenyl) 1-deuteroformamide (33).[9] To a 50 mL round bottom

flask were added NaO$_2$CD (1.36 g, 20.0 mmol), 8 mL of anhydrous ethyl ether, a magnetic

stirring bar, and 0.02 g of n-Bu$_4$NCl. The mixture was stirred at room temperature, and 1 g

(12.7 mmol) of acetyl chloride was added. The resulting mixture was stirred at room

temperature for 4 h. The mixture was cooled to 0 °C, and a solution of 2-iodoaniline (1.0 g,

5.0 mmol) in 1.4 mL of ethyl ether was added. The reaction was allowed to proceed at 0 °C

for 20 min then quenched with 3 mL of methanol. Acetone (20 mL) was added, and the

resulting solution was filtered. The ethyl ether was removed under reduced pressure, and the

resulting solid was recrystallized from 2:3 methanol/water. Yield: 64%. ^{1}H NMR (300

MHz, CDCl$_3$) δ 6.85 (m, 1 H), 7.33 (m, 1 H), 7.78 (m, 1 H), 8.28 (d, J = 8.3 Hz, 1 H). The

deuterium incorporation was determined by GC-MS analysis to be greater than 98%.

Preparation of N-phenyl 1-deuteroformamide (35). To a 50 mL round bottom flask were

added NaO$_2$CD (1.36 g, 20.0 mmol), 8 mL of anhydrous ethyl ether, a magnetic stirring bar,

and 0.02 g of n-Bu$_4$NCl. The mixture was stirred at room temperature, and 1 g (12.7 mmol)

of acetyl chloride was added. The resulting mixture was stirred at room temperature for 4 h.

The mixture was cooled to 0 °C, and a solution of aniline (465.0 mg, 5.0 mmol) in 1.4 mL of

ethyl ether was added. The reaction was allowed to proceed at 0 °C for 20 min then

quenched with 3 mL of methanol. Acetone (20 mL) was added, and the resulting solution

was filtered. The ethyl ether was then removed under reduced pressure, and the resulting

solid was recrystallized from 2:3 methanol/water. Yield: 63%. ^{1}H NMR (300 MHz, CDCl$_3$)

δ 7.08 (m, 4H), 7.30 (m, 4 H), 7.56 (d, J = 1.3 Hz, 2 H) 7.75 (br s, 1 H), 8.72 (br s, 1 H); ^{13}C

NMR (300 MHz, CDCl$_3$) δ 118.99, 120.49, 125.01, 125.49, 129.29, 129.96, 137.12, 137.35,

160.10, 163.34. The spectral properties of this compound were identical to those in the

literature.[10] The deuterium incorporation was determined by GC-MS analysis to be 70%.

Preparation of *N*-phenylformamide (36). To a 50 mL round bottom flask were added

NaO$_2$CH (1.36 g, 20.0 mmol), 8 mL of anhydrous ethyl ether, a magnetic stirring bar, and

0.02 g of *n*-Bu$_4$NCl. The mixture was stirred at room temperature, and 1 g (12.7 mmol) of

acetyl chloride was added. The resulting mixture was stirred at room temperature for 4 h.

The mixture was cooled to 0 °C, and a solution of aniline (487.0 mg, 5.0 mmol) in 1.4 mL of

ethyl ether was added. The reaction was allowed to proceed at 0 °C for 20 min and then

quenched with 3 mL of methanol. Acetone (20 mL) was added, and the resulting solution

was filtered. The ethyl ether was then removed under reduced pressure, and the resulting

solid was recrystallized from 2:3 methanol/water. Yield: 80%. ^{1}H NMR (300 MHz, CDCl$_3$)

δ 7.08 (m, 4 H), 7.25 (m, 4 H), 7.56 (m, 2 H), 8.67 (s, 1 H), 8.71 (d, J = 11.3 Hz, 1 H), 8.86

(br s, 1 H), 9.40 (br s, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 119.01, 120.56, 125.01, 125.49,

129.28, 129.96, 137.16, 137.43, 160.36, 163.61. The other spectral properties of this

compound were identical to those in the literature.[11]

Preparation of N-formyl-7-iodo-2,3-dihydroindole (43). This compound was prepared using a procedure slightly modified from that of Somei.[12] A solution of thallium tris-trifluoroacetate (TTFA) (3.6 g, 9.6 mmol) in 11 mL of trifluoroacetic acid (TFA) was added to a solution of N-formyl-2,3-dihydroindole (878.0 mg) in TFA (9 mL) and the reaction mixture was stirred at room temperature for 3 h. After evaporation of the solvent under reduced pressure, the residue was dried *in vacuo* at room temperature. A solution of KI (7.2 g) in 48 mL of water was added to the residue and stirred at room temperature for 2 h. After addition of CH_2Cl_2-MeOH (95:5, v/v) to the reaction mixture, the resulting mixture was filtered through silica gel to remove solid particles. The organic layer was separated, and the water layer was extracted with CH_2Cl_2. The combined organic layers were washed with 5% aqueous $NaHSO_3$ and brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel with ethyl acetate/hexanes (1:1) as an eluent. 1-Formyl-7-iodo-2,3-dihydroindole was obtained. Yield: 53%; mp 93-94 °C. IR (neat) 3063, 2962, 1645, 1357; ^1H NMR (300 MHz, $CDCl_3$) δ 3.04 (t, J = 8.0 Hz, 2 H), 4.13 (t, J = 8.0 Hz, 2 H), 6.75 (t, J = 7.6 Hz, 1 H), 7.20 (d, J = 1.0 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 9.74 (s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.64, 46.02, 125.75, 126.14, 136.57, 139.66, 143.17, 160.60; HRMS cacld for C_9H_8INO: 272.96507. Found: 272.96553. Anal. calcd for C_9H_8INO: C, 39.59; H, 2.95; N, 5.13. Found: C, 39.65; H, 3.09; N, 5.03.

Preparation of N-deuteroformyl-2,3-dihydroindole. To a 50 mL round bottom flask were added NaO_2CD (1.36 g, 20.0 mmol), 8 mL of anhydrous ethyl ether, a magnetic stirring bar, and 0.02 g of n-Bu_4NCl. The mixture was stirred at room temperature, and 1 g (12.7 mmol) of acetyl chloride was added. The resulting mixture was stirred at room temperature for 4 h. The mixture was cooled to 0 °C, and a solution of indoline (705.0 mg, 5.0 mmol) in 1.4 mL

of ethyl ether was added. The reaction was allowed to proceed at 0 °C for 20 min then

quenched with 3 mL of methanol. Acetone (20 mL) was added, and the resulting solution

was filtered. The ethyl ether was then removed under reduced pressure, and the resulting

solid was recrystallized from 2:3 methanol/water. Yield: 70%. ^{1}H NMR (300 MHz, CDCl$_3$)

δ 2.88 (m, 2 H), 3.78 (m, 2 H), 6.87 (m, 1 H), 6.89 (m, 3 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ

27.21, 44.63, 109.55, 124.25, 124.57, 126.10, 132.01, 132.29, 141.16,

Preparation of N-deuteroformyl-7-iodo-2,3-dihydroindole (52). This compound was

prepared using a procedure slightly modified from that of Somei.[12] A solution of thallium

tris-trifluoroacetate (TTFA) (3.6 g, 9.6 mmol) in 11 mL of trifluoroacetic acid (TFA) was

added to a solution of N-deuteroformyl-2,3-dihydroindole (873.0 mg) in TFA (9 mL) and the

reaction mixture was stirred at room temperature for 3 h. After evaporation of the solvent

under reduced pressure, the residue was dried in vacuo at room temperature. A solution of

KI (7.2 g) in 48 mL of water was added to the residue and stirred at room temperature for 2

h. After addition of CH$_2$Cl$_2$-MeOH (95:5, v/v) to the reaction mixture, the resulting mixture

was filtered through silica gel to remove solid particles. The organic layer was separated,

and the water layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed

with 5% aq NaHSO$_3$ and brine and dried over Na$_2$SO$_4$. After evaporation of the solvent, the

residue was subjected to column chromatography on silica gel with ethyl acetate/hexanes

(1:1) as an eluent. N-Deuteroformyl-7-iodo-2,3-dihydroindole was obtained. Yield: 44%.

^{1}H NMR (300 MHz, CDCl$_3$) δ 3.05 (t, J = 8.1 Hz, 2 H), 4.14 (t, J = 8.1 Hz, 2 H), 6.75 (t, J =

7.7 Hz, 1 H), 7.20 (m, 1 H), 7.63 (d, J = 8.0 Hz, 1 H). The deuterium incorporation was

determined by GC-MS analysis to be 66%.

Preparation of N-formyl-2,3-dihydroindole (53). To a 50 mL round bottom flask were

added NaO₂CH (1.36 g, 20.0 mmol), 8 mL of anhydrous ethyl ether, a magnetic stirring bar,

and 0.02 g of n-Bu₄NCl. The mixture was stirred at room temperature, and 1 g (12.7 mmol)

of acetyl chloride was added. The resulting mixture was stirred at room temperature for 4 h.

The mixture was cooled to 0 °C, and a solution of indoline (705.0 mg, 5.0 mmol) in 1.4 mL

of ethyl ether was added. The reaction was allowed to proceed at 0 °C for 20 min then

quenched with 3 mL of methanol. Acetone (20 mL) was added, and the resulting solution

was filtered. The ethyl ether was then removed under reduced pressure, and the resulting

solid was recrystallized from 2:3 methanol/water. Yield: 80%. The spectral properties of

this compound were identical to those in the literature.[13]

Preparation of 8-iodo-1-naphthaldehyde (54). To a 100 mL round bottom flask were

added 1 g (3.5 mmol) of 1-hydroxymethyl-8-iodonaphthalene, 7.9 g (91.0 mmol) of

manganese(IV) oxide (MnO₂), a magnetic stirring bar, and 50 mL of chloroform. The

reaction was stirred and refluxed over night at 60 °C. The reaction mixture was then filtered,

and the solvent was removed under reduced pressure. The solid was recrystallized from

methanol. Yield: 70%. ¹H NMR (300 MHz, CDCl₃) δ 6.94 (t, J = 7.6 Hz, 1 H), 7.27 (t, J =

7.5 Hz, 1H), 7.64 (m, 3 H), 1.09 (d, J = 7.2 Hz, 1 H), 11.47 (s, 1 H); ¹³C NMR (300 MHz,

CDCl₃) δ 90.02, 125.99, 127.78, 129.86, 130.21, 133.49, 134.49, 135.57, 136.57, 136.35,

141.33, 191.58. The spectral properties of this compound were identical to those in the

literature.[14]

Preparation of 8-iodo-1-naphthaldehyde-d (59). KMnO₄ (445.0 mg, 2.8 mmol) was

added portionwise to a vigorously stirred mixture of 1-hydroxymethyl-8-iodonaphthalene

(500.0 mg, 1.8 mmol) and 3 N H₂SO₄ (5.0 mL) in an ice bath. After stirring for several

hours, the reaction mixture was treated with $NaHSO_3$ and extracted with ether. The ether layer was extracted with 10% NaOH (aq). The alkaline solution was acidified with HCl and extracted with chloroform. $MgSO_4$ was added, and then the organic layer was filtered and the solvent removed. The yield of 8-iodo-1-naphthoic acid was 64%. The 8-iodo-1-naphthoic acid was next dissolved in 3 mL of anhydrous 1,2-dimethoxyethane. It was then added dropwise to an ice cold stirred mixture of titanium(IV) chloride (209.0 mg, 1.0 mmol) and sodium borodeuteride (125.0 mg, 3.3 mmol) in 10 mL of anhydrous 1,2-dimethoxyethane. Stirring was continued for 1 day at room temperature, and the reaction was then quenched by the addition of 50 mL of ice water. The aqueous solution was extracted with benzene (2 x 60 mL). The extract was washed with satd NaCl solution and dried with $MgSO_4$. The organic layer was filtered and removed under reduced pressure. The resulting oil was used further without purification. The oil was added to a 100 mL round bottom flask. To this flask was added 7.9 g (91.0 mmol) of manganese(IV) oxide (MnO_2), a magnetic stirring bar, and 50 mL of chloroform. The reaction was stirred and refluxed over night at 60 °C. The reaction mixture was then filtered, and the solvent was removed under reduced pressure. The solid was recrystallized from methanol. Overall yield: 35%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (m, 1 H), 7.51 (m, 1 H), 7.88 (m, 3 H), 8.25 (d, J = 7.2 Hz, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 90.13, 126.14, 127.88, 129.93, 130.38, 130.51, 134.40, 135.86, 141.48, 142.79, 191.84. The deuterium incorporation was determined by GC-MS analysis to be 47%.

Preparation of *o*-iodophenyl formate (63). To a 50 mL round bottom flask were added NaO_2CH (1.36 g, 20.0 mmol), 8 mL of anhydrous ethyl ether, a magnetic stirring bar, and 0.02 g of *n*-Bu_4NCl. The mixture was stirred at room temperature, and 1 g (12.7 mmol) of

acetyl chloride was added. The resulting mixture was stirred at room temperature for 4 h.

The mixture was cooled to 0 °C, and a solution of 2-iodophenol (1.0 g, 4.5 mmol) in 1.4 mL

of ethyl ether was added. The reaction was allowed to proceed at 0 °C for 20 min and then

quenched with 3 mL of methanol. Acetone (20 mL) was added, and the resulting solution

was filtered. The ethyl ether was then removed under reduced pressure, and the resulting

solid was recrystallized from chloroform. Yield: 44%. IR (neat) 3062, 2958, 2927, 1744

cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (m, 1 H), 7.13 (m, 1 H), 7.36 (m, 1 H), 7.84 (d, J =

5.9 Hz, 1 H), 8.38 (s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 90.11, 122.96, 128.41, 129.89,

139.99, 150.76, 158.58; HRMS calcd for $C_7H_5O_2I$: 347.93343. Found: 347.93388.

Standard Procedure for the Migration Chemistry. The aryl iodide (0.25 mmol), 5 mol %

of $Pd(OAc)_2$ (2.8 mg, 0.01 mmol), 5 mol % of dppm (4.8 mg, 0.01 mmol), CsPiv (117.0 mg,

0.50 mmol), and n-butanol (925.0 mg, 10.00 mmol) were added to a 4 dram vial equipped

with a magnetic stirring bar and a Teflon-lined screw cap. DMF (4 mL) was added. The vial

was placed in a mineral oil bath at 100 °C for 1 day. The reaction mixture was cooled to

room temperature and then quenched with 30 mL of aq NaCl. The aqueous layer was

extracted 3 times with 30 mL of ethyl ether. The organic layer was dried using $MgSO_4$.

Filtration and evaporation of the ethyl ether under reduced pressure produced the crude

product, which was further purified by silica gel chromatography.

n-**Butyl N-phenylcarbamate (25).** Compound 25 was isolated as a light yellow oil (42%

yield): ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.38 (m, 2 H), 1.59 (m, 2 H),

4.15 (t, J = 6.6 Hz, 2 H), 6.59 (br s, 1 H), 7.03 (m, 1 H), 7.27 (m, 2 H), 7.37 (m, 2 H). The

spectral properties of this compound are identical to those in the literature.[15]

N-Phenyl-2,2-dimethylpropanamide (26). Compound 26 was isolated as a viscous yellow oil (15% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.29 (s, 9 H), 7.06 (m, 1 H), 7.29 (m, 3 H), 7.48 (m, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 27.86, 39.82, 120.16, 124.41, 129.18, 138.24, 176.76; HRMS calcd for C$_{11}$H$_{15}$NO: 177.115364. Found: 177.115592. The spectral properties of this compound are identical to those in the literature.[16]

Methyl *N*-phenylcarbamate (37). Compound 37 was isolated as a light yellow oil (14% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.78 (s, 3 H), 6.66 (br s, 1 H), 7.07 (m, 1 H), 7.25 (m, 2 H), 7.37 (m, 2 H). The spectral properties of this compound are identical to those in the literature.[17]

Ethyl *N*-phenylcarbamate (38). Compound 38 was isolated as a light yellow oil (18% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.22 (t, *J* = 7.0 Hz, 3 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 7.06 (m, 1 H), 7.28 (m, 2 H), 7.33 (m, 2 H). The spectral properties of this compound are identical to those in the literature.[18]

n-Butyl 2,3-dihydro-1*H*-indolo-7-carboxylate (45). Compound 45 was isolated as a light yellow oil (47% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.94 (t, *J* = 7.4 Hz, 3 H), 1.42 (m, 2 H), 1.70 (m, 2 H), 3.01 (t, *J* = 8.3 Hz, 2 H), 3.66 (t, *J* = 8.3 Hz, 2 H), 4.24 (t, *J* = 6.6 Hz, 2 H), 6.51 (t, *J* = 7.0 Hz, 1 H), 7.14 (dd, *J* = 1.3, 5.7 Hz, 1 H), 7.55 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 14.04, 19.56, 28.81, 31.13, 47.07, 64.29, 102.66, 116.22, 124.44, 126.60, 127.99, 128.56, 154.77.

n-Butyl naphthalene-1-carboxylate (55). Compound 55 was isolated as an orange oil (35% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.99 (t, *J* = 5.5 Hz, 3 H), 1.50 (m, 2 H), 1.80 (m, 2 H), 4.41 (t, *J* = 5.0 Hz, 2 H), 7.48 (m, 3 H), 7.87 (d, *J* = 5.6 Hz, 1 H), 8.01 (d, *J* = 6.2 Hz, 1 H), 8.17 (d, *J* = 5.5 Hz, 1 H), 8.89 (d, *J* = 6.2 Hz, 1 H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 14.07,

19.64, 31.08, 65.21, 124.73, 126.05, 126.39, 127.76, 127.90, 128.74, 130.26, 131.59, 133.42, 134.06, 167.94. The spectral properties of this compound are identical to those in the literature.[19]

n-**Butyl salicylate (65).** Compound **65** was isolated as a light yellow oil (32% yield): IR (neat) 3156, 3050, 2958, 1675, 1213 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.59 (t, J = 5.6 Hz, 3 H), 1.45 (m, 2 H), 1.73 (m, 2 H), 4.32 (t, J = 5.0 Hz, 2 H), 6.85 (m, 1 H), 6.95 (m, 1 H), 7.41 (m, 1 H), 7.83 (d, J = 1.2 Hz, 1 H), 10.84 (s, 1 H); HRMS calcd for C$_{11}$H$_{14}$O$_3$: 194.09429. Found: 194.09467. The spectral properties of this compound are identical to those in the literature.[20]

sec-**Butyl salicylate (71).** Compound **71** was isolated as a light yellow oil (30% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.00 (m, 3 H), 1.54 (m, 2 H), 5.10 (q, J = 6.2 Hz, 1 H), 6.87 (m, 1 H), 6.96 (d, J = 8.4 Hz, 1 H), 7.42 (m, 1 H), 7.83 (d, J = 1.4 Hz, 1 H), 10.94 (s, 1 H). The spectral properties of this compound are identical to those in the literature.[21]

References

1. (a) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Hafner, K.; Rees, C. W.;

    Trost, B. M.; Lehn, J-M.; Schleyer, P. v-R.; Zahradnik, R., Eds.; Springer-Verlag:

    Berlin, 1980. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Katritzky, A. R.;

    Meth-Cohn, O.; Rees, C. W., Eds.; Academic Press: London, 1985. (c) Tsuji, J.

    Palladium Reagents and Catalysts, John Wiley & Sons: New York, 1995.

2. (a) Larock, R. C.; Ilkka, S. J. *Tetrahedron Lett.* **1986**, *27*, 2211. (b) Larock, R. C.;

    Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629. (c) Larock, R. C.;

    Leung, W.-Y. *J. Org. Chem.* **1990**, *55*, 6244. (d) Larock, R. C.; Lu, Y.-D.; Bain, A. C.;

    Russell, C. E. *J. Org. Chem.* **1991**, *56*, 4589. (e) Larock, R. C.; Wang, Y.; Lu, Y.;

    Russell, C. E. *J. Org. Chem.* **1994**, *59*, 8107.

3. (a) Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1987**, *28*, 4977. (b)

    Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1988**, *29*, 6399. (c)

    Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172. (d)

    Larock, R. C. Yang, H. *Synlett* **1994**, 748. (e) Larock, R. C.; Yang, H.; Pace, P.; Cacchi,

    S; Fabrizi, G. *Tetrahedron Lett.* **1998**, *39*, 237. (f) Larock, R. C.; Yang, H.; Pace, P.;

    Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **1998**, *39*, 1885. (g) Larock, R. C.; Pace, P.;

    Yang, H. *Tetrahedron Lett.* **1998**, *39*, 2515. (h) Larock, R. C.; Yang, H.; Pace, P.;

    Narayanan, K.; Russell, C. E.; Cacchi, S.; Fabrizi, G. *Tetrahedron* **1998**, *54*, 7343. (i)

    Larock, R. C.; Pace, P.; Yang, H.; Russell, C. E.; Cacchi, S.; Fabrizi, G. *Tetrahedron*

    1998, *54*, 9961.

4. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

5. (a) Pope, B. M.; Sheu S.-J.; Stanley, R. L.; Tarbell, D. S.; Yamamoto, Y. *J. Org. Chem.* **1978**, *43*, 2410. (b) Stanley, R. L.; Tarbell, D. S. *J. Org. Chem.* **1977**, *42*, 3686. (c) Dean, C. S.; Tarbell, D. S. *J. Org. Chem.* **1971**, *36*, 1180. (d) Dean, C. S.; Tarbell, D. S.; Friederang, A. W. *J. Org. Chem.* **1770**, *35*, 3393.

6. Wade, L. G. *Organic Chemistry, 2nd Edition*; Prentice Hall: Englewood Cliffs, New Jersey, 1991.

7. Ward, J. A., M.S. Thesis, *Iowa State University*, **1982**.

8. Curtin, D. Y.; Hurwitz, M. J. *J. Am. Chem. Soc.* **1952**, *74*, 5383.

9. (a) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (b) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R. *J. Med. Chem.* **1998**, *41*, 1060. (c) Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. *Synthesis* **2000**, 429.

10. (a) Cadogan, W. *J. Chem. Soc. B* **1971**, *583*, 584. (b) Hammerum, S. *Org. Mass Spectrom.* **1975**, *10*, 896.

11. (a) Ishii, Y.; Takendo, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Satoshi, S. *J. Org. Chem.* **1996**, *61*, 3088. (b) Claramunt, R. M.; Sanz, D.; Maria, M. D. S.; Jimenez, J. A.; Jimeno, M. L.; Elguero, J. *Heterocycles* **1998**, *47*, 301. (c) Barnett, R. *J. Chem. Soc., Chem. Commun.* **1972**, 758.

12. Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146.

13. (a) Carlier, D. R.; Lockshin, M. D.; Filsoa, M. P. *J. Org. Chem.* **1994**, *59*, 3232. (b) Kikugawa, Y.; Kashimura, M. *Synthesis* **1982**, 785. (c) Combrisson, R. *Tetrahedron* **1976**, *32*, 1507.

14. (a) Bailey, R. J.; Card, P. J.; Shechter, H. *J. Am. Chem. Soc.* **1983**, *105*, 6096. (b) Shea, K. M.; Lee, K. L.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 2353.

15. (a) McGhee, W.; Riley, D.; Christ, K.; Yi, P.; Parnas, B. *J. Org. Chem.* **1985**, *60*, 2820. (b) MacKay, D.; Taylor, D.; Wigle, N. J.; Ian, D. *J. Org. Chem.* **1987**, *52*, 1288.

16. (a) Leardini, R.; Zanardi, G. *Synthesis* **1982**, 225. (b) Wender, P. A.; Allan, W. W. *Tetrahedron* **1983**, *39*, 3767.

17. (a) Nishio, T.; Kato, A.; Kashima, C.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1980**, 607. (b) Arndsten, B. A.; Sleiman, H. F.; Chang, A. K.; McElwee-White, L. *J. Am. Chem. Soc.* **1991**, *113*, 4871. (c) Burgess, H.; Donnelly, J. A. *Tetrahedron* **1991**, *47*, 111.

18. (a) Mason, S.; Mothes, V.; Thuillier, A. *Tetrahedron* **1984**, *40*, 1573. (b) Moore, H. W.; Hernandez, L.; Kunert, D. M.; Mercer, F.; Annlic, S. *J. Am. Chem. Soc.* **1981**, *103*, 1769.

19. Cia, M-Z.; Song, C-S.; Huang, X. *J. Chem. Soc., Perkin Trans. 1* **1997**, *16*, 2273.

20. Mohammed, A. A.; Yoshihisa, G.; Kiuchi, F.; Tsuda, Y.; Kondo, K. *Chem. Pharm. Bull.* **1991**, *39*, 1043.

21. (a) Kaminska, J. E.; Kaminski, Z. J.; Gora, J. *Synthesis* **1999**, 593. (b) Rossi, R. *J. Org. Chem.* **1974**, *39*, 855.

GENERAL CONCLUSIONS

In this dissertation the scope and limitations of several palladium-catalyzed processes have been presented. In particular, new palladium-catalyzed methodology for the heteroannulation of cyclic and bicyclic alkenes by functionally-substituted aryl iodides has been developed. Also, palladium methodology for the synthesis of tetrasubstituted alkenes by the ternary coupling of an aryl iodide, an alkyne, and an organometallic has been developed. Lastly, an investigation of palladium migration chemistry where the palladium has migrated from an aryl group to an acyl group has been performed.

In Chapter 1, a reasonably efficient, palladium(0)-catalyzed synthesis of benzofuran, carbazole, and indoline derivatives has been developed. The key to the success of these heteroannulation processes lies in the correct choice of the cyclic or bicyclic alkene. o-Hydroxyaryl iodides give good yields of heteroannulation product when allowed to react with appropriate alkenes. Reactions of the o-hydroxyaryl iodides with indene and 1,2-dihydronaphthalene afford only low yields of heteroannulation products due to competing reaction pathways, which lead to Heck products. The electronics of the aryl iodide is important for formation of the desired heteroannulation product. The heteroannulation of o-aminoaryl iodides onto alkenes is greatly facilitated by employing ethylene glycol as the solvent and DMG as an additive. Good yields of heteroannulation products from o-aminoaryl iodides have been obtained.

In Chapter 2, our preliminary results indicate the feasibility of employing palladium(0)-catalyzed, intermolecular methodology for the regio- and stereoselective synthesis of tetrasubstituted alkenes. After optimization of our model system, good yields of

the desired alkene have been produced. The electronics of the aryl iodide are important for the success of the reaction. Various alkynes (other than diphenylacetylene) can be employed in the reaction as well. When the organometallic reagent is varied, tin and boronic acid reagents give high yields, and silicon reagents give lower yields.

In Chapter 3, the reaction conditions under which palladium will undergo intramolecular migration from an aryl group to an acyl group have been investigated. We have optimized the reaction conditions by varying the phosphine ligand, the base, and the solvent, but have found that the original reaction conditions produced the best yields of migration product. We have noted during our studies of this palladium migration process that other interesting rearrangements can also occur, because certain functional groups are better leaving groups than palladium. These results together suggest that palladium migration from an aryl group to an acyl group can and does occur.

ACKNOWLEDGEMENTS