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Preparation of allylic ketones via acylation of allylic
mercurials and palladium(0)-catalyzed coupling of aryl iodides,
nonconjugated dienes, and nucleophiles

Lu, Yong-de, Ph.D.

Iowa State University, 1991

Preparation of allylic ketones via acylation of allylic mercurials

and

Palladium(0)-catalyzed coupling of aryl iodides,
nonconjugated dienes, and nucleophiles

by

Yong-de Lu

A Dissertation Submitted to the
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Iowa State University
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GENERAL INTRODUCTION

The dissertation consists of two parts made up of a total of four papers suitable for publication in a journal. The first part of this dissertation discusses the acylation of allylic mercurials by acyl chlorides promoted by aluminum chloride. A variety of allylic mercurials and acyl chlorides can be employed successfully in this reaction. This reaction provides a convenient route to allylic ketones. A modified literature procedure to prepare allylic mercuric iodides from the corresponding allylic halides and metallic mercury is also presented in this part.

The second part of this dissertation discusses the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes, and nucleophiles, which generates more than one carbon-carbon bond or carbon-heteroatom bond at a time via palladium migration chemistry.

The second part of this thesis is divided into three sections. The first section deals with the palladium-catalyzed coupling of aryl iodides and nonconjugated dienes using carbon nucleophiles. The reaction results in a high degree of regioselectivity and stereoselectivity. Applications of nitrogen and oxygen nucleophiles in this unique coupling reaction are reported in the second section. A variety of amines and the azide anion have been used as representative nitrogen nucleophiles and only one regio- and stereoisomer is isolated in good yields. When oxygen nucleophiles, such as acetate anion and phenoxide anion, are used in the coupling process, a mixture of regio- and stereoisomers is obtained. The focus of the third section is the application of the three-component coupling methodology to the synthesis of analogues of some naturally occurring pyridine alkaloids. The palladium-catalyzed coupling-migration approach is the key step and the total synthesis is accomplished in only two steps.

A general summary comes after the four papers.

PART I. PREPARATION OF ALLYLIC KETONES

VIA ACYLATION OF ALLYLIC MERCURIALS

INTRODUCTION

The use of organometallic compounds for the synthesis of ketones has been known for more than a century.[1] Over the past several decades, reactions involving electrophilic acylation of organometallics to form ketones have been well studied and reviewed.[2,3] Organometallic derivatives of aluminum, boron, cadmium, copper, iron, lead, magnesium, mercury, nickel, rhodium, silicon, sodium, tin, zirconium, and zinc have been shown to react with acid halides to yield ketones, in some cases catalyzed by a palladium compound. These reactions can be represented by the general equation 1.[2,4]

$$R^1\overset{O}{\overset{\|}{C}}X + R^2M \longrightarrow R^1\overset{O}{\overset{\|}{C}}R^2 + MX \qquad (1)$$
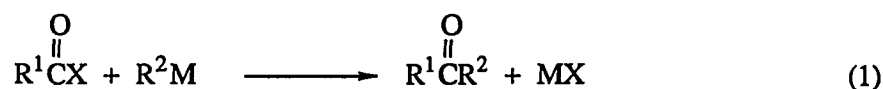
In this introduction, no effort has been made to cover the literature on the acylation of organometallics reported before 1987, except mercury, since an excellent book[3] covering this subject is available. An attempt has been made to cover all primary literature related to the application of organometallics to the synthesis of ketones via acylation through 1990. Included are organometallics of copper, magnesium, titanium, thallium, and zinc, which will be discussed first. Then, the acylation of organomercurials, particularly allylic mercurials, will be examined in detail.

Copper reagents have proven to be very useful in organic synthesis.[5] Their synthetic utility would be enhanced further if highly functionalized copper compounds could be prepared. Rieke and co-workers have reported that highly reactive copper can be prepared by the lithium naphthalide reduction of the complex copper(I) iodide/triphenylphosphine. This copper reacts with functionalized alkyl halides to give organocopper reagents which can be effectively trapped with acid chlorides to give functionalized ketones in good yields (eq 2).[6]

Ester, nitrile, chloride, remote epoxide, and, to some extent, ketone groups can be tolerated by this approach, because the preparation of the copper reagent does not involve an organolithium

$$Br(CH_2)_nY \xrightarrow[\text{CuI / PPh}_3]{\text{Li naphthalide}} \xrightarrow{\text{PhCOCl}} Ph\overset{\overset{\displaystyle O}{\|}}{C}(CH_2)_nY \qquad (2)$$

Y = Cl, CO$_2$Et, CN	n = 2-7	60-80%
COCH$_3$	4	19%
epoxide	6	58%
	1-2	0%
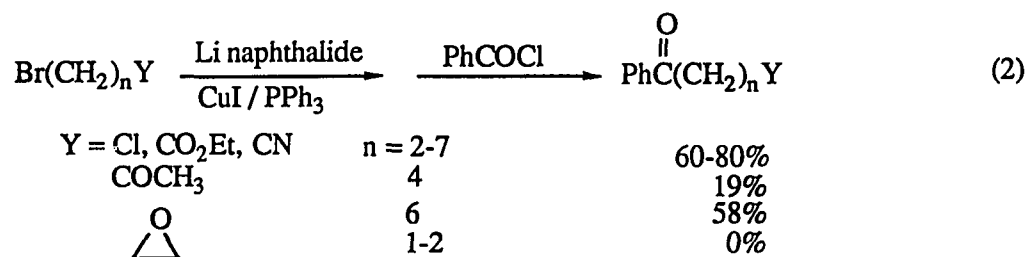
or Grignard reagent. It is noted that epoxide functionality must be located in such a position that intramolecular epoxide attack by the organocopper species cannot occur. Anyway, this methodology increases the utility of organocopper reagents for ketone synthesis.

Knochel et al.[7] have found that a new class of highly functionalized copper reagents RCu(CN)ZnI can be prepared by the reaction of a soluble copper salt CuCN• 2LiX (X = Cl, Br) with various zinc organometallics (eq 3). Meanwhile, Gaudemar[8] developed a mild

$$R^1\text{-I} \xrightarrow[\text{THF, 25-40 }^0\text{C}]{\text{activated Zn}} R^1\text{-ZnI} \xrightarrow[\text{0 }^\circ\text{C, 10 min}]{\text{CuCN• 2LiX}} R^1\text{-Cu(CN)ZnI} \xrightarrow[\text{0 }^\circ\text{C, 3 h}]{R^2\text{COCl}} R^1\overset{\overset{\displaystyle O}{\|}}{C}R^2 \qquad (3)$$

$$R^1 = n\text{-Bu, } i\text{-Pr, cyclohexyl, EtO}_2C(CH_2)_3, NC(CH_2)_3 \qquad\qquad 81\text{-}94\%$$
$$R^2 = n\text{-C}_5H_{11}, \text{cyclohexyl, Ph}$$
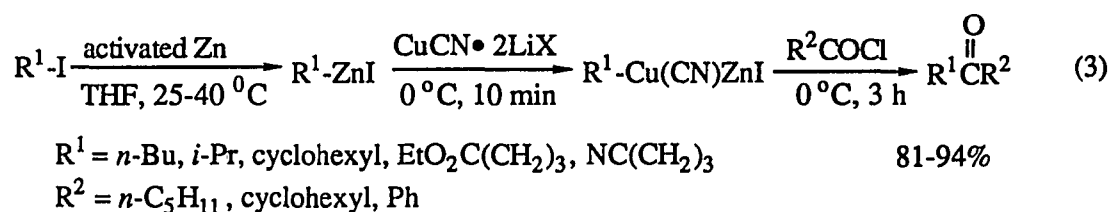
synthesis of polyfunctional zinc organometallics by treating various functionalized iodides with activated zinc in THF. The copper reagents react rapidly with acid chlorides and furnish the ketones in high yields (see eq 3). Under the standard conditions, the copper species do not react with epoxides and ketones. However, they react with allylic halides regioselectively and afford the S$_N$ 2' substitution products. Therefore, it is expected that the high tolerance of important groups like an ester, nitrile, or ketone, as well as the high stability of these new copper reagents RCu(CN)ZnI will allow them to find broad application in organic synthesis.

Several decades ago, organozinc reagents were found unsatisfactory when used in the preparation of ketones.[2] However, it has been reported in the recent literature that organozinc reagents can be readily prepared by the reaction of alkyl iodides with a zinc-copper couple in uncommon solvents (carbonate esters, butyl phosphate, sulfolane). Treating the organozinc reagent formed with an acyl chloride gives good yields of the corresponding ketones.[9] Yoshida et al.[10] have also found that β-, γ- and δ- zinc ketones or zinc alkenes can be prepared by treating the corresponding iodoketone or iodoalkene with zinc-copper couple in HMPA-benzene or DMF-benzene, and this functionalized zinc reagent can then be reacted with a variety of acid chlorides in the presence of a palladium(0) catalyst to yield the corresponding diketone or unsaturated ketone (eqs 4 and 5). They found that β-zinc ketones and their

$$
\underset{\substack{O \\ \parallel}}{RC(CH_2)_nI} + Zn\text{-}Cu \xrightarrow[C_6H_6]{HMPA} \underset{\substack{O \\ \parallel}}{RC(CH_2)_nZnI} \xrightarrow[Pd(PPh_3)_4]{R'COCl} \underset{\substack{O \quad O \\ \parallel \quad \parallel}}{RC(CH_2)_nCR'} \quad (4)
$$

R = Me, Et, Ph   n = 2-6   R' = Me, Et, vinyl, Ph   53-91%

$$
CH_3CHICH_2CH\text{=}CH_2 + Zn\text{-}Cu \xrightarrow[\substack{2. Pd(PPh_3)_4, \\ PhCOCl}]{1. DMF\text{-}C_6H_6} \underset{\substack{O \\ \parallel}}{PhCCH(CH_3)CH_2CH\text{=}CH_2} \quad (5)
$$
78%

higher homologues are rather stable and undergo neither an intramolecular proton abstraction to form zinc enolates nor nucleophilic attack at the carbonyl to form zinc cycloalkanolates.

Marko and co-workers[11] have allowed triorganothallium reagents to react with acid chlorides to form ketones successfully. Triorganothallium reagents, which were easily prepared, in situ, from diorganothallium(III) halides and organolithium or organomagnesium derivatives, reacted readily and chemoselectively with acid chlorides to give high yields of alkyl and phenyl ketones. Selective group transfer was accomplished in the case of a mixed triorganothallium derivative (eq 6).

$$\text{Me}_2\text{TlC}\!\!=\!\!\text{CPh} \; + \; \text{R}\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{Cl} \quad \xrightarrow[\;20\,^{\circ}\text{C}\;]{\text{Et}_2\text{O}} \quad \text{R}\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{C}\!\!=\!\!\text{CPh} \qquad (6)$$

$$\text{R} = \text{Me, } n\text{-nonyl} \qquad\qquad 73\text{-}77\%$$

The acylation of an organomanganese iodide or bromide with a carboxylic acid chloride, in ether, allowed the preparation of a large array of ketones in excellent yield.[12,13] Recently, Cahiez and co-workers have successfully prepared organomanganese chlorides in THF, instead of ether, in high yields,[13] and these organomanganese reagents were efficiently acylated by carboxylic acid chlorides in the same solvent THF (eq 7).[14] Alkyl, aryl, alkenyl,

$$\text{MnCl}_2 \cdot 2\,\text{LiCl} \quad \xrightarrow[\substack{\text{or } n\text{-BuLi} \\ \text{THF}}]{n\text{-BuMgCl}} \quad n\text{-BuMnCl} \quad \xrightarrow[\text{THF}]{\text{PhCOCl}} \quad n\text{-Bu}\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{Ph} \qquad (7)$$

$$\begin{aligned}\text{from } n\text{-BuMgCl:} &\quad 90\% \\ \text{from } n\text{-BuLi:} &\quad 88\%\end{aligned}$$
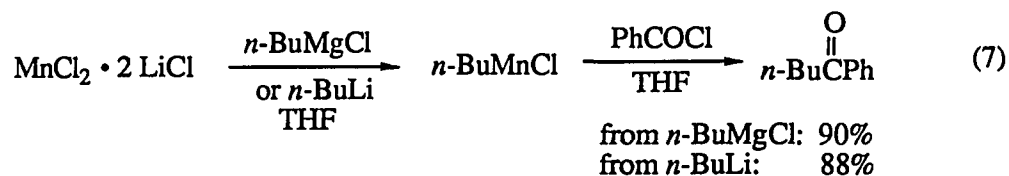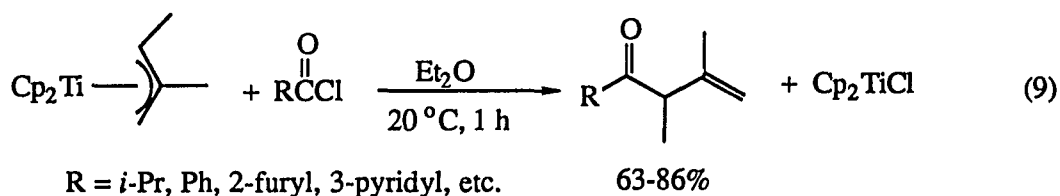
and alkynylmanganese halides are readily acylated by acid chlorides to give the corresponding ketones in good yield (75 - 95%). Allylic ketones can also be prepared successfully from the corresponding allylic manganese chloride without rearrangement (eq 8).[14] This is the first time that an allylic manganese halide has been acylated in good yield by a carboxylic acid chloride.

$$(\text{CH}_3)_2\text{C}\!\!=\!\!\text{CHCH}_2\text{MnCl} + n\text{-C}_7\text{H}_{15}\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{Cl} \quad \xrightarrow[\text{-10 to 20}\,^{\circ}\text{C}]{\text{THF}} \quad (\text{CH}_3)_2\text{C}\!\!=\!\!\text{CHCH}_2\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{C}_7\text{H}_{15} \qquad (8)$$

$$89\%$$
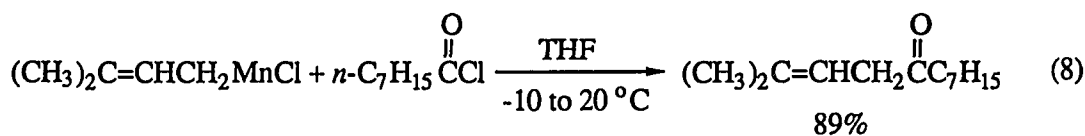
In addition to the σ-bonded organometallic reagents used to prepare ketones, it has been found that π-bonded organometallics can also be applied to the preparation of ketones via acylation. Titanium(III) π-allylic complexes, prepared by the interaction of a 1,3-diene with Cp$_2$TiCl$_2$ and n-propylmagnesium bromide, have been found to react with carboxylic acid chlorides under mild conditions to give high yields of the related β, γ-unsaturated ketones
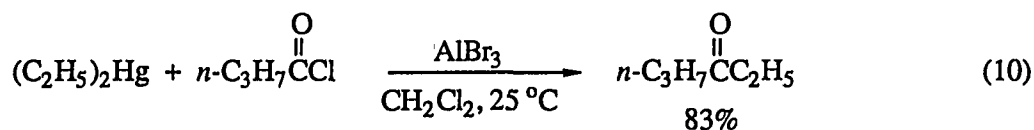
(eq 9).[15] The reaction takes place regioselectively at the most substituted carbon atom of the π-allylic ligand.

$$Cp_2Ti \overset{}{\underset{}{\longrightarrow}} + R\overset{O}{\overset{\|}{C}}Cl \xrightarrow[20\,^\circ C,\ 1\ h]{Et_2O} R\overset{O}{\overset{\|}{\diagup}}\diagdown + Cp_2TiCl \qquad (9)$$

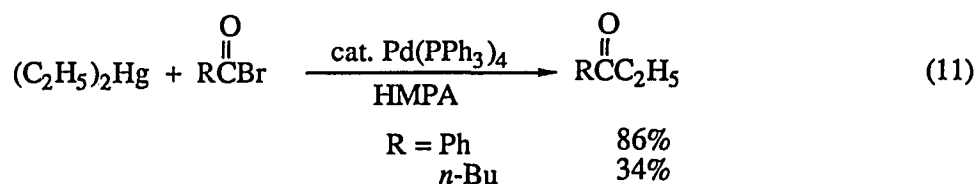R = *i*-Pr, Ph, 2-furyl, 3-pyridyl, etc.　　63-86%

It is well known that organomercurials should be handled with respect due to their high toxicity. However, the majority of organomercurials are fairly high-melting crystalline solids whose handling requires no undue precautions. They are generally of sufficiently low volatility that they can be easily weighed out in air on the laboratory bench and transfered to a reaction flask. This is especially true of the most common organomercurials of type RHgX, particularly the organomercuric halides, which generally have much higher melting points and are much less powerful skin irritants than the diorganomercurials R_2Hg. The remarkable chemical stability of most organomercurials allows one to incorporate essentially all important organic functional groups in these organometallics. These characteristics thus allow one to run synthetic reactions employing organomercurials under a wide variety of conditions. The more reactive organometallic reagents, such as organolithium and magnesium compounds, which were developed in the early part of the twentieth century, accommodate very little in the way of functionality. Therefore, another purpose of this part of my dissertation is to rejuvenate interest in the organometallic chemistry of less reactive main group elements like mercury.

Although the reaction of organomercurials and alkyl halides is severely limited, the reaction with acid halides is more general and can afford a useful route to ketones. Simple alkylmercurials can be acylated under the appropriate conditions to give good yields of ketones. Thus, diethylmercury reacts directly with acid chlorides under forcing conditions to give low

yields of ketones;[16] however, the addition of aluminum bromide affords high yields of ketones even at room temperature (eq 10).[17] It is unclear whether one or both organic groups on

$$(C_2H_5)_2Hg + n\text{-}C_3H_7\overset{\overset{\displaystyle O}{\|}}{C}Cl \xrightarrow[\text{CH}_2\text{Cl}_2, 25\,^\circ\text{C}]{\text{AlBr}_3} n\text{-}C_3H_7\overset{\overset{\displaystyle O}{\|}}{C}C_2H_5 \quad (10)$$
$$83\%$$

the mercury can be utilized in this reaction. Catalytic amounts of Pd(PPh3)4 in HMPA also promote the acylation of diethylmercury (eq 11).[18] Unfortunately, the reaction requires the

$$(C_2H_5)_2Hg + R\overset{\overset{\displaystyle O}{\|}}{C}Br \xrightarrow[\text{HMPA}]{\text{cat. Pd(PPh}_3)_4} R\overset{\overset{\displaystyle O}{\|}}{C}C_2H_5 \quad (11)$$

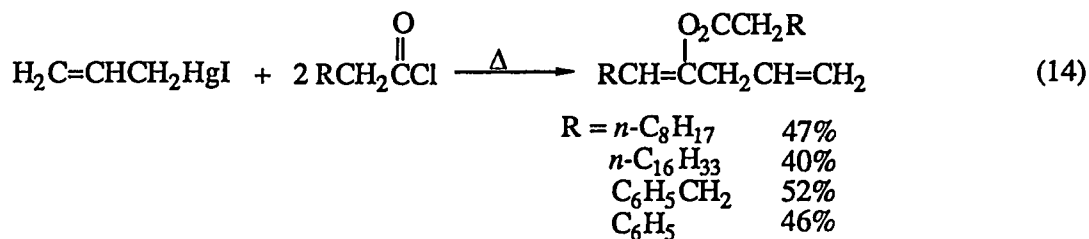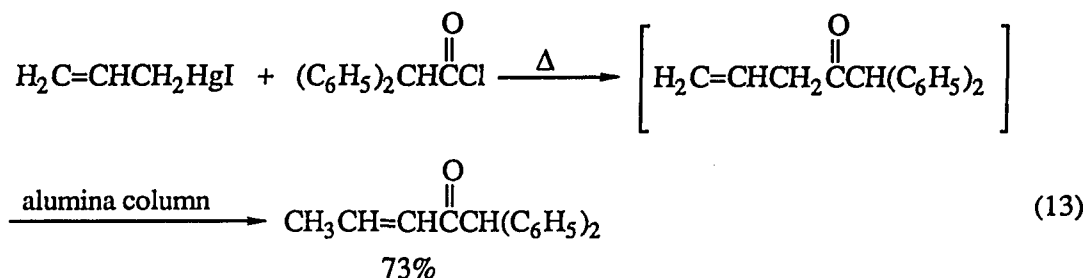$$\begin{array}{cc} R = Ph & 86\% \\ n\text{-Bu} & 34\% \end{array}$$

use of hexamethylphosphoramide (HMPA), which is expensive and toxic, and the reaction fails apparently when alkyl- and arylmercuric chlorides are employed. Lower yields are obtained when aliphatic acid bromides are employed in this reaction.

The reaction of benzylmercuric chloride, acetyl chloride and aluminum bromide affords two unexpected products (eq 12).[19] Both products appear to arise via initial acylation in the para position of the benzene ring to produce a cyclohexadiene which can either rearrange to
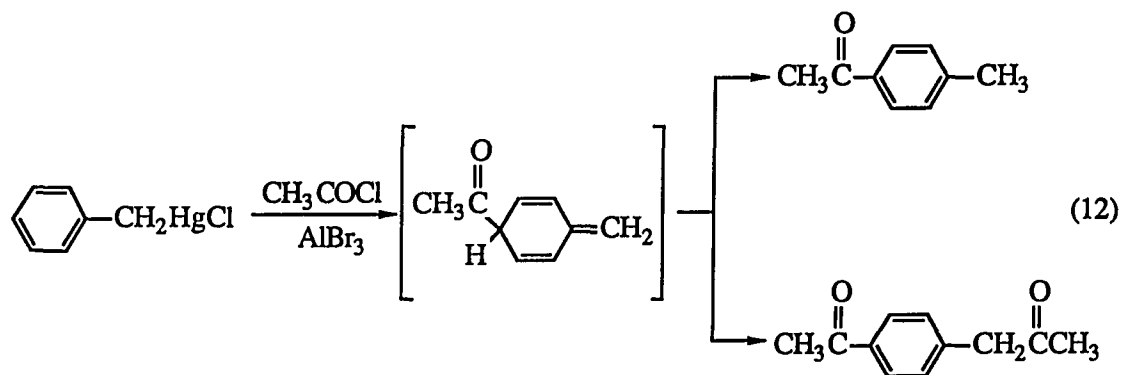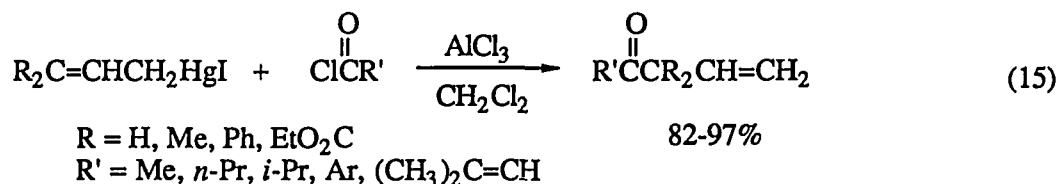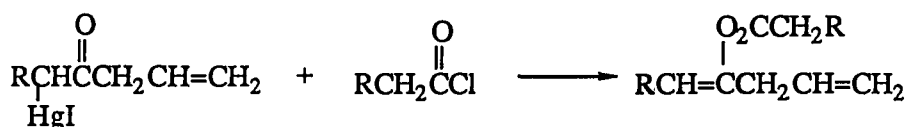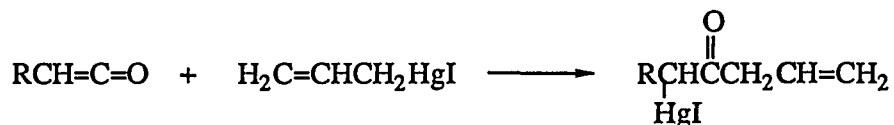
give the minor product or undergo further acylation to produce the major product, the diketone.

The reaction of allylmercuric iodide and an acid chloride in the absence of a Lewis acid also provides unexpected products and none of the anticipated allyl ketone is observed (eqs 13 and 14).[20] The infrared spectrum of the crude reaction mixture of the former reaction (eq 13)

$$H_2C=CHCH_2HgI \ + \ (C_6H_5)_2CH\overset{O}{\overset{\|}{C}}Cl \ \xrightarrow{\ \Delta\ } \ \left[H_2C=CHCH_2\overset{O}{\overset{\|}{C}}CH(C_6H_5)_2 \right]$$

$$\xrightarrow{\text{alumina column}} \ CH_3CH=CH\overset{O}{\overset{\|}{C}}CH(C_6H_5)_2 \tag{13}$$
$$73\%$$

$$H_2C=CHCH_2HgI \ + \ 2\,RCH_2\overset{O}{\overset{\|}{C}}Cl \ \xrightarrow{\ \Delta\ } \ RCH=\overset{O_2CCH_2R}{\overset{|}{C}}CH_2CH=CH_2 \tag{14}$$

$$\begin{array}{ll} R = n\text{-}C_8H_{17} & 47\% \\ n\text{-}C_{16}H_{33} & 40\% \\ C_6H_5CH_2 & 52\% \\ C_6H_5 & 46\% \end{array}$$
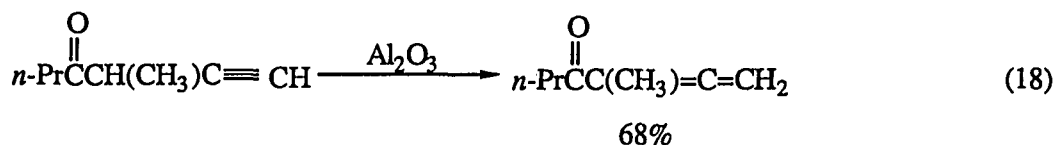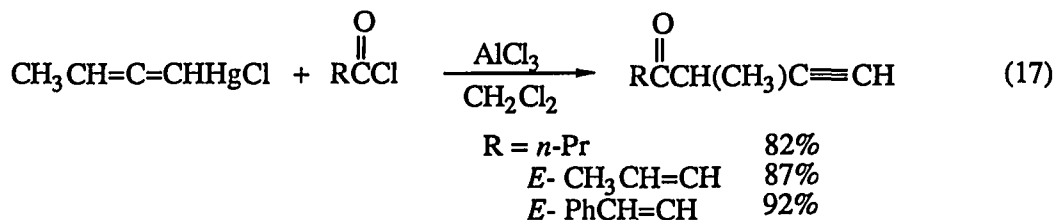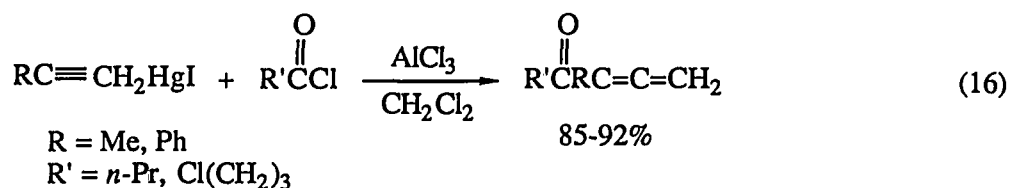
shows that the reaction of diphenylacetyl chloride with allylmercuric iodide does afford the expected allyl ketone which, however, isomerizes into the diphenylmethyl propenyl ketone during the purification procedure. The product of Equation 14 appears to arise via ketene formation and insertion into the allylmercurial, followed by acylation of the resulting α-mercurated ketone (Scheme I).

Larock and the author of this dissertation have reported that the AlCl₃-promoted acylation of allylic mercuric iodides with acid chlorides did yield the anticipated allylic ketones and no isomerization product was observed (eq 15).[21] Considerable functionality can be

Scheme I

$$RCH_2\overset{\overset{\displaystyle O}{\|}}{C}Cl \quad + \quad H_2C=CHCH_2HgI \quad \longrightarrow \quad RCH=C=O \quad + \quad CH_3CH=CH_2$$

$$RCH=C=O \quad + \quad H_2C=CHCH_2HgI \quad \longrightarrow \quad R\underset{\underset{\displaystyle HgI}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH=CH_2$$

$$R\underset{\underset{\displaystyle HgI}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH=CH_2 \quad + \quad RCH_2\overset{\overset{\displaystyle O}{\|}}{C}Cl \quad \longrightarrow \quad RCH=\underset{\underset{\displaystyle |}{}}{C}CH_2CH=CH_2 \overset{O_2CCH_2R}{\underset{}{|}}$$

$$R_2C=CHCH_2HgI \quad + \quad Cl\overset{\overset{\displaystyle O}{\|}}{C}R' \quad \xrightarrow[CH_2Cl_2]{AlCl_3} \quad R'\overset{\overset{\displaystyle O}{\|}}{C}CR_2CH=CH_2 \qquad (15)$$

R = H, Me, Ph, EtO$_2$C   82-97%
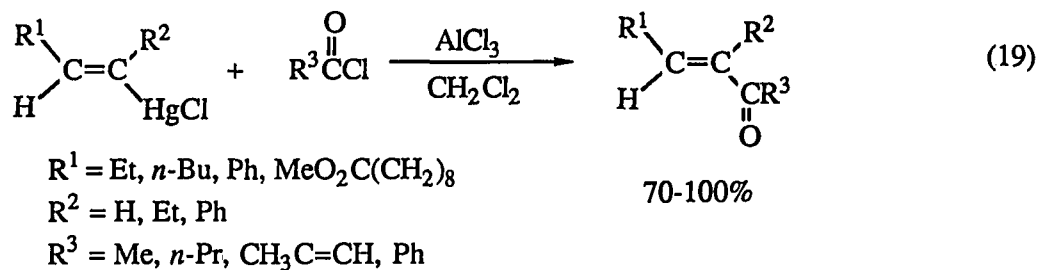R' = Me, *n*-Pr, *i*-Pr, Ar, (CH$_3$)$_2$C=CH

accommodated by this reaction and all reactions proceed with allylic rearrangement, even when it means that the double bond is removed from conjugation. Furthermore, allylic mercuric iodides can be readily prepared from allylic halides and mercury(0) under mild conditions in good to excellent yields. This process is the subject of this chapter.

Larock and co-workers[22,23] have also found that the low-temperature reaction of carboxylic acid chlorides, aluminum halides, and propargylic and allenic organomercurials affords the corresponding rearranged allenic and propargylic ketones, respectively, in high yields (eqs 16 and 17). It is of interest to note that the propargylic ketones rearrange smoothly to the corresponding allenic ketones when passed through a column of aluminum oxide. In fact, this isomerization process provides a unique route to allenic ketones (eq 18).[22]
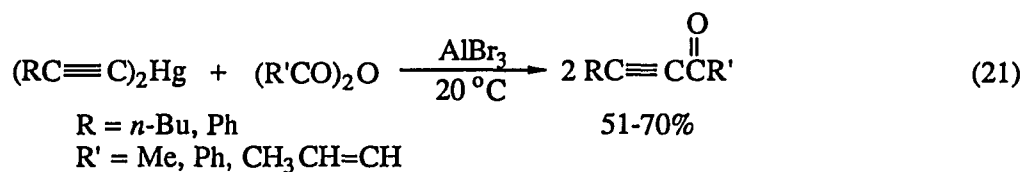
$$RC{\equiv}CH_2HgI \ + \ R'\overset{\overset{O}{\|}}{C}Cl \ \xrightarrow[CH_2Cl_2]{AlCl_3} \ R'\overset{\overset{O}{\|}}{C}RC{=}C{=}CH_2 \qquad (16)$$

R = Me, Ph

R' = n-Pr, Cl(CH$_2$)$_3$

85-92%

$$CH_3CH{=}C{=}CHHgCl \ + \ R\overset{\overset{O}{\|}}{C}Cl \ \xrightarrow[CH_2Cl_2]{AlCl_3} \ R\overset{\overset{O}{\|}}{C}CH(CH_3)C{\equiv}CH \qquad (17)$$

R = n-Pr   82%

E- CH$_3$CH=CH   87%

E- PhCH=CH   92%

$$n\text{-Pr}\overset{\overset{O}{\|}}{C}CH(CH_3)C{\equiv}CH \ \xrightarrow{Al_2O_3} \ n\text{-Pr}\overset{\overset{O}{\|}}{C}C(CH_3){=}C{=}CH_2 \qquad (18)$$
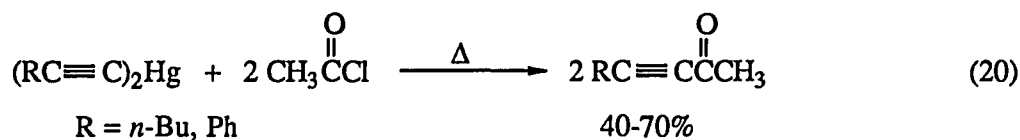
68%

While vinylmercurials do not react directly with acid chlorides, the addition of an equivalent of aluminum chloride promotes rapid acylation and affords excellent yields of α,β-unsaturated ketones with retention of configuration (eq 19).[24,25] Unlike the alkyl- and arylmercuric

$$\underset{H}{\overset{R^1}{>}}C{=}C\underset{HgCl}{\overset{R^2}{<}} \ + \ R^3\overset{\overset{O}{\|}}{C}Cl \ \xrightarrow[CH_2Cl_2]{AlCl_3} \ \underset{H}{\overset{R^1}{>}}C{=}C\underset{\underset{O}{\overset{\|}{C}R^3}}{\overset{R^2}{<}} \qquad (19)$$

R^1 = Et, n-Bu, Ph, MeO$_2$C(CH$_2$)$_8$

R^2 = H, Et, Ph
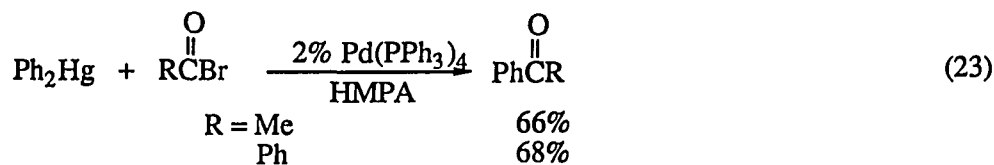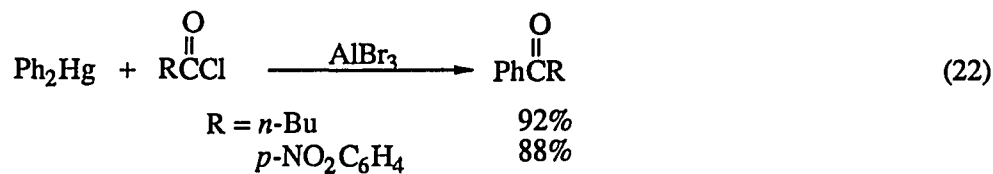
R^3 = Me, n-Pr, CH$_3$C=CH, Ph

70-100%

chlorides, the reaction of vinylmercuric chlorides with acid chlorides occurs very quickly, often in minutes at room temperature. A number of other reagents, such as Al, AlBr$_3$, TiCl$_4$, [ClRh(CO)$_2$]$_2$ and Pd(PPh$_3$)$_4$, also facilitate acylation, but the yields are generally lower and mixtures of stereoisomers are observed. Mechanistically, the AlCl$_3$ reaction may be proceeding

by addition of the acid chloride across the carbon-carbon double bond, followed by mercuric chloride elimination.

Dialkynylmercurials are sufficiently reactive towards aliphatic acid halides that both groups are transferred in refluxing heptane (eq 20).[26] Acid anhydrides can also be employed in these reactions under mild conditions, if aluminium bromide is added (eq 21).

$$(RC{\equiv}C)_2Hg \ + \ 2\ CH_3\overset{\text{O}}{\underset{\text{||}}{C}}Cl \ \xrightarrow{\ \Delta\ } \ 2\ RC{\equiv}C\overset{\text{O}}{\underset{\text{||}}{C}}CH_3 \qquad\qquad (20)$$

$$R = n\text{-Bu, Ph} \qquad\qquad\qquad 40\text{-}70\%$$

$$(RC{\equiv}C)_2Hg \ + \ (R'CO)_2O \ \xrightarrow[\text{20 °C}]{AlBr_3} \ 2\ RC{\equiv}C\overset{\text{O}}{\underset{\text{||}}{C}}R' \qquad\qquad (21)$$

$$R = n\text{-Bu, Ph}$$
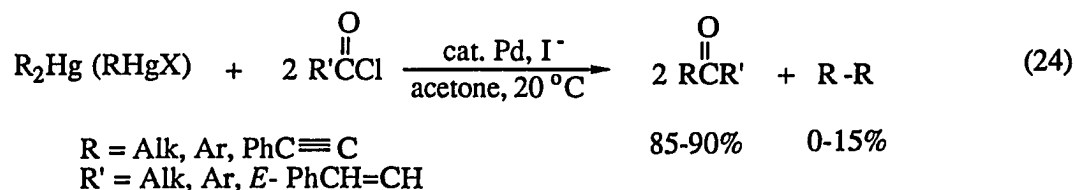$$R' = \text{Me, Ph, } CH_3CH{=}CH \qquad\qquad 51\text{-}70\%$$

Although simple arylmercuric halides and diarylmercurials will react at high temperature with acid halides,[27] better yields of ketones are obtained by adding aluminum halides[18,28,29] or by using Pd(PPh3)4 as a catalyst[18] (eqs 22 and 23). In the former reaction, it is unclear

$$Ph_2Hg \ + \ R\overset{\text{O}}{\underset{\text{||}}{C}}Cl \ \xrightarrow{AlBr_3} \ Ph\overset{\text{O}}{\underset{\text{||}}{C}}R \qquad\qquad (22)$$

$$R = n\text{-Bu} \qquad\qquad 92\%$$
$$p\text{-}NO_2C_6H_4 \qquad 88\%$$

$$Ph_2Hg \ + \ R\overset{\text{O}}{\underset{\text{||}}{C}}Br \ \xrightarrow[\text{HMPA}]{2\%\ Pd(PPh_3)_4} \ Ph\overset{\text{O}}{\underset{\text{||}}{C}}R \qquad\qquad (23)$$

$$R = \text{Me} \qquad\qquad 66\%$$
$$\text{Ph} \qquad\qquad 68\%$$

whether one or both organic groups on mercury can be utilized. When using the palladium catalyst, organomercuric chlorides apparently fail to work. The literature also contains a number of examples of heteroatom-containing arylmercurials which react directly with acid halides. These include organomercurials derived from diphenyl ether,[30] furans,[31] benzofuran,[32] thiophenes,[33] benzothiophene,[34] and selenophene.[35] Yields vary substantially from compound to compound, but the acylation of these arylmercurials can prove synthetically useful.

Bumagin and co-workers[36,37] have reported that the reaction of organomercurials with acid chlorides in acetone in the presence of a catalytic amount of a palladium complex and iodide anion gives high yields of unsymmetrical ketones (eq 24). Unfortunately, small

$$R_2Hg\ (RHgX)\ +\ 2\ R'\overset{O}{\overset{\|}{C}}Cl\ \xrightarrow[\text{acetone, 20\,°C}]{\text{cat. Pd, I}^-}\ 2\ R\overset{O}{\overset{\|}{C}}R'\ +\ R\text{-}R \qquad (24)$$

R = Alk, Ar, PhC≡C
R' = Alk, Ar, E- PhCH=CH

85-90%   0-15%

amounts of homocoupling products (R-R) were observed along with the desired ketones. The selectivity of the reaction towards the ketone can be increased by carrying out the reaction with a suitable combination of reactants in the absence of oxygen.

The following chapters of this part of my dissertation will discuss the preparation of allylic mercuric iodides and their application to the synthesis of allylic ketones via $AlCl_3$ promoted acylation.

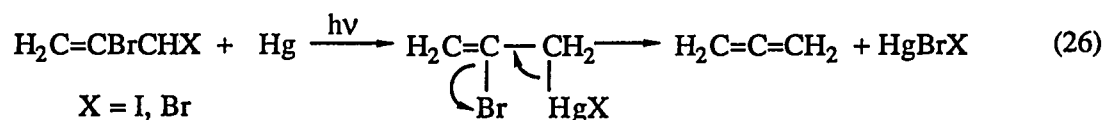# PREPARATION OF ALLYLIC MERCURIC IODIDES

A large number of allylic mercuric halides have been reported to be prepared from the corresponding allylic halides upon direct reaction with metallic mercury. In 1855 and 1865, Zinon[38] and Linnemann[39] first isolated crystalline allylmercuric iodide when allyl iodide was reacted with metallic mercury directly. Later on, a wide variety of allylic mercurials were prepared by Russian workers using similar methods.

Reutov and Nesmeyanov[40] have reported that the reaction of metallic mercury with organic halides is activated by ultraviolet light and by Bz_2O_2, indicating the radical character of the reaction. It was also reported that organic iodides or bromides reacted with mercury to yield organomercurials. For example, the reaction of allyl bromide with metallic mercury affords allylmercuric bromide in differing yields depending on the reaction conditions employed (eq 25). The first result was obtained by running the reaction in a quartz tube. In a
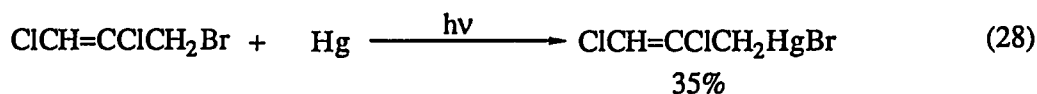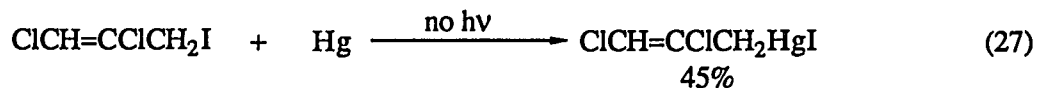
$$H_2C=CHCH_2Br \ + \ Hg \longrightarrow H_2C=CHCH_2HgBr + \ polymer \qquad (25)$$

hv / 48 h, quartz tube	9%	
hv / 48 h, glass tube	20%	no polymer
no light (dark) / 25 d	32%	no polymer
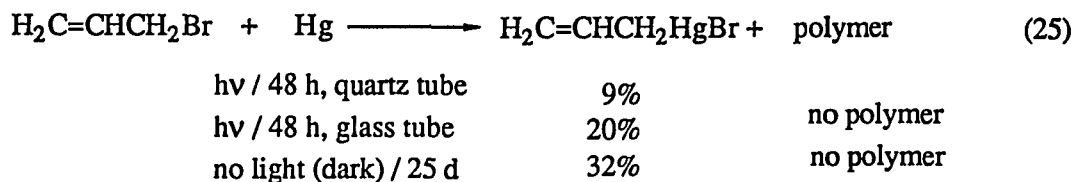
glass tube, the yield of RHgBr rose to 20% and the polymer failed to form. Without light, allyl bromide reacts very slowly with mercury and in twenty five days gave a 32% yield of the desired product.[41] Under the same conditions, allyl chloride failed to react, as did cinnamyl chloride.[40,41] Unexpectedly, when cinnamyl bromide was allowed to react with metallic mercury at room temperature, the desired cinnamylmercuric bromide was obtained in 82% yield, even without irradiation and only shaking the suspension of mercury and RBr in ethanol for about fifteen minutes.[40]

Friedlina and co-workers have further reported that upon reaction with metallic mercury, with or without irradiation by ultraviolet light, 1,2-dibromo-2-propene, and 1-iodo-2-bromo-2-propene, similar to 1,2-dihaloalkanes, do not form organic mercury compounds, but mercury halide and allene (eq 26).[42] However, the β-chloroallylmercuric iodide was successfully

$$H_2C=CBrCHX + Hg \xrightarrow{h\nu} H_2C=C \overset{CH_2}{\underset{Br}{\big\langle}} \underset{HgX}{\big\rangle} \longrightarrow H_2C=C=CH_2 + HgBrX \qquad (26)$$

X = I, Br

obtained from 2-chloro-1-iodo-2-propene in 36% yield. This compound decomposes upon heating or during storage with evolution of allene. The presence of a chlorine atom in a position gamma to the halomercury group stabilizes β-haloallylmercuric halides (eqs 27 and 28).[42]

$$ClCH=CClCH_2I + Hg \xrightarrow{no\ h\nu} ClCH=CClCH_2HgI \qquad (27)$$
$$45\%$$

$$ClCH=CClCH_2Br + Hg \xrightarrow{h\nu} ClCH=CClCH_2HgBr \qquad (28)$$
$$35\%$$

Formation of organomercury compounds probably proceeds as a result of a homolytic reaction, which may be represented by Scheme II.[43]

Scheme II

$$R\text{-}X \xrightarrow{h\nu} R\bullet + \bullet X$$
$$R\text{-}X + \bullet Hg \bullet \longrightarrow R\bullet + \bullet HgX$$
$$R\bullet + \bullet Hg \bullet \longrightarrow \bullet HgR$$
$$\bullet HgR + R\text{-}X \longrightarrow RHgX + R\bullet$$
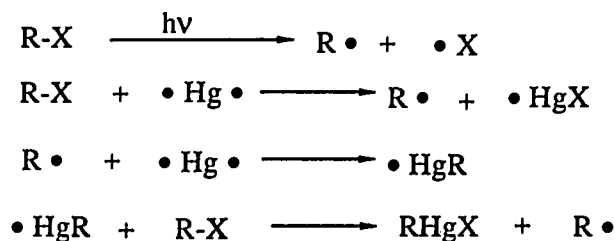
Table 1. Direct mercuration of allylic halides with metallic mercury.

Allylic Halide	Allylic Mercurial	% Yield	Reference
$H_2C=CHCH_2I$	$H_2C=CHCH_2HgI$	---	39
$H_2C=CClCH_2I$	$H_2C=CClCH_2HgI$	36	44
$ClCH=CClCH_2I$	$ClCH=CClCH_2HgI$	45	44
$Cl_2C=CHCH_2I$	$Cl_2C=CHCH_2HgI$	67	45
$Cl_2C=CClCH_2I$	$Cl_2C=CClCH_2HgI$	24	44
$Cl_2C=CBrCH_2I$	$Cl_2C=CBrCH_2HgI$	31	44
$H_2C=CHCH_2Br$	$H_2C=CHCH_2HgBr$	32	41
$PhCH=CHCH_2Br$	$PhCH=CHCH_2HgBr$	82	41
$Cl_2C=CBrCH_2Cl$	$Cl_2C=CBrCH_2HgCl$	45	44
$Cl_2C=CClCH_2Cl$	$Cl_2C=CClCH_2HgCl$	28	44

In summary, all examples of the reaction of allylic halides with metallic mercury reported in the previous literature are listed in Table 1.

In 1884, Henry [44] reported that the reaction of propargyl iodide and metallic mercury in the sunlight afforded an organomercury derivative. Unfortunately, this compound was never fully characterized as being either the allenic or propargylic derivatives (eq 29). Therefore, the

$$HC\equiv CCH_2I \quad + \quad Hg \quad \xrightarrow{h\nu} \quad HC\equiv CCH_2HgI \quad or \quad H_2C=C=CHHgI \quad (29)$$

results reported by Henry were reinvestigated by Larock and Chow, who developed a general route to allenic and propargylic mercurials via the direct reaction of propargylic iodides and metallic mercury under irradiation by sunlight.[45] Initial studies were directed toward the development of a general procedure for the mercuration reaction. Using 1-iodo-2-butyne as the

model substrate, optimal conditions were obtained and the reaction afforded 1-iodomercurio-2-butyne in 80% yield with a complete absence of the allenic isomer (eq 30).

$$CH_3C\equiv CCH_2I \quad + \quad Hg \quad \xrightarrow{\quad h\nu \quad} \quad CH_3C\equiv CCH_2HgI \qquad (30)$$
$$80\%$$
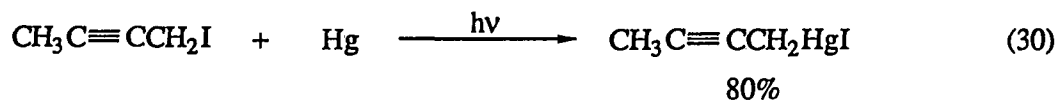
The procedure involved mixing two equivalents of mercury and one equivalent of propargylic iodide in a sealed test tube flushed with nitrogen before sealing, vigorously shaking the tube until the mercury was finely dispersed, and setting the tube in the sunlight for about two hours, followed by setting the tube overnight in the refrigerator and purifying the product in an appropriate manner. This general procedure was applied to a variety of organic halides. The results of this study are summarized in Tables 2 and 3.[23a]

While pure crystalline allylmercuric iodide was isolated nearly a century ago, no yield was reported in the literature.[38,39] A successful synthesis of propargylic or allenic mercurials

Table 2. Mercuration of allenic and propargylic iodides.

Organic Iodide	Product	% Isolated Yield
$CH_3CH=C=CHI$	---	---
$(CH_3)_2C=C=CHI$	---	---
$HC\equiv CCH_2I$	$H_2C=C=CHHgI$	55
$CH_3CHIC\equiv CH$	$CH_3CH=C=CHHgI$	80
$CH_3CHIC\equiv CPh$	$CH_3CH=C=CPhHgI$	66
$CH_3C\equiv CCH_2I$	$CH_3C\equiv CCH_2HgI$	83
$C_6H_5C\equiv CCH_2I$	$C_6H_5C\equiv CCH_2HgI$	68
$MeO_2C(CH_2)_3C\equiv CCH_2I$	$MeO_2C(CH_2)_3C\equiv CCH_2HgI$	35

Table 3. Mercuration of allenic and propargylic bromides.

Organic Bromide	Product	% Isolated Yield
$(CH_3)_2C=C=CHBr$	---	---
$HC\equiv CCH_2Br$	---	---
$CH_3C\equiv CCH_2Br$	---	---
$C_6H_5C\equiv CCH_2Br$	$C_6H_5C\equiv CCH_2HgBr$	72
$HC\equiv CCHBrCH_3$	---	---
$CH_3C\equiv CCHBrC_2H_5$	---	---
$C_6H_5C\equiv CCHBrCH_3$	---	---
$HC\equiv CCBr(CH_3)_2$	$(CH_3)_2C=C=CHHgBr$	60

by the direct reaction of corresponding propargylic iodides and metallic mercury has been described by Chow.[23a] The likelihood that allylic mercuric iodides might be prepared in a similar manner encouraged us to examine this approach. This method appeared particularly attractive, since it should accommodate a wide range of organic functionality. Therefore, the reaction reported by Zinon[38] was reinvestigated in order to develop both a general and a convenient route to allylic mercurials. Using allyl iodide as the model substrate, optimal conditions were eventually arrived at which afforded the expected allylmercuric iodide in a yield as high as 98% (eq 31).

$$H_2C=CHCH_2I \ + \ Hg \ \xrightarrow[\ 25\,°C\ ]{\ THF\ } \ H_2C=CHCH_2HgI \qquad (31)$$

$$\mathbf{1}$$
$$98\%$$
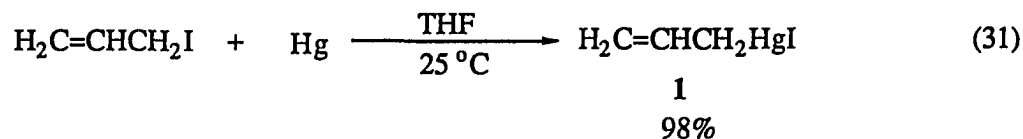
At the first stage of our studies, the procedure used by Chow in the preparation of propargylic or allenic mercurials was utilized for the preparation of allylmercuric iodide. It

involved mixing two equivalents of metallic mercury and one equivalent of the allyl iodide in a Pyrex tube flushed with nitrogen before sealing it, and vigorously shaking the tube until the mercury was finely dispersed. The tube was then placed in the sunlight until the liquid allyl iodide was no longer present (prolonged exposure to sunlight resulted in the presence of red HgI_2). After storing the tube overnight in a refrigerator, the product was dissolved in THF, the solution was filtered and the solvent removed. The yield of the crude product only reached 60%.

As indicated in equation 30, when a propargylic iodide was used as the substrate, after the mercury was added and finely dispersed by shaking, the reaction time was about two hours upon continued exposure to the sunlight. In the case of allyl iodide, however, only twenty minutes in the sunlight were needed before red spots (HgI_2) were observed. This strongly indicated that the reaction of allyl iodide with metallic mercury proceeds much faster than when the propargylic iodides are used under the same irradiation conditions. Furthermore, from the results represented in equation 25,[40] it is apparent that strong ultraviolet irradiation is not necessary for the formation of the desired allylic mercurials. These results prompted us to examine the direct mercuration reaction of allyl iodide under still milder conditions. When a reaction tube was placed in indirect sunlight (room light or diffuse light), the red spots would appear about thirty minutes later, and a 70% yield was obtained after appropriate purification.

In order to carry out the direct mercuration reaction under still milder conditions, THF was added as a solvent and a suspension of mercury in the THF solution of allyl iodide was stirred vigorously for almost four hours at room temperature in room light. To our delight, a nearly quantitative yield (98%) was obtained.

Since other allylic iodides are difficult to prepare and handle, we examined the mercuration of allylic bromides. It was found that the reaction of allyl bromide with metallic mercury was more difficult than the reaction with allyl iodide; none of the desired product was isolated under the best conditions used in the allyl iodide mercuration. Even placing the

reaction flask in an ultrasonic bath for four hours, while irradiating in sunlight or by a high

pressure mercury lamp (HANOVIA 679 A36), failed to initiate the mercuration of allyl

bromide. Allyl chloride, likewise, proved to be inert to metallic mercury under the same

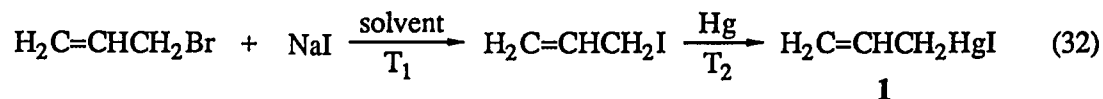conditions used for allyl bromide. The overall results are summarized in Table 4.

Table 4. Preparation of allylmercuric halides by the reaction of allyl halides
with metallic mercury.

$H_2C=CHCH_2X$ X	Reaction Conditions[a]	$H_2C=CHCH_2HgX$ X	Yield[b] %
I	sunlight/ 20 min/ no solvent	I	60
I	roomlight/ 30 min/ no solvent	I	73
I	roomlight/ 4 h/ THF	I	98
Br,Cl	sunlight/ 8-10 h/ no solvent	Br,Cl	0
Br,Cl	sunlight or irradiation/ 5-10 h/ THF	Br,Cl	0
Br,Cl	ultrasonic bath/ 4 h/ THF	Br,Cl	0

[a] All reactions were carried out at room temperature.
[b] All yields are isolated yields.

Since allylic bromides or chlorides are readily available and fail to react with metallic

mercury directly, a two-step route to allylic mercuric iodides from allylic bromides or chlorides

was designed and investigated. First, the allylic bromide was converted to the

corresponding allylic iodide by nucleophilic displacement with iodide anion. Next, the allylic

iodide generated in situ was treated with metallic mercury (eq 32). Various solvents,

$$H_2C=CHCH_2Br \ + \ NaI \ \xrightarrow[T_1]{solvent} \ H_2C=CHCH_2I \ \xrightarrow[T_2]{Hg} \ H_2C=CHCH_2HgI \qquad (32)$$
$$\mathbf{1}$$

including acetone which is generally considered the standard solvent in such halide

displacement reactions by most organic chemists, have been examined. As one can see from

Table 5. Preparation of allylmercuric iodide by the one-pot reaction of allyl bromide, sodium iodide, and metallic mercury.[a]
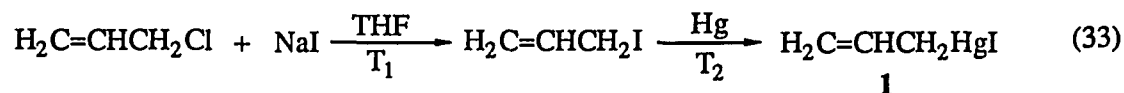
Solvent	T_1 (h)	T_2 (h)	% Isolated Yield
$CH_3COC_2H_5$	24	18	42
CH_3COCH_3	2	4	61
THF[b]	2	4	71
THF	2	8	92
THF	2	12	92

[a] Reaction was run at room temperature in the presence of 2.0 equiv of NaI and 4 g of Hg(0).

[b] Anhydrous, dried by refluxing in the presence of metallic sodium.

the results shown in Table 5, the highest yield of compound 1 was obtained when allyl bromide was allowed to react with sodium iodide in tetrahydrofuran (THF) for 2 hours (T_1) and continuously stirred for another 8 - 12 hours (T_2) after the metallic mercury was added to the reaction mixture. It appears that THF as a solvent offers a number of advantages over acetone and, therefore, is the solvent of choice for this reaction. It is not necessary to remove the sodium salts produced in the first step, so this is really a convenient procedure. Moreover, another advantage is that the product formed in THF is much cleaner than that formed in acetone, because the solubility of the sodium halide in THF is less than in acetone.

Allyl chloride was also allowed to react with sodium iodide and metallic mercury in THF under the same experimental conditions as allyl bromide (eq 33) . In order to optimize the

$$H_2C=CHCH_2Cl \ + \ NaI \ \xrightarrow[T_1]{THF} \ H_2C=CHCH_2I \ \xrightarrow[T_2]{Hg} \ H_2C=CHCH_2HgI \qquad (33)$$
$$\underset{1}{}$$

reaction conditions, various reaction times in both steps (T_1 and T_2) were carefully examined. The data described in Table 6 indicate that the highest yield of compound 1 was obtained when the reaction time of the first step was 4 hours, and the second reaction step was run for 24

Table 6. Preparation of allylmercuric iodide by the one-pot reaction of allyl chloride, sodium iodide, and metallic mercury.[a]

Entry	Reaction Time T_1 (h)	Reaction Time T_2 (h)	% Isolated Yield
1	2	8	58
2	2	30	58
3	4	24	72
4	2 [b]	24	70
5	48	3	69

[a] Reaction was run in THF at room temperature in the presence of 2.0 equiv of NaI and 4 g of Hg(0).

[b] Refluxing in THF.

hours. These data suggest that the nucleophilic displacement of chloride by iodide is the rate determining step.

In order to demonstrate the synthetic utility of the two-step iodide displacement-mercuration procedure for the synthesis of allylic mercuric iodides from allylic bromides and chlorides, a variety of allylic bromides and chlorides was allowed to react with sodium iodide and metallic mercury in THF as described above (procedure A). The results shown in Table 7 indicate that a variety of substituted allylic chlorides, and bromides can be employed successfully in this process. Most mercuration reactions of allylic chlorides and bromides were run under the conditions illustrated in equations 32 and 33, except those shown in entries 7 - 9 in Table 7. Procedure A did not work well with all allylic halides, but a simplified procedure (procedure B) which involves mixing all reagents together from the start and stirring the appropriate period of time at 0 °C generally provides reasonable yields for those more difficult compounds (entries 7 - 9).

Table 7. Preparation of Allylic Mercuric Iodides.

Entry	Allylic Halide	Procedure	Reaction Time T_1 ; T_2 (h)		Allylic Mercurial	% Isolated Yield
	$H_2C=CHCH_2X$				$H_2C=CHCH_2HgI$ (1)	
1	X = I	a	- ;	4		98
2	X = Br	A	2 ;	8		92
3	X = Cl	A	4 ;	24		78
4	$H_2C=C(CH_3)CH_2Cl$	A	8 ;	24	$H_2C=C(CH_3)CH_2HgI$ (2)	79
5	E-$CH_3CH=CHCH_2Br$	A	4 ;	24	E- $CH_3CH=CHCH_2HgI$ (3)	78
6	E-$PhCH=CHCH_2Br$	A	4 ;	24	E- $PhCH=CHCH_2HgI$ (4)	38[b]
7	$(CH_3)_2C=CHCH_2Br$	B	6		$(CH_3)_2C=CHCH_2HgI$ (5)	44
8	E-$EtO_2CCH=CHCH_2Br$	B	3		E- $EtO_2CCH=CHCH_2HgI$ (6)	43
9	$H_2C=C(CO_2CH_3)CH_2Br$	B	1		$H_2C=C(CO_2CH_3)CH_2HgI$ (7)	47

[a] Commercial available allyl iodide was used directly, omitting the sodium iodide step.

[b] The corresponding cinnamylmercuric bromide can be prepared in higher yield by shaking with mercury(0) for 15 minutes in 95% ethanol (see reference 41).

Crotyl bromide with a methyl group attached to the allyl moiety could theoretically react with the metallic mercury to afford isomeric allylic mercurials. However, the results presented in Table 7 show clearly that the reaction proceeds with no evidence of rearrangement (entry 5). The direct mercuration of crotyl bromide under sunlight in the absence of solvent failed to give any of the desired product; during the course of our investigation, diethyl ether was also used as a solvent, but only a 5% yield of compound 3 was obtained.

Methallyl chloride showed high reactivity using the iodide displacement-mercuration procedure. The yield of compound 2 reached as high as 79% (see entry 4, Table 7). ^{1}H NMR spectral data for compound 2 indicate only two singlets [δ 3.94 (4H), 1.80 (2H)] proving the existence of an equilibrating process. This results were consistent with the data reported by Winstein and co-workers.[46]

When allylic bromides containing an ester group were employed in the iodide displacement-mercuration process using procedure B, the expected allylic mercurials 6 and 7

were isolated (see entries 8 and 9 in Table 7). Presumably, many other functional groups can also be readily accommodated by this process.

Several secondary allylic iodides, bromides, and chlorides were examined to see if one can prepare the corresponding secondary allylic mercurials. 3-Iodo-1-butene was allowed to react with metallic mercury in THF at room temperature for 4 hours, but none of the desired product could be detected. Neither 3-bromocyclohexene nor 3-chlorocyclohexene reacted with mercury(0) as desired.

As mentioned in the introductory section, the formation of organomercury compounds from organic halides and mercury appears to proceed by a radical chain mechanism.[27c] To establish the free radical nature of the reaction, oxygen was chosen as a radical chain inhibitor and Galvinoxyl as a radical scavenger to see if these additives could suppress or interrupt the radical chain reaction. By comparing the results shown in equation 34, one can see that the
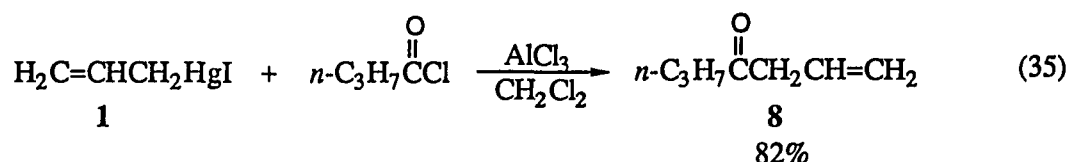
$$H_2C=CHCH_2I \quad + \quad Hg \xrightarrow[25\,^\circ C,\,4\,h]{THF} H_2C=CHCH_2HgI \qquad (34)$$
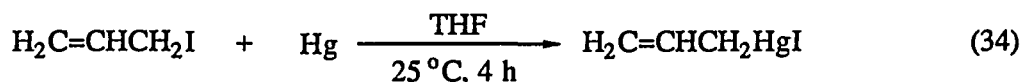
Reaction Conditions	% Isolated Yield
Dark, in absence of oxygen	95
Dark, in presence of oxygen	8
Dark, in absence of oxygen, Galvinoxyl added	5

direct mercuration of allyl iodide with metallic mercury can be considered a spontaneously initiated radical chain process. That means neither photoinitiation nor use of a chemical initiator are needed to initiate the radical chain reaction. Normally, a secondary carbon radical shows much more stability than its primary counterpart. However, the experimental fact is that only primary allylic iodides react with mercury to form the corresponding allylic mercurials. The high sensitivity of the reaction to steric effects suggests that a bulky mercury atom may be involved in the initiation process.

PREPARATION OF ALLYLIC KETONES

As discussed in the introductory section, although alkyl,[16-18] aryl,[17,18,27-29] vinylic, 24,25 allenic,[22,23] propargylic,[22,23] and alkynyl[26] mercurials undergo facile acylation by acyl halides either directly or preferably in the presence of aluminum chloride or Pd(PPh3)4,[47] only one example of the direct reaction of allylmercuric iodide with acyl halides has previously been reported [20] and none of the anticipated allyl ketone was observed (eqs 13 and 14). Now with a variety of allylic mercurials in hand, we set out to examine their reaction with acyl halides. Following previous successful work on the acylation of vinylic, allenic, and propargylic mercurials with acyl halides promoted by aluminum chloride, we examined the AlCl3-promoted acylation of allylic mercurials under conditions very similar to those reported previously.[24,25]

The reaction of allylmercuric iodide and butyryl chloride was chosen as a model reaction for study (eq 35). Allylmercuric iodide was prepared from commercially available allyl iodide

$$H_2C=CHCH_2HgI \quad + \quad n\text{-}C_3H_7\overset{\overset{\displaystyle O}{\|}}{C}Cl \quad \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{AlCl}_3} \quad n\text{-}C_3H_7\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH=CH_2 \qquad (35)$$

$$\mathbf{1} \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \mathbf{8}$$
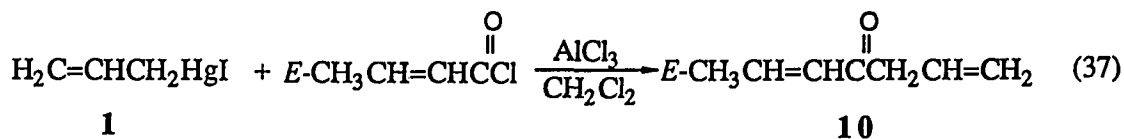$$82\%$$

and mercury(0) using the procedure represented in equation 31 in almost quantitative yield. Allylmercuric iodide was treated with butyryl chloride and AlCl3 (1.1 equiv) in dichloromethane for 10 minutes at 0 °C to afford 1-hepten-4-one in 82% yield, without even optimizing conditions. In order to further improve the yield of allyl ketone, 2.2 equiv of AlCl3 was examined under the same conditions as those indicated in equation 35; however, only an 80% yield of compound 8 was isolated. This result demonstrates that the amount of aluminum chloride does not have a pronounced effect on the yield of the reaction.

Benzoyl chloride was then chosen as the acyl chloride to react with allylmercuric iodide under the standard conditions established during optimization of the model reaction. However, the ^{1}H NMR spectrum of the products of the reaction indicated the existence of a significant amount of impurities which appeared to contain two benzoyl fragments. The extra peaks seemed to arise via further reaction of the desired product with another equivalent of benzoyl chloride. In order to avoid this type of side reaction, a combination of short reaction time and higher reaction temperature was selected. Finally, it was found that the acylation of allylmercuric iodide (1) with benzoyl chloride proceeded at room temperature in only 4 minutes to afford the desired allylic ketone 9 in 87% isolated yield (eq 36).

$$H_2C=CHCH_2HgI \ + \ PhCCl \xrightarrow[25\,°C,\ 4\ min]{AlCl_3\ /\ CH_2Cl_2} PhCCH_2CH=CH_2 \qquad (36)$$

1

9

87%
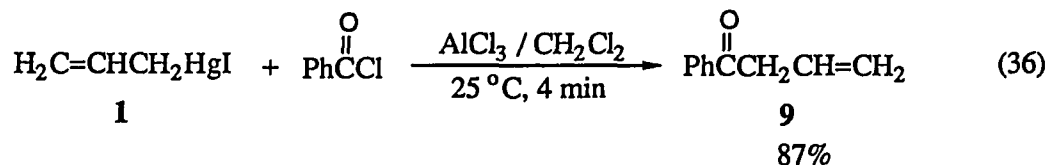
Crotonyl chloride was allowed to react with allylmercuric iodide (1) in the presence of 1.1 equivalent of AlCl₃. Various combinations of reaction time and temperature were examined. The results shown in equation 37 indicate that when the reaction was run in refluxing dichloromethane for 4 minutes, a nearly quantitative yield of 1,5-heptadien-4-one was obtained.

$$H_2C=CHCH_2HgI \ + \ E\text{-}CH_3CH=CHCCl \xrightarrow[CH_2Cl_2]{AlCl_3} E\text{-}CH_3CH=CHCCH_2CH=CH_2 \qquad (37)$$

1

10

Reaction Temperature (°C)	Reaction time (min)	Isolated Yield (%)
0	8	58
25	6	64
40	4	97

With these encouraging results in hand, optimization of the acylation process using various allylic mercurials and acyl chlorides focussed on the use of different combinations of reaction time and temperature. Our results are summarized in Table 8. The isolated yields obtained were generally greater than 85%. All reactions proceeded in a matter of minutes at room temperature or temperatures as low as -78 °C. Alkyl, aryl, and functionally substituted allylic mercurials were all found to work well. Considerable functionality should be accommodated by this reaction. While allenic [22] and vinylic [24,25] mercurials react under similar conditions with aliphatic and α,β-unsaturated acyl chlorides, but not aromatic acyl chlorides, and while propargylic [22] mercurials only react well with aliphatic acyl chlorides, allylic mercurials give excellent yields with all three types of acyl chlorides.

All reactions proceeded with allylic rearrangement, even when it means that the double bond was removed from conjugation. The acylations of E-2-butenylmercuric iodide and E-3-methyl-2-butenylmercuric iodide under appropriate conditions with n-butyryl chloride gave 3-methyl-1-hepten-4-one and 3,3-dimethyl-1-hepten-4-one, respectively (see entries 6 and 7 in Table 8). These results can be rationalized by the mechanism proposed by Mukaiyama[21] in which electrophilic attack of the aluminium chloride complexed butyryl chloride occurs at the γ-carbon atom of the allyl moiety of the allylic mercurial.

It is of interest to note the results of the reaction between 3-methyl-2-butenylmercuric iodide (5) and various acyl chlorides (see entries 7-9 in Table 8). The existence of substantial steric hindrance on the γ-carbon atom of the allylic moiety should make electrophilic attack of the acyl group more sluggish. However, the fact is that excellent yields of the desired allylic ketones 14 - 16 were formed under very mild conditions. It appears that steric hindrance is not an important factor in the acylation of allylic mercurials promoted by aluminum chloride.
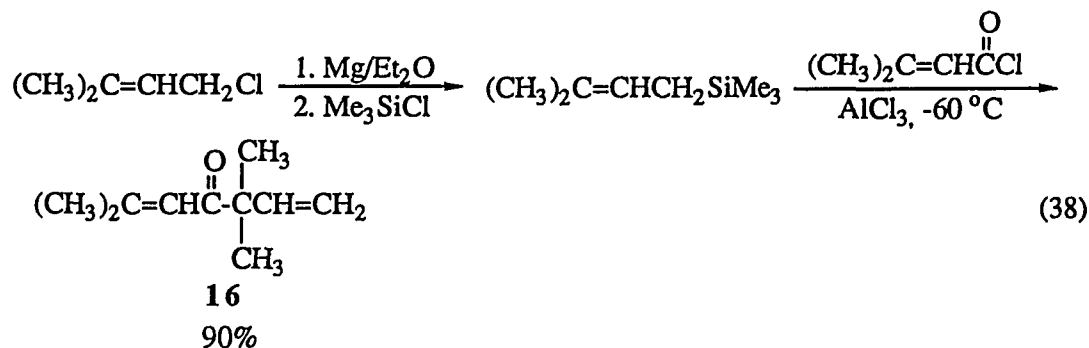
Calas and co-workers[48] have found that allylic silanes, in the presence of Lewis acids, such as AlCl$_3$, can readily react with acid chlorides to afford the corresponding allylic ketones. Using this methodology, a naturally occurring monoterpene Artemisia ketone was synthesized
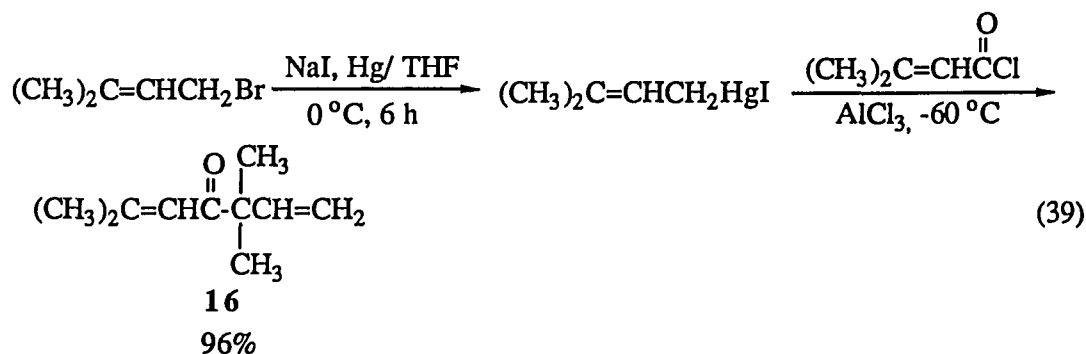
Table 8. Preparation of allylic ketones.

Entry	Allylic Mercurial	Acide Chloride	Reaction Conditions °C, min	Allylic Ketone (compound number)	% Isolated Yield
1	1	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	0, 10	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{CH}=\text{CH}_2$ (8)	82
2		$(\text{CH}_3)_2\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	-78, 7	$(\text{CH}_3)_2\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{CH}=\text{CH}_2$ (11)	84
3		$E\text{-}\text{CH}_3\text{CH}=\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	40, 4	$E\text{-}\text{CH}_3\text{CH}=\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{CH}=\text{CH}_2$ (10)	97
4		$\text{Ph}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	25, 6	$\text{Ph}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{CH}=\text{CH}_2$ (9)	87
5		$p\text{-CH}_3\text{OC}_6\text{H}_4\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	0, 10	$p\text{-CH}_3\text{OC}_6\text{H}_4\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{CH}=\text{CH}_2$ (12)	90
6	3	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	0, 7	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\underset{\text{CH}_3}{\text{C}}\text{HCH}=\text{CH}_2$ (13)	70
7	5	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	0, 10	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\underset{\text{CH}_3}{\overset{\text{OCH}_3}{\text{C}}}\text{CH}=\text{CH}_2$ (14)	86
8		$(\text{CH}_3)_2\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	-60, 15	$(\text{CH}_3)_2\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\underset{\text{CH}_3}{\overset{\text{OCH}_3}{\text{C}}}\text{CH}=\text{CH}_2$ (15)	93
9		$(\text{CH}_3)_2\text{C}=\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	-60, 15	$(\text{CH}_3)_2\text{C}=\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\underset{\text{CH}_3}{\overset{\text{OCH}_3}{\text{C}}}\text{CH}=\text{CH}_2$ (16)	96
10	4	$\text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	-78, 10	$\text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\underset{\text{Ph}}{\text{C}}\text{HCH}=\text{CH}_2$ (17)	82
11		$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	25, 10	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\underset{\text{Ph}}{\text{C}}\text{HCH}=\text{CH}_2$ (18)	69
12	6	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}$	25, 10	$n\text{-C}_3\text{H}_7\overset{\text{O}}{\overset{\|}{\text{C}}}\underset{\text{CO}_2\text{Et}}{\text{C}}\text{HCH}=\text{CH}_2$ (19)	89

a All reactions were run by adding 2 mmol of allylic mercurial to 20 mL of CH_2Cl_2 containing 2.2 mmol of AlCl_3 and 2 mmol of acyl chloride. After the appropriate reaction time, the reaction was quenched with 5% NaHCO_3, washed with 3 M $\text{Na}_2\text{S}_2\text{O}_3$ and saturated aq. NaCl, dried, and the solvent removed.
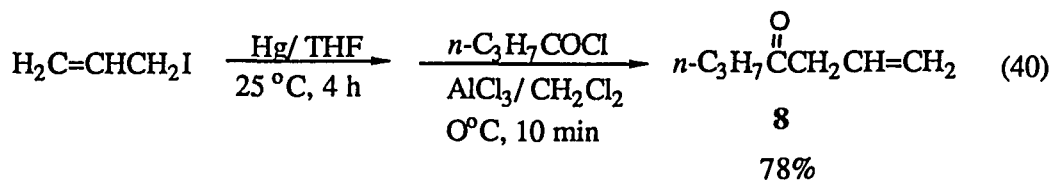
successfully (eq 38).[49] The intermediate allylic silane was made from the corresponding allylic chloride through a Grignard reagent.

$$(CH_3)_2C=CHCH_2Cl \xrightarrow[\text{2. Me}_3\text{SiCl}]{\text{1. Mg/Et}_2\text{O}} (CH_3)_2C=CHCH_2SiMe_3 \xrightarrow[\text{AlCl}_3,\ -60\ ^\circ\text{C}]{(CH_3)_2C=CHCCl}^{\overset{O}{\underset{||}{}}}$$

$$(CH_3)_2C=CH\overset{\overset{O}{\underset{||}{}}}{C}-\overset{\overset{CH_3}{\underset{|}{}}}{C}CH=CH_2 \atop \underset{CH_3}{|}$$

$$\textbf{16}$$
$$90\%$$

(38)

The high reactivity of 3-methyl-2-butenylmercuric iodide towards acylation with acyl chlorides prompted us to examine the synthesis of the naturally occurring Artemisia ketone (**16**). The result shown in equation 39 and entry 9 in Table 8 demonstrates one of the advantages of our approach. The intermediate allylic mercurial can be readily prepared from the corresponding allylic bromide in only one step and the yield of Artemisia ketone is higher than that obtained by the silane procedure.

$$(CH_3)_2C=CHCH_2Br \xrightarrow[\text{0 °C, 6 h}]{\text{NaI, Hg/ THF}} (CH_3)_2C=CHCH_2HgI \xrightarrow[\text{AlCl}_3,\ -60\ ^\circ\text{C}]{(CH_3)_2C=CHCCl}^{\overset{O}{\underset{||}{}}}$$

$$(CH_3)_2C=CH\overset{\overset{O}{\underset{||}{}}}{C}-\overset{\overset{CH_3}{\underset{|}{}}}{C}CH=CH_2 \atop \underset{CH_3}{|}$$

$$\textbf{16}$$
$$96\%$$

(39)

By employing the crude allylic mercurial obtained from the first step after a change of solvent, one can simplify the overall process further. In this manner, allylmercuric iodide can be converted to 1-hepten-4-one in one pot in an overall yield of 78% (eq 40). The reaction of

$$H_2C=CHCH_2I \xrightarrow[\text{25 °C, 4 h}]{\text{Hg/ THF}} \xrightarrow[\substack{\text{AlCl}_3/\text{CH}_2\text{Cl}_2 \\ \text{0°C, 10 min}}]{n\text{-C}_3\text{H}_7\text{COCl}} n\text{-C}_3\text{H}_7\overset{\overset{\text{O}}{\|}}{\text{C}}\text{CH}_2\text{CH=CH}_2 \quad (40)$$

8

78%

allyl iodide with metallic mercury was carried out under the previously developed conditions. This was followed by filtering the unreacted mercury, replacing the THF solvent by dichloromethane, and adding $AlCl_3$ and butyryl chloride into the flask. The acylation was then run at 0 °C for 10 min.

Several acylation reactions were attempted without success. When the acylation was run using a benzoyl chloride derivative bearing electron-withdrawing substituents on the benzene ring, the yield of the desired allylic ketone was found to be reduced dramatically. For example, allylmercuric iodide was allowed to react with 3,5-dinitrobenzoyl chloride in the presence of $AlCl_3$ and dichloromethane under various conditions. The results described in equation 41 indicate that the best yield of the corresponding allylic ketone only reached 15%.

$$H_2C=CHCH_2HgI \quad + \quad \underset{O_2N\diagdown\diagup NO_2}{\overset{COCl}{\diagup\diagdown}} \quad \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{AlCl}_3} \quad \underset{O_2N\diagdown\diagup NO_2}{\overset{COCH_2CH=CH_2}{\diagup\diagdown}} \quad (41)$$
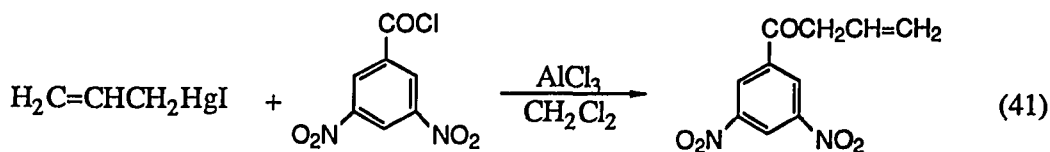
Reaction Temperature (°C)	Reaction Time (min)	Isolated Yield (%)
25	6	6
0	10	11
-40	6	15

The spot on TLC analysis due to the mercurial disappeared quickly as $AlCl_3$ was added to the reaction mixture. Therefore, it appears that some reaction between the allylic mercurial and

AlCl$_3$ predominates. In contrast, when a benzoyl chloride derivative with an electron-donating substituent on the aromatic ring was used as the acyl chloride in the acylation of allylic mercurials, an excellent yield of the corresponding allylic ketone was obtained (see entry 5 in Table 8).

Other unsuccessful acyl chlorides are o-chlorobenzoyl chloride and chloro-substituted aliphatic acid chlorides, such as chloroacetyl chloride, γ-chlorobutyryl chloride and dichloroacetyl chloride. Ethoxycarbonyl-substituted aliphatic acid chlorides, such as ethyl malonyl chloride and ethyl succinyl chloride also failed to give any of the desired products. However, when the ethoxycarbonyl group was attached to the allylic mercurial, a high yield of the desired allylic ketone was observed (see entry 12 in Table 8). An electron-withdrawing functional group when incorporated in the acyl chloride dramatically reduces the yield of allylic ketone formed in the acylation of allylic mercurials.

When methallylmercuric iodide was treated with n-butyryl chloride in the presence of AlCl$_3$ at 0 °C for 10 min, only an unexpected product 2-chloro-2-methyl-4-heptanone was isolated in 22% yield (eq 42). We were unable to readily eliminate HCl from the

$$H_2C=C(CH_3)CH_2HgI \;+\; n\text{-}C_3H_7\overset{\displaystyle O}{\overset{\|}{C}}Cl \;\xrightarrow[\text{0 °C, 10 min}]{\text{AlCl}_3/\text{CH}_2\text{Cl}_2}\; n\text{-}C_3H_7\overset{\displaystyle O}{\overset{\|}{C}}CH_2\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle Cl}{|}}{C}}\text{-}CH_3 \qquad (42)$$

<div align="center">22%</div>
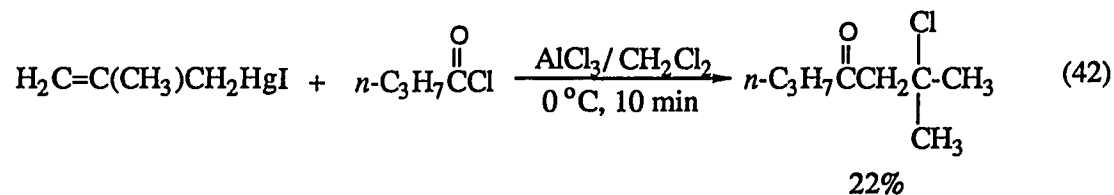
β-chloroketone on treatment with base. It was thought that the addition of hydrogen chloride to the double bond probably occurs during the work-up procedure. To prevent this unexpected reaction, the reaction mixture was quenched with 5% NaHCO$_3$ at low temperature (-78 °C). However, this procedure proved unsuccessful in eliminating the side product.

CONCLUSION

The results presented in this part of the dissertation are the first observed examples of the acylation of allylic mercurials by an acyl chloride promoted by aluminum chloride. This carbon-carbon bond forming reaction proceeds with allylic rearrangement. A variety of allylic mercurials and acyl chlorides including aliphatic, aromatic, and α-, β-unsaturated acyl chlorides can be employed successfully in this reaction. However, acyl chlorides containing an electron-withdrawing substituent often failed. This reaction provides a convenient new synthetic route to allylic ketones.

This part of the dissertation also presents a modified literature procedure to prepare allylic mercuric iodides from the corresponding allylic halides and metallic mercury in good yields. A considerable amount of functionality can be tolerated in this procedure. Unfortunately, secondary allylic mercurials cannot be synthesized when this procedure is employed.

EXPERIMENTAL SECTION

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on an IBM IR/98 FT-IR spectrometer or on a Beckmann 4250 spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O]. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Reagents

All allylic halides and acyl chlorides were used as purchased from Aldrich or Fluka and were distilled prior to use. Methyl α-(bromomethyl)acrylate was synthesized according to the procedure reported by Cassady and co-workers.[50] Aluminum chloride and metallic mercury were purchased from Fluka.

The preparation of compound 1

To a 100 ml round bottom flask flushed with nitrogen, equipped with a magnetic stirrer and sealed with a septum was placed 4.0 g of metallic mercury (0.02 mol). Then a solution of allyl iodide (1.56 g, 0.09 mol) in 10 ml of dry THF was injected into the flask though the septum. The reaction mixture was allowed to stir for 4 hours at room temperature without irradiation. The mixture was filtered through Celite to remove the unreacted mercury. The

mercury residue was washed with THF (2 × 15 ml). After removal of the solvent from the combined solvent layers in vacuo, crude allylmercuric iodide, a white powder, was obtained: 3.27g, 98% yield; mp 130-131°C (lit.[47]129-131°C, lit[51] 133-135 °C); ^{1}H NMR (DMSO-d_6) δ 2.50 (br s, 2 H, C$\underline{H}_2$CH=CH$_2$), 4.82 (br s, 2 H, CH=C$\underline{H}_2$), 6.06 (dt, J = 8.7 Hz, J = 17.7 Hz, 1 H, C$\underline{H}$=CH$_2$); ^{1}H NMR (DMSO-d_6, HgI$_2$) δ 3.70 (d, J = 11.0 Hz, 4 H, C$\underline{H}_2$CH=C$\underline{H}_2$), 6.04 (p, J = 11.0 Hz, 1 H, CH$_2$C$\underline{H}$=CH$_2$) (consistent with lit [47]); IR (KBr) 3076, 2928, 2924, 1619 (C=C), 1428, 1392, 1188, 1090, 1036, 986, 764, 679 cm^{-1}. Anal. Calcd for C$_3$H$_5$HgI: C, 9.87; H, 1.37. Found: C, 9.57; H, 1.45.

General procedure for the preparation of allylic mercuric iodides from allylic halides (procedure A)

In an dry 50 ml one-necked, round bottom flask flushed with nitrogen, equipped with a magnetic stirrer and sealed with a septum, was placed 3 g of sodium iodide (0.02 mol) and 10 ml of dry THF. After stirring for 30 min, 0.01 mol of allylic bromide or chloride was injected into the flask and the reaction mixture was allowed to stir under nitrogen for another 2-4 h at room temperature. Then 4.0 g of metallic mercury was added to the flask, which was flushed with nitrogen again. Stirring was continued for the period of time required. The reaction mixture was filtered through Celite which was washed with THF (2 × 15 ml). Ether was then added to the combined organic solution, which was washed with water (2 × 15 ml) and dried over anhydrous magnesium sulfate. After removal of the solvent, the crude product was obtained. Recrystallization can be performed using ethanol as the solvent if necessary.

General procedure for the preparation of allylic mercuric iodides from allylic halides (procedure B)

In an dry 50 ml one-necked, round bottom flask equipped with a magnetic stirrer was placed 3 g of sodium iodide (0.02 mol), 4.0 g of metallic mercury, and 10 ml of dry THF. After flushing with nitrogen for 5 min and sealing the flask with a septum, 0.01 mol of allylic

bromide or chloride was injected into the flask and the reaction mixture was allowed to stir under nitrogen at room temperature for the period of time required. The reaction mixture was filtered through Celite which was washed with THF (2 × 15 ml). Ether was then added to the combined organic solution, which was washed with water (2 × 15 ml) and dried over anhydrous magnesium sulfate. After removal of the solvent, the crude product was obtained. Recrystallization can be performed using ethanol as the solvent if necessary.

Spectral data for allylic mercuric iodides prepared by the above general procedures

Methallylmercuric iodide (2) Compound **2** was prepared in 79% yield when methallyl bromide was allowed to react with sodium iodide and metallic mercury using procedure A : mp. 200 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.73 (s, 3 H, CH_3), 3.58 (br s, 4 H, $\underline{CH}_2C(CH_3)=\underline{CH}_2$); ^{1}H NMR (DMSO-$d_6$, HgI_2) δ 1.73 (s, 3 H, CH_3), 3.57 (sharp s, 4 H, $\underline{CH}_2C(CH_3)=\underline{CH}_2$); IR (KBr) 3078, 2970, 2935, 1626 (C=C), 1439, 1414, 1369, 1283, 1099, 878 (C=CH_2), 766, 716 cm^{-1}. Anal. Calcd for C_4H_7HgI: C, 12.56; H, 1.84. Found: C, 12.29; H, 1.98.

E-Crotylmercuric iodide (3) Compound **3** was prepared in 78% yield when E-crotyl bromide was allowed to react with sodium iodide and metallic mercury using procedure A: mp. 103-105 °C (lit.[52] 102-105 °C); ^{1}H NMR (CDCl$_3$) δ 1.73 (d, J = 6.3 Hz, 3 H, CH_3), 2.77 (d, J = 7.2 Hz, 2 H, CH_2), 5.35 - 5.77 (m, 2 H, CH=CH); IR (KBr) 3011, 2908, 2876, 1614 (C=C), 1447, 1094, 959 (E-CH=CH), 741 cm^{-1}.

E-Cinnamylmercuric iodide (4) Compound **4** was prepared in 38% yield when E-cinnamyl bromide was treated with sodium iodide and metallic mercury using procedure A: mp. 76-78 °C; ^{1}H NMR (CDCl$_3$) δ 2.39 (d, J = 10.2 Hz, 2 H, CH_2), 6.25 (dt, J = 15.9 Hz, J = 10.2 Hz, 1 H, CH=$C\underline{H}CH_2$), 6.43 (d, J = 15.9 Hz, 1 H, PhCH=C), 7.20 - 7.34 (m, 5

H, Aryl); IR (KBr) 3059, 2926, 2841, 1600 (C=C), 1449, 1443, 964 (E- CH=CH), 758,

741, 690 cm^{-1}. Anal. Calcd. for C_9H_9HgI: C, 24.20; H, 2.03. Found: C, 23.12; H, 2.01.

3-Methyl-2-butenylmercuric iodide (5) Compound 5 was prepared in 44% yield when

3-methyl-2-butenyl bromide was allowed to react with sodium iodide and metallic mercury

using procedure B: mp. 66-67 °C; ^{1}H NMR (CDCl$_3$) δ 1.74 (d, J = ~1 Hz, 3 H, CH$_3$), 1.76

(d, J = ~1 Hz, 3 H, CH$_3$), 2.75 (d, J = 6.9 Hz, 2 H, CH$_2$), 5.74 (br t, J = 6.9 Hz, 1 H,

C=CH); IR (KBr) 3078, 2970, 2934, 1626 (C=C), 1439, 1414, 1369, 1283, 1099, 876,

764, 716 cm^{-1}. Anal. Calcd for C_5H_9HgI: C, 15.14; H, 2.29. Found: C, 15.06; H, 2.24.

E- Ethyl 4-(iodomercurio)crotonate (6) Compound 6 was prepared in 43% yield when

ethyl 4-bromocrotonate was allowed to react with sodium iodide and metallic mercury using

procedure B: mp. 117-118 °C; ^{1}H NMR (CDCl$_3$) δ 1.27 (t, J = 7.2 Hz, 3 H, CH$_3$), 2.88 (d,

J = 9.0 Hz, 2 H, C=CCH$_2$), 4.19 (q, J = 7.2 Hz, 2 H, CH$_2$), 5.79 (d, J = 16.8 Hz, 1 H,

COCH=C), 7.17 (dt, J = 16.8 Hz, J = 9.0 Hz, 1 H, CH=CHCH$_2$); IR (KBr) 2982, 2914,

1699 (C=O), 1624 (C=C), 1366, 1319, 1287, 1128, 980 (E -CH=CH), 876 cm^{-1}. Anal.

Calcd for $C_6H_9HgIO_2$: C, 16.35; H, 2.06. Found: C, 16.54; H, 1.99.

Methyl 2-(iodomercuriomethyl)acrylate (7) Compound 7 was prepared in 47% yield

when methyl 2-(bromomethyl)acrylate was allowed to react with sodium iodide and metallic

mercury using procedure B: mp. 56-57 °C; ^{1}H NMR (DMSO-d$_6$) δ 2.60 (s, 2 H, CH$_2$Hg),

3.69 (s, 3 H, CH$_3$), 5.59 (s, 1 H, H$_2$C=C), 5.82 (s, 1 H, H$_2$C=C); IR (KBr) 2949, 1711

(C=O), 1610 (C=C), 1200, 1173, 926, 890 (C=CH$_2$) cm^{-1}. Anal. Calcd for $C_6H_9HgIO_2$: C,

16.35; H, 2.06. Found: C, 16.11; H, 1.96.

General procedure for the acylation of allylic mercuric iodides

To a 25 ml dry round-bottom flask equipped with a magnetic strirrer and flushed with nitrogen was added 25 ml of distilled dichloromethane, 0.3 g of aluminum chloride (2.2 mmol) and the acyl chloride (2.0 mmol). After stirring at the appropriate temperature for 10 min, the allylic mercuric iodide (2.0 mmol) was added directly (no solvent was used) to the flask under nitrogen and the reaction mixture was stirred for the period of time required. Normally a red or orange color appears. The mixture was poured into 30 ml of 5% ammonium chloride solution and stirred for 5 min. The mixture was then separated and the organic layer was washed with 5% sodium bicarbonate solution, 3M sodium thiosulfate and water (two to three times each), and finally dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the crude product was obtained. Further distillation may be performed if necessary.

Spectral data for the allylic ketones prepared using the above general procedure

1-Hepten-4-one (8)   Compound 8[53] was prepared in 82% yield when allylmercuric iodide (1) was allowed to react with n-butyryl chloride using the general procedure: ^{1}H NMR (CDCl3) δ 0.92 (t, J = 7.5 Hz, 3 H, CH3), 1.67 (sextet, J = 7.5 Hz, 2 H, CH2C$\underline{H}$2CH3), 2.42 (t, J = 7.5 Hz, 2 H, COC$\underline{H}$2CH2), 3.17 (d, J = 6.9 Hz, 2 H, COCH2C=), 5.13 (dd, J = 16.8 Hz, J = ~1 Hz, 1 H, E-H2C=C), 5.18 (dd, J = 9.6 Hz, J = ~1 Hz, 1 H, Z-H2C=C), 5.88 - 6.10 (m, 1 H, CH2C$\underline{H}$=CH2); IR (neat) 3081, 2976, 1700 (C=O), 1635 (C=C), 1460, 997, 921 cm-1; mass spectrum m/z 112.17250 (calcd for C7H12O, 112.17241)

2-Methyl-5-hexen-3-one (9)   Compound 9[54] was synthesized in 84% yield when allylmercuric iodide (1) was allowed to react with isobutyryl chloride using the general procedure: ^{1}H NMR (CDCl3) δ 1.10 (d, J = 7.8 Hz, 6 H, CH3), 2.67 (septet, J = 7.8 Hz, 1 H, CHC=O), 3.23 (d, J = 6.9 Hz, 2 H, CH2C=), 5.13 (dd, J = 15.6 Hz, J = ~1 Hz, 1 H, E-H2C=C), 5.17 (dd, J = 9.0 Hz, J = ~1 Hz, 1 H, Z-H2C=C), 5.89 - 5.60 (m, 1 H,

$CH_2C\underline{H}=CH_2$); IR (neat) 3082, 2974, 2935, 1723(C=O), 1634 (C=C), 1469, 1385, 1038, 995, 920 cm^{-1}; mass spectrum m/e 112.17211 (calcd for $C_7H_{12}O$, 112.17241).

E-1,5-Heptadien-4-one (10)   Compound 10[55] was prepared in 97% yield when allylmercuric iodide (1) was allowed to react with crotonyl chloride using the general procedure: ^{1}H NMR (CDCl$_3$) δ 1.91 (dd, J = 6.6 Hz, J = 1.4 Hz, 3 H, CH$_3$), 3.31 (d, J = 6.9 Hz, 2 H, COCH$_2$), 5.14 (dd, J = 15.6 Hz, J = ~1 Hz, 1 H, E-H$_2$C=C), 5.18 (dd, J = 10.00 Hz, J = ~1 Hz, 1 H, Z-C=CH$_2$), 5.90 - 5.99 (m, 1 H, CH$_2$C$\underline{H}$=CH$_2$), 6.15 (dq, J = 15.6 Hz, J = 1.4 Hz, 1 H, COCH=C), 6.89 (dq, J = 6.6 Hz, J = 15.6 Hz, 1 H, COC=CH); IR (neat) 3076, 1695 (C=O), 1675 (C=C), 1633 (C=C), 993, 973 (E- CH=CH), 917 cm^{-1}; mass spectrum m/z 110.15620 (calcd for $C_7H_{10}O$, 110.15639).

1-Phenyl-3-buten-1-one (11)   Compound 11[56] was prepared in 87% yield when allylmercuric iodide (1) was allowed to react with benzoyl chloride using the general procedure: ^{1}H NMR (CDCl$_3$) δ 3.76 (d, J = 6.6 Hz, 2 H, COCH$_2$), 5.20 (dd, J = 8.3 Hz, J = ~1 Hz, 1 H, Z- H$_2$C=C), 5.23 (dd, J = 17.0 Hz, J = ~1 Hz, 1 H, E- H$_2$C=C), 6.05 - 6.14 (m, 1 H, CH$_2$C$\underline{H}$=CH$_2$), 7.46 - 7.97 (m, 5 H, Aryl); IR (neat) 3081, 2960, 1690(C=O), 1665 (C=C), 1580, 981, 910, 762, 710 cm^{-1}; mass spectrum m/z 146.18913 (calcd for $C_{10}H_{10}O$, 146.18892).

1-(4-Methoxyphenyl)-3-buten-1-one (12)   Compound 12[57] was prepared in 90% yield when allylmercuric iodide (1) was allowed to react with 4-methoxybenzoyl chloride using the general procedure: ^{1}H NMR (CDCl$_3$) δ 3.72 (d, J = 6.6 Hz, 2 H, COCH$_2$), 3.89 (s, 3 H, CH$_3$), 5.20 (dd, J = 15.3 Hz, J = ~1 Hz, 1 H, E-H$_2$C=C), 5.22 (dd, J = 9.0 Hz, J = ~1 Hz, 1 H, Z-H$_2$C=C), 6.09-6.15 (m, 1 H, CH$_2$C$\underline{H}$=CH$_2$), 6.93 (d, J = 8.7 Hz, 2 H, Aryl), 7.95 (d, J = 8.7 Hz, 2 H, Aryl); IR (neat) 3088, 2986, 1668 (C=O), 1595 (C=C), 1443, 1302, 1259,

1227, 1028, 835, 812 cm^{-1}; mass spectrum m/z 176.08360 (calcd for $C_{11}H_{12}O_2$, 176.08373).

3-Methyl-1-hepten-4-one (13)   Compound 13[58] was prepared in 70% yield when *E*-crotylmercuric iodide (3) was allowed to react with n-butyryl chloride using the general procedure: ^{1}H NMR (CDCl$_3$) δ 0.90 (t, J = 7.5 Hz, 3 H, CH$_2$C<u>H</u>$_3$), 1.17 (d, J = 6.9 Hz, 3 H, CHC<u>H</u>$_3$), 1.58 (sextet, J = 7.5 Hz, 2 H, CH$_2$C<u>H</u>$_2$CH$_3$), 2.43 (t, J = 7.5 Hz, 2 H, COCH$_2$), 3.20 (p, J = 6.9 Hz, 1 H, C<u>H</u>(CH$_3$)), 5.13 (dd, J = 8.1 Hz, J = ~1 Hz, 1 H, *Z*-H$_2$C=C), 5.16 (dd, J = 17.4 Hz, J = ~1 Hz, 1 H, *E*-H$_2$C=C), 5.71-5.86 (m, 1 H, CH$_2$C<u>H</u>=CH$_2$); IR (neat) 3080, 2900, 1720 (C=O), 1640 (C=C), 1460, 1380, 1020, 980, 915, 730 cm^{-1}; mass spectrum m/z 126.19945 (calcd for $C_8H_{14}O$, 126.19928).

3,3-dimethyl-1-hepten-4-one (14)   Compound 14[59] was prepared in 86% yield when 3-methyl-2-butenylmercuric iodide (5) was allowed to react with n-butyryl chloride using the general procedure: ^{1}H NMR (CDCl$_3$) δ 0.88 (t, J = 7.5 Hz, 3 H, CH$_2$C<u>H</u>$_3$), 1.22 (s, 6 H, C(CH$_3$)$_2$), 1.57 (tq, J = 7.2 Hz, J = 7.5 Hz, 2 H, CH$_2$C<u>H</u>$_2$CH$_3$), 2.43 (t, J = 7.2 Hz, 2 H, COCH$_2$), 5.13 (dd, J = 10.3 Hz, J = ~1 Hz, 1 H, *Z*-H$_2$C=C), 5.13 (dd, J = 17.4 Hz, J = ~1 Hz, 1 H, *E*-H$_2$C=C), 5.91 (dd, J = 10.2 Hz, J = 17.4 Hz, 1 H, C<u>H</u>=CH$_2$); IR (neat) 2983, 2934, 1709 (C=O), 1635 (C=C), 1464, 1379, 1366, 978, 913 cm^{-1}; mass spectrum m/z 252.39824 (calcd for $C_9H_{16}O$, 252.39800).

2,4,4-Trimethyl-5-hexen-3-one (15)   Compound 15 was prepared in 93% yield when 3-methyl-2-butenylmercuric iodide (5) was allowed to react with isobutyryl chloride using the general procedure: ^{1}H NMR (CDCl$_3$) δ 1.03 (d, J = 6.6 Hz, 6 H, CH(C<u>H</u>$_3$)$_2$), 1.23 (s, 6 H, C(CH$_3$)$_2$), 3.07 (septet, J = 6.6 Hz, 1 H, CHCO), 5.16 (dd, J = 17.2 Hz, J = ~1 Hz, 1 H, *E*-H$_2$C=C), 5.18 (dd, J = 10.2 Hz, J = ~1 Hz, 1 H, *Z*-H$_2$C=C), 5.88 (dd, J = 10.2 Hz, J = 17.2

Hz, 1 H, C$\underline{H}$=CH$_2$);   IR (neat) 2976, 2935, 1711 (C=O), 1636 (C=C), 1470, 1381, 995, 920

cm^{-1};   mass spectrum m/z 140.12004   (calcd for C$_9$H$_{16}$O, 140.12012).

2,5,5-Trimethyl-2,6-heptadien-4-one (16)   Compound 16[60] was prepared in 96%

yield when 3-methyl-2-butenylmercuric iodide (5) was allowed to react with 3-methyl-2-

butenoyl chloride using the general procedure: ^{1}H NMR (CDCl$_3$) δ 1.22 (s, 6 H, C(CH$_3$)$_2$),

1.88 (s, 3 H, =C(CH$_3$)$_2$), 2.12 (s, 3 H, =C(CH$_3$)$_2$), 5.13 (dd, J = 17.4 Hz, J = ~1 Hz, 1 H,

E-H$_2$C=C), 5.15 (dd, J = 10.8 Hz, J = ~1 Hz, 1 H, Z-H$_2$C=C), 5.93 (dd, J = 10.8 Hz, J =

17.4 Hz, 1 H, C$\underline{H}$=CH$_2$), 6.24 (br s, 1 H, CH=C);   IR (neat) 2976, 2935, 1684 (C=O), 1622

(C=C),, 1447, 1379, 977, 918, 735 cm^{-1}.   Anal. Calcd for C$_{10}$H$_{16}$O: C, 78.89; H, 10.59.

Found: C, 78.69; H, 10.52.

3-Phenyl-4-penten-2-one (17)   Compound 17[61] was prepared in 82% yield when

E-cinnamylmercuric iodide (4) was allowed to react with acetyl chloride using the general

procedure: ^{1}H NMR (CDCl$_3$) δ 2.12 (s, 3 H, CH$_3$), 4.36 (d, J = 8.1 Hz, 1 H, PhCH), 5.07

(dd, J = 17.1 Hz, J = ~1 Hz, 1 H, E-H$_2$C=C), 5.22 (dd, J = 10.2 Hz, J = ~1 Hz, 1 H, Z -

C=CH$_2$), 6.24 (ddd, J = 8.1 Hz, J = 10.2 Hz, J = 17.1 Hz, 1 H, CHC$\underline{H}$=CH$_2$), 7.21 - 7.37

(m, 5 H, Aryl);   IR (neat) 3030, 1713 (C=O), 1637 (C=C), 991, 924, 756, 702 cm^{-1};   mass

spectrum m/z 160.00888 (calcd for C$_{11}$H$_{12}$O, 160.00882).

3-Phenyl-1-hepten-4-one (18)   Compound 18 was prepared in 82% yield when

E-cinnamylmercuric iodide (4) was allowed to react with n-butyryl chloride using the general

procedure: ^{1}H NMR (CDCl$_3$) δ 0.82 (t, J = 7.5 Hz, 3 H, CH$_3$), 1.56 (sextet, J = 7.5 Hz,

2 H, CH$_2$), 2.41 (t, J = 7.5 Hz, 2 H, COCH$_2$), 4.36 (d, J = 8.1 Hz, 1 H, COCH), 5.07 (dd, J

= 17.1 Hz, J = ~1 Hz, 1 H, E-H$_2$C=C), 5.20 (dd, J = 11.0 Hz, J = ~1 Hz, 1 H, Z-H$_2$C=C),

6.24 (ddd, J = 8.1 Hz, J = 11.0 Hz, J = 17.1 Hz, 1 H, CHC$\underline{H}$=CH$_2$), 7.21 - 7.36 (m, 5 H,

Aryl); IR (neat) 3028, 2968, 1876, 1713 (C=O), 1605 (C=C), 991, 922, 754, 700 cm^{-1};

mass spectrum m/z 188.27034 (calcd for $C_{13}H_{16}O$, 188.27001).

Ethyl 2-ethenyl-3-oxo-hexanoate (19)   Compound 19 was prepared in 89% yield when

ethyl 4-(iodomecurio)crotonate (6) was allowed to react with n-butyryl chloride using the

general procedure: ^{1}H NMR (CDCl$_3$) δ 0.98 (t, J = 7.5 Hz, 3 H, CH$_2$CH$_2$CH$_3$), 1.27 (t, J =

7.2 Hz, 3 H, OCH$_2$CH$_3$), 1.67 (sextet, J = 7.5 Hz, 2 H, CH$_2$CH$_2$CH$_3$), 2.34 (t, J = 7.5 Hz,

2 H, COCH$_2$), 3.09 (d, J = 6.9 Hz, 1 H, COCH), 4.15 (q, J = 7.2 Hz, 2 H, OCH$_2$CH$_3$),

5.14 - 5.18 (m, 2 H, C=CH$_2$), 5.86 - 6.00 (m, 1 H, CH=CH$_2$); IR (neat) 3086, 2970,

1711(C=O), 1645 (C=O), 1462, 1286, 1182, 1097, 1032, 924 cm^{-1}. Anal. Calcd for

$C_{10}H_{16}O_3$: C, 65.15; H, 8.75. Found: C, 65.03; H, 8.69.

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PART II. PALLADIUM(0)-CATALYZED COUPLING OF ARYL IODIDES,
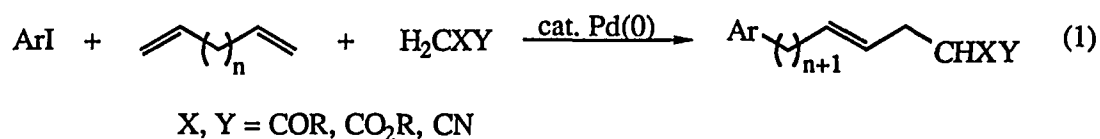NONCONJUGATED DIENES, AND NUCLEOPHILES

SECTION I. PALLADIUM(0)-CATALYZED COUPLING OF ARYL IODIDES,
NONCONJUGATED DIENES, AND CARBON NUCLEOPHILES

INTRODUCTION

Modern palladium chemistry developed very rapidly after the Wacker process was invented in 1958.[1] Since then a large number of new reactions involving palladium compounds have been discovered. One important aspect of palladium chemistry is the application of these reactions to organic synthesis.

Palladium compounds are convenient reagents, because they are usually stable and easy to handle. Toxicity is also not a serious problem. However, palladium is still a rather expensive metal with a high molecular weight, so stoichiometric consumption of palladium compounds is not tolerable in organic synthesis. It is generally most desirable to use palladium compounds in catalytic amounts. Although many palladium reactions have been discovered in the last thirty years, further developments in this field are expected through application of catalytic palladium chemistry to organic synthesis.

Synthetic methodology, which allows for a rapid increase in molecular complexity, is extremely valuable in modern synthetic organic chemistry, particularly when it generates more than one carbon-carbon bond at a time, accommodates considerable functionality, and is broad in scope. The purpose of this dissertation section is to report just such methodology involving the palladium-catalyzed coupling of aromatic iodides, nonconjugated dienes, and carbon nucleophiles in the manner shown below (eq 1).
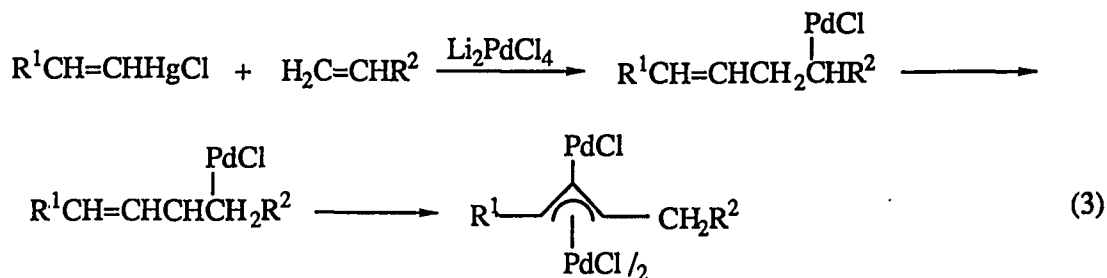
$$ArI \quad + \quad \text{(diene)}_n \quad + \quad H_2CXY \quad \xrightarrow{\text{cat. Pd(0)}} \quad Ar\text{(chain)}_{n+1}CHXY \quad (1)$$

$$X, Y = COR, CO_2R, CN$$

π-Allylpalladium compounds were first reported in 1957.[2] Since that time, a number of procedures have been reported for their preparation.[3] π-Allylpalladium compounds have

recently become valuable intermediates in organic synthesis,[4] particularly for the synthesis of naturally occurring organic compounds, such as terpenes,[5] pheromones,[6] antibiotics,[7] alkaloids,[8] and vitamins.[9]

The most generally useful methods for preparing π-allylpalladium compounds appear to be the direct allylic hydrogen substitution of alkenes by palladium salts[10] and the insertion of palladium(0) reagents into allylic substrates.[4a,11] Another important method for the synthesis of π-allylpalladium compounds involves the addition of σ-bonded organopalladium compounds to conjugated dienes. Heck et al.[12] reported that organopalladium compounds formed by the transmetallation of organomercurials add to various conjugated dienes to afford π-allylpalladium compounds (eq 2).

$$\text{RHgCl} \quad + \quad \diagup\!\!\!\!\diagdown \quad \xrightarrow{\text{LiPdCl}_3} \quad R\diagup\!\!\!\!\diagup\!\!\!\!\diagdown\underset{\underset{\text{Pd}/_2}{|}}{} \qquad (2)$$

R = Me, aryl, benzylic
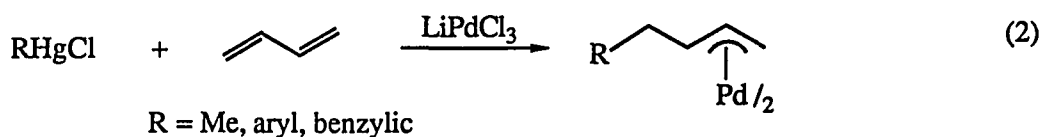
Reactions of vinylpalladium complexes with alkenes provide another route to π-allylpalladium compounds. Larock and co-workers found that vinylmercurials readily react with dilithium tetrachloropalladate and simple alkenes[13] or cyclic alkenes[14] to afford good to excellent yields of π-allylpalladium compounds (eq 3). Apparently this reaction involves the generation and subsequent addition of a vinylpalladium species to the carbon-carbon double
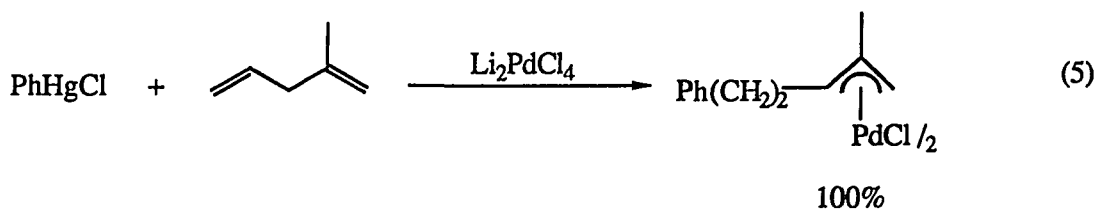
$$R^1CH=CHHgCl \quad + \quad H_2C=CHR^2 \xrightarrow{\text{Li}_2\text{PdCl}_4} R^1CH=CHCH_2\overset{\overset{\text{PdCl}}{|}}{C}HR^2 \longrightarrow$$

$$R^1CH=CHCH\overset{\overset{\text{PdCl}}{|}}{}CH_2R^2 \longrightarrow R^1\!\!\diagup\!\!\overset{\overset{\text{PdCl}}{|}}{\diagup\!\!\diagdown}\!\!-CH_2R^2 \qquad (3)$$
$$\text{PdCl}/_2$$

bond of an alkene to produce a σ-bonded homoallylic palladium complex, which rearranges via palladium hydride elimination - readdition to afford the π-allylpalladium compound.

In order to extend this type of palladium migration to other systems, especially those in which the palladium was even further removed from the carbon-carbon double bond, Larock and Takagi[15] also prepared π-allylpalladium compounds by organopalladium additions to nonconjugated dienes (eq 4). This reaction clearly involves initial organopalladium addition

$$\text{RHgCl} \quad + \quad \diagdown\!\!\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown_n \quad \xrightarrow{\text{Li}_2\text{PdCl}_4} \quad R(CH_2)_{n+1}\diagup\!\!\diagdown \atop \underset{PdCl/_2}{} \qquad (4)$$

$$R = Me, Ph, MeO_2C \qquad n = 1 - 4$$
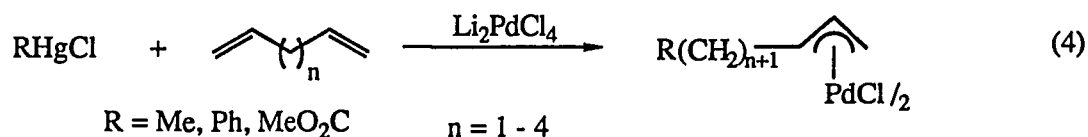
to the less hindered double bond of the diene, followed by a series of palladium hydride elimination - readdition reactions until a π-allylpalladium compound is formed. The palladium species was observed to migrate as far as four carbon atoms prior to π-allylpalladium compound formation.

Another important feature of these organopalladium additions to nonconjugated dienes is the high regioselectivity observed. Thus, the organopalladium addition to 4-methyl-1,4-pentadiene occurred on the least substituted double bond exclusively, followed by palladium migration to form the π- allylpalladium compound shown (eq 5).

$$\text{PhHgCl} \quad + \quad \diagup\!\!\diagdown\!\!\diagup\!\!\diagdown \quad \xrightarrow{\text{Li}_2\text{PdCl}_4} \quad Ph(CH_2)_2\diagup\!\!\diagdown \atop \underset{PdCl/_2}{} \qquad (5)$$

$$100\%$$

At the same time, Bender et al.[16] reported that bromo- or iodobenzene, instead of organomercurials, reacts with 1,4-pentadiene and piperidine under palladium catalysis to afford

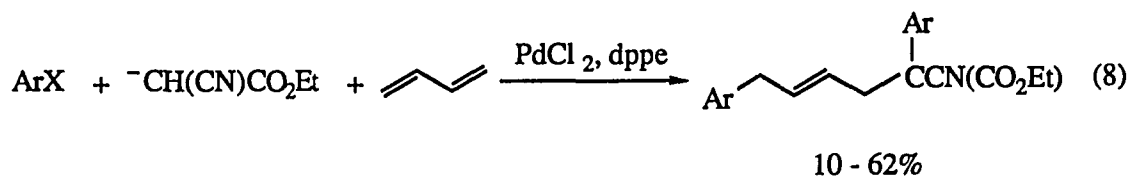an allylic amine and 1-phenyl-1,4-pentadiene (eq 6). This reaction is believed to proceed by a

$$\text{PhBr} + \text{(1,4-pentadiene)} + \text{(piperidine, N-H)} \xrightarrow[\text{P(o-tol)}_3]{1\% \text{ Pd(OAc)}_2} \text{Ph}\sim\sim\text{N(piperidine)} \quad 49\%$$

$$+ \quad \text{(Ph-CH}_2\text{CH}_2\text{-CH(N-piperidine)-CH=CH}_2) \quad + \quad \text{(Ph-CH(CH}_3\text{)-CH=CH-CH}_2\text{-N-piperidine)} \quad + \quad \text{Ph}\sim\sim \quad (6)$$

$$3\% \qquad\qquad 8\% \qquad\qquad 24\%$$
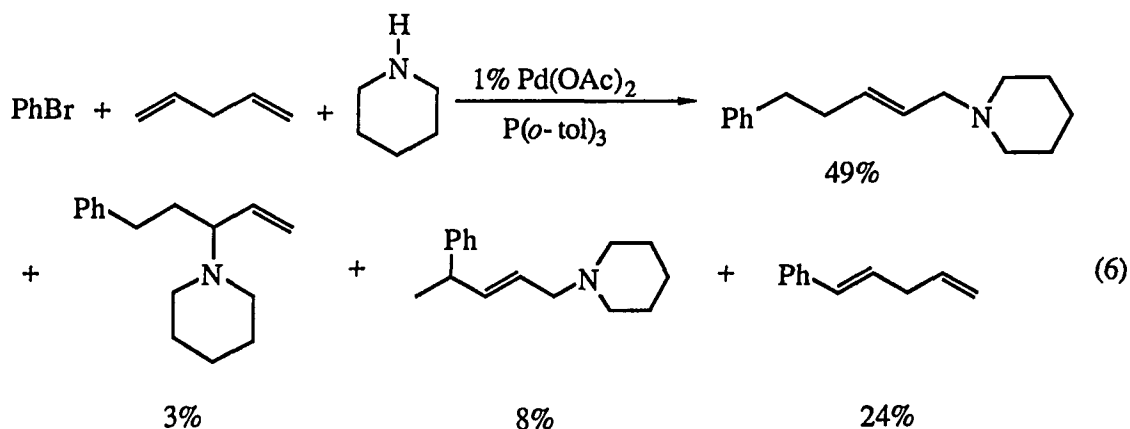
mechanism similar to that described in equations 4 and 5. It is noteworthy that π-allylpalladium intermediates readily undergo attack by an amine to form a carbon-nitrogen bond.

It is known that π-allylpalladium compounds undergo a variety of nucleophilic displacement reactions by carbon and heteroatom nucleophiles to form carbon-carbon and carbon-heteroatom bonds.[4,17] These reactions have been extensively used in organic synthesis. O'Connor et al.[18] also reported the formation of two carbon-carbon bonds in a single palladium-catalyzed step (eq 7). The reaction of 1-bromo-2-methylpropene, isoprene,

$$\text{(CH}_3)_2\text{C=CH-Br} + \text{(isoprene)} \xrightarrow[\text{NaCH(CO}_2\text{Me)}_2]{\text{cat. Pd(OAc)}_2, \text{ PPh}_3} \text{(2,6-dimethylhepta-2,5-dien-1-yl)}\text{CH(CO}_2\text{Me)}_2 \quad (7)$$

$$22\%$$
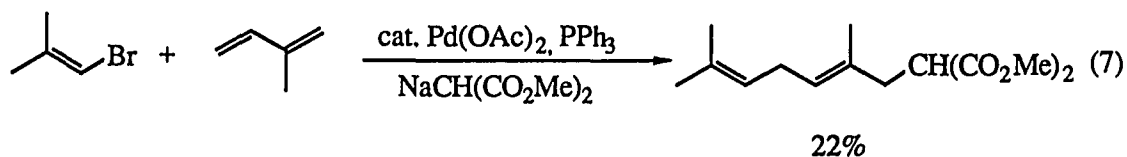
and dimethyl sodiomalonate affords dimethyl (2,6-dimethylhepta-2,5-dien-1-yl) malonate in 22% yield.

Another example of the formation of two new bonds in one catalytic cycle was recently reported by Uno et al.[19] The reaction of butadiene with aryl halides and stabilized carbanions under palladium-catalyzed conditions gives arylation/alkylation products of the diene in which three carbon-carbon bonds are formed from three components in one catalytic step (eq 8).
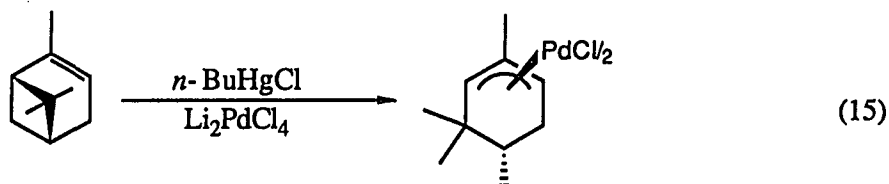
$$\text{ArX} + {}^-\text{CH(CN)CO}_2\text{Et} + \underset{}{} \xrightarrow{\text{PdCl}_2,\ \text{dppe}} \text{Ar} \underset{}{} \overset{\overset{\text{Ar}}{|}}{\text{CCN(CO}_2\text{Et)}} \quad (8)$$

$$10 - 62\%$$

Soderberg and co-workers[20] recently demonstrated that cyclic nonconjugated dienes, such as 1,4-cyclohexadiene, can give π-allylpalladium compounds via initial addition of palladium(II) and nucleophiles across the less hindered double bond, followed by subsequent migration of palladium towards the remaining double bond (eq 9). They also found that

$$\underset{\text{KOAc/HOAc}}{\xrightarrow{\text{(MeCN)}_2\text{PdCl}_2}} \quad \underset{\text{PdCl}/2}{\text{AcO}} \quad \underset{\text{PPh}_3}{\xrightarrow{\text{NaH(CO}_2\text{Me)}_2}} \quad \underset{\text{CH(CO}_2\text{Me)}_2}{\text{AcO}} \quad (9)$$
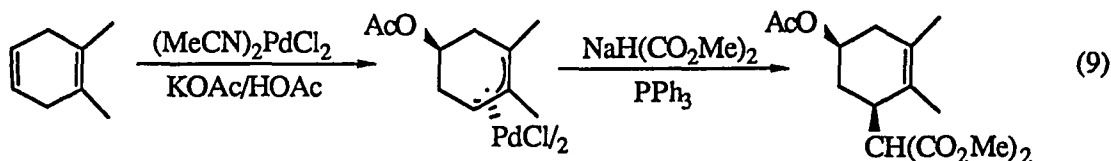
nucleophilic displacement of the π-allylpalladium product by carbanions occurs on the face of the π-allyl unit opposite to the palladium. However, Larock and Takagi[15b] found that the reaction of 1,4-cyclohexadiene with phenylmercuric chloride and Li$_2$PdCl$_4$ did not give the anticipated π-allylpalladium compound under their reaction conditions. It is not clear why the intermediate organopalladium compound in this case is so unstable.

The unique ability of palladium to migrate along carbon chains through palladium hydride elimination and subsequent readdition has also been employed by Larock et al.[21] to synthesize vinyl lactones (eq 10). Obviously, this annulation process proceeds via intramolecular

$$R^1 \diagdown \diagup R^2 \atop H \diagup \diagdown HgCl \quad + \quad \diagup\!\!\!\diagdown\!\!\!\diagdown_n CO_2H \quad \xrightarrow[-20 \text{ to } 25\,^\circ C]{PdCl_2/\,MeCN} \quad \left[R^1\!\!-\!\!\overset{R^2}{\diagup\!\!\!\diagdown}\!\!-\!\!(CH_2)_{n+1}CO_2H \atop PdCl/_2 \right]$$

$$R^1 = \text{Alkyl, Ph} \qquad n = 1, 2$$
$$R^2 = \text{H, Me}$$

$$\xrightarrow{2\ K_2CO_3} \qquad R^1\!\!\diagdown\!\!\diagup\!\!R^2 \cdots O \diagup\!\!\diagdown O \quad \text{(10)}$$

$$35\text{-}85\%$$

displacement of a π-allylpalladium intermediate which was formed through palladium migration. Later on, the same authors [22] reported a new procedure for the synthesis of the lactones shown in equation 10 by employing vinyl iodides, bromides, and triflates, rather than organomercurials, and a catalytic amount of palladium (eq 11).

$$R^1\!\!\diagdown\!\!\diagup\!\!R^2 \atop H\diagup\!\!\diagdown X \quad + \quad \diagup\!\!\!\diagdown\!\!\!\diagdown_n CO_2H \quad \xrightarrow[\substack{TBAC,\ i\text{-}Pr_2NEt \\ DMF,\ 80\,^\circ C,\ 20\ h}]{5\%\ Pd(OAc)_2} \quad R^1\!\!\diagdown\!\!\diagup\!\!R^2 \cdots O\diagup\!\!\diagdown O \quad \text{(11)}$$

$$n = 1, 2$$
$$X = \text{I, Br, OTf}$$
$$R^1 = \text{Alkyl, Ph} \qquad\qquad 30\text{-}70\%$$
$$R^2 = \text{H, Me}$$

Larock et al.[23] have also successfully employed the unique ability of palladium to migrate along carbon chains to prepare a series of long chain aldehydes and ketones in good to excellent yields via palladium-catalyzed coupling of aryl halides and non-allylic unsaturated alcohols (eq 12). The mechanism of this useful reaction undoubtedly involves arylpalladium generation and addition to the carbon-carbon double bond, palladium migration via reversible palladium hydride elimination and subsequent readdition, and eventually enol formation.

$$\text{ArI} + \underset{\substack{R^1 \quad OH \\ \text{(structure)}}}{} \xrightarrow[\substack{\text{LiCl, LiOAc} \\ \text{TBAC, DMF} \\ 25\,^\circ\text{C, 4 d}}]{\text{cat. Pd(OAc)}_2} \underset{4 \sim 5}{Ar\cdots R^2} + \underset{1}{\cdots R^2} \quad (12)$$

$$R^1, R^2 = H, Me \qquad n = 1 - 8 \qquad 77 - 94\%$$

Seven years ago, Larock and Varaprath[24] found that π-allylpalladium compounds were readily available by organopalladium additions to vinylic cyclopropanes and vinylic cyclobutanes (eqs 13 and 14). This reaction apparently involves the formation of (cycloalkylcarbinyl)palladium

$$\text{RHgCl} + \underset{\text{(cyclopropane)}}{} \xrightarrow{\text{Li}_2\text{PdCl}_4} R\cdots \overset{\text{PdCl/}_2}{} \quad (13)$$

$$\text{RHgCl} + \underset{\text{(cyclobutane)}}{} \xrightarrow{\text{Li}_2\text{PdCl}_4} R\cdots \overset{\text{PdCl/}_2}{} \quad (14)$$

intermediates which undergo ring-opening and subsequent palladium migration to afford the π-allylpalladium products (Scheme I).

Scheme I

$$\text{RHgCl} + \text{Li}_2\text{PdCl}_4 \longrightarrow \text{RPdCl}_3{}^{2-}$$

$$\text{RPdCl}_3{}^{2-} + \underset{\text{(structure)}}{} \longrightarrow \underset{\substack{R \\ PdCl_3{}^{2-}}}{} \longrightarrow R\cdots PdCl_3{}^{2-}$$

$$\rightleftharpoons R\cdots \underset{HPdCl_3{}^{2-}}{} \rightleftharpoons R\cdots \underset{PdCl_3{}^{2-}}{} \longrightarrow R\cdots \underset{PdCl_3{}^{2-}}{}$$

Larock et al.[25] also used this type of ring-opening process to prepare enantiomerically pure π-allylpalladium compounds (eq 15). Formation of the enantiomerically pure

$$
\text{(15)}
$$

π-allylpalladium compound is best explained mechanistically by a sequence involving stereospecific palladium hydride addition and elimination steps and cyclobutylcarbinyl palladium ring-opening (Scheme II).

Scheme II
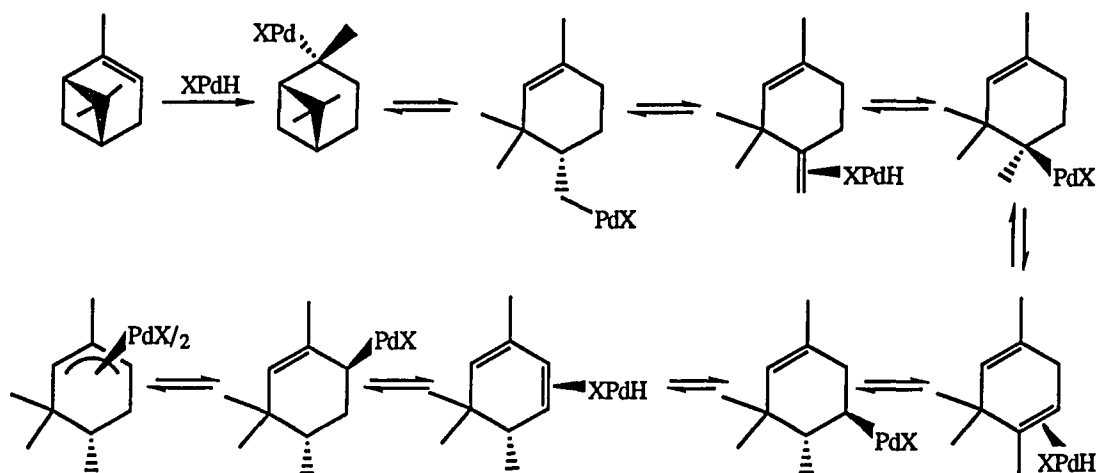
The remarkable ability of palladium to migrate along carbon chains was also employed by Larock and Ilkka[26] in the arylation of 4,5-epoxy-1-pentene with phenylmercuric chloride and a stoichiometric amount of palladium to afford an allylic alcohol in 68% yield (eq 16). They

$$\text{PhHgCl} \quad + \quad 2 \quad \overset{\text{O}}{\underset{}{\diagup\hspace{-0.3em}\diagdown\hspace{-0.3em}\diagup}} \quad \xrightarrow[\substack{5\% \text{ sat'd NH}_4\text{Cl} \\ 0\,^{\circ}\text{C, 10 h}}]{\text{Li}_2\text{PdCl}_4/\text{THF}} \quad \text{Ph}\diagdown\hspace{-0.3em}\diagup\hspace{-0.3em}\diagdown\hspace{-0.3em}\diagup\text{OH} \qquad (16)$$

$$68\%$$
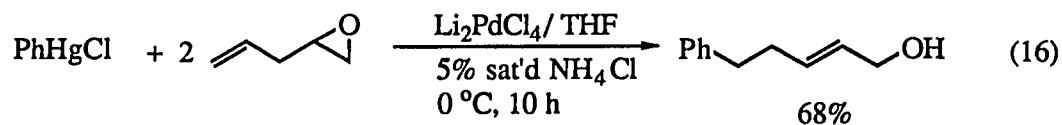
have also recently developed a valuable, very general, new process for the synthesis of aryl

allylic alcohols, which employs a catalytic amount of palladium, a variety of olefinic epoxides,

and organic halides rather than organometallic reagents (eq 17).[27] This arylation

process most likely proceeds as illustrated in Scheme III.

$$\text{Ar-I} \quad + \quad 2 \quad \overset{\text{O}}{\underset{n}{\diagup\hspace{-0.3em}\diagdown\hspace{-0.3em}\diagup}} \quad \xrightarrow[\substack{\text{TBAC, }i\text{-Pr}_2\text{NEt} \\ \text{LiO}_2\text{CH, LiCl} \\ 50\,^{\circ}\text{C, 1 day}}]{\text{cat. Pd(OAc)}_2,\ \text{DMF}} \quad \text{Ar}\diagdown\hspace{-0.3em}\diagup\hspace{-0.3em}\diagdown\hspace{-0.3em}\diagup\text{OH} \qquad (17)$$

$$n = 1 - 4, 10 \qquad\qquad\qquad 50 - 80\%$$
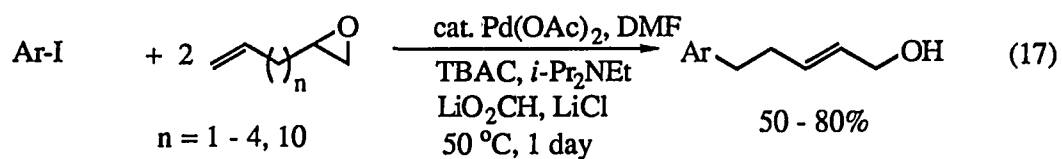
Scheme III
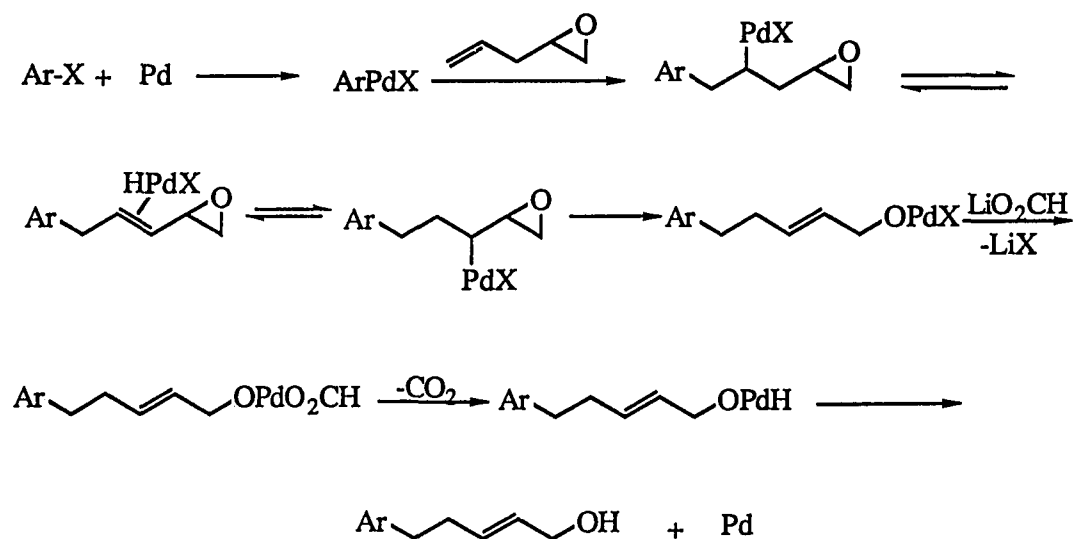
From the above discussion, one should note that there are only a few examples of

palladium-catalyzed reactions proceeding through π-allylpalladium intermediates in which two

new bonds are formed in a single step (eqs 6 - 10). Only two examples have been reported in the literature using π-allylpalladium intermediates prepared from nonconjugated dienes via remote palladium migration (eqs 6 and 9).

Recently Bain[28] explored the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and nucleophiles in DMF at 100 °C for 4 days, using potassium carbonate as a base. Under her reaction conditions only carbon nucleophiles gave decent yields of the desired coupling products which were always contaminated with trace amounts of possible regioisomers and stereoisomers. For example, when iodobenzene was allowed to react with 5 equivalents of 1,5-hexadiene and 5 equivalents of ethyl acetoacetate in the presence of a catalytic amount of bis(benzylideneacetone)palladium(0) [Pd(dba)$_2$], the desired coupling product was obtained in 67% yield contaminated with possible isomers (eq 18). Unfortunately,

(18)

major   minor

67%

when other aryl iodides were employed instead of iodobenzene, poor yields of coupling products were observed. This work also proved to be irreproduceable by myself and others apparently due to the manner in which the reagents were weighed out and added to the reaction mixture. When using nitrogen or oxygen nucleophiles, The Bain procedure gave poor results and obviously needed further improvement.

Therefore, we have decided to reinvestigate the various reaction variables to optimize the reaction conditions and to broaden the scope of the process. The results described in this section involve the development of a new, very general palladium-catalyzed process for the coupling of aryl iodides, nonconjugated dienes, and carbon nucleophiles. In the next section, an application of the newly established procedure to nitrogen and oxygen nucleophiles will be discussed in detail, and in the last section the attempted application of this unique palladium migration methodology to the synthesis of some naturally occurring pyridine alkaloids will be described.

COUPLING OF PHENYL IODIDE, 1,5-HEXADIENE AND DIETHYL MALONATE

As mentioned in the introductory section, Larock et al.[15] observed that π-allylpalladium compounds can be prepared by the reaction of organomercurials, nonconjugated dienes, and Li_2PdCl_4 in good to excellent yields via palladium migration (see eq 4). Heck[16] has also found that the palladium-catalyzed arylation or vinylation of a 1,4-diene proceeds by a similar mechanism to generate π-allylpalladium intermediates which give allylic amines when trapped with amine nucleophiles (see eq 6). Recently Soderberg and Hall[97] have demonstrated that 1,4-cyclohexadiene affords a π-allylpalladium compound that undergoes nucleophilic displacement by dimethyl malonate anion to form a malonate derivative (see eq 9). These results clearly indicate that palladium can migrate along a carbon chain and generate a π-allylpalladium intermediate that can further react with a variety of nucleophiles to form functionalized olefinic derivatives.

In order to efficiently perform palladium-catalyzed multiple bond formation in a single step, it is necessary to optimize the reaction conditions (solvent, reaction temperature, reaction time, selection of catalysts, bases, and ligands, etc.). The coupling of iodobenzene, 1,5-hexadiene, and diethyl malonate was chosen as a model system due to the commercial availability of the starting materials and the feasibility of product isolation (eq 19).
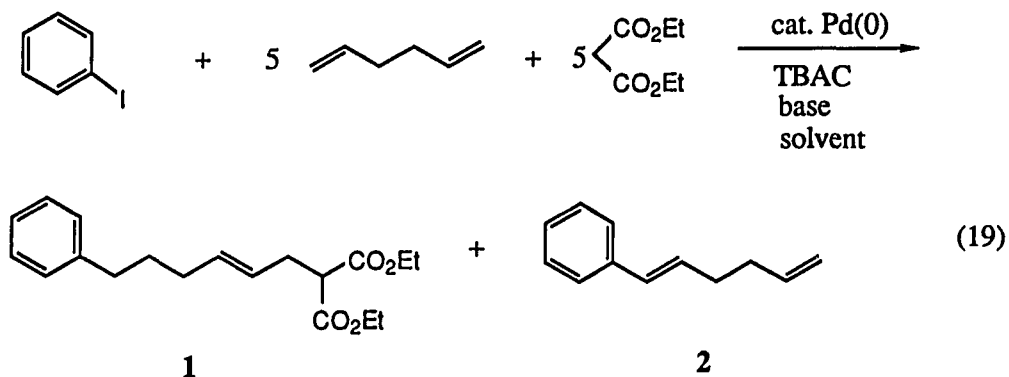
Bain[28] reported in her M.S.Thesis that the coupling reaction of iodobenzene, 1,5-hexadiene, and diethyl malonate proceeded in the presence of 5% bis(dibenzylideneacetone)palladium(0) [Pd(dba)$_2$], 1.1 equivalents of tetra-n-butylammonium chloride (TBAC), and 2.5 equivalents of potassium carbonate in DMF at 100 °C for 4 days to afford the coupling product **1** in 85% yield. However, under these same conditions, Fried[29] ran this reaction three times and isolated compound **1** in yields of only 34%, 22%, and 20% . The author of this dissertation isolated compound **1** in 55% yield. Since Bain's best yield of **1** was not reproduceable, efforts were made to reinvestigate the reaction conditions.

According to Jackson's work,[30] the presence of dimethylsulfoxide (DMSO) facilitates nucleophilic displacement of π-allylpalladium compounds by stabilized carbon nucleophiles. DMSO was therefore tested as a solvent. The results of this work are listed in Table 1.

Table 1. Effect of solvents on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and diethyl malonate.[a]

Solvent	Reaction Time (h)	% Isolated Yield of Compound 1							
		6	8	12	18	24	48	72	96
DMF		--	--	29	--	34	36	43	40
1 : 1 DMF/DMSO		40	--	52	--	58	69	48	--
DMSO		42	53	68	76	71	40	--	--
1 : 1 DMSO/HMPA		--	--	--	--	47	--	--	--
HMPA		--	--	--	--	--	46	--	--

[a] Reaction was run in the presence of 5% Pd(dba)$_2$, 2.5 equiv of KHCO$_3$, and 1.1 equiv of TBAC at 80 °C.

It appears that pure DMSO gives higher yields than pure DMF, HMPA, or a mixture of DMF or HMPA and DMSO, and DMSO is the solvent of choice for this coupling reaction. When DMSO is used as the solvent, the reaction time required is shorter, and the yield of compound **1** is higher.

Trost and Fullerton[31] suggested that the presence of an additional ligand facilitates substitution in the π-allylpalladium system. Tsuji et al.[32] in their very early work also employed DMSO as a co-solvent for reactions with simple π-allylpalladium compounds. Dimethylsulfoxide probably fulfills the role of an additional ligand.

In an attempt to further increase the reaction selectivity, a variety of reaction temperatures and times were carefully examined for the palladium-catalyzed coupling of phenyl iodide, 1,5-hexadiene and diethyl malonate (see eq 19). The data listed in Table 2 indicates that the best yield of the desired coupling product 1 was obtained at 80 °C in 18 h, when potassium bicarbonate was used as the base and DMSO as the solvent. It was found that reducing the reaction temperature did not effectively suppress the formation of the Heck product 2.

Table 2. Effect of reaction temperature on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and diethyl malonate.[a]

Reaction Temp. (°C)	Reaction Time (h)	% Isolated Yield	
		Compound 1	Compound 2
60	24	48	36
80	18	76	15
100	8	73	17
120	8	68	18

[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$, 1.1 equiv of TBAC, and 2.5 equiv of KHCO$_3$ at 80 °C.

With a good solvent and reaction temperature in hand, the coupling reaction of iodobenzene, 1,5-hexadiene, and diethyl malonate was allowed to proceed in the presence of 5% Pd(dba)$_2$ and 1.1 equivalents tetra-n-butylammonium chloride (TBAC) in DMSO, using a variety of inorganic bases. The results presented in Table 3 reveal that the best yield of compound 1 was obtained by using sodium bicarbonate as the base. Also, the yield of coupling product was very similar when employing either sodium or potassium as the cation.

Table 3. Effect of bases on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and diethyl malonate.[a]

| Base | Reaction Time (h) | % Isolated Yield of Compound 1 | | | |
		12	18	24	48
K_2CO_3		40	53	52	48
Na_2CO_3		52	67	64	62
$KHCO_3$		68	76	71	40
$NaHCO_3$		59	68	82	73

[a] Reaction was run in DMSO in the presence of 5% $Pd(dba)_2$, 1.1 equiv of TBAC, and 2.5 equiv of base at 80 °C.

The addition of a base is a key to the successful performance of the palladium-catalyzed cross coupling process, presumably because it is required to abstract the hydrogen atom from the malonate to create the necessary carbanion nucleophile, and the palladium(0) catalyst must be regenerated via the decomposition of the hydridopalladium iodide which is probably also promoted by the base.

Triethylamine, diisopropylethylamine (i-Pr$_2$NEt) , and acetate bases are popular bases that are often used in palladium mediated coupling reactions. However, when these bases were employed in the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and diethyl malonate in DMF, a complicated mixture was observed with a significant amount of Heck product 2. An explanation for this may be that the acetate anion or amine can function both as a base and a nucleophile.[33] Coupling of an aryl iodide, and a nonconjugated diene with nitrogen or oxygen nucleophiles will be discussed in Section II of this part of the dissertation.

In comparison to $Pd(dba)_2$, several other palladium catalysts, such as tetrakis(triphenylphosphine)palladium(0) [Pd(PPh$_3$)$_4$], palladium acetate, and palladium chloride were examined in the coupling of iodobenzene, 1,5-hexadiene and diethyl malonate. It is of interest to note that only a monocoupling product 1-phenyl-1,5-hexadiene (2) (Heck

product) was isolated in 70% yield when Ph(PPh$_3$)$_4$ was used as the catalyst, and none of the

desired product **1** was detected (eq 20). However, when Pd(OAc)$_2$ or PdCl$_2$ was used as

$$
\text{PhI} + 5 \diagup\!\!\!\!\diagdown\!\!\!\!\diagup\!\!\!\!\diagdown + 5 \begin{array}{c} \text{CO}_2\text{Et} \\ \text{CO}_2\text{Et} \end{array} \xrightarrow[\substack{1.1\ \text{TBAC} \\ 2.5\ \text{NaHCO}_3 \\ \text{DMSO} \\ 80\ ^\circ\text{C},\ 12\ \text{h}}]{5\%\ \text{Pd(PPh}_3)_4} \quad \underset{\substack{70\% \\ \mathbf{2}}}{\text{Ph}\diagup\!\!\!\!\diagdown\!\!\!\!\diagup\!\!\!\!\diagdown} \quad (20)
$$
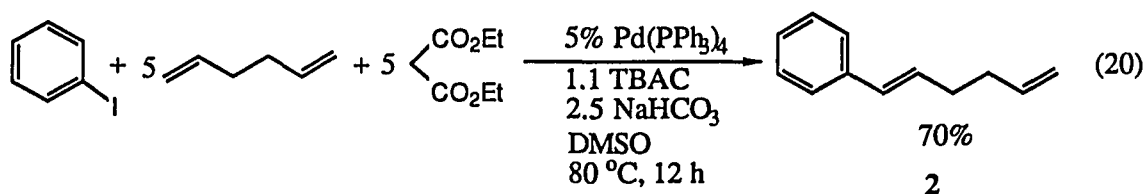
the catalyst in the coupling reaction under the conditions described in equation 20, a low yield

(40 ~ 50%) of the desired product **1** was isolated, alongside a significant amount of Heck

product **2**. The result of equation 20 reveals that the triphenylphosphine ligand blocks the

palladium migration process effectively, and therefore triphenylphosphine cannot be used as a

ligand in the palladium migration system.

Compound **2** is the sole reaction side product and normally exists in the crude product

before purification. Generation of the Heck product (**2**) seriously reduces the yield of desired

coupling product **1**. Therefore, suppressing the formation of the Heck product effectively is

very important, while optimizing the reaction conditions for the palladium-catalyzed coupling of

aryl iodides, nonconjugated dienes, and nucleophiles.

It was found that the amount of catalyst Pd(dba)$_2$ used in the three component coupling

system did not significantly effect the yield of the desired coupling product **1**. For laboratory

convenience and economical reasons, 5% Pd(dba)$_2$ was utilized throughout this project.

A systematic investigation of the reaction stoichiometry was carried out and the results

shown in Table 4 indicate that the reactant stoichiometry is not a particularly important factor in

the reaction. Both five and two equivalents of diene or malonate work well (entries 4 and 7).

It is of interest to note that in order to maintain the product yield at a high level, the amount of

Table 4. Effect of reaction stoichiometry on the palladium-catalyzed coupling of
iodobenzene, 1,5-hexadiene, and diethyl malonate.[a]

Entry	Iodobenzene (equiv)	1.5-Hexadiene (equiv)	Diethyl malonate (equiv)	Time (h)	% Yield[b]
1	1	1	1	24	29
2	1	1	2	24	68
3	1	2	1	48	65
4	1	2	2	24	81
5	1	2	5	12	76
6	1	5	2	24	62
7	1	5	5	24	82

[a] Reaction was run in DMSO in the presence of 5% $Pd(dba)_2$, 1.1 equiv of TBAC, and 2.5 equiv of $NaHCO_3$ at 80 °C.
[b] Isolated yield of compound 1.

malonate used should be either larger than or equal to the amount of diene employed in the coupling reaction. Otherwise, the reaction either requires a longer reaction time (entry 3) or a poor yield is obtained (entry 6). It seems likely that nucleophilic displacement of the palladium in the π-allylpalladium compound is the rate determining step in the overall coupling process. The reason that five equivalents of 1,5-hexadiene were often used in the coupling reaction was to make up for any material lost during the reaction due to the fact that its boiling point (66 °C) is lower than the reaction temperature (80 °C).

Tetra-n-butylammonium chloride (TBAC) was first employed by Jeffery,[34] to promote the palladium-catalyzed vinylation of aryl, vinylic, and alkynyl halides. In order to determine the importance of TBAC in our palladium-catalyzed coupling system, TBAC was omitted from one reaction. The reaction was completed in 24 hours, but afforded the desired coupling product 1 in only 46% yield, plus a 36% yield of the Heck product 2. On the other hand, the use of extra TBAC did not offer significant advantages in the coupling reaction. For example, when 2.2 equivalents of TBAC were used in the coupling reaction, the desired product 1 was obtained in 75% yield under our best conditions. Therefore, the addition of one equivalent of

TBAC is enough for efficient performance of the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and carbon nucleophiles.

The coupling process most likely proceeds as illustrated in Scheme IV. A likely mechanism for the formation of compound **1** involves oxidative addition of the aryl iodide to palladium(0), arylpalladium addition to one of the carbon-carbon double bonds of the diene, palladium migration through a series of reversible palladium hydride eliminations and subsequent readditions, formation of a π-allylpalladium intermediate, and eventual carbanion displacement of the palladium moiety.

Scheme IV

Ar-I + Pd ⟶ ArPdI
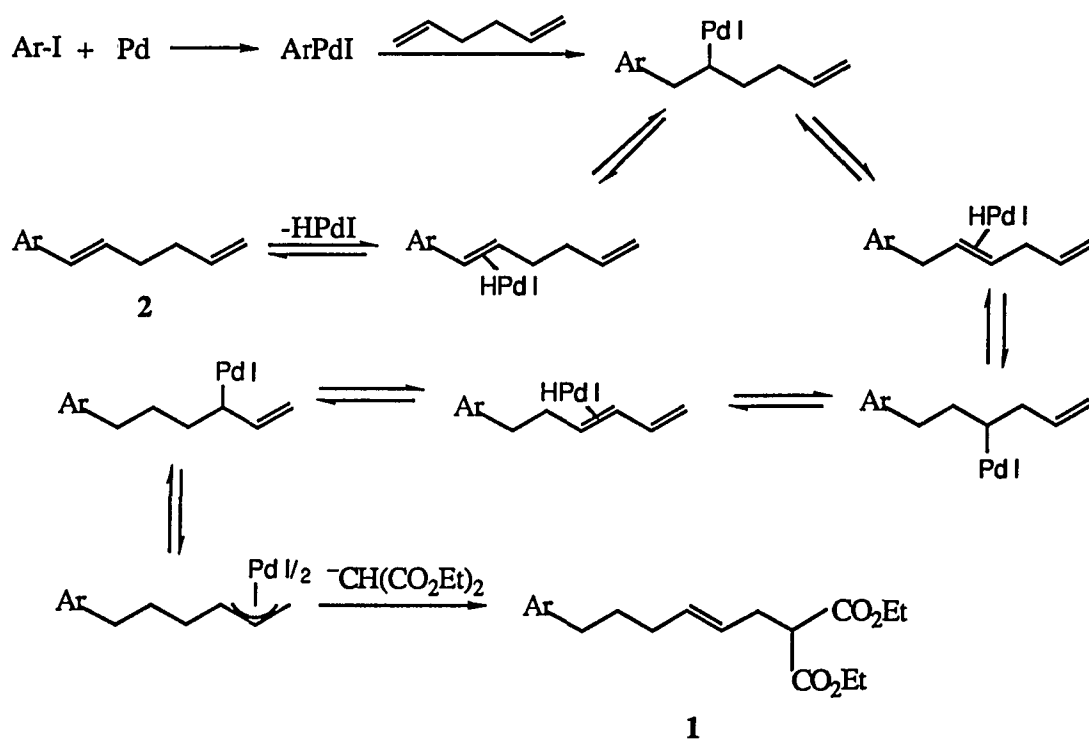
A similar reaction pathway can account for the formation of the Heck product (2). This involves an initial addition of the arylpalladium to one of the carbon-carbon double bonds of the diene, followed by elimination of palladium hydride to form a hydridopalladium-styrene derivative π-complex. Dissociation of the π-complex generates compound 2 (see Scheme IV).

The oxidative addition of aryl halides to Pd(0) and subsequent olefin insertion are well known processes.[81c-e] Careful spectroscopic examination of the product provides no evidence of aryl addition to the internal carbon of the carbon-carbon double bond of the diene as sometimes is observed in related reactions.[23,27]

Larock et al[14,15,22] previously reported the unique ability of organopalladium compounds generated by organomercurial transmetallation to add to carbon-carbon double bonds of nonconjugated dienes and migrate palladium along the carbon chain to form π-allylpalladium compounds. However, the elimination of palladium hydride in that process and its subsequent reaction with the starting diene to form a second different π-allylpalladium product suggested a potential synthetic limitation of this methodology. Fortunately, only minor amounts of the Heck product and $CH_3(CH_2)_2CH=CHCH_2CH(CO_2Et)_2$ are observed as side products under our reaction conditions, even though the reaction is run in the presence of a base, a carbanion, and a very polar solvent, any of which might be expected to displace palladium hydride from any of the intermediate palladium hydride diene π-complexes.

It is also noteworthy that only the E- isomer of product 1 was observed arising from nucleophilic attack of the carbanion at the remote end of the π-allylpalladium intermediate. The *syn* conformation of π-allylpalladium complexes is normally more stable than the *anti* conformation,[35] especially when a long carbon chain is attached to one terminus of the π-allyl complex (eq 21). Subsequent nucleophilic attack on the *syn* conformation of the π-allylpalladium complex results in the formation of the E- isomer of compound 1. The reaction does show a high degree of stereoselectivity. The stereochemistry of compound 1 has been

$$\underset{syn}{\text{Ar}\diagup\diagdown\diagup\diagdown\underset{\text{PdX/}_2}{\overset{\text{H}}{\underset{\text{H}\ \text{H}}{\diagup\diagdown}}}\text{H}} \quad \longleftarrow\ \longrightarrow \quad \underset{anti}{\text{Ar}\diagup\diagdown\diagup\diagdown\diagup\text{H}}\qquad (21)$$
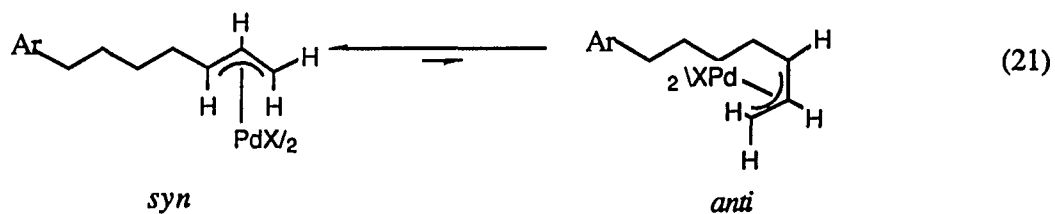
established by 300 MHz ^{1}H NMR and FT-IR spectroscopy.

In summary, after a thorough examination of a variety of reaction conditions, an optimal procedure was obtained for the model system. This procedure was efficient and gave an excellent yield of the coupling product.

COUPLING OF ARYL IODIDES, NONCONJUGATED DIENES, AND CARBON NUCLEOPHILES

In order to demonstrate the synthetic utility of the procedure established during the model system study, the reaction of a variety of carbon nucleophiles, nonconjugated dienes, and aryl iodides was carefully examined to see if the corresponding functionalized olefinic compound could be prepared in good yields. First, a series of stabilized carbon nucleophiles were allowed to react with iodobenzene and 1,5-hexadiene in the presence of 5% $Pd(dba)_2$, 1.1 equivalents of n-Bu$_4$NCl (TBAC) and 2.5 equivalents of $NaHCO_3$ at 80 °C. Our results are summarized in Table 5.

As mentioned in the previous section, the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and a variety of stabilized carbon nucleophiles proceeds regioselectively. No evidence was obtained for the existence of the regioisomer formed by nucleophilic attack on the internal carbon of the π-allyl unit . By examining the results shown in Table 5, one notices that only the E-configuration about the double bond was observed and that the phenyl group exclusively adds to the terminal carbon of 1,5-hexadiene, which has already been observed in our model system.

The palladium-catalyzed coupling of iodobenzene, 1,5 hexadiene and ethyl acetoacetate proceeded smoothly under our standard conditions (entry 2 in Table 5). The yield of desired product 3 was 71%.

The reaction between iodobenzene, 1,5-hexadiene, and ethyl cyanoacetate (entry 4 in Table 5) was studied. There is no coupling product $Ph(CH_2)_3CH=CHCH_2C(Ph)(CN)CO_2Et$ observed, even though Takahashi et al.[19] have isolated a similar product from the analogous reaction of 1,3-butadiene (see eq 8). Takahashi's results can be explained by the initial formation of the aryl cyanoacetate formed from a reaction between the cyanoacetate and the aryl halide (eq 22).[36] This species then attacks the π-allylpalladium intermediate yielding the

68

Table 5. Palladium-catalyzed coupling of iodobenzene and 1,5-hexadiene with carbon nucleophiles.[a]
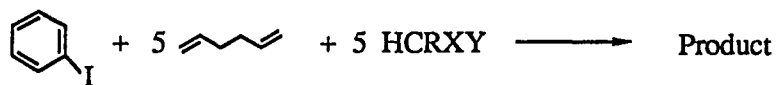
Entry	HCRXY	Time (h)	Product		% Yield[b]
1	CO$_2$Et / CO$_2$Et	24	structure	(1)	82
2	COMe / CO$_2$Et	12	structure	(3)	71
3	COMe / COMe	24	structure	(4)	60
4	CN / CO$_2$Et	12	structure	(5)	81
5	SO$_2$Ph / CO$_2$Me	8	structure	(6)	77
6	dimedone	24	structure	(7)	58
7	2-methyl-1,3-cyclohexanedione	12	structure	(8)	64
8	structure	12	structure	(9)	64

[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$, 1.1 equiv of TBAC, and 2.5 equiv of NaHCO$_3$ at 80 °C, using 5 equiv of 1,5-hexadiene and 5 equiv of carbon nucleophile.

[b] Isolated yield.

$$\text{ArX} + {}^-\text{CH(CN)CO}_2\text{Et} \xrightarrow{\text{cat. Pd(0)}} \overset{\overset{\displaystyle \text{Ar}}{|}}{\text{H}}\overset{}{\text{C}}\text{CN(CO}_2\text{Et)} + \text{X}^- \qquad (22)$$
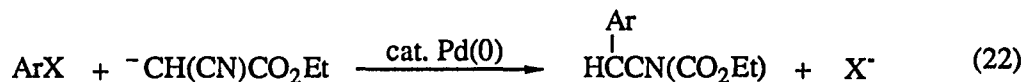
diaryl substituted cyanoacetate. The different results can be explained by the fact that the cyanoacetate anion was generated in situ from cyanoacetate and sodium hydride, and a much larger amount of the aryl iodide was used.

After obtaining a high yield of product **5**, it was thought that malononitrile might give a good yield of coupling product. Unfortunately, this reaction failed to give the expected product for no apparent reason (eq 23).

$$\text{PhI} + 5 \underset{\text{2}}{\diagup\!\diagdown\!\diagup\!\diagdown} + 5\overset{\text{CN}}{\underset{\text{CN}}{\diagdown}} \xrightarrow[\substack{1.1\ \text{TBAC} \\ 2.5\ \text{NaHCO}_3 \\ \text{DMSO, } 80\ °\text{C}}]{5\%\ \text{Pd(dba)}_2} \quad \underset{0\%}{\text{Ph}\overset{}{\diagup\!\diagup}\underset{\text{CN}}{\diagup\!\diagdown}\text{CN}} \qquad (23)$$
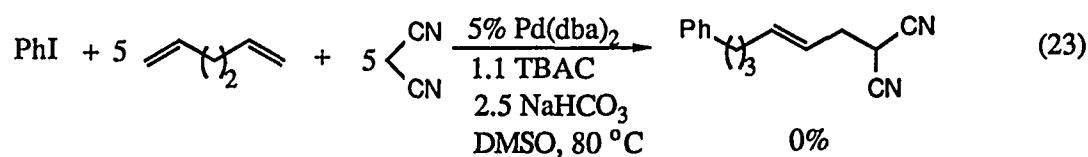
The reaction of a β-diketone with iodobenzene and 1,5-hexadiene produced an approximately 3: 2 keto-enol mixture of compound **4** (entry 3 in Table 5). Atkins et al.[37] have also found that the reaction of a β-diketone with allylic alcohols in the presence of palladium acetate and triphenylphosphine affords a keto-enol mixture of product (eq 24).

$$\diagup\!\diagdown\!\diagup\!\diagdown\!\diagup\!\diagdown\text{OH} + \overset{\text{O}\quad\text{O}}{\diagdown\!\diagup\!\diagdown\!\diagup\!\diagdown} \xrightarrow[\text{PPh}_3]{\text{Pd(OAc)}_2} \quad \diagup\!\diagdown\!\diagup\!\diagdown\!\diagup\!\diagdown\overset{=\text{O}}{\underset{=\text{O}}{\diagdown}} \qquad (24)$$

keto and enol forms
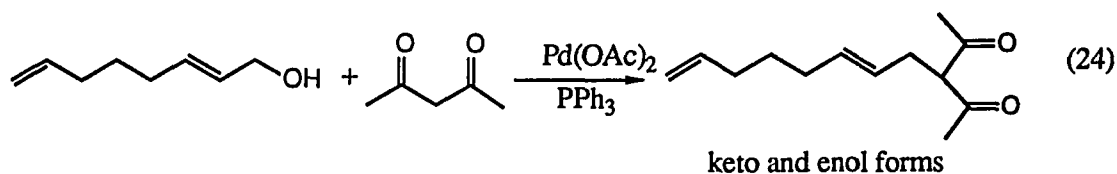
Several cyclic diketones were examined as alternative nucleophiles for the coupling with iodobenzene and 1,5-hexadiene in the presence of a catalytic amount of Pd(dba)$_2$. When 5,5-dimethylcyclohexa-1,3-dione was used as a carbon nucleophile, the anticipated coupling

compound **7** was isolated in 58% yield, and existed almost entirely in the enolic form. This is evident from the fact that its ^{1}H NMR spectrum shows a 2 H doublet at δ 3.10 (=CHC$\underline{H}_2$C(CO)=COH), rather than a 2 H doublet of doublets at ~δ 2.70, as would be expected for the β-diketone structure. Meanwhile, the IR spectrum shows a broad enolic OH stretch at ~3500 cm^{-1}.

In order to avoid the formation of a keto-enol mixture, a cyclic β-diketone with only one α-hydrogen, such as 2-methylcyclohexa-1,3-dione was employed in the reaction. The expected coupling product **8** was obtained in 64% yield.

When a ketolactone was allowed to react with iodobenzene and 1,5-hexadiene in the presence of a catalytic amount of Pd(dba)$_2$ at 80 °C, the product **9** was obtained in 64% yield (entry 8 in Table 5).

As shown in entry 5 of Table 5, the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and methyl phenylsulfonylacetate under our standard conditions afforded the anticipated product **6** in 77% yield. It therefore appears that a carbanion stabilized by a sulfonyl group can be successfully employed in our coupling system. Further work may include the examination of other sulfur stabilized carbanions to determine if they would work under our reaction conditions.

When methyl phenylsulfinylacetate was used as the nucleophile in the coupling of iodobenzene and 1,5-hexadiene under the same reaction conditions as those listed in entry 5, Table 5, the expected product underwent sulfenic acid elimination to form a conjugated diene derivative **10** in only 11% yield. The predominant product in this reaction was 1-phenyl-1,5-hexadiene (**2**) (Heck product)which was obtained in 83% yield (eq 25).

Ph-I + 5 /\/\/ + 5 $PhSOCH_2CO_2Me$ $\xrightarrow[\substack{1.1 \text{ TBAC} \\ 2.5 \text{ NaHCO}_3 \\ \text{DMSO, } 80\,^\circ C}]{5\% \text{ Pd(dba)}_2}$

$$\left[Ph\diagdown\diagup\diagdown\diagup\underset{\underset{SOPh}{|}}{\overset{CO_2Me}{|}} \right] \quad + \quad Ph\diagdown\diagup\diagdown\diagup \qquad (25)$$

                                                      2
                                                     83%

$\big\downarrow$ -HOSPh

$Ph\diagdown\diagup\diagdown\diagup\diagdown CO_2Me$

10
11%
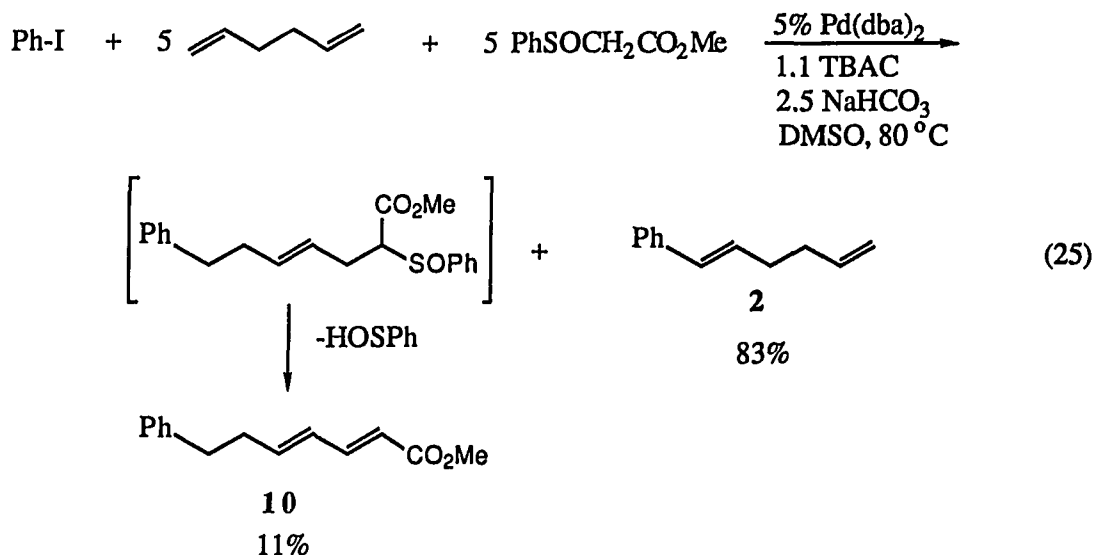
For comparison, methyl phenylthioacetate was allowed to react with iodobenzene and 1,5-hexadiene under the same reaction conditions shown in equation 25, and only Heck product (2) was observed (81%) (eq 26).

Ph-I + 5 /\/\/ + 5 $PhSCH_2CO_2Me$ $\xrightarrow[\substack{1.1 \text{ TBAC} \\ 2.5 \text{ NaHCO}_3 \\ \text{DMSO, } 80\,^\circ C}]{5\% \text{ Pd(dba)}_2}$ $Ph\diagdown\diagup\diagdown\diagup$ (26)

                                                                                       2
                                                                                      81%
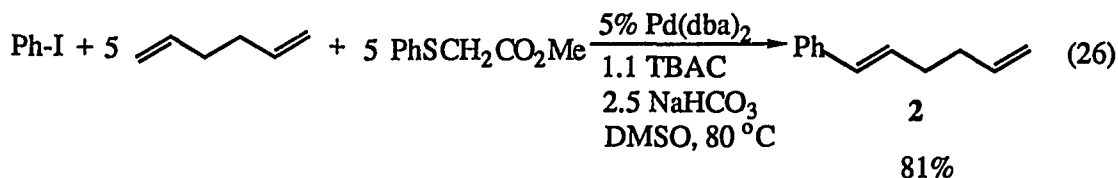
Trost [38] has pointed out that the ability to achieve alkylation appears to correlate with the pKa of the carbon acid; the more acidic the substrate is, the better the alkylation proceeds. Data from Bordwell [39] indicated that upon increasing the oxidation state of sulfur, as in CH_3SO and CH_3SO_2, an additional increase in the acidity of the adjacent carbon atom (13 to 17 pKa units greater than the CH_3S group) is observed. The sequence of acidity is therefore as follows.

$$PhSO_2CH_2CO_2CH_3 > PhSOCH_2CO_2CH_3 > PhSCH_2CO_2CH_3$$

It is not clear whether the phenylthio- or phenylsulfinyl group affects the palladium migration.

It was of interest to try other longer dienes with more carbon atoms between the carbon-carbon double bonds. Cyclic nonconjugated dienes were also examined under the standard conditions. The results are summarized in Table 6.

The reactions work well for both acyclic and cyclic dienes with 1 to 10 carbon atoms between the two carbon-carbon double bonds. The number of carbon atoms that palladium migrates was extended from 2 to 10 (entries 1-4 in Table 6). These results indicate that the length of unconjugated diene does effect the yield, but that palladium can migrate along any carbon chain by a series of palladium hydride eliminations and readditions until the formation of a π-allylpalladium complex occurs at the other end of the diene. It appears that the hydridopalladium π-complex intermediates which are formed in the palladium migration process are surprisingly stable.

Larock and Takagi[92b] have shown that the reaction of 2,4-dimethyl-1,4-hexadiene with ethylmercuric chloride yields approximately a 3 : 2 mixture of syn and $anti$ π-allylpalladium isomers in 25% yield (eq 27). This reaction clearly demonstrates that palladium can migrate

$$\text{EtHgCl} \quad + \quad \overset{\displaystyle }{\text{\Large \textasciicircum}} \quad \xrightarrow[\substack{0 \text{ to } 25\,^{\circ}\text{C} \\ 25\%}]{\text{Li}_2\text{PdCl}_4} \quad \underset{\substack{\text{PdCl}/2 \\ syn : anti = 3 : 2}}{\text{\Large \textasciicircum}} \qquad (27)$$
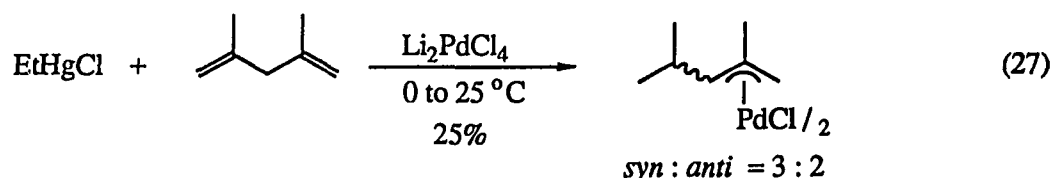
past a branched carbon to generate a π-allylpalladium complex. The low yield is attributed to steric hindrance to olefin insertion due to increased substitution about the double bonds of the diene. In order to determine if an analogous intermediate could be generated from 2,5-dimethyl-1,5-hexadiene, the reaction of this diene with iodobenzene and diethyl malonate

Table 6. Palladium-catalyzed coupling of iodobenzene and diethyl malonate with nonconjugated dienes.[a]

$$\text{(iodobenzene)} + 5 \text{ diene} + 5 \text{ H}_2\text{C(CO}_2\text{Et)}_2 \longrightarrow \text{Product}$$
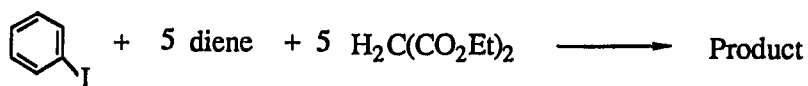
Entry	Diene	Time (h)	Product		% Yield[b]
1		24		(1)	82
2		24		(11)	66
3	[c]	24		(12)	55
4	[c]	24		(13)	52
5		36		(14)	63
6		36		(15)	60
7		12		(16)	88
8		12		(17)	57

[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$, 1.1 equiv of TBAC, and 2.5 equiv of NaHCO$_3$ at 80 °C, using 5 equiv of of nonconjugated diene and 5 equiv of diethyl malonate.

[b] Isolated yield.

[c] 2.0 Equiv of diene were used.

was studied (entry 5 in Table 6). The anticipated product was obtained in 63% yield as the

E-isomer **14** (eq 28). It seems that substituted diene double bonds apparently do not

$$\text{Ph-I} + 5 \quad \diagup\!\!\!\diagdown\!\!\!\diagup\!\!\!\diagdown\!\!\!\diagup \;\; + \; 5 \; \diagdown\!\!\!\!<\begin{array}{c} CO_2Et \\ CO_2Et \end{array} \xrightarrow[\substack{1.1\ TBAC \\ 2.5\ NaHCO_3 \\ DMSO,\ 80\ ^\circ C}]{5\%\ Pd(dba)_2} \text{Ph} \diagup\!\!\!\diagdown\!\!\!\diagup\!\!\!\diagdown\!\!\!< \begin{array}{c} CO_2Et \\ CO_2Et \end{array} \qquad (28)$$

14
63%
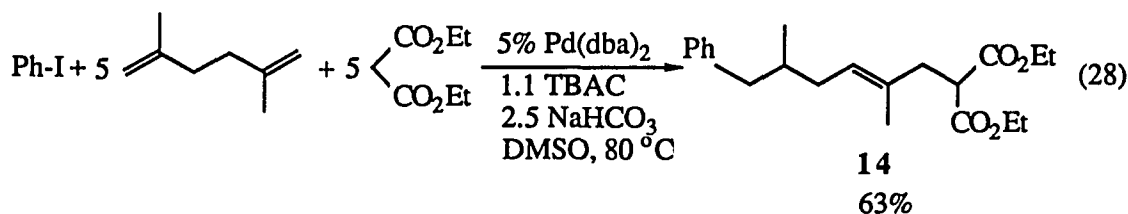
significantly affect the yield of the migration product under our standard reaction conditions.

Examination of the result in entry 6 in Table 6 also reveals that the reaction of 2-methyl-

1,5-hexadiene with iodobenzene and diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1

equivalents of TBAC, and 2.5 equivalents of NaHCO$_3$ at 80 °C afforded compound **15** in 60%

yield as a single regioisomer and stereoisomer. The absence of other regioisomers of

compound **15** clearly indicates that the phenyl group added exclusively to the least substituted

carbon-carbon double bond of the diene. The selectivity of this addition is believed to occur

because the less substituted double bond coordinates more readily with the arylpalladium

halide. Larock and Takagi[15b] have also observed that organopalladium compounds add to the

least substituted double bond of the diene exclusively (see eq 5). In contrast to the results of

Bender et al.[16] products derived from the organic moiety adding to the internal carbon of the

double bond were not seen.

In order to determine if palladium can migrate around a carbon ring, 1,4-cyclohexadiene

and 1,5-cyclooctadiene were allowed to react with iodobenzene and diethyl malonate under our

standard conditions (entries 7 and 8 in Table 6). The isomerically pure product **16** and **17**

were isolated in yields of 88% and 57%, respectively. The stereochemical assignment of **16**

was accomplished by COSY-2D ^{1}H NMR spectroscopy, which is totally consistent with the

structure anticipated mechanistically. The eight membered ring structure of compound **17** is believed to possess a *trans*-configuration by mechanistic arguments, although the spectral data are too complicated to interpret. It is known that both organopalladium additions to the carbon-carbon double bond and palladium hydride eliminations occur in a *syn* fashion, and that nucleophilic attack of a carbanion on a π-allylpalladium compound occurs from the face of the π-allyl unit opposite to that of the palladium atom[10,20] (Scheme V).
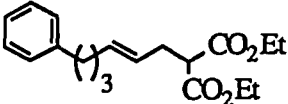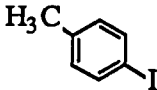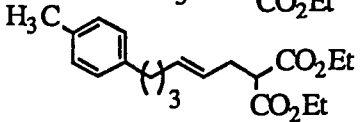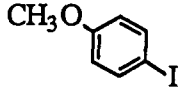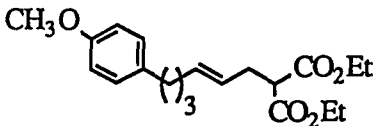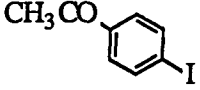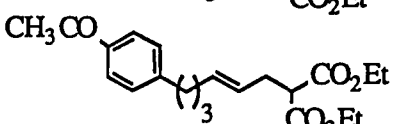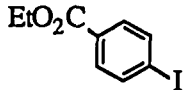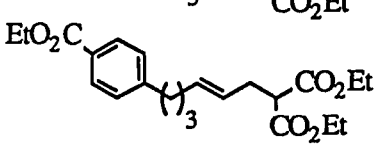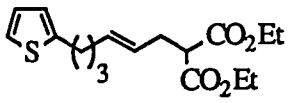
Scheme V
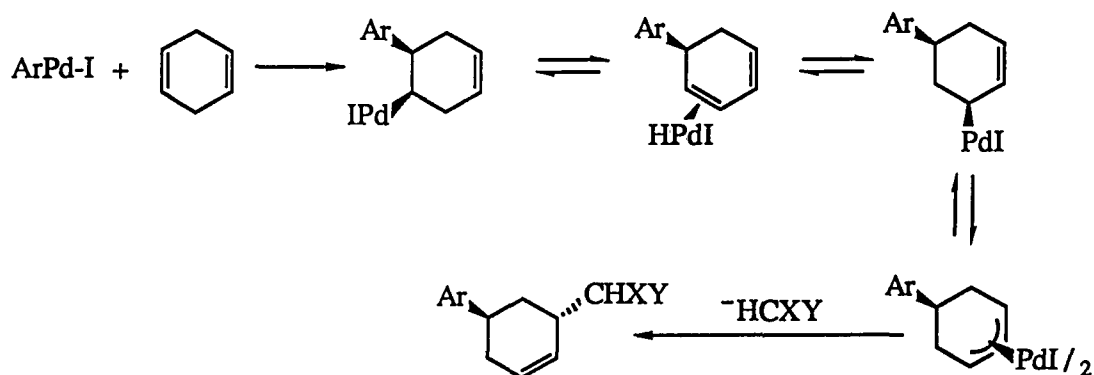
Finally, it was of interest to determine if other aryl iodides could be successfully coupled with nonconjugated dienes and diethyl malonate. These results are listed in Table 7.

By examining the results shown in Table 7, one can see that moderate to good coupling product yields can be obtained when a wide variety of aryl iodides were allowed to react with 1,5-hexadiene and diethyl malonate in the presence of a catalytic amount of palladium(0), 1.1 equivalents of *n*-Bu4NCl, and 2.5 equivalents of sodium bicarbonate at 80 °C. The reactions proceed with a high degree of regioselectivity and stereoselectivity, giving solely the *E* configuration of the coupling product with the aryl group attached to the terminal carbon of the diene. It is also noteworthy that several important functional groups can be accommodated by this reaction, and that the presence or absence of electron-donating or -withdrawing groups on

Table 7. Palladium-catalyzed coupling of 1,5-hexadiene and diethyl malonate with aryl
iodides.[a]

Aryl Iodide + 5   + 5 $H_2C(CO_2Et)_2$ $\longrightarrow$ Product
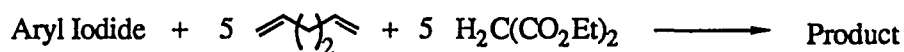
Entry	Aryl Iodide	Time (h)	Product		% Yield[b]
1		24		(1)	82
2		12		(18)	64
3		12		(19)	54
4		6		(20)	56
5		12		(21)	37
6		12		(22)	59

[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$, 1.1 equiv of TBAC, and
2.5 equiv of NaHCO$_3$ at 80 °C, using 5 equiv of 1,5-hexadiene and 5 equiv of diethyl
malonate.
[b] Isolated yield.

the aryl iodide has only a minor effect on the yield of the reaction. It seems likely that the

oxidative addition of the aryl iodide to palladium(0) is not the rate-determining step in the

overall process, since similar reaction times are observed for aryl iodides bearing electron-

donating and electron-withdrawing groups.

The reaction of 1,5-hexadiene and diethyl malonate with ethyl 4-iodobenzoate produced the desired coupling product in a yield lower than expected, because similar Rf values for the target molecule and the starting diethyl malonate caused difficulty in isolating the product. When extra malonate was removed in vacuo by mechanical pumping, a significant amount of the desired product was lost. However, were the reaction to be scaled up, it seems likely that vacuum distillation could be utilized to separate these two compounds, because of the large difference in their boiling points.

Attempts to extend the process to aryl iodides bearing more than one halogen atoms were not successful. Thus, 1,2-diiodobenzene was allowed to react with 5 equivalents of 1,5-hexadiene and diethyl malonate in the presence of a catalytic amount of $Pd(dba)_2$, 1.1 equivalents of n-Bu_4NCl and 2.5 equivalents of $NaHCO_3$ in DMSO at 80 °C. A monosubstituted product was obtained in a low yield (21%), rather than the anticipated disubstituted one (eq 29). The addition of ten equivalents of diene to the reaction mixture still failed to yield any of the desired disubstituted product.
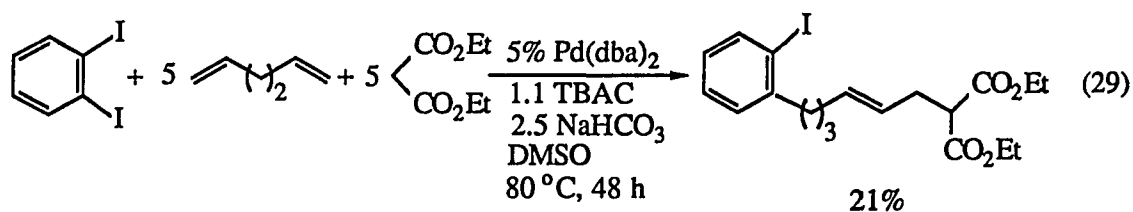
CONCLUSION

The results presented in this section of the dissertation provide a unique synthetic methodology in which more than one carbon-carbon bond is generated in a single one pot process. The process involves the palladium-catalyzed coupling of aromatic iodides, nonconjugated dienes, and carbon nucleophiles.

This process is remarkably versatile, giving good yields for a wide variety of carbon nucleophiles. It works well for both acyclic and cyclic nonconjugated dienes containing from 1 to 10 carbon atoms between the carbon-carbon double bonds. This implies that palladium can migrate quite a long distance (at least up to 10 carbons) along carbon-carbon chains to form π-allylpalladium compounds.

This process results in a high degree of regioselectivity and stereoselectivity. The initial addition of the arylpalladium takes place at the less hindered double bond of the nonconjugated diene and no evidence of aryl addition to the internal carbon was observed. Only products formed from carbanion attack at the remote end of the carbon chain are observed and all products are exclusively the E isomers.

Further work has focused on an examination of analogous reactions using a variety of heteroatom-containing nucleophiles which will be discussed in the next section of this dissertation.

EXPERIMENTAL SECTION

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded either on an IBM IR/98 FT-IR spectrometer or a Beckmann 4250 spectrometer. GC-MS data were recorded on a Finnigan MS-50 mass spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Gas chromatographic analyses were performed on an HP 5890 gas chromatography equipped with a HP-1 Megabore column. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O]. Flash chromatography was carried out on 230 - 400 mesh silica gel or aluminum oxide (activated neutral, Brockman I). A Harrison Research Chromatotron (Model 7924) with 1 mm silica gel plates (60 PF-254, EM-Science) was used to purify some of the products obtained as mixtures.

Reagents

All aryl iodides, nonconjugated dienes and carbon nucleophiles were used as purchased from Aldrich, Fluka and Wiley without prior purification. Tetra-*n*-butylammonium chloride was purchased from Lancaster Co. and kept dry in a desiccator. Sodium bicarbonate was available from Fisher Inc. The solvent dimethylsulfoxide (DMSO) and others were purchased from Fischer and used without further purification. Pd(dba)$_2$ and Pd(OAc)$_2$ were generously provided by Johnson Matthey, Inc.

General procedure for the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and carbon nucleophiles

To a culture tube (16 x 125 mm) with a micromagnetic stirring bar were added sodium bicarbonate (0.105 g, 1.25 mmol), tetra-n-butylammonium chloride (0.153 g, 0.55 mmol) and bis(dibenzylideneacetone)palladium(0) (0.014 g, 0.025 mmol). After passing nitrogen gas though the tube for several minutes, the tube was sealed by a septum and 2 mL of solvent dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then the aryl iodide (0.50 mmol) was added, followed by the nonconjugated diene (2.50 mmol) and the nucleophile (2.50 mmol). The culture tube was sealed with a screw cap lined with Teflon after the addition of all reagents and the reaction mixture was stirred at 80 °C for the period of time required. The reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous ammonium chloride solution (10 mL), and extracted with diethyl ether three times (10 mL x 3). The ether layer was backwashed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to remove the solvent. Finally, the product was isolated by flash chromatography on a silica gel column.

Spectral data for coupling products prepared by the above general procedure

(E)-$C_6H_5(CH_2)_3CH=CHCH_2CH(CO_2C_2H_5)_2$ (1)   Compound 1 was isolated in 82% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1 equivalent of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 24 h. ^{1}H NMR (CDCl$_3$) δ 1.25 (t, J = 7.2 Hz, 6 H, CH$_3$), 1.65 (quintet, J = 7.2 Hz, 2 H, PhCCH$_2$), 2.00 (q, J = 7.2 Hz, 2 H, CH$_2$C=), 2.55 - 2.60 (m, 4 H, PhCH$_2$, CH$_2$CCO$_2$), 3.37 (t, J = 7.5 Hz, 1 H, CHCO$_2$), 4.17 (q, J = 7.2 Hz, 4 H, CO$_2$CH$_2$), 5.38 (dt, J = 7.2 Hz, J = 15.3 Hz, 1 H, vinyl), 5.55 (dt, J = 7.2 Hz, J = 15.3 Hz, 1 H, vinyl), 7.29 - 7.14 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.11, 30.96, 31.88 (2C), 35.22, 52.30, 61.28, 125.64, 125.86,

128.23, 128.39, 133.36, 142.85, 168.98 (C=O); IR (neat) 3085, 2982, 2935, 1730 (C=O), 1335 - 1177 (br C-O), 970 (E-CH=CH), 780, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.44; H, 8.30.

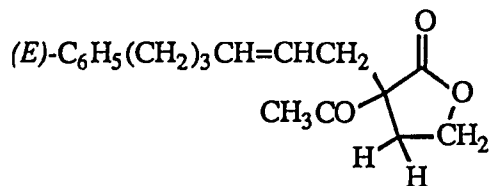**(E)-$C_6H_5(CH_2)_3CH=CHCH_2CH(COCH_3)CO_2C_2H_5$ (3)** Compound **3** was isolated in 71% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of ethyl acetoacetate in the presence of 5% Pd(dba)$_2$, 1.1 equivalent of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 12 h. ^{1}H NMR (CDCl$_3$) δ 1.26 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.66 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$), 2.00 (q, J = 7.2 Hz, 2 H, CH$_2$C=), 2.22 (s, 3 H, CH$_3$CO), 2.51 - 2.60 (m, 4 H, PhCH$_2$, CH$_2$CCO$_2$), 3.47 (t, J = 7.5 Hz, 1 H, CHCO$_2$), 4.17 (q, J = 7.2 Hz, 2 H, CO$_2$CH$_2$), 5.35 (dt, J = 8.7 Hz, J = 15.2 Hz, 1 H, vinyl), 5.50 (dt, J = 8.7 Hz, J = 15.2 Hz, 1 H, vinyl), 7.27 - 7.14 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.16, 29.02, 30.96, 31.28, 31.98, 35.23, 59.80, 61.28, 125.64, 125.96, 128.23, 128.38, 133.30, 142.25, 169.38 (C=O), 202.51 (C=O); IR (neat) 3085, 2982, 2935, 1730 (C=O), 1716 (C=O), 1300 - 1200 (br C-O), 972 (E-CH=CH), 780, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.86; H, 8.33.

(E)-$C_6H_5(CH_2)_3CH=CHCH_2CH(COCH_3)_2$ (4) Compound **4** was isolated in 60% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of acetylacetone in the presence of 5% Pd(dba)$_2$, 1.1 equivalents of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 24 h. ^{1}H NMR (CDCl$_3$) δ 1.67 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$), 2.05 - 2.11 (m, 2 H, CH$_2$C=), 2.11 (s, 3 H, CH$_3$CO), 2.17 (s, 3 H, CH$_3$C(OH)=, enol form), 2.53 - 2.59 (m, 4 H, PhCH$_2$, CH$_2$CCO$_2$), 2.92(d, J = ~1 Hz, 2 H, CH$_2$C=C(OH), enol form), 3.68 (t, J = 7.5 Hz, 1 H, CHCO$_2$), 5.24 - 5.35 (m, 1 H, vinyl), 5.39 - 5.42 (m, 2 H, CH=CH, enol form), 5.47 - 5.58 (m, 1 H,

vinyl), 7.14 - 7.29 (m, 5 H, aryl), 16.50 (s, 1 H, OH); ^{13}C NMR (CDCl$_3$) δ 22.86, 29.12,

30.16, 31.18, 31.28, 35.23, 68.69, 108.14, 125.67, 127.76, 128.22, 128.32, 130.57,

133.36, 142.25, 192.08 (C=O, enol form), 203.59 (C=O); IR (neat) 3600 (br OH, enol

form), 3026, 2930, 2858, 1724 (C=O), 1701 (C=C-C=O, enol form), 1605 (br), 1452, 1421,

1358, 978 (*E*-CH=CH), 748, 700 cm^{-1}.   Anal. Calcd for C$_{17}$H$_{22}$O$_2$: C, 79.03; H, 8.58.

Found: C, 79.10; H, 8.51.

(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$CH(CN)CO$_2$C$_2$H$_5$ (5)   Compound 5 was isolated

in 81% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-

hexadiene and 5.0 equivalents of ethyl cyanoacetate in the presence of 5% Pd(dba)$_2$, 1.1

equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 24 h. ^{1}H

NMR (CDCl$_3$) δ 1.31 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.71 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$),

2.02 (dt, J = 7.5 Hz, J =7.2 Hz, 2 H, CH$_2$C=), 2.58 - 2.65 (m, 4 H, PhCH$_2$, CH$_2$CCN),

3.51 (t, J = 6.6 Hz, 1 H, CHCN), 4.25 (q, J = 7.2 Hz, 2 H, CO$_2$CH$_2$), 5.40 (dt, J = 7.2 Hz,

J = 15.1 Hz, 1 H, vinyl), 5.56 (dt, J = 7.2 Hz, J = 15.1 Hz, 1 H, vinyl), 7.29 - 7.14 (m, 5 H,

aryl); ^{13}C NMR(CDCl$_3$) δ 13.98, 30.70, 31.84, 32.95, 35.15, 38.09, 65.51, 116.18,

123.17, 125.64, 128.22, 128.95, 136.05, 142.13, 165.58 (C=O); IR (neat) 3085, 2986,

2250 (C≡N), 1741(C=O), 1300 -1200 (br), 972 (*E*-CH=CH), 750, 700 cm^{-1}. Anal. Calcd for

C$_{17}$H$_{21}$O$_2$N: C, 75.24; H, 7.80. Found: C, 74.87; H, 7.83.

(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$CH(SO$_2$C$_6$H$_5$)CO$_2$CH$_3$ (6)   Compound 6 was

isolated in 77% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of

1,5-hexadiene and 5.0 equivalents of methyl phenylsulfonylacetate in the presence of 5%

Pd(dba)$_2$, 1.1 equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for

8 h. ^{1}H NMR (CDCl$_3$) 1.61 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$), 1.95 (dt, J = 7.5 Hz, J =

6.9 Hz, 2 H,CH$_2$C=), 2.54 (t, J = 7.5 Hz, 2 H, PhCH$_2$), 2.61 - 2.71 (m, 2 H, CH$_2$CSO$_2$),

3.63 (s, 3 H, CO$_2$CH$_3$), 3.98 (dd, J = 4.2 Hz, J = 11.0 Hz, 1 H, CHSO$_2$), 5.25 (dt, J = 7.5 Hz, J = 15.0 Hz, 1 H, vinyl), 5.54 (dt, J = 7.5 Hz, J = 15.0 Hz, 1 H, vinyl), 7.11 - 7.27 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 29.99, 30.69, 31.80, 35.04, 52.79, 70.60, 123.17, 125.64, 128.19, 128.28, 129.00, 129.22, 134.26, 135.17, 136.95, 142.07, 165.85 (C=O); IR (neat) 3063, 3026, 2932, 1744 (C=O), 1448, 1437, 1327 (SO$_2$), 1202, 1084, 970 (E-CH=CH), 741, 689 cm^{-1}; mass spectrum m/z 372.48380 (calcd for C$_{21}$H$_{24}$O$_4$S, 372.48374).
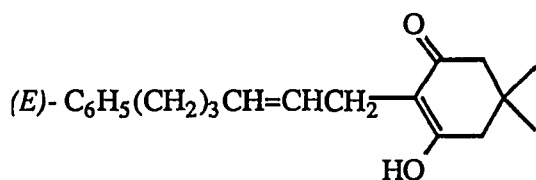
(E)- C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$—

HO   (7)   Compound 7 was isolated in 60% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of 5,5-dimethyl-1,3-cyclohexanedione in the presence of 5% Pd(dba)$_2$, 1.1 equivalents of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 24 h. The enolic form of compound 7 predominates in the product mixture. ^{1}H NMR (CDCl$_3$) δ 1.06 (s, 6 H, CH$_3$), 1.68 (quintet, J = 7.6 Hz, 2 H, PhCCH$_2$), 2.00 (dt, J = 7.2 Hz, J = 7.6 Hz, 2 H, CH$_2$C=), 2.20 (br s, 4 H, CH$_2$CO, CH$_2$C(OH)=), 2.60 (t, J = 7.6 Hz, 2 H, PhCH$_2$), 3.10 (d, J = 5.1 Hz, 2 H, CH$_2$C(CO)=), 5.36 - 5.48 (m, 1H, vinyl), 5.61 - 5.72 (m, 1 H, vinyl), 7.14 - 7.29 (m, 5 H, aryl), 15.84 (br s, 1 H, OH); IR (neat) 3400 (br OH), 3063, 2961, 2934, 1738 (C=O), 1607 (C=O enolic form), 1377, 1246, 966 (E-CH=CH), 740, 700 cm^{-1}. mass spectrum m/z 298.42649 (calcd for C$_{20}$H$_{26}$O$_2$, 298.42620).
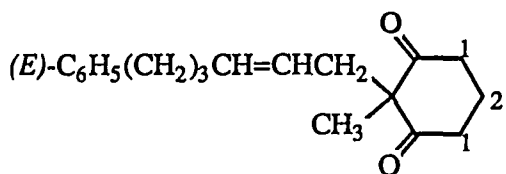
(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$

CH$_3$

(8) Compound **8** was isolated in 64%

yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and

5.0 equivalents of 2-dimethyl-1,3-cyclohexanedione in the presence of 5% Pd(dba)$_2$, 1.1

equivalents of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 12 h. ^{1}H

NMR (CDCl$_3$) δ 1.21 (s, 3 H, CH$_3$), 1.16 - !.25 (m, 2 H, 2-H$_2$), 1.63 (quintet, J = 7.5 Hz, 2

H, PhCCH$_2$), 2.00 (dt, J = 7.2 Hz, J = 7.5 Hz, 2 H, CH$_2$C=), 2.48 - 2.67 (m, 8 H, PhCH$_2$,

CH$_2$C(CH$_3$), 1-H$_4$), 5.24 (dt, J = 7.8 Hz, J = 15.3 Hz, 1H, CH=C), 5.49 (dt, J = 7.8 Hz, J

= 15.3 Hz, 1 H, CH=C), 7.14 - 7.29 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 17.47, 18.87,

30.90, 31.88, 35.14, 38.03, 40.69, 65.51, 123.59, 125.53, 128.12, 128.26, 134.99,

142.12, 209.75 (C=O); IR (neat) 3026, 2934, 2872, 1726 (C=O), 1699 (C=O), 1454, 1026,

972 (*E* - CH=CH), 750, 700 cm^{-1}; mass spectrum m/z 284.44560 (calcd for C$_{19}$H$_{24}$O$_2$,

284.44567).   Anal. Calcd for C$_{19}$H$_{24}$O$_2$: C, 80.24; H, 8.51. Found: C, 78.79; H, 8.66.

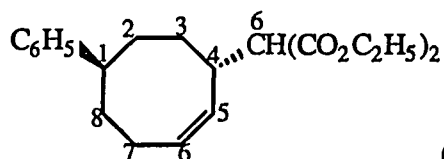*(E)*-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$

CH$_3$CO

H   H

CH$_2$

(9) Compound **9** was isolated in 64%

yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and

5.0 equivalents of 2-acetylbutyrolactone in the presence of 5% Pd(dba)$_2$, 1.1 equivalents of n-

Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 12 h. ^{1}H NMR (CDCl$_3$) δ

1.67 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$), 2.04 (dt, J = 7.0 Hz, J = 7.5 Hz, 2 H, CH$_2$C=),

2.26 (d, J = 6.3 Hz, 2 H, CH$_2$CCO), 2.34 (s, 3 H, CH$_3$C=O), 2.61 (t, J = 7.5 Hz, 2 H,

PhCH$_2$), 2.69 - 2.76 (m, 1 H, CH$_2$CH$_2$O), 2.82 -2.90 (m, 1 H, CH$_2$CH$_2$O), 4.17 - 4.27 (m,

2 H, CO$_2$CH$_2$), 5.20 (dt, J = 7.2 Hz, J = 15.5 Hz, 1 H, vinyl), 5.65 (dt, J = 7.2 Hz, J = 15.5

Hz, 1 H, vinyl), 7.16 -7.30 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 25.83, 28.58, 30.83,

31.94, 35,19, 37.92, 61.21, 66.20, 122.85, 125.66, 128.20, 128.28, 126.01, 142.04,

175.13 (C=O), 202.11(C=O); IR (neat) 3061, 2926, 1765 (C=O), 1713 (C=O), 1167 (C-O),

1028, 972 (*E*-CH=CH), 912, 735, 700 cm^{-1};   mass spectrum m/z 286.15632 (calcd for

C$_{18}$H$_{22}$O$_3$, 286.15689).   Anal. Calcd for C$_{18}$H$_{22}$O$_3$: C, 75.49; H, 7.74. Found: C, 74.88;

H, 7.57.

(*E*)-C$_6$H$_5$(CH$_2$)$_5$CH=CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (11)   Compound **11** was isolated

in 66% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,7-

octadiene and 5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1

equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 24 h. ^{1}H

NMR (CDCl$_3$) δ 1.16 (t, J = 7.2 Hz, 6 H, CH$_3$'s), 1.12 - 1.29 (m, 4 H, CH$_2$'s), 1.50

(quintet, J = 5.4 Hz, 2 H,PhCCH$_2$), 1.96 (q, J = 6.3 Hz, 2 H, CH$_2$C=), 2.45 - 2.52 (m, 4 H,

PhCH$_2$, CH$_2$CCO$_2$), 3.26 (t, J = 7.5 Hz, 1 H, CHCO$_2$), 4.08 (q, J = 7.2 Hz, 4 H, CO$_2$CH$_2$),

5.25 (dt, J = 8.4 Hz, J = 15.2 Hz, 1 H, vinyl), 5.40 (dt, J = 8.4 Hz, J = 15.2 Hz, 1 H,

vinyl), 7.06 -7.19 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.07, 28.68, 29.12, 31.29, 31.81,

32.33, 35.85, 52.25, 61.21, 125.27, 125.50, 128.14, 128.28, 133.72, 142.68, 168.96

(C=O); IR (neat) 3060, 2982, 2856, 1734 (C=O), 1452, 1336-1177 (br C-O), 970 (*E*-

CH=CH), 750, 700 cm^{-1};   mass spectrum m/z 346.21439 (calcd for C$_{21}$H$_{30}$O$_4$, 346.21441).

Anal. Calcd for C$_{21}$H$_{30}$O$_4$: C, 72.80; H, 8.72. Found: C, 71.46; H, 8.56.

(*E*)-C$_6$H$_5$(CH$_2$)$_9$CH=CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (12)   Compound **12** was isolated

in 55% yield from the coupling of 1.0 equivalent of iodobenzene, 2.0 equivalents of 1,11-

dodecadiene and 5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1

equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 24 h. ^{1}H

NMR (CDCl₃) δ 1.25 (t, J = 7.2 Hz, 6 H, CH₃'s), 1.21 - 1.28 (br m, 12 H, CH₂'s), 1.60 (br

s, 2 H, PhCCH₂), 1.95 (q, J = 6.3 Hz, 2 H, CH₂C=), 2.54 - 2.62 (m, 4 H, ArCH₂,

CH₂CCO₂), 3.36 (t, J = 7.6 Hz, 1 H, CHCO₂), 4.17 (q, J = 7.2 Hz, 4 H, CO₂CH₂), 5.34

(dt, J = 7.8 Hz, J = 15.3 Hz, 1 H, vinyl), 5.52 (dt, J = 7.8 Hz, J = 15.3 Hz, 1 H, vinyl),

7.16 -7.29 (m, 5 H, aryl); ¹³C NMR (CDCl₃) δ 14.43, 28.01, 29.50 (br 6 C), 31.87, 32.33,

35.98, 52.43, 61.25, 125.13, 125.75, 128.28, 128.42, 133.94, 142.87, 169.01 (C=O); IR

(neat) 3020, 2936, 2860, 1730 (C=O), 1455, 1360 - 1150 (br C-O), 1060, 940 (E-CH=CH),

740, 700 cm⁻¹; mass spectrum m/z 402.57520 (calcd for C₂₅H₃₈O₄, 402.57531).

(E)-C₆H₅(CH₂)₁₁CH=CHCH₂CH(CO₂C₂H₅)₂ (13)   Compound **13** was

isolated in 52% yield from the coupling of 1.0 equivalent of iodobenzene, 2.0 equivalents of

1,13-tetradecadiene and 5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)₂,

1.1 equivalents of n-Bu₄NCl and 2.5 equivalents of NaHCO₃ in DMSO at 80 °C for 24 h. ¹H

· NMR (CDCl₃) δ 1.26 (t, J = 7.2 Hz, 6 H, CH₃'s), 1.21 - 1.28 (br m, 16 H, CH₂'s), 1.59 (br

s, 2 H, PhCCH₂), 1.95 (q, J = 6.3 Hz, 2 H, CH₂C=), 2.54 - 2.62 (m, 4 H, ArCH₂,

CH₂CCO₂), 3.36 (t, J = 7.5 Hz, 1 H, CHCO₂), 4.17 (q, J = 7.2 Hz, 4 H, CO₂CH₂), 5.34

(dt, J = 7.2 Hz, J = 15.5 Hz, 1 H, vinyl), 5.52 (dt, J = 7.2 Hz, J = 15.5 Hz, 1 H, vinyl),

7.16 -7.29 (m, 5 H, aryl); ¹³C NMR (CDCl₃) δ 14.10, 28.10, 29.62 (br 8 C), 31.88 , 32.21,

35.99, 52.50, 61.23, 125.19, 125.76, 128.08, 128.58, 133.94, 142.89, 169.90 (C=O); IR

(neat) 3020, 2940, 2860, 1720 (C=O), 1450, 1280 - 1120 (br C-O), 1080, 960 (E -CH=CH),

720, 700 cm⁻¹; mass spectrum m/z 430.30910 (calcd for C₂₇H₄₂O₄, 430.30832).

(E)-C₆H₅CH₂CH(CH₃)CH₂CH=C(CH₃)CH₂CH(CO₂C₂H₅)₂ (14)

Compound **14** was isolated in 63% yield from the coupling of 1.0 equivalent of iodobenzene,

5.0 equivalents of 2,5-dimethyl-1,5-hexadiene and 5.0 equivalents of diethyl malonate in the

presence of 5% Pd(dba)$_2$, 1.1 equivalents of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 36 h. ^{1}H NMR (CDCl$_3$) δ 0.81 (d, J = 6.3 Hz, 3 H, C$\underline{H}_3$CH), 1.24 (t, J = 7.2 Hz, 6 H, C$\underline{H}_3$CH$_2$), 1.59 (s, 3 H, CH$_3$C=), 1.71 - 1.89 (m, 2 H, CH$_2$C=), 1.94 - 2.02 (m, 1 H, PhCCH$_2$), 2.35 (dd, J = 7.8 Hz, J = 13.2 Hz, 1 H, one of ArCH$_2$), 2.57 - 2.63 (m, 3 H, one of ArCH$_2$, CH$_2$CCO$_2$), 3.55 (t, J = 8.1 Hz, 1 H, CHCO$_2$), 4.16 (q, J = 7.2 Hz, 4 H, CO$_2$CH$_2$), 5.26 (t, J = 6.9 Hz, 1 H, vinyl), 7.11 - 7.28 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.04, 15.82 , 19.23, 34.57, 35.56, 38.55, 42.90, 50.79, 61.14, 125.50, 127.87, 128.10, 128.90, 131.77, 141.22, 168.89 (C=O); IR (neat) 3020, 2928, 2860, 1750 (C=O), 1734 (C=O), 1454, 1369, 1279 - 1175 (br C-O), 840 (CH=C), 740, 700 cm^{-1}. Anal. Calcd for C$_{21}$H$_{30}$O$_4$: C, 72.80 ; H, 8.73. Found: C, 72.48 ; H, 8.90.

(E)-C$_6$H$_5$(CH$_2$)$_3$CH=C(CH$_3$)CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (15) Compound 15 was isolated in 60% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 2-methyl-1,5-hexadiene and 5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1 equivalents of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 36 h. ^{1}H NMR (CDCl$_3$) δ 1.24 (t, J = 7.2 Hz, 6 H, C$\underline{H}_3$CH$_2$), 1.60 (s, 3 H, CH$_3$C=), 1.63 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$), 2.01 (dt, J = 6.9 Hz, J = 7.2 Hz, 2 H, CH$_2$C=), 2.57 (t, J = 6.3 Hz, 2 H, PhCH$_2$), 2.58 (d, J = 6.3 Hz, 2 H, CH$_2$CCO$_2$), 3.54 (t, J = 6.3 Hz, 1 H, CHCO$_2$), 4.16 (q, J = 7.2 Hz, 4 H, CO$_2$CH$_2$), 5.26 (t, J = 6.9 Hz, 1 H, vinyl), 7.13 - 7.28 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.04, 15.72 , 27.37, 31.17, 35.26, 38.05, 50.80, 61.19, 125.53, 127.17, 128.14, 128.30, 131.12, 142.32, 168.09 (C=O); IR (neat) 3028, 2980, 2860, 1750 (C=O), 1730 (C=O), 1452, 1369, 1280 - 1180 (br C-O), 840 (CH=C), 740, 700 cm^{-1}; mass spectrum m/z 332.19858 (calcd for C$_{20}$H$_{28}$O$_4$, 332.19877).

(16)
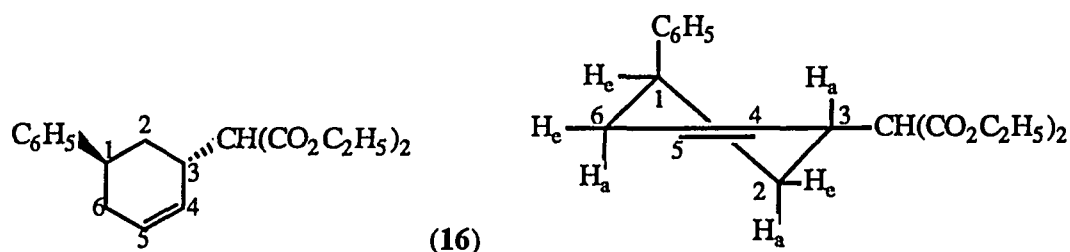
Compound **16** was isolated in 88% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,4-cyclohexadiene and 5.0 equivalents of diethyl malonate in the presence of 5% $Pd(dba)_2$, 1.1 equivalents of n-Bu$_4$NCl and 2.5 equivalents of $NaHCO_3$ in DMSO at 80 °C for 12 h. ^{1}H NMR (CDCl$_3$) δ 1.22 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.28 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.77 (br d, J = 13.5 Hz, J = 4.2 Hz, J = 2.7 Hz, 1 H, 2-H$_e$), 1.98 (ddd, J = 13.5 Hz, J = 11.1 Hz, J = 4.2 Hz, 1 H, 2-H$_a$,), 2.16 (m, 1 H, 6-H$_a$), 2.42 (dt, J = 18.2 Hz, J = 4.8 Hz, 6-H$_e$), 2.88 (br s, 1 H, 3-H$_a$), 2.98 (br s, 1 H, 1-H$_e$), 3.45 (d, J = 10.5 Hz, 1 H, CHCO$_2$), 4.16 (q, J = 7.2 Hz, 2 H, CO$_2$CH$_2$), 4.25 (q, J = 7.2 Hz, 2 H, CO$_2$CH$_2$), 5.70 - 5.73 (br d, J = 10.2 Hz, 1 H, 4-H), 5.85 - 5.92 (m, 1 H, 5-H), 7.20 -7.33 (m, 5 H, aryl); ^{1}H- ^{1}H COSY spectrum afforded the following proton connectivities: 2-H$_e$ / 3-H$_a$; 2-H$_e$ / 1-H$_e$ (1.77 ppm); 2-H$_a$ / 3-H$_a$ (1.98 ppm); 6-H$_a$ / 1-H$_e$; (2.16 ppm); 3-H$_a$ / 2-H (2.88 ppm); ^{13}C NMR (CDCl$_3$) δ 18.80, 32.48, 32.94, 34.12, 35.50, 56.68, 61.05, 125.94, 126.60, 127.02, 128.15, 129.10, 145.71, 168.01 (C=O); IR (neat) 3028, 2960, 2876, 1755 (C=O), 1734 (C=O), 1240 - 1180 (br C-O), 1034, 740, 700 cm^{-1}; mass spectrum m/z 316.39750 (calcd for C$_{19}$H$_{24}$O$_4$, 316.39712).

(17)   Compound **17** was isolated in 57% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-cyclooctadiene and

5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1 equivalents of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 12 h. ^{1}H NMR (CDCl$_3$) δ 1.27 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.28 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.55 - 1.75 (m, 6 H, 2-H$_2$, 3-H$_2$, 8-H$_2$), 2.00 (m, 1 H, 1-H$_1$), 2.30 - 2.51 (m, 2 H, 7-H$_2$), 2.75 - 2.86 (m, 1 H, 4-H$_1$), 3.35 (d, J = 11.7 Hz, 1 H, CH$_2$CCO$_2$), 4.20 (q, J = 7.2 Hz, 2 H, CO$_2$CH$_2$), 4.23 (q, J = 7.2 Hz, 2 H, CO$_2$CH$_2$), 5.52 - 5.81 (m, 2 H, 5-H$_1$, 6-H$_1$), 7.18 -7.31 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.07, 27.49, 28.04, 30.85, 35.67, 42.95, 45.54, 50.95, 53.60, 54.54, 61.14 (CO$_2$CH$_2$), 61.19 (CO$_2$CH$_2$), 125.89, 127.18, 128.23, 145.08, 168.70 (C=O), 169.36 (C=O); IR (neat) 3020, 2980, 2941, 2864, 1753 (C=O), 1732 (C=O), 1450, 1302 - 1173 (br C-O), 1032, 740, 700 cm^{-1} ; mass spectrum m/z 344.19820 (calcd for C$_{21}$H$_{28}$O$_4$, 344.19877).

***(E)-p*-CH$_3$C$_6$H$_4$(CH$_2$)$_3$CH=CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (18)** Compound **18** was isolated in 64% yield from the coupling of 1.0 equivalent of *p*-tolyl iodide, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1 equivalents of n-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 24 h. ^{1}H NMR (CDCl$_3$) δ 1.25 (t, J = 7.2 Hz, 6 H, CH$_3$), 1.63 (quintet, J = 8.7 Hz, 2 H,ArCCH$_2$), 2.02 (q, J = 7.5 Hz, 2 H, CH$_2$C=), 2.31 (s, 3 H, CH$_3$), 2.51 -2.60 (m, 4 H, ArCH$_2$, CH$_2$CCO$_2$), 3.36 (t, J = 8.7 Hz, 1 H, CHCO$_2$), 4.18 (q, J = 7.2 Hz, 4 H, CO$_2$CH$_2$), 5.38 (dt, J = 6.9 Hz, J = 15.3 Hz, 1 H, vinyl), 5.52 (dt, J = 6.9 Hz, J = 15.3 Hz, 1 H, vinyl), 7.01- 7.07 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.07, 21.08, 30.81, 31.12, 31.87, 35.90, 52.17, 61.30, 125.75, 128.81, 128.94, 133.36, 136.08, 139.09, 168.90 (C=O); IR (neat) 2982, 2934, 1734 (C=O), 1447, 1369 - 1177 (br C-O), 1036, 970 (*E*-CH=CH), 830 cm^{-1}; mass spectrum m/z 332.44062 (calcd for C$_{20}$H$_{28}$O$_4$, 332.44025).

(E)-p-CH$_3$OC$_6$H$_4$(CH$_2$)$_3$CH=CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (19)   Compound **19**

was isolated in 54% yield from the coupling of 1.0 equivalent of *p*-anisyl iodide, 5.0

equivalents of 1,5-hexadiene and 5.0 equivalents of diethyl malonate in the presence of 5%

Pd(dba)$_2$, 1.1 equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for

24 h. ^{1}H NMR (CDCl$_3$) δ 1.25 (t, J = 7.2 Hz, 6 H, CH$_3$), 1.63 (quintet, J = 7.5 Hz, 2 H,

ArCCH$_2$),1.99 (dt, J = 7.5 Hz, J = 6.9 Hz, 2 H, CH$_2$C=), 2.52 (t, J = 7.5 Hz, 2 H, ArCH$_2$),

2.58 (dd, J = 6.9 Hz, J = 7.8 Hz, CH$_2$CCO$_2$), 3.37 (t, J = 7.8 Hz, 1 H, CHCO$_2$), 3.78 (s, 3

H, CH$_3$O), 4.18 (q, J = 7.2 Hz, 4 H, CO$_2$CH$_2$), 5.37 (dt, J = 7.2 Hz, J = 15.3 Hz, 1 H,

vinyl), 5.54 (dt, J = 7.2 Hz, J = 15.3 Hz, 1 H, vinyl), 6.80 (d, J = 8.7 Hz, 2 H, aryl), 7.06

(d, J = 8.7 Hz, 2 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.10, 31.12, 31.83 (br 2 C), 34.23,

52.27, 55.17, 61.22, 113.63, 125.75, 129.20, 133.36, 134.40, 157.63, 168.91 (C=O);   IR

(neat) 2984, 2961, 1734 (C=O), 1514, 1335 - 1151 (br C-O), 1036, 970 (*E*-CH=CH), 830

cm $^{-1}$;   mass spectrum m/z 348.19387 (calcd for C$_{20}$H$_{28}$O$_5$, 348.19368).

(E)-p-CH$_3$COC$_6$H$_4$(CH$_2$)$_3$CH=CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (20)   Compound **20**

was isolated in 56% yield from the coupling of 1.0 equivalent of *p*-iodoacetophenone iodide,

5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of diethyl malonate in the presence of 5%

Pd(dba)$_2$, 1.1 equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for

6 h. ^{1}H NMR (CDCl$_3$) δ 1.26 (t , J = 7.2 Hz, 6 H, CH$_3$'s), 1.67 (quintet, J = 7.5 Hz, 2 H,

ArCCH$_2$), 2.01 (dt, J = 6.6 Hz, J = 7.5 Hz, 2 H, CH$_2$C=), 2.59 (s, 3 H, CH$_3$CO), 2.57 -

2.66 (m, 4 H, ArCH$_2$, CH$_2$CCO$_2$), 3.37 (t, J = 7.5 Hz, 1 H, CHCO$_2$), 4.19 (q, J = 7.2 Hz, 4

H, CO$_2$CH$_2$), 5.38 (dt, J = 8.7 Hz, J = 15.3 Hz, 1 H, vinyl), 5.53 (dt, J = 8.7 Hz, J = 15.3

Hz, 1 H, vinyl), 7.24 (d, J = 8.4 Hz, 2 H, aryl), 7.87 (d, J = 8.4 Hz, 2 H, aryl); ^{13}C NMR

(CDCl$_3$) δ 14.01, 26.55, 30.55, 31.82 (br 2 C), 35.15, 52.11, 61.82, 128.15, 128.45,

128.58, 132.94, 134.93, 148.21, 168.92 (C=O), 197.78 (C=O); IR (neat) 2984, 2935, 1732

(C=O), 1684 (C=O), 1607 (C=C), 1447, 1302 - 1151 (br C-O), 1034, 970 (*E*-CH=CH), 568

cm^{-1}; mass spectrum m/z 360.19439 (calcd for $C_{21}H_{28}O_5$, 360.19368).

(E)-p-$C_2H_5O_2CC_6H_4(CH_2)_3CH=CHCH_2CH(CO_2C_2H_5)_2$ (21)   Compound

21 was isolated in 37% yield from the coupling of 1.0 equivalent of ethyl *p*-iodobenzoate, 5.0

equivalents of 1,5-hexadiene and 5.0 equivalents of diethyl malonate in the presence of 5%

Pd(dba)$_2$, 1.1 equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for

12 h. ^{1}H NMR (CDCl$_3$) δ 1.25 (t, J = 7.2 Hz, 6 H, C$\underline{H}_3$CH$_2$), 1.38 (t, J = 7.2 Hz, 3 H,

C$\underline{H}_3$CH$_2$), 1.67 (quintet, J = 7.5 Hz, 2 H, ArCCH$_2$), 2.00 (q, J = 7.5 Hz, 2 H, CH$_2$C=),

2.56 - 2.65 (m, 4 H, ArCH$_2$, CH$_2$CCO$_2$), 3.34 - 3.39 (m, 1 H, CHCO$_2$), 4.18 (q, J = 7.2

Hz, 4 H, CO$_2$CH$_2$), 4.36 (q, J = 7.2 Hz, 2 Hz, CO$_2$CH$_2$), 5.38 (dt, J = 8.7 Hz, J = 15.3 Hz,

1 H, vinyl), 5.53 (dt, J = 8.7 Hz, J = 15.3 Hz, 1 H, vinyl), 7.21 (d, J = 8.4 Hz, 2 H, aryl),

7.94 (d, J = 8.4 Hz, 2 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.08, 14.24, 30.31, 31.14, 31.87,

35.14, 52.13, 60. 63, 61.34, 125.87, 127.60, 128.24, 129.53, 133.65, 147.43, 166. 41

(C=O),168.92 (C=O),   IR (neat) 2984, 2935, 1734 (C=O), 1610 (C=C), 1464, 1333 - 1105

(br C-O), 1034, 970 (*E*-CH=CH), 856, 764, 704 cm^{-1}. This compound is too unstable to

obtain high resolution mass spectral data; the result presented here is done by a solids probe:

m/z 390 (M$^+$, 8.23), 344 (M$^+$ - C$_2$H$_5$OH, 34.29), 131 (100.00).

(*E*) - (CH$_2$)$_3$CH=CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (**22**)   Compound **22** was isolated
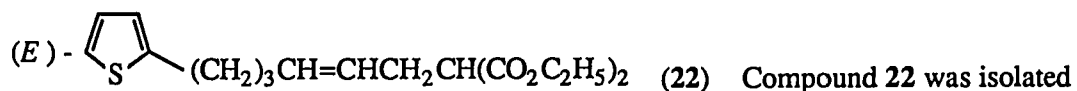
in 59% yield from the coupling of 1.0 equivalent of 2-iodothiophene, 5.0 equivalents of 1,5-

hexadiene and 5.0 equivalents of diethyl malonate in the presence of 5% Pd(dba)$_2$, 1.1

equivalents of *n*-Bu$_4$NCl and 2.5 equivalents of NaHCO$_3$ in DMSO at 80 °C for 12 h. ^{1}H

NMR (CDCl$_3$) δ 1.26 (t , J = 7.2 Hz, 6 H, CH$_3$), 1.71 (quintet, J = 7.2 Hz, 2 H,

C$_4$H$_3$SCH$_2$C$\underline{H}_2$), 2.04 (dt, J = 6.9 Hz, J = 7.2 Hz, 2 H, CH$_2$C=), 2.59 (dd, J = 6.6 Hz, J =

7.5 Hz, 2 H, CH_2CCO_2), 2.79 (t, J = 7.2 Hz, 2 H, $C_4H_3SCH_2$), 3.37 (t, J = 7.5 Hz, 1 H,

$CHCO_2$), 4.18 (q, J = 7.2 Hz, 4 H, CO_2CH_2), 4.36 (q, J = 7.2 Hz, 2 Hz, CO_2CH_2), 5.53 -

5.58 (m, 2 H, vinyl), 6.76 (dd, J = 1.5 Hz, J = 3.3 Hz, 1 H, aryl), 6.90 (dd, J = 3.3 Hz, J =

5.1 Hz, 1 H, aryl), 7.10 (dd, J = 1.5 Hz, J = 5.1 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ

29.09, 31.18, 31.11, 31.83, 35.25, 52.22, 61.21, 124.02, 126.17, 128.60, 127.59, 132.95,

145.17, 168.94 (C=O); IR (neat) 3072, 2982, 1734 (C=O), 1443, 1369 - 1153 (br C-O),

1036, 972 (E-CH=CH), 851 cm^{-1}; mass spectrum m/z 324.43864 (calcd for $C_{17}H_{24}O_4S$,

324.43940).

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SECTION II. PALLADIUM(0)-CATALYZED COUPLING OF ARYL IODIDES,

NONCONJUGATED DIENES, AND HETEROATOM NUCLEOPHILES

INTRODUCTION

The development of synthetic methodology for the formation of more than one carbon-carbon or carbon-nitrogen bond at a time is a growing area in synthetic organic chemistry. In Section I of Part II of this dissertation, our study of the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and carbon nucleophiles was discussed. It seemed likely that that procedure could be extended to the use of heteroatom-containing nucleophiles. We now report the success of that endeavor.

The most important heteroatom-containing nucleophiles used in the palladium displacement of π-allylpalladium compounds are nitrogen nucleophiles. Amines are among the most popular nitrogen nucleophiles. As mentioned in the introductory section of Section I, Stakem and Heck[1] have already reported that allylic amines were observed as the major product, when bromobenzene was allowed to react with 1,4-pentadiene in the presence of piperidine under palladium-catalyzed conditions (eq 1). A π-allylpalladium intermediate
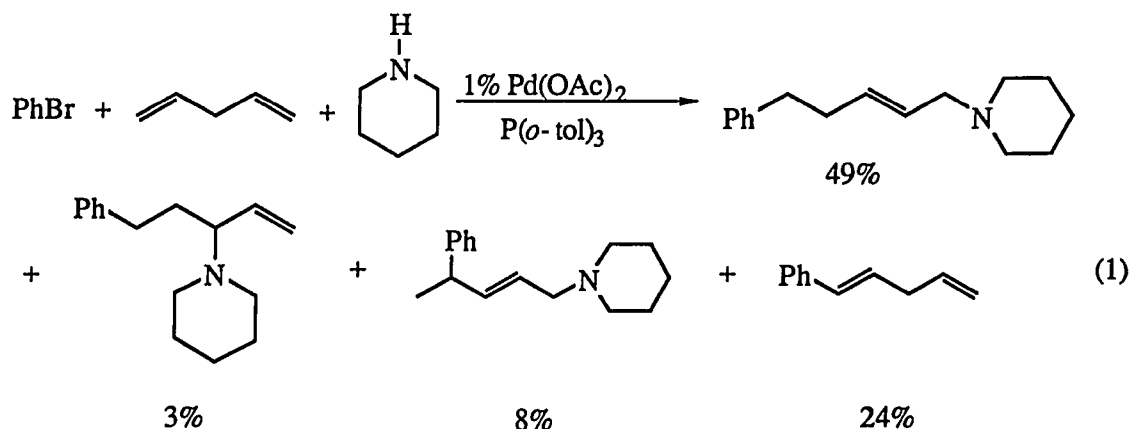
formed in situ readily undergoes a palladium displacement reaction by the amine to form a carbon-nitrogen bond.

In a similar manner, O'Connor et al.[2] found that both secondary and primary amines participate in the reactions of iodobenzene and conjugated dienes to form allylic amines. The primary amine shows an enhanced tendency to attack the internal π-allylic terminus due to the decreased steric requirements of this amine nucleophile (eqs 2 and 3).

$$\text{Ph-I} + \diagup\diagdown + \underset{\text{N-H}}{\bigcirc} \xrightarrow[\text{PPh}_3, 130\,^{0}\text{C}]{1\%\ \text{Pd(OAc)}_2} \text{Ph} \diagdown\diagup\diagdown\text{N}\bigcirc + \text{Ph}\diagdown\diagup \qquad (2)$$

$$66\% \qquad\qquad\qquad 15\%$$

$$\text{Ph-I} + \diagup\diagdown + n\text{-BuNH}_2 \xrightarrow[\text{PPh}_3, 130\,^{0}\text{C}]{1\%\ \text{Pd(OAc)}_2} \text{Ph}\diagdown\diagup\diagdown\text{NH-}n\text{-Bu} \qquad (3)$$

$$37\%$$

$$+ \quad \text{Ph}\diagdown\underset{}{\overset{\text{NH-}n\text{-Bu}}{\diagup}}\diagup \quad + \quad \text{Ph}\diagdown\diagup\diagdown$$

$$12\% \qquad\qquad 16\%$$
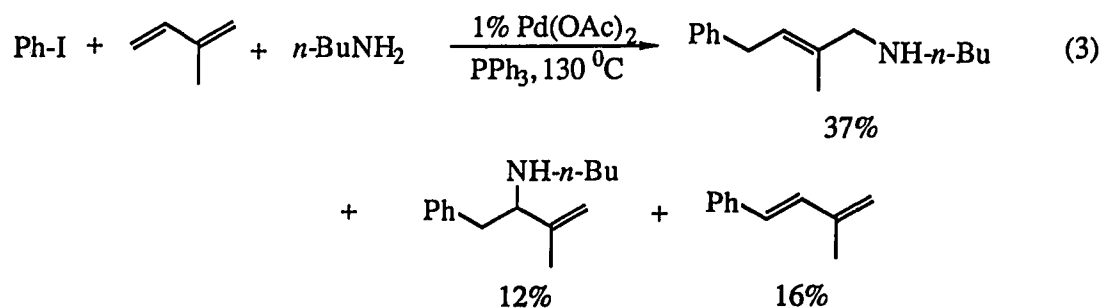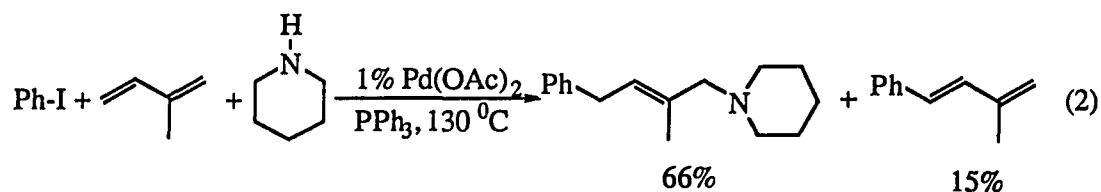
Patel et al.[3] reported that tertiary 2,5-dienylamines were produced in moderate to good yields when vinylic halides and morpholine or piperidine were allowed to react with conjugated dienes in the presence of a palladium catalyst (eq 4).

$$\underset{\text{Br}}{\diagup}\diagdown + \diagup\diagdown\diagup + \underset{\text{N-H}}{\bigcirc} \xrightarrow[\text{P(}o\text{-tol)}_3]{1\%\ \text{Pd(OAc)}_2} \diagdown\diagup\diagdown\diagup\diagdown\text{N}\bigcirc \qquad (4)$$

$$60\%$$
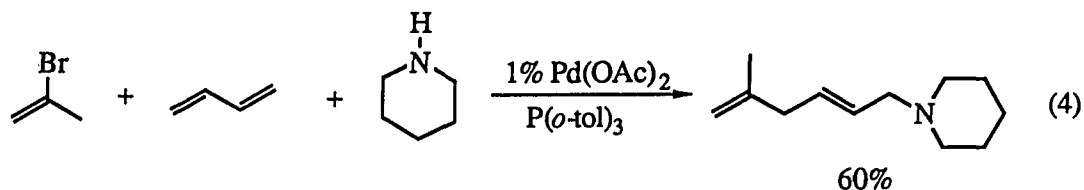
Conjugated dienes can be converted to pyrroles[4] in low to moderate yields by use of the displacement reaction of a π-allylpalladium complex with an amine nucleophile (Scheme I).

<u>Scheme I</u>

54%
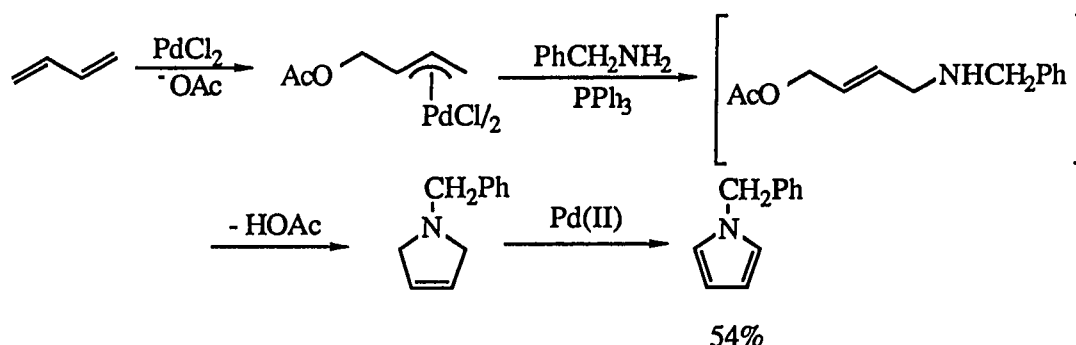
The reaction involves three steps: (1) reaction of the diene with $PdCl_2$ in the presence of an acetate anion to form the 1-acetoxymethyl-π-allylpalladium intermediate, (2) reaction of the π-allylpalladium intermediate with a primary amine to form a 4-amino-2-alken-1-yl acetate that easily cyclizes under the reaction conditions to a pyrroline, and (3) oxidation of the pyrroline to the pyrrole with additional Pd(II).

Palladium-catalyzed exchanges of allyl hydroxyl;[5] acetate;[5,6] and phenyl,[4,5] benzyl, and alkyl ether[4] substrates with secondary amines generally proceed in good to excellent yields. Equation 5 illustrates one of these examples. Apparently these exchange processes involve nucleophilic attack by amines on π-allylpalladium intermediates formed in situ.

95%

$$(5)$$
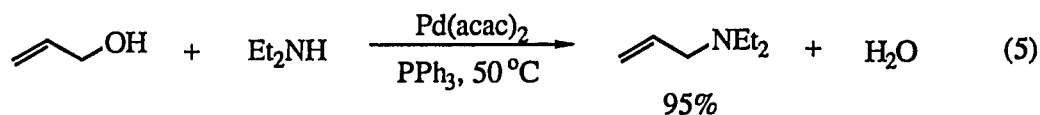
The stereochemistry of the exchange reaction with amine nucleophiles varies with the reaction conditions. Formation of the π-allylpalladium intermediate occurs with inversion. Nucleophilic attack on this intermediate can either involve an S_N2 displacement on the π-allylic

unit to give net retention of the initial structure or attack of the amine on the palladium metal, followed by reductive elimination, to give a net inversion at the carbon (Scheme II).[7]

Scheme II

$$\text{OAc} \longrightarrow [\text{allyl}]\text{-Pd}^+(\text{L})(\text{L}) \quad \xrightarrow{R_2NH} \quad [\text{allyl}]\text{-NR}_2$$

$$\xrightarrow{R_2NH} \quad L\text{-Pd}(\text{L})\text{-NR}_2 \longrightarrow [\text{allyl}]\text{-NR}_2$$
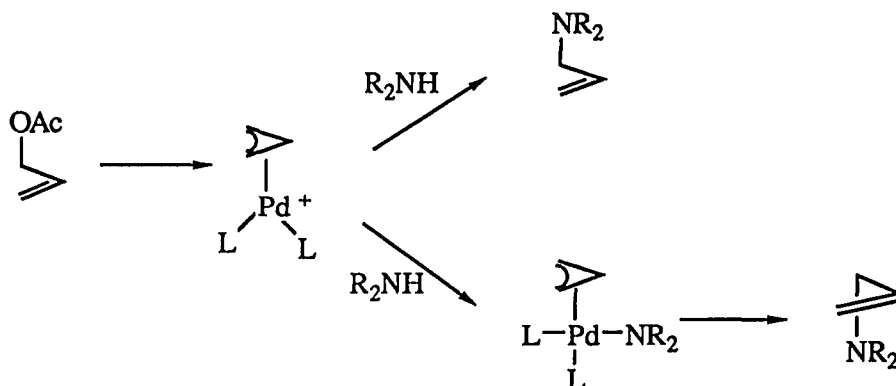
Few oxygen nucleophiles have been found to be useful in the displacement reaction of π-allylpalladium compounds. The palladium-catalyzed exchange of allylic groups with various nucleophiles is well known.[5,6] For example, the phenoxy group in allyl phenyl ether may be replaced by other alkoxy groups, such as p-methylphenoxy, p-chlorophenoxy, benzyloxy, methoxy, ethoxy, and isopropoxy, employing $PdCl_2(PPh_3)_2$-NaOPh as the catalyst.[5] Unfortunately, low to moderate yields of isomeric mixtures (where possible) are obtained in most cases. Replacement of a phenoxy group by a carboxylate group occurs similarly in modest yields with $Pd(OAc)_2$-PPh$_3$ as the catalyst.[5] Allylic acetate groups can be replaced by other carboxylate groups, as well as by phenoxy and alkoxy groups, using the $PdCl_2(PPh_3)_2$-NaOPh catalyst.[6] These reactions appear to involve a mobile equilibrium that may proceed in either direction depending on the reaction conditions.

Deardorff and co-workers[8] previously described a palladium-catalyzed route to *cis* 4-phenoxy-2-cyclopenten-1-ol based on the reaction of phenol with cyclopentadiene

monoepoxide (eq 6).

$$(6)$$

80%
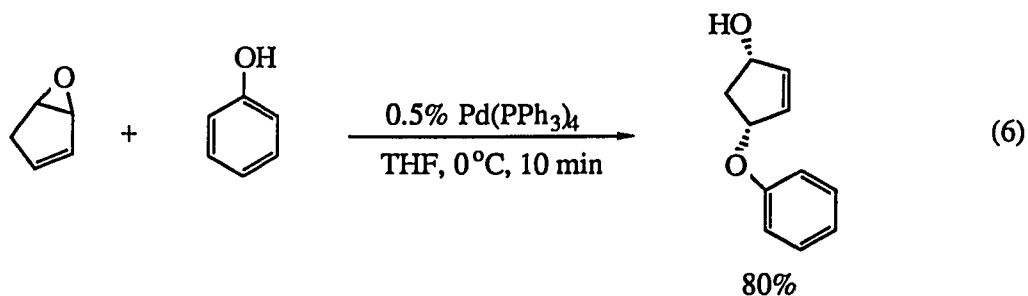
Later they[9] extended this chemistry to the synthesis of unsymmetrically protected diols

using silyl protected phenols (eq 7). Even though a good example of the intermolecular attack

$$(7)$$

R = H	23%
R = NO$_2$	87%
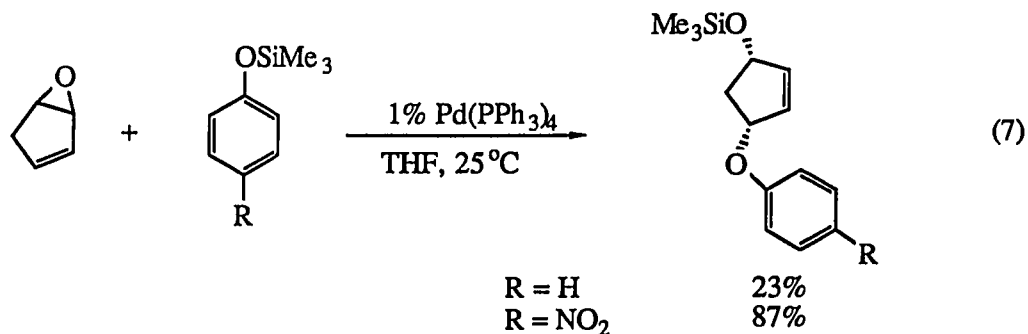
of the phenoxide nucleophile in palladium chemistry is evident, this reaction appears limited to

only cyclopentadiene monoepoxide and sterically less hindered phenols.

Recently, Deardorff et al.[10] disclosed an efficient procedure by which a cyclopentanoid

was obtained stereoselectively via nucleophilic attack of phenoxide on a π-allylpalladium

complex generated from an allylic acetate (eq 8).

$$(8)$$

90%
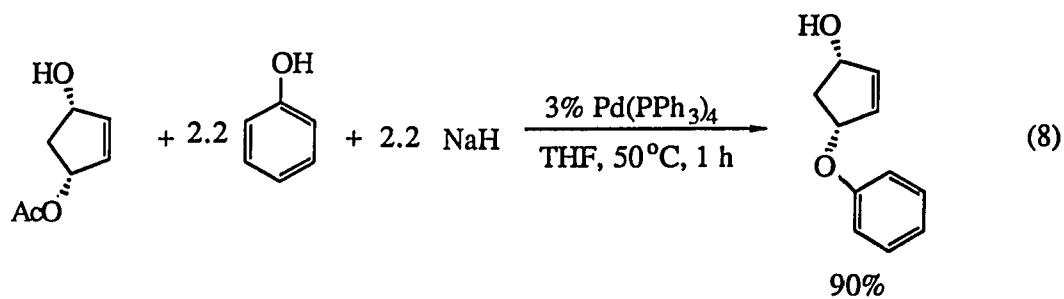
Larock and Stolz-Dunn[11] recently reported that a mixture of regio- and stereoisomers was obtained upon palladium-catalyzed reaction of phenol and vinylic oxetanes (eqs 9 and 10). With low amounts of the palladium catalyst and a low reaction temperature (see eq 9),

$$
\text{(vinylic oxetane)} + 1.2 \; \text{(phenol, OH)} \xrightarrow[\text{THF, } 0\,^{\circ}\text{C, 10 min}]{1.0\% \; \text{Pd(PPh}_3)_4} \quad \underset{\text{OPh}}{\text{(product)}} \text{OH} \quad + \quad \text{PhO} \text{(product)} \text{OH} \quad (9)
$$

84%   16%

$$
\text{(vinylic oxetane)} + 1.2 \; \text{(phenol, OH)} \xrightarrow[\text{THF, } 40\,^{\circ}\text{C, 3.5 h}]{9\% \; \text{Pd(PPh}_3)_4} \quad \underset{\text{OPh}}{\text{(product)}} \text{OH} \quad + \quad \text{PhO} \text{(product)} \text{OH} \quad (10)
$$

23%   58%
(E /Z = 87 / 13)
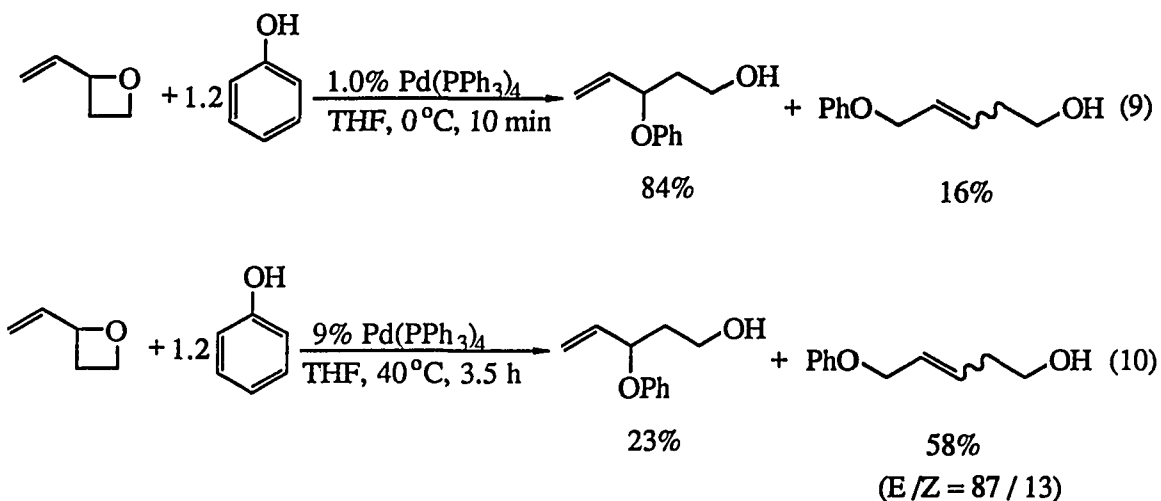
the kinetic product was obtained as the major product (84% yield); with greater amounts of the palladium catalyst and a higher reaction temperature (see eq 10), the thermodynamic product was observed as the major product (58% yield).

The synthetic utility of the intramolecular nucleophilic displacement by nucleophiles of a π-allylpalladium intermediate generated in situ is revealed by the number of publications in this area which have recently emerged.[12]

Trost and Genet[13] reported the use of an intramolecular reaction of π-allylpalladium intermediates with amine nucleophiles to construct typical alkaloid skeletons represented by 6-azabicyclo[3.2.1]oct-3-ene (eq 11) and 2,3,3a,4,5,7a-hexahydro-1H -indole (eq 12).

(11)

67%

(12)

>50%
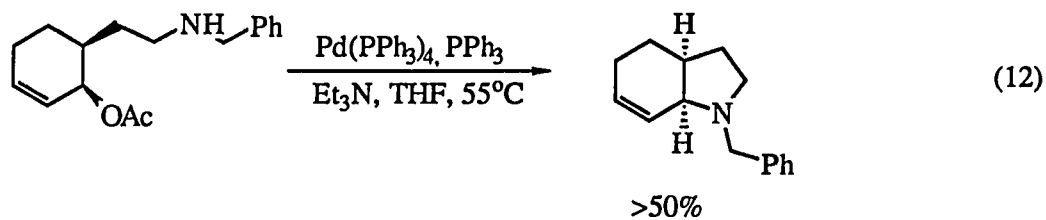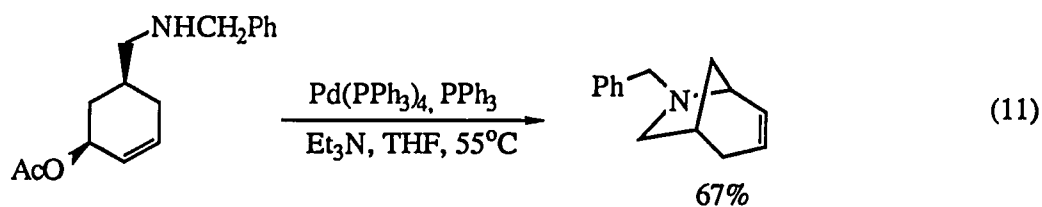
Trost and Godleski[14] disclosed an exceptionally facile synthesis of (+)-ibogamine in which the nucleophilic displacement of a π-allylpalladium intermediate by an amine is a key step (eq 13).

(13)

(+)-ibogamine
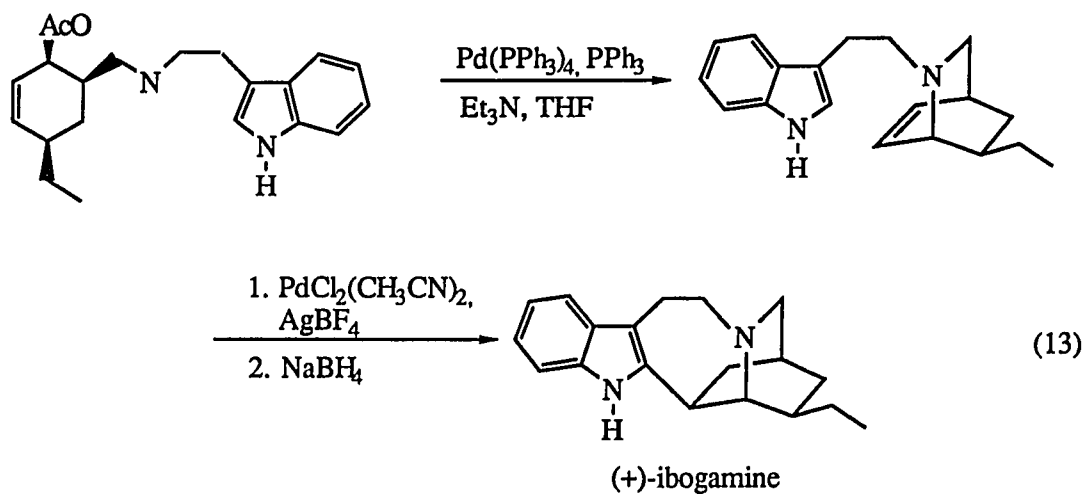
Larock et al.[15] reported the palladium-promoted reaction of conjugated or nonconjugated dienes, or vinylcyclopropane with functionalized organomercurials. These substrates in the

presence of a palladium(II) salt initially form a π-allylpalladium species that is intramolecularly displaced by oxygen or nitrogen nucleophiles (eq 14). Later on, they extended this approach

$$\text{(14)}$$

XH = NHAc, OH
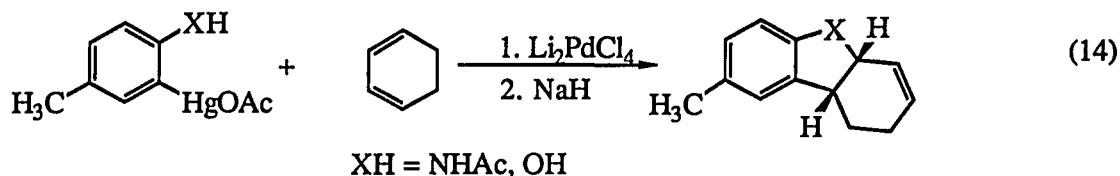
to the use of heteroatom-substituted dienes (eq 15).[16] Unfortunately, most of these processes require stoichiometric amounts of the palladium salt and necessitate the preparation of toxic organomercurials.

$$\text{(15)}$$
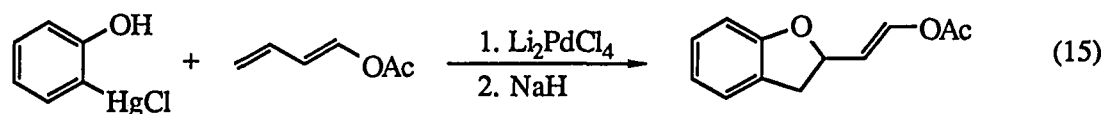
To overcome these disadvantages, Larock et al.[17] recently developed a new palladium-catalyzed heteroannulation of 1,3-dienes using functionalized aryl halides, rather than toxic organometallics, to afford a variety of oxygen and nitrogen heterocycles in good yields (eq 16).

$$\text{(16)}$$
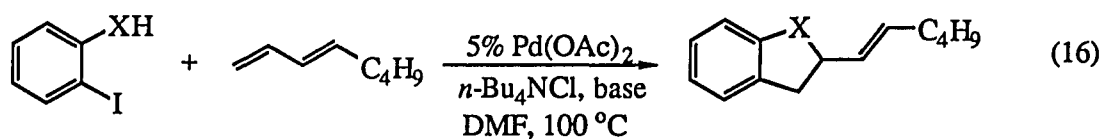
XH	base	% yield
OH	NaOAc	75
NHAc	Na_2CO_3	63
NHTs	Na_2CO_3	84

More recently, Larock et al. [18] reported the success of this same methodology for the regioselective annulation of 1,2-dienes (eq 17).

$$
\text{(structure)} \quad + \quad n\text{-}C_8H_{17}CH=C=CH_2 \quad \xrightarrow[\substack{n\text{-}Bu_4NCl, \text{ base} \\ DMF, 100\,^{\circ}C}]{5\% \ Pd(OAc)_2} \quad \text{(product)} \quad (17)
$$

XH	R	base	% yield
OH	MeCO	K_2CO_3	71
NHTs	H	Na_2CO_3	85
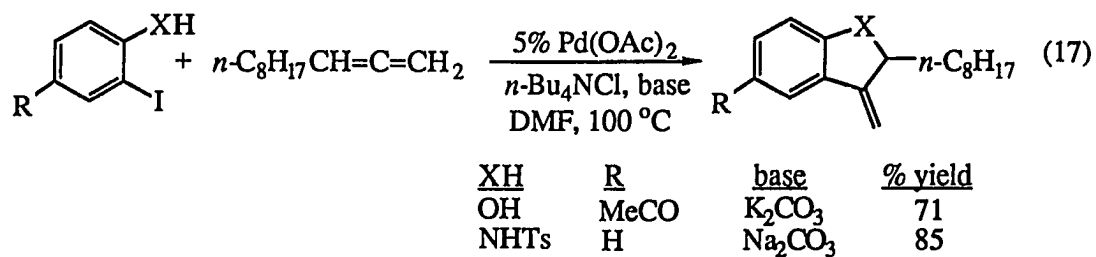
Larock and co-workers have reported that the intramolecular nucleophilic displacement by carboxylate of π-allylpalladium complexes formed in situ by addition of σ-organopalladium intermediates to 1,3-dienes[15] (eq 18) and allenes (eq 19)[19] produces good yields of lactones.

$$
\text{(structure)} \quad + \quad \text{(structure)} \quad \xrightarrow[CH_3CN, 0\,^{\circ}C]{LiPdCl_3} \quad \left[\text{(structure)} \right] \quad \xrightarrow{K_2CO_3} \quad \text{(structure)} \quad (18)
$$

$$
71\%
$$

$$
\text{(structure)} \quad + \quad \text{(structure)} \quad \xrightarrow[CH_3CN]{PdCl_2} \quad \left[\text{(structure)} \right] \quad \xrightarrow{Na_2CO_3} \quad \text{(structure)} \quad (19)
$$
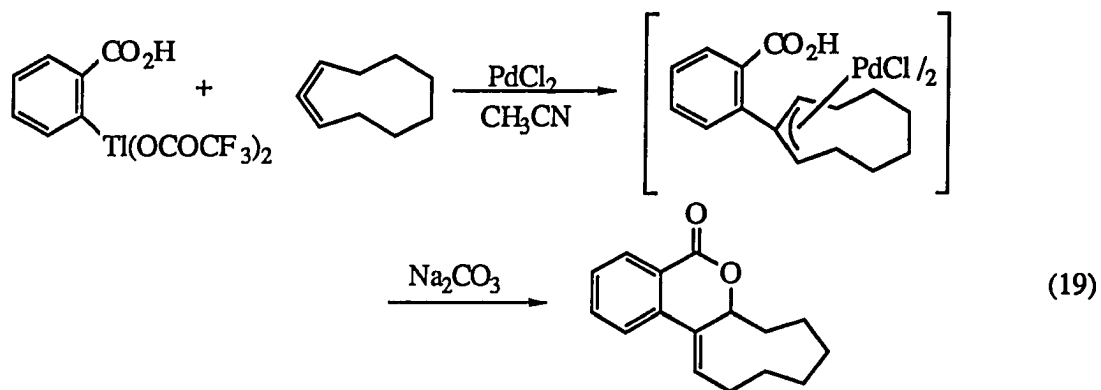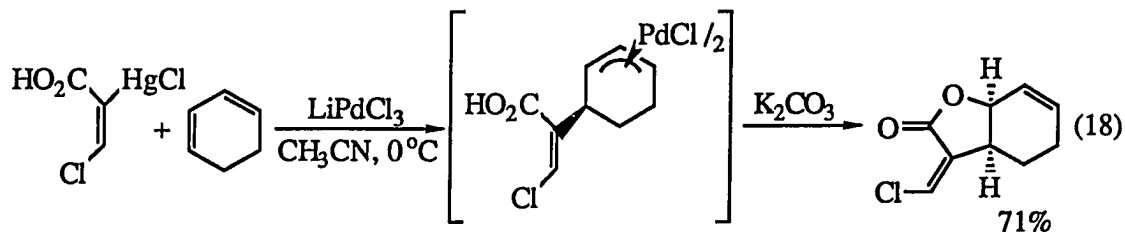
The palladium-mediated addition of alkenyl organomercurials to unsaturated acids also produces lactones by carboxylate attack on a π-allylpalladium intermediate that is formed after palladium migration (eq 20).[20]

$$n\text{-}C_8H_{17}\diagup\diagdown_{HgCl} + \diagup\diagdown\diagup_{CO_2H} \xrightarrow[\substack{CH_3CN \\ -20\,^\circ C}]{PdCl_2} \left[n\text{-}C_8H_{17}\diagup\diagdown\diagup\overset{PdCl}{\underset{}{\diagup}}\diagdown\diagup_{CO_2H} \right]$$

$$\longrightarrow \left[\underset{n\text{-}C_8H_{17}}{\overset{HO_2C}{\diagdown}}\diagup\underset{PdCl\,/_2}{\diagdown} \right] \xrightarrow[80\,^\circ C]{Na_2CO_3} n\text{-}C_8H_{17}\diagup\diagdown\diagup\diagdown\diagup O \diagdown\diagup O \tag{20}$$

Trost and Tanaglia[21] reported that while simple alcohols are poor nucleophiles towards π-allylpalladium complexes in intermolecular reactions, they participate without complications in intramolecular reactions (eq 21).

$$\underset{\substack{OH \\ OH}}{}\overset{()_n}{\diagup}\diagdown_{OAc} \xrightarrow[THF,\,25\,^\circ C]{Pd_2(dba)_3\cdot CHCl_3,\ PPh_3} HO\diagup\diagdown\overset{()_n}{\underset{O}{}}\diagdown \tag{21}$$

n = 1   86%
n = 2   96%
n = 3   25%

Stork and Poirier[22] reported another example of intramolecular π-allylpalladium displacement by an alcohol in which a clean transfer of chirality from an alkenylcarbinol to a tetrahydrofuran was accomplished (eq 22).

$$HO\diagup\diagdown\diagup\diagdown\overset{\underset{H}{}}{}OCO\text{-}\bigcirc\!\!\begin{smallmatrix}Cl\\ \\Cl\end{smallmatrix} \xrightarrow[\substack{Et_3N \\ MeCN,\,35\,^\circ C}]{5\%\ Pd(PPh_3)_4} \underset{O}{}\overset{}{}\diagup\diagdown\diagup \tag{22}$$

95% (80% ee)

Trost and Angle[23] have reported an unusual approach to the formation of a carboxylate nucleophile in situ by capturing the oxygen leaving group in the palladium-catalyzed reaction of vinyl epoxides with carbon dioxide (eq 23). Intramolecular displacement of palladium by this carbonate anion yields a cyclic carbonate.

$$\text{(23)}$$

95%
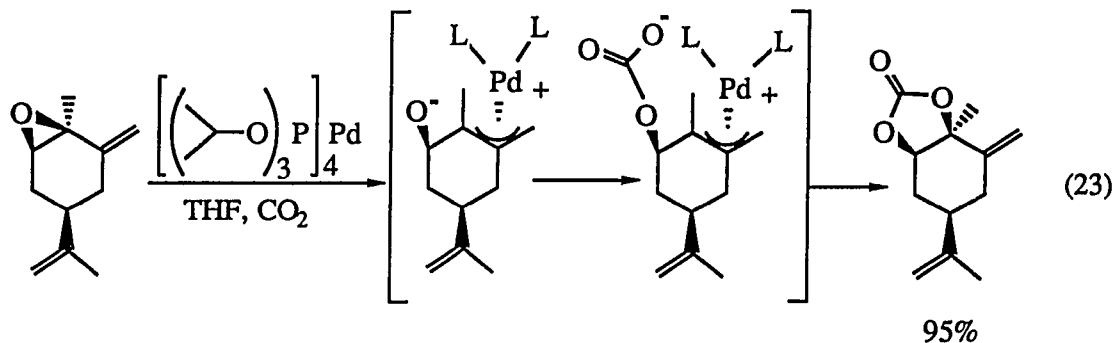
Trost and Runge[24] reported the first example in which enolates from β-ketoesters may undergo preferential oxygen rather than carbon alkylation (eq 24). However, prolonged treatment with a palladium(0) catalyst converted the O-alkylated product to the C-alkylated one.

$$\text{(24)}$$

87%   77%
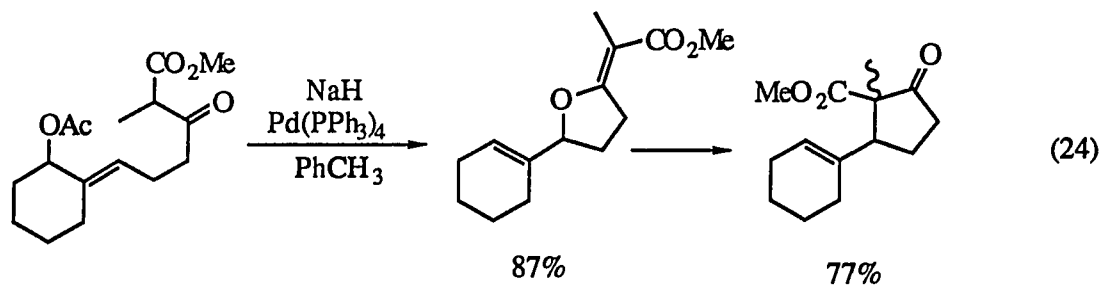
The following section will discuss our development of the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and heteroatom-containing nucleophiles, particularly nitrogen and oxygen nucleophiles, via palladium migration chemistry.

COUPLING INVOLVING NITROGEN NUCLEOPHILES

As stated in the introductory section of this section, amines are among the most frequently used heteroatom nucleophiles used in π-allylpalladium displacement reactions. As a natural extension from carbon nucleophiles, nitrogen nucleophiles were extensively explored in our palladium migration chemistry.

In an attempt to make the palladium-catalyzed coupling reactions of aryl iodides, nonconjugated dienes and nucleophiles more general, the previously established carbon nucleophile procedure was used as a starting point. The reaction of iodobenzene, 1,5-hexadiene and piperidine was chosen as a model system for optimizing the reaction conditions (eq 25). Unfortunately, Heck product **2** was observed to be the major product in 36% yield,
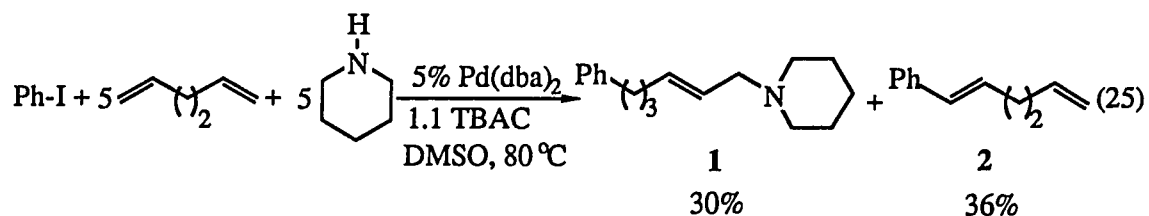
rather than the anticipated migration-displacement product **1**. We did not use any inorganic base because the amine itself is a base. In the presence of an amine base, the initial hydridopalladium species is apparently displaced from the carbon chain to form an aryl diene (**2**).

In order to modify the reaction conditions and keep the reaction system as similar as possible to that used in the carbon nucleophile displacement process, the amount of tetra-*n*-butylammonium chloride (TBAC) was first considered as a variable. When 2.2 equivalents of TBAC were used in the model reaction, instead of 1.1 equivalents, the yield of compound **1** was increased to 48%, and that of compound **2** was decreased to 27%. Apparently the

ammonium salt, TBAC, favors the formation of the migration product. However, the use of additional amounts of TBAC (3-4 equivs) did not show any further advantages in the formation of the migration product.

In an attempt to further improve the selectivity of the coupling reaction (see eq 25), the effect of the reaction temperature and time on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and piperidine was next examined. The results are summarized in Table 1.

Table 1. Effect of reaction temperature and time on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and piperidine.[a]

		% Isolated Yield	
Reaction Temp (^{0}C)	Reaction time (h)	1	2
60	36	45	30
80	24	48	27
100	12	72	14
120	8	53	22

[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$ and 2.2 equiv of TBAC.

The data listed in Table 1 demonstrate that the best yield of the desired coupling product 1 was obtained at 100 °C in 12 hours. Neither higher nor lower temperatures seem to effectively suppress the formation of the Heck product 2.

To make certain that dimethylsulfoxide is still the solvent of choice, solvent variations were also explored. Several polar aprotic solvents were examined on the model system (eq 25) under the best reaction conditions shown in Table 1. The results presented in Table 2 clearly indicate that the reaction using DMF as the solvent gave lower yields of coupling products, while the yield was slightly improved when DMA was employed as the solvent. Neat DMSO is still the solvent of choice for the amine nucleophile system. Fortunately, after modifying the reaction temperature, the amount of TBAC and the solvent employed, our earlier standard

Table 2. Effect of solvent in the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and piperidine.[a]

| | % Isolated Yield | |
Solvent	Compound 1	Compound 2
DMF	53	24
DMA	61	25
DMSO	72	14

[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$, 2.2 equiv of TBAC at 100 °C for 12 h.

procedure with only minor modifications proved its generality for use in our palladium migration chemistry.

The allylic amine product (1) was believed to possess the E-configuration about the carbon-carbon double bond based on the assumption that the *syn-* π-allylpalladium complex is the more stable and the predominant conformation, especially when a long carbon chain is linked to one terminus of the π-allyl unit (see eq 19 of Section I). Accordingly, when the amine nucleophile attacks the primary terminus of the π-allyl unit, an E-isomer should be obtained. Indeed, the E-configuration of the double bond is evidenced by the coupling constant between the two vinylic hydrogens in ^{1}H NMR spectrum (J = 15.3 Hz), and the presence of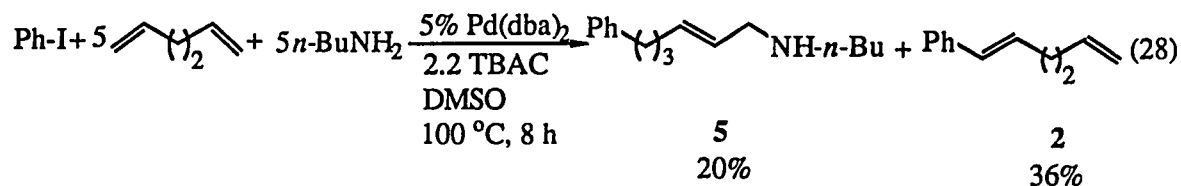 an absorption band at ~960 cm^{-1} in the out of plane bending region of the infrared spectrum. During their study of the reactions of π-allylpalladium intermediates with amines, Stakem and Heck[25] also observed that only the E-isomers of the allylic amines were formed.

Careful spectroscopic examination of the product provides no evidence for aryl addition to the internal carbon of the diene carbon-carbon double bond, consistent with the results obtained earlier using carbon nucleophiles.

It is noteworthy that the amine nucleophile exclusively attacks the terminal carbon of the π-allyl unit. No product of internal attack was observed when piperidine was used as the

nucleophile. Therefore, this reaction does show a high degree of regioselectivity and stereoselectivity.

The coupling process using amines as the nucleophile most likely proceeds as illustrated in Scheme III. A plausible mechanism for the formation of compound **1** involves the oxidative addition of the aryl iodide to a palladium(0) species. Arylpalladium addition to one of the carbon-carbon double bonds of the diene is followed by palladium migration by a sequence of palladium hydride eliminations and readditions to produce a π-allylpalladium intermediate which is eventually displaced by a nucleophile to afford the desired adduct. A palladium (0) species is regenerated by the amine-promoted decomposition of the hydridopalladium iodide.

Scheme III

Ph-I + Pd(0) ———→ PhPdI
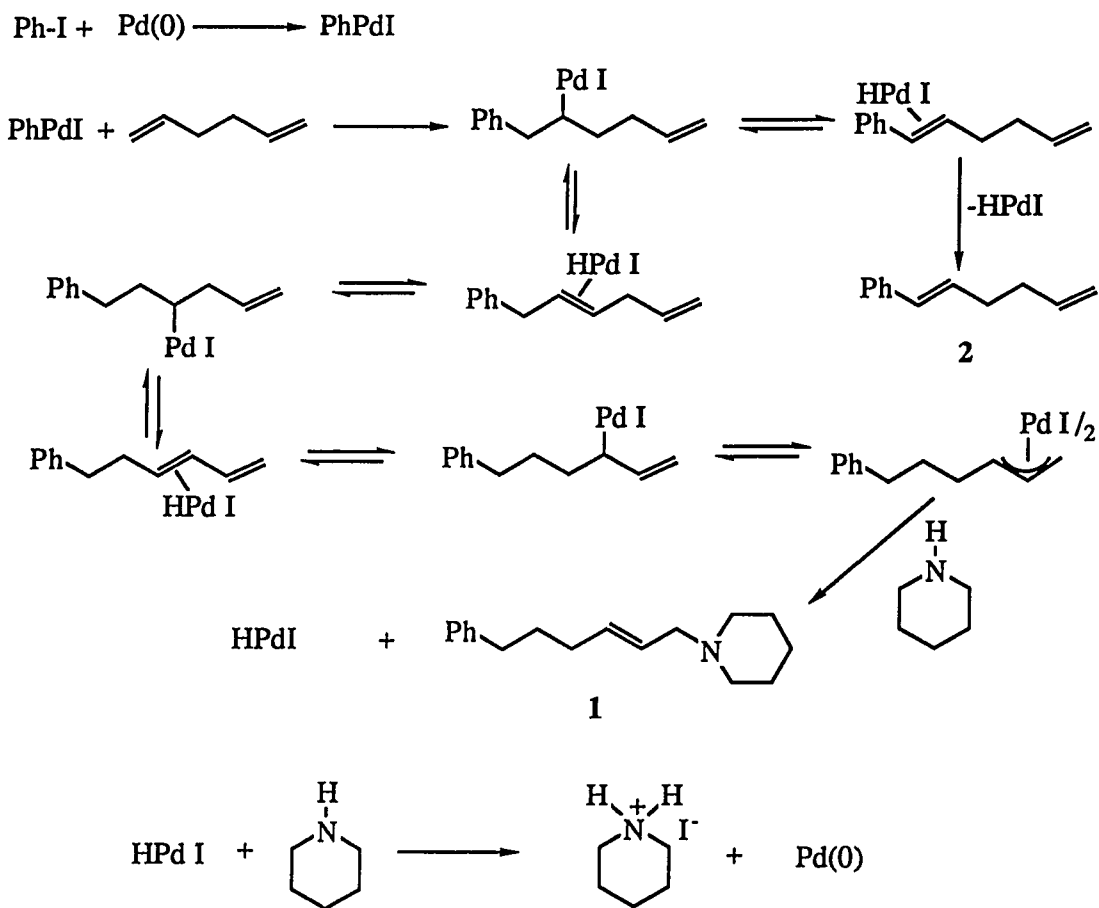
The generation of Heck product **2** can be explained mechanistically by dissociation of the hydridopalladium-diene π-complex as indicated in Scheme III.

Since a good yield of piperidine coupling product **1** was obtained after modifying the amounts of TBAC used and the reaction temperature employed, no other variations were explored at this time with our model system.

Pyrrolidine was also allowed to react with iodobenzene and 1,5-hexadiene in the presence of a catalytic amount of Pd(dba)$_2$, and 2.2 equivalents of TBAC at 100 °C for only three hours to afford the allylic tertiary amine **3** in 63% yield and Heck product **2** in 25% yield (eq 26).

$$\text{Ph-I} + 5 \underset{2}{\diagup\!\!\!\diagdown} + 5 \underset{\underset{H}{N}}{\diagdown} \xrightarrow[\substack{2.2\ \text{TBAC} \\ \text{DMSO} \\ 100\,°\text{C, 3 h}}]{5\%\ \text{Pd(dba)}_2} \underset{\substack{3 \\ 63\%}}{\text{Ph}\diagup\!\!\!\diagdown_3\diagdown\!\!\!N\diagdown} + \underset{\substack{2 \\ 25\%}}{\text{Ph}\diagup\!\!\!\diagdown_2} \quad (26)$$
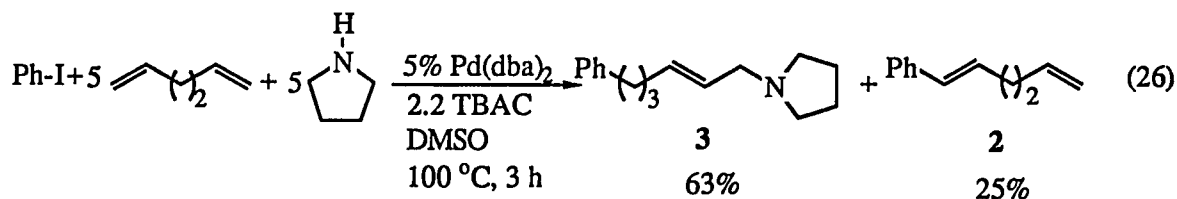
It is worth pointing out that a short reaction time seems to favor the formation of the desired amine adduct and suppresses the Heck product. It is thought that the π-allylpalladium nucleophilic displacement step might be the rate determining step in the overall process, because in changing the nucleophile from carbon to nitrogen, we found that the overall reaction rate increased dramatically.

An attempt was also made to investigate different combinations of reaction temperature and reaction time to see which combination is best suited for the performance of this unique palladium-catalyzed multiple coupling reaction. Amine product **3** was obtained in only a 41% yield alongside a 23% yield of Heck product **2**, when the reaction shown in equation 26 was carried out at 80 °C for 12 hours. It is quite clear that a high reaction temperature and a shorter reaction time is better than a lower reaction temperature with a longer reaction time.

Morpholine was employed as a secondary amine nucleophile in the reaction with iodobenzene and 1,5-hexadiene, under conditions similar to those described in equation 26. The desired allylic tertiary amine product **4** was isolated in an excellent 72% yield when the reaction was run at 100 °C for only 4 hours (eq 27). Prolonging the reaction time from 4 hours to 12 hours at 100 °C ultimately reduced the yield of **4** to 58%. The E-configuration of the double bond in compound **4** is evidenced by the coupling constant between the two vinyl hydrogens in the ^{1}H NMR spectrum (J = 15.3 Hz).
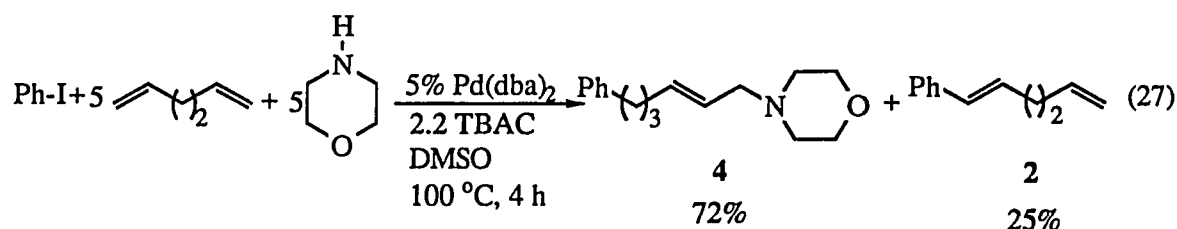
With these encouraging results in hand, we set out to explore the use of primary amines as the nitrogen nucleophiles. It is known that most primary amines have pK_b values similar to secondary amines,[26] but that the reduced steric hindrance of the primary amine often makes such amines strong kinetic bases.

At this point, the important role of the ammonium salt in these amine nucleophilic displacement reactions should be emphasized. When the reaction presented in equation 26 was scaled up, tetra-n-butylammonium chloride (TBAC) purchased from Lancaster was in short supply. TBAC purchased from Chemical Dynamics Company was therefore utilized as an alternative in the reaction. Unfortunately, only a 24% yield of the desired amine product **3** was isolated, along with a significant amount of Heck product **2** (42% yield). Therefore, it should be emphasized that different sources of TBAC exhibit different effects on the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and amine nucleophiles.

Initial application of the optimized conditions established using secondary amines as the nucleophile to the coupling of iodobenzene and 1,5-hexadiene proved to be quite disappointing

when primary amines were employed. The reaction of iodobenzene with 5 equivalents of 1,5-hexadiene and 5 equivalents of n-butylamine in the presence of a catalytic amount of Pd(dba)$_2$ and 2.2 equivalents of TBAC in DMSO solvent at 100 °C for 8 hours gave the desired allylic amine product 5 in only a 20% yield, alongside a 36% yield of Heck product 2 (eq. 28). It

$$\text{Ph-I} + 5 \diagdown\diagup\diagdown_2\diagdown\diagup\diagdown + 5\,n\text{-BuNH}_2 \xrightarrow[\substack{2.2\ \text{TBAC} \\ \text{DMSO} \\ 100\,^\circ\text{C, 8 h}}]{5\%\ \text{Pd(dba)}_2} \text{Ph}\diagdown\diagup\diagdown_3\diagdown\diagup\diagdown\text{NH-}n\text{-Bu} + \text{Ph}\diagdown\diagup\diagdown\diagup\diagdown_2\diagdown \qquad (28)$$

$$\underset{20\%}{\mathbf{5}} \qquad\qquad \underset{36\%}{\mathbf{2}}$$

was suspected that the primary amine played an important role in the displacement of the hydridopalladium species from its diene π-complex. We therefore decided to investigate the relationship between the yield of 5 and the ratio of n-butylamine to iodobenzene under the reaction conditions shown in equation 28.

From the data shown in Table 3, one can see that the best yield of amine adduct 5 was obtained when only 2.5 equivalents of n-butylamine was employed instead of 5 equivalents in the coupling reaction. It does appear that the presence of the less hindered base, n-butylamine, promotes the dissociation of the hydridopalladium-diene π-complex and favors generation of the Heck product.

Table 3. Effect of the ratio of n-butylamine to iodobenzene on the coupling of iodobenzene, 1,5-hexadiene, and n-butylamine.[a]

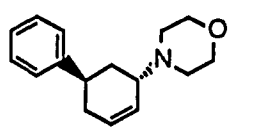|	% Isolated Yield	
Equiv of n-BuNH$_2$	Compound 5	Compound 2
5	20	36
2.5	50	32
1.5	37	40

[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$, 2.2 equiv of TBAC in DMSO at 100 °C for 8 h.

Since aniline is a weaker base than ordinary primary alkylamines, the reaction of

iodobenzene and 1,5-hexadiene with aniline under conditions similar to those presented in

equation 27 proceeded slowly; after 30 hours of reaction, the GC analysis showed that

iodobenzene was totally consumed, and only a 30% yield of aniline coupling product was

obtained. However, when 2.5 equivalents of sodium bicarbonate was added to the reaction

mixture, the reaction was much faster than the previous one, and the desired product was

isolated in a higher yield (66%) (eq 29). A plausible explanation is that the presence of sodium

$$Ph\text{-}I + 5 \diagdown\hspace{-4pt}\diagup_2\hspace{-4pt}\diagdown\hspace{-4pt}\diagup + 5 \underset{\text{NH}_2}{\bigcirc} \xrightarrow[\substack{2.2\ \text{TBAC} \\ \text{DMSO, 100 °C}}]{5\%\ \text{Pd(dba)}_2} Ph\diagdown\hspace{-4pt}\diagup_3\diagdown\hspace{-4pt}\underset{\underset{\text{H}}{\text{N}}}{\diagup}\bigcirc + Ph\diagdown\hspace{-4pt}\diagup\diagdown\hspace{-4pt}\diagup_2\hspace{-4pt}\diagdown \quad (29)$$

	6	**2**
in absence of NaHCO₃	30%	25%
in presence of NaHCO₃ (2.5 equiv)	66%	28%
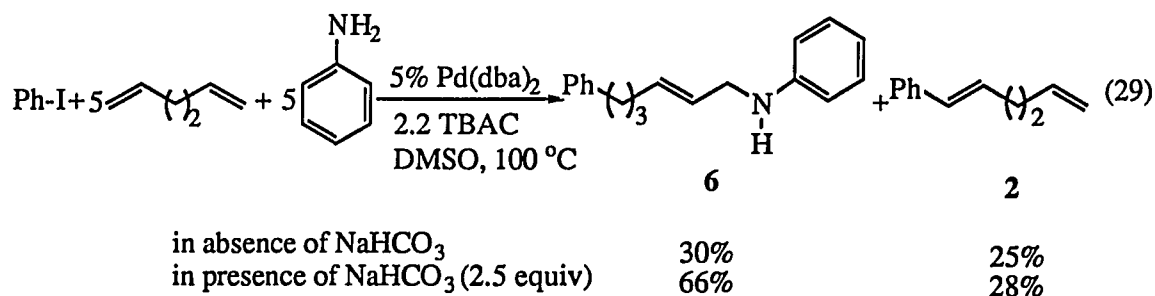
bicarbonate favors the removal of hydrogen iodide from the hydridopalladium species and

promotes the regeneration of palladium(0), which can now re-enter the catalytic cycle.

However, it is disappointing to find that N-methyl aniline failed to participate in the palladium-

catalyzed coupling of iodobenzene and 1,5-hexadiene, even in the presence of an inorganic

carbonate base.

In order to demonstrate the synthetic utility of the modified procedure established in our

model studies. A variety of amine nucleophiles, including primary and secondary amines, and

nonconjugated dienes were examined to determine if the corresponding allylic amines can be

prepared in good yields. Our results are summarized in Tables 4 and 5.

It is of interest to note from Tables 4 and 5 that the palladium-catalyzed coupling of

iodobenzene, nonconjugated dienes, and amine nucleophiles proceeds regioselectively and

Table 4. Palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and amine nucleophiles.[a]
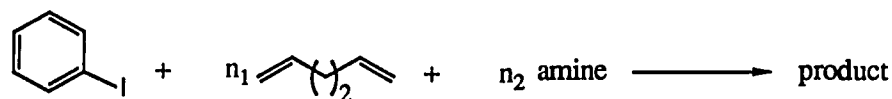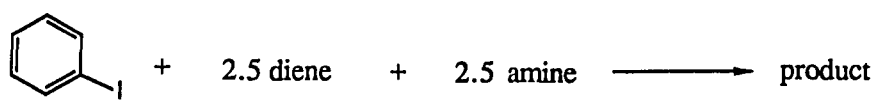
Entry	Amine	n_1	n_2	Time (h)	Product		% Yield[b]
1	H_2N	5.0	2.5	8		(5)	50
2	H_2N	2.5	2.5	12		(7)	60
3	H_2N	2.5	2.5	24		(8)	51
4	HN	2.5	2.5	10		(9)	65
5		5.0	5.0	12		(1)	72
6		5.0	5.0	3		(3)	63
7		5.0	5.0	4		(4)	72
8[c]	H_2N	2.5	2.5	24		(6)	66
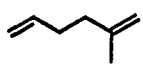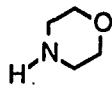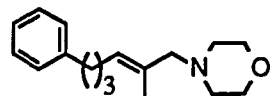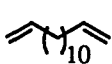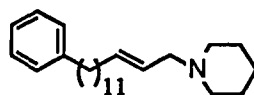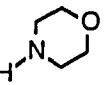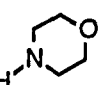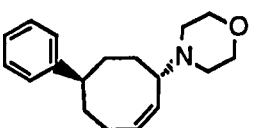
[a] Reaction was run in DMSO in the presence of 5% Pd(dba)$_2$, 2.2 equiv of TBAC in DMSO at 100 °C.
[b] Isolated yield.
[c] In the presence of 2.5 equiv of NaHCO$_3$.

Table 5. Palladium-catalyzed coupling of iodobenzene, nonconjugated dienes, and amine nucleophiles.[a]

 + 2.5 diene + 2.5 amine ⟶ product

Entry	Diene	Amine	Time (h)	Product		% Yield[b]
1			24		(10)	62
2			36		(11)	30
3			12		(12)	78
4			24		(13)	42

[a] Reaction was run with 2.5 equiv of amine and diene in the presence of 5% Pd(dba)$_2$, 2.2 equiv of TBAC in DMSO at 100 °C.

[b] Isolated yield.

stereoselectively. Regardless of the amine, only one regioisomer and one stereoisomer were isolated. No evidence was obtained for the existence of any regioisomer formed by attack of the amine nucleophile on the internal carbon of the π-allyl unit. By examining the results shown in Tables 4 and 5, one can see that only E-stereoisomers are isolated and the phenyl group always adds to the terminal carbon of the diene.

O'Connor et al.[2] reported previously that the reactions of iodobenzene and isoprene with primary amines were extremely sluggish at 100 °C, but proceeded at a reasonable rate at 125-130 °C. Their reactions using n-butylamine showed an enhanced tendency of the amine to attack the secondary carbon of the π-allylic system. In sharp contrast to these reports, the

reaction of iodobenzene and 1,5-hexadiene with *n*-butylamine proceeded smoothly under our

reaction conditions (in 8 hours) and the desired product was formed regioselectively.

The results in Table 4 indicate that both primary and secondary amines work well and

good yields of allylic secondary and tertiary amines are obtained with a high degree of regio-

and stereoselectivity. However, when a smaller nucleophile, methylamine as a 40% aqueous

solution, was employed in the palladium-catalyzed coupling of iodobenzene and

1,5-hexadiene, Heck product **2** dominated the reaction mixture. When dry methylamine gas

was added to the reaction mixture, only the starting material iodobenzene was recovered, and

neither the desired product nor Heck product were detected.

An examination of the results in Table 5 reveals that the use of 2-methyl-1,5-hexadiene in

the coupling of iodobenzene and morpholine in the presence of a catalytic amount of $Pd(dba)_2$

and 2.2 equiv of TBAC results in the formation of the amine adduct **10** in 62% yield as the

sole regioisomer (entry 1 in Table 5). The absence of any regioisomers clearly demonstrated

that the phenyl group exclusively added to the least substituted carbon-carbon double bond of

the diene. Similar results were observed when using carbon nucleophiles (see entry 6 in Table

14 of Section I). The unique ability of palladium to migrate along a long carbon chain under

our reaction conditions was proved by the modest yield of compound **11** (entry 2 in Table 5).

These results indicate that it does not matter how long the carbon chain is, the allylic product is

still formed, although the yield is reduced. It is incredible that palladium is capable of

migrating up to ten carbons via repeated interconversions between palladium σ- and π-

complexes without evident dissociation, especially in the presence of a polar solvent plus a

strong organic base.

From entries 3 and 4 in Table 5 it should be emphasized that palladium is capable of

migrating along a carbon ring to form only one stereoisomer, either **12** or **13** in yields of 78%

and 42%, respectively. The stereochemistry of compound **12** was assigned by ^{1}H NMR and

COSY spectral data which is consistent with the structure anticipated mechanistically. The

eight membered ring structure of compound **13** is believed to possess a *trans*-configuration by mechanistic arguments. The spectral data unfortunately were too complicated to interpret stereochemically.

During our studies on the syntheses of the pyridine alkaloid analogues (see Section III of Part II), we found that the palladium-catalyzed coupling of 3-iodopyridine, 1,5-hexadiene and benzylmethylamine in the presence of 2.2 equivalents of TBAC failed to produce the desired coupling product. Lithium chloride was then used to replace TBAC, and surprisingly, a good yield of the desired product was obtained (see eqs 8 and 9 in Section III of Part II). Since lithium chloride is cheaper than TBAC and easy to handle, it was of interest to examine if lithium chloride can also be used in the palladium-catalyzed three-component coupling when using nitrogen nucleophiles. For comparison, the coupling of iodobenzene, 1,5-hexadiene, and benzylmethylamine were designed to proceed in the presence of either TBAC or lithium chloride under the same reaction conditions. The results presented in equation 30 indicate that lithium

$$\text{Ph-I} + 5 \underset{2}{\diagup\!\!\!\diagdown\!\!\!\diagup} + 5\ \text{PhCH}_2\text{NHMe} \xrightarrow[\substack{\text{DMSO} \\ 100\ ^\circ\text{C, 12 h}}]{5\%\ \text{Pd(dba)}_2} \underset{3}{\text{Ph}\diagdown\!\!\!\diagup}\diagup\!\!\!\diagdown\underset{\text{Me}}{\text{NCH}_2\text{Ph}} \quad (30)$$

2.2 TBAC	55%
1.0 LiCl	60%
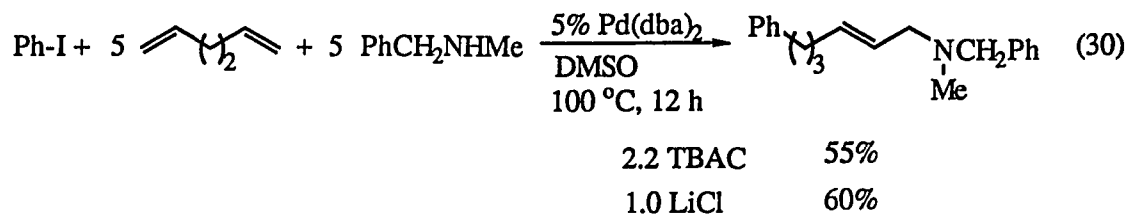
chloride can be used to replace TBAC in the palladium-catalyzed coupling of aryl iodides and nonconjugated dienes with amine nucleophiles.

The palladium-catalyzed amination of allylic compounds with secondary amines has been extensively studied and has proven to be efficient for the synthesis of tertiary allylic amines[5-7,27] However, palladium-catalyzed reactions with ammonia or primary amines cannot be applied to the synthesis of primary or secondary allylic amines, because polyallylation results in contamination by secondary and tertiary allylic amines. Therefore, primary amines

have been prepared from *N*-protected primary allylic amines such as 4,4'-dimethoxybenzhydrylamines,[28] *p*-toluenesulfonamides,[29] phthalimides,[30] and di-*t*-butyl iminodicarbonates,[31] obtainable by palladium(0)-catalyzed reactions. For the synthesis of secondary allylic amines, the preparation of *N*-allylic hydroxylamines by palladium-catalyzed reactions and subsequent reduction have been reported.[32]

So far a variety of secondary and tertiary amines with a relatively long carbon chain have been synthesized in good yields using our nitrogen atom coupling process via palladium migration. However, it is known that small molecular weight primary amines cannot be used as a nitrogen nucleophile in the coupling reaction. How to develop this methodology to prepare long carbon chain primary amines is indeed a challenge.

It is already known that N-alkylphthalimides may be converted into the corresponding primary amine by hydrolysis or hydrazinolysis (Gabriel primary amine synthesis)[33] and phthalimide can be used as a nucleophile in the palladium-catalyzed allylic exchange reaction of allylic esters and phenyl ethers to give allylic products.[27] We thought that if a long chain allylic phthalimide could be prepared by the palladium-catalyzed coupling using phthalimide as a nucleophile, hydrazinolysis of this intermediate would afford the corresponding long carbon chain primary amine. Unfortunately, the reaction of iodobenzene and 1,5-hexadiene using phthalimide as the nucleophile and Pd(dba)$_2$ as the catalyst, under the best reaction conditions described in Tables 4 and 5 failed to give any anticipated *N*-allylic phthalimide derivative, regardless of the presence or absence of an inorganic base (eq. 31). The starting iodobenzene

$$\text{Ph-I} + 5 \quad \diagup\hspace{-0.3em}\diagdown\hspace{-0.3em}\diagup_2\hspace{-0.3em}\diagdown \quad + \quad 2.5\,\text{HN}\!\!\diagdown\hspace{-0.2em}\text{(phthalimide)} \quad \xrightarrow[\substack{2.2\,\text{TBAC} \\ (\text{NaHCO}_3 \\ \text{or Na}_2\text{CO}_3) \\ \text{DMSO, 80 °C}}]{5\%\ \text{Pd(dba)}_2} \quad \text{Ph}\!\diagdown\hspace{-0.2em}\diagup_3\hspace{-0.2em}\diagdown\!\text{N}\!\!\diagdown\hspace{-0.2em}\text{(phthalimide)} \qquad (31)$$

0%

was recovered, even though the reaction was run for 4 days. It is not clear why the palladium catalyst was killed in the presence of phthalimide under our conditions.

As an alternative to phthalimide, we turned to amide nucleophiles.[30] Benzenesulfonamide was selected and treated with iodobenzene and 1,5-hexadiene under the same conditions as shown in entry 8 of Table 4. The desired allylic phenylsulfonamide product was isolated, but only in a low yield of 34% (eq 32).

$$Ph\text{-}I + 5 \quad \text{[diene]}_2 \quad + 2.5\ H_2NSO_2Ph \quad \xrightarrow[\substack{2.2\ TBAC \\ 2.5\ NaHCO_3 \\ DMSO,\ 100\,^\circ C}]{5\%\ Pd(dba)_2} \quad Ph\text{[chain]}_3 \text{-}NHSO_2Ph \qquad (32)$$

$$34\%$$

The ease with which an organic azide is reduced to form a primary amine,[34] and the report that sodium azide can be used as a nucleophile in the catalytic transformation of allylic acetates to allylic azides through a π-allylpalladium intermediate (eq 33)[35] encouraged

$$R\text{[chain]}OAc \quad + \quad NaN_3 \quad \xrightarrow[THF\text{-}H_2O]{Pd(PPh_3)_4} \quad R\text{[chain]}N_3 \qquad (33)$$

us to examine whether sodium azide could be used as an alternative nitrogen nucleophile in the palladium-catalyzed coupling reaction of aryl iodides and nonconjugated dienes.

Due to the limited solubility of sodium azide in organic solvents, a mixture of DMSO and water in a 4 : 1 ratio was used as a solvent in the preliminary study. Equation 34 shows the

$$PhI + 5\quad\text{[diene]}_2 \quad + n\ NaN_3 \quad \xrightarrow[\substack{DMSO\ (20\%\ H_2O) \\ 2.2\ TBAC,\ 100\,^\circ C}]{5\%\ Pd(dba)_2} \quad Ph\text{[chain]}_3\text{-}N_3 + Ph\text{[chain]}_2 \qquad (34)$$

$$\mathbf{14} \qquad\qquad\qquad \mathbf{2}$$

reaction conditions under which the stoichiometry of the sodium azide cross coupling reaction

was investigated. Table 6 shows that essentially the same yields of the desired allylic
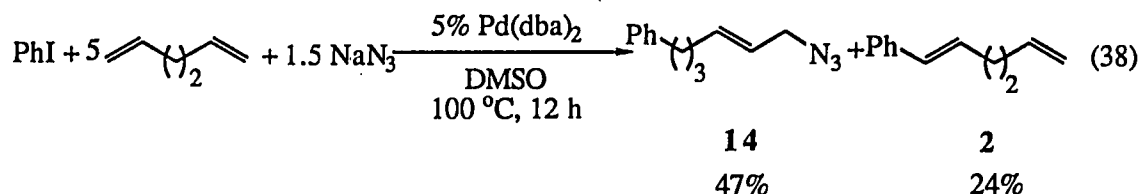
Table 6. Effect of varying the amount of sodium azide on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and sodium azide.[a]

| Equiv of NaN₃ | % Isolated Yield | |
n	14	2
1.1	33	32
1.5	34	22
2.5	33	27
5.0	22	39

[a] Reaction was run with 5 equiv of 1,5-hexadiene in the presence of 5% $Pd(dba)_2$, 2.2 equiv of TBAC in DMSO (20% H_2O) at 100 °C for 12 h.

azide were obtained when 1.1 to 2.5 equivalents of sodium azide were used. The yield seemed

to drop when still more sodium azide was used.

The water content in the DMSO solvent was also varied using reaction conditions similar

to those shown in equation 36, except that 1.5 equivalents of NaN_3 were employed. However,

the results in Table 7 demonstrate that the water content is unimportant for the DMSO-

Table 7. Effect of the water content in DMSO on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and sodium azide.[a]

| Ratio of Solvent | | % Isolated Yield | |
DMSO	:	H_2O	14	2
10		0	40	22
9		1	35	25
8		2	34	22
7		3	39	21

[a] Reaction was run with 5 equiv of 1,5-hexadiene in the presence of 5% $Pd(dba)_2$, 2.2 equiv of TBAC at 100 °C for 12 h.

mediated, palladium-catalyzed coupling reaction when using sodium azide as the nucleophile. Thus, commercial DMSO could be employed in this coupling reaction without further treatment.

In 1983 Spencer[36] reported that the use of sodium acetate as a base, and the polar solvent N,N-dimethylformamide, in the palladium-catalyzed vinylation of arenes greatly increased the turnover of the palladium (eq 35). Jeffery[37] subsequently found that the addition of

$$
\text{ArX} \quad + \quad \overset{}{\diagdown\!\!\diagup}\text{E} \quad \xrightarrow[\substack{\text{NaOAc} \\ \text{DMF, 120 °C}}]{\text{cat. Pd(OAc)}_2 \text{ PR}_3} \quad \text{Ar}\diagdown\!\!\diagup\diagup\text{E} \qquad (35)
$$
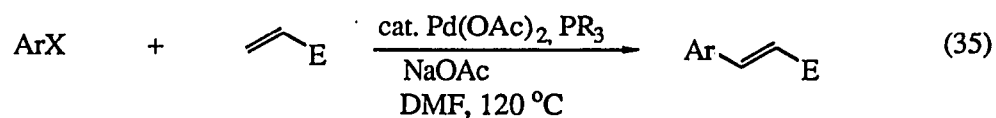
tetra-n-butylammonium chloride (TBAC) to such reactions allowed the palladium-catalyzed vinylation of aryl, vinylic and alkynyl halides to proceed at room temperature (eq 36).

$$
\text{RX} \quad + \quad \overset{}{\diagdown\!\!\diagup}\text{E} \quad \xrightarrow[\substack{\text{NaOAc} \\ \text{TBAC} \\ \text{DMF, 25 °C}}]{\text{cat. Pd(OAc)}_2 \text{ PR}_3} \quad \text{R}\diagdown\!\!\diagup\diagup\text{E} \qquad (36)
$$

R = aryl, vinylic, alkynyl
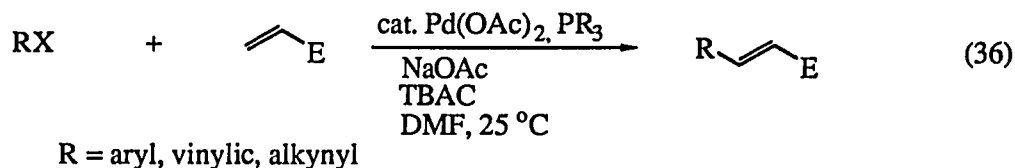
Larock and co-workers[38] have extended Jeffery's conditions to the use of non-activated cyclic alkenes (eq 37). However, the role of TBAC in affording high yields of coupling product in shorter reaction times is not well understood.

$$
\text{RI} \quad + \quad \pentagon \quad \xrightarrow[\substack{\text{base, TBAC} \\ \text{DMF, 25 °C}}]{\text{cat. Pd(OAc)}_2} \quad \text{R}\!\!-\!\!\pentagon \qquad (37)
$$
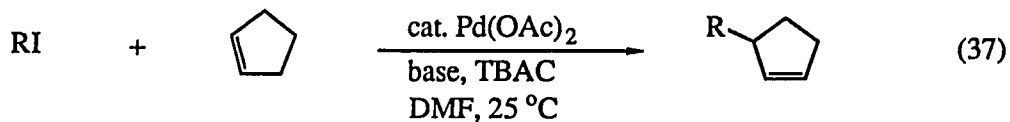
Recently, Amatore et al.[39] reported the electrical reduction of $Cl_2Pd(PPh_3)_2$ to give low coordinated zerovalent palladium complexes that are stabilized by chloride anions. These complexes were formulated as $[x(n\text{-}Bu_4N)Cl_xPd^0(PPh_3)_2]_n$ analogous to the $LiClPd(0)(PPh_3)_n$ intermediate reported by Negishi et al.,[40] which has recently been postulated to be the effective species in some palladium-catalyzed cross-coupling reactions by Stille and Scott.[41] Amatore found that the rate of oxidative addition of PhI to these complexes is faster than the addition of PhI to $Pd(PPh_3)_4$ or $Pd(PPh_3)_3$. Similar types of intermediates might also be involved in the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes, and carbon or amine nucleophiles, because TBAC significantly promotes these reactions.

To make clear the importance of TBAC when using the azide nucleophile, a study of the effect of TBAC on the coupling reaction was carried out both in the absence and in the presence of different amounts of TBAC. The results in Table 8 demonstrate that TBAC is not a very

Table 8. Effect of varying amounts of TBAC on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene, and sodium azide.[a]

| Equiv of TBAC | Time (h) | % Isolated Yield | |
		14	2
0	12	32	15
1	12	39	22
2.2	12	40	22

[a] Reaction was run in the presence of 5% $Pd(dba)_2$ at 100 °C in DMSO using 1.5 equiv of NaN_3.

important component in the palladium-catalyzed coupling of iodobenzene and 1,5-hexadiene when sodium azide is used as the nucleophile, even though the addition of one to two equivalents of TBAC improves the reaction yield slightly. The reaction studied in Table 8 was scaled up to 2 mmol, without using TBAC, and the yield of the desired allylic azide 14

was 47%, alongside a 24% yield of Heck product (eq 38).

$$PhI + 5 \underset{2}{\diagdown} + 1.5\ NaN_3 \xrightarrow[\substack{DMSO \\ 100\ °C,\ 12\ h}]{5\%\ Pd(dba)_2} Ph\underset{3}{\diagdown} N_3 + Ph\underset{2}{\diagdown} \quad (38)$$

<div align="center">

14   **2**

47%   24%

</div>

Recently Safi et al.[42] developed a palladium(0)-catalyzed reaction of various allylic esters with trimethylsilyl azide under anhydrous conditions. For example, the reaction of cinnamyl acetate with trimethylsilyl azide in the presence of a catalytic amount of dipalladium-tris(dibenzylideneacetone) in THF afforded the primary (E)-cinnamyl azide in good yield (eq 39). Since trimethylsilyl azide readily dissolves in most organic solvents, it was of interest to

$$Ph\diagup\diagdown OAc + Me_3SiN_3 \xrightarrow[THF,\ 50\,°C]{Pd_2(dba)_3,\ PPh_3} Ph\diagup\diagdown N_3 \quad (39)$$

<div align="center">85%</div>
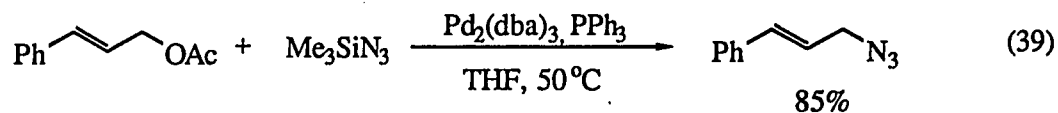
use this azide as an azide nucleophile in the coupling of iodobenzene and 1,5-hexadiene in the presence of 5% Pd(dba)₂ in DMSO. Unfortunately, neither the expected product **14**, nor Heck product **2**, were observed in this reaction (eq 40). Variation of the solvent (DMF, THF)

$$PhI + 5 \underset{2}{\diagdown} + 1.5\ Me_3SiN_3 \xrightarrow[DMSO,\ 100\ °C]{5\%\ Pd(dba)_2} Ph\underset{3}{\diagdown} N_3 \quad (40)$$

<div align="center">

14

0%

</div>
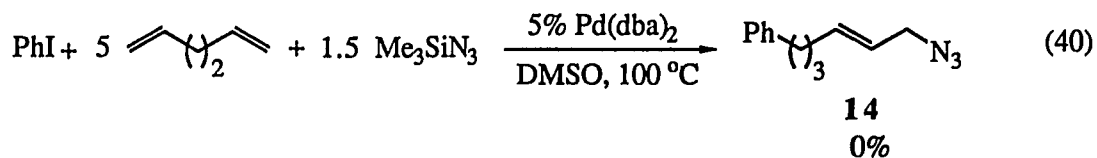
and the reaction temperature (60 °C) also failed to initiate the coupling reaction. However, the GC trace showed that the reaction did produce some small amounts of compound **14** and compound **2** when 2.5 equivalents of sodium bicarbonate was added to the reaction mixture.

Unfortunately, the starting material iodobenzene was not totally consumed even when the reaction was run for five days.

The reduction of this allylic azide catalyzed by palladium on charcoal readily converted the allylic azide to the corresponding saturated primary amine under mild conditions. A detailed study of this reaction will be presented in the next section.

COUPLING INVOLVING OXYGEN NUCLEOPHILES

As mentioned in the introduction of this section, allylic esters or ethers are the most frequently used substrates for the palladium-catalyzed displacement reaction by nitrogen nucleophiles. There are only a few examples of oxygen nucleophiles being used in the intermolecular displacement reaction of π-allylpalladium compounds. For example, allylic acetate groups may be replaced by other carboxylate groups or phenoxy groups using palladium as a catalyst. Most publications related to the oxygen displacement of π-allylpalladium intermediates involve intramolecular reactions.[12]

According to Spencer,[36] both sodium and potassium acetate are efficient bases in the palladium-catalyzed vinylation of aryl iodides. Later, Jeffery[37] disclosed that the addition of TBAC so greatly promotes this reaction that it can be run at room temperature. Since these reaction conditions are analogous to those used in our coupling process, we expected that Heck product 2 would become the major product. Nonetheless, we have studied such reactions and report here the success of that effort.

To find the best reaction conditions, the palladium-catalyzed coupling between iodobenzene, 1,5-hexadiene, and an acetate salt was chosen for the model study. The initial study was performed in the presence of 5% Pd(dba)$_2$ in DMSO at 100 °C, as well as in the absence of TBAC which kept reaction conditions as simple as possible (eq 41).

$$PhI + 5 \overset{}{\diagup\!\!\diagdown}\!\!\diagup_{2}\!\!\diagdown + 1.5\,MOAc \xrightarrow[\text{DMSO, 100 °C}]{5\%\ Pd(dba)_2} Ph\!\diagdown\!\!\diagup_{3}\!\!\diagdown\!\!\diagup\!\!\diagdown_{OAc} + Ph\!\diagup\!\!\diagdown\!\!\diagup_{2}\!\!\diagdown \quad (41)$$

$$\mathbf{15} \qquad\qquad\qquad \mathbf{2}$$
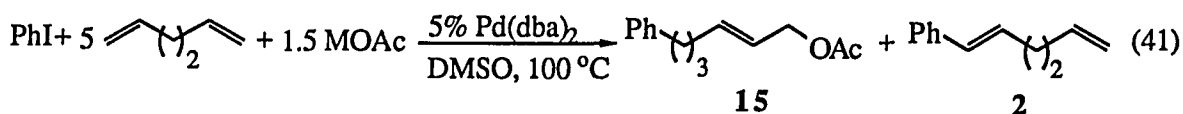
Based on the discussion in the previous section, it has been suggested that the formation of Heck product 2 involves an initial addition of the arylpalladium to one of the carbon-carbon double bond of the diene, followed by β-hydride elimination from the σ-palladium intermediate

to generate a palladium-styrene π-complex. The subsequent dissociation of the π-complex affords a palladium hydride species and the Heck product. Obviously, the presence of a strong base promotes the dissociation process (Scheme IV).

Scheme IV
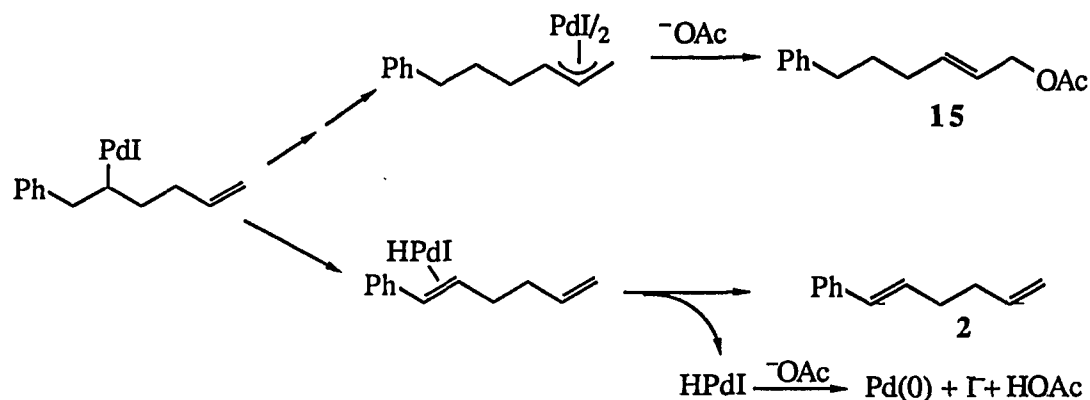
A possible method of inhibiting the formation of Heck product 2 is the use of a weaker base sodium bicarbonate, which has been proven successful in the case of carbon nucleophiles (see Section I in Part II). During the model system study, an acetate salt was used as both the nucleophile and the base. It was expected that the lower basicity of the acetate salt would be important in limiting the formation of the Heck product 2.

Since the activity of an acetate anion is influenced by its different countercations, a variety of acetate salts was investigated in our model reaction. Thus, the reaction was examined with Li, Na, and K cations and the results in Table 9 indicate that although the Heck product 2 predominates in the product mixture in each case, lithium acetate is the best choice of acetate salt. Potassium acetate particularly favors the formation of side product 2.

The reason for the better performance of the lithium cation than sodium and potassium cations in suppressing the formation of the side product 2 is probably due to the small size of

Table 9. Effect of alkali metal acetate on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and acetate.[a]

| Alkali Metal | % Isolated Yield | |
	15	2
Li	25	30
Na	20	33
K	11	54

[a] Reaction was run for 24 h in the presence of 5% Pd(dba)$_2$ at 100 °C in DMSO using 1.5 equiv of acetate and 5 equiv of 1,5-hexadiene.

the lithium cation, which promotes the formation of a tight ion pair with the acetate anion and in turn reduces its effective basicity. Conversely, the fact that potassium cation favors the formation of 2 can be explained by its larger size among the three alkali metals.

The addition of one or two equivalents of TBAC increases both the reaction rate and the yield of the palladium-catalyzed coupling when using carbon or amine nucleophiles. Thus, TBAC was used as an additive in the palladium-catalyzed coupling of iodobenzene and 1,5-hexadiene with LiOAc and NaOAc as nucleophiles (see eq 41). The data presented in Table 10 indicates: (1) TBAC increases the yields of both the main product 15 and the side product 2

Table 10. Effect of TBAC on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and lithium acetate or sodium acetate.[a]

| Equiv of TBAC | % Isolated Yield | | | |
| | 15 | | 2 | |
n	LiOAc	NaOAc	LiOAc	NaOAc
0	25	20	30	33
1	32	28	35	46
2	31	29	34	45
3	30	27	32	34

[a] Reaction was run in the presence of 5% Pd(dba)$_2$ in DMSO at 100 °C for 12 h, using 1.5 equiv of acetate and 5 equiv of 1,5-hexadiene.

(no improvement in reaction selectivity is observed), (2) lithium acetate is a more suitable nucleophile than is sodium acetate in this coupling reaction, although there is not a big difference in yield, and (3) the use of one equivalent of TBAC in the reaction seems to be enough, because the addition of more TBAC did not show an increased yield or increased selectivity for formation of compound **15.**

An attempt to improve the reaction selectivity was made by introducing lithium chloride as another additive, because the lithium cation showed considerable promise in the above studies and lithium chloride possesses the ability to stabilize the active zerovalent palladium species by the formation of complexes such as $LiClPd(0)(PPh_3)_n$.[40,41] Recently, Larock and Leung[43] also reported the successful use of lithium chloride in the synthesis of aryl allylic alcohols via palladium migration chemistry. The interesting results in Table 11 clearly demonstrate that

Table 11. Effect of lithium chloride on the palladium-catalyzed coupling of iodobenzene, 1,5 - hexadiene and lithium acetate.[a]

		% Isolated Yield	
Equiv of LiCl	Reaction Time (day)	15	2
0	0.5	32	35
1	1	36	32
1.5	2	40	31
2.0	3	30	28

[a] Reaction was run in the presence of 5% $Pd(dba)_2$ at 100 °C in DMSO using 1.5 equiv of acetate, 5 equiv of 1,5-hexadiene, and 1.0 equiv of TBAC.

lithium chloride is efficacious in improving the reaction selectivity, because with 1.5 equivalent of LiCl the coupling product **15** was obtained as the major product. However, LiCl obviously slows the rate of the reaction.

Since lithium acetate functions as a nucleophile and a base in the reaction, it is possible that more than one equivalent of lithium acetate should be employed in the coupling reaction. Therefore, different amounts of lithium acetate were studied under the conditions described in equation 42. To our delight, Table 12 indicates that the yield of coupling product **15** was improved up to 56% when three equivalents of lithium acetate were used.

$$\text{PhI} + 5 \underset{2}{\diagup\hspace{-0.5em}\diagdown\diagup} + \ n \ \text{LiOAc} \ \xrightarrow[\substack{1.0 \text{ TBAC} \\ 1.5 \text{ LiCl} \\ \text{DMSO, } 100\,^\circ\text{C}}]{5\% \ \text{Pd(dba)}_2} \ \underset{\mathbf{15}}{\text{Ph}\underset{3}{\diagup\hspace{-0.5em}\diagdown}\diagup\diagdown\text{OAc}} + \ \underset{\mathbf{2}}{\text{Ph}\diagup\diagdown\diagup\diagdown} \quad (42)$$
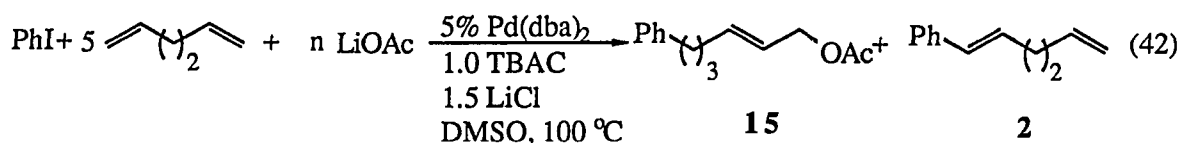
Table 12. Effect of the amount of lithium acetate on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and lithium acetate.[a]

Equiv of LiOAc	Reaction Time (day)	% Isolated Yield	
		15	**2**
1.5	2	40	31
3.0	2	56	20
5.0	2	41	35

[a] Reaction was run in the presence of 5% Pd(dba)$_2$ at 100 °C in DMSO using 5 equiv of 1,5-hexadiene, 1.0 equiv of TBAC, and 1.5 equiv of LiCl.

Also, various amounts of catalyst bis(dibenzylideneacetone)palladium(0) were tried to optimize the yield of **15** in the coupling reaction, but no significant differences were found with different amounts of the palladium catalyst (5%, 7.5% and 10%). For economic reasons, 5% of the palladium catalyst was used in all subsequent reactions.

Tetra-n-butylammonium acetate dissolves in polar aprotic solvents, which makes this salt another candidate as an acetate salt that also is commercially available. The palladium-catalyzed coupling (eq 39) of iodobenzene and 1,5-hexadiene with tetra-n-butylammonium acetate (TBAA) was totally inhibited in the absence of lithium chloride, and only the Heck product **2**

was isolated in 72% yield. However, the addition of lithium chloride dramatically promotes the

formation of the desired coupling product **15** (eq 43) and the best yield was obtained when

three equivalents of LiCl was utilized in this reaction (Table 13).

$$\text{PhI} + 5 \overset{}{\diagdown} (\ )_2 \diagup + 1.5\,n\text{-Bu}_4\text{NOAc} \xrightarrow[\substack{\text{DMSO, 100 °C} \\ n \text{ LiCl}}]{5\% \text{ Pd(dba)}_2} \quad \underset{\textbf{15}}{\text{Ph} (\ )_3 \text{OAc}} + \underset{\textbf{2}}{\text{Ph} (\ )_2} \quad (43)$$
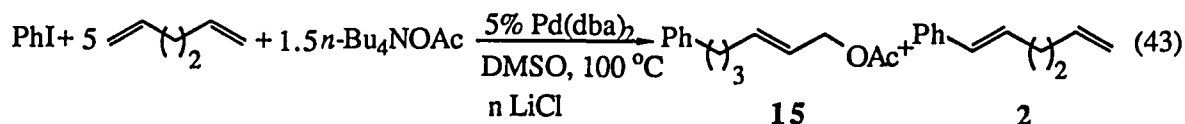
Table 13. The effect of different amounts of lithium chloride on the reaction shown in
equation 43.[a]

		% Isolated Yield	
Equiv of LiCl	Reaction Time	**15**	**2**
0	12 h	--	72
1	18 h	25	40
2	3 days	45	34
3	4 days	53	30
4	5 days	50	32

[a] Reaction was run in the presence of 5% Pd(dba)$_2$ at 100 °C in DMSO using 1.5 equiv
of TBAA, and 5 equiv of 1,5-hexadiene.

It appears that the lithium cation and the chloride anion are also important components

which promote the formation of the coupling product **15**. By comparing these conditions with

those when using lithium acetate as the nucleophile, it was considered that four species (AcO$^-$,

Cl$^-$, Li$^+$, and n-Bu$_4$N$^+$) may play roles in the palladium-catalyzed coupling of iodobenzene,

1,5-hexadiene and acetate. Table 14 shows the effect of these four variants on the yield of the

coupling process. Entries 15, 17 and 18 in Table 14 demonstrate three combinations of

reagents that give the highest yield of **15** and low yields of **2**. Of these three combinations

two procedures have received additional attention: Procedure A --- 3 equivalents of LiOAc, 1.5

equivalents of LiCl, 1.0 equivalent of n-Bu$_4$NCl (TBAC); Procedure B --- 3 equivalents of

LiOAc, 3 - 4 equivalents of LiCl.

Table 14. Effect of different species on the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and acetate.[a]

| Entry | AcO⁻ | Cl⁻ | Li⁺ | $n\text{-Bu}_4\text{N}^+$ | % Isolated Yield | |
					15	2
1	1.5	--	1.5	--	25	30
2	3.0	--	3.0	--	22	44
3	5.0	--	5.0	--	22	55
4	1.0	--	--	1.0	0	70
5	3.0	--	--	3.0	0	72
6	5.0	--	--	5.0	0	71
7	1.5	1.0	1.5	1.0	32	35
8	1.5	1.0	1.0	1.5	25	40
9	1.5	2.0	2.0	1.5	45	34
10	1.5	2.0	2.5	1.0	31	30
11	1.5	2.5	3.0	1.0	40	31
12	1.5	3.0	3.5	1.0	30	28
13	3.0	1.0	3.0	1.0	30	40
14	3.0	1.0	4.0	--	41	40
15*	3.0	2.5	4.5	1.0	56	20
16	3.0	3.0	3.0	3.0	30	40
17*	3.0	3.0	6.0	--	53	27
18*	3.0	4.0	7.0	--	48	33
19	3.0	5.0	8.0	--	32	36
20	5.0	2.5	6.5	1.0	41	35
21	5.0	3.0	4.0	4.0	28	53
22	5.0	3.0	6.0	2.0	37	46
23	5.0	3.0	8.0	--	46	38

[a] Reaction was run in the presence of 5% Pd(dba)_2 at 100 °C in DMSO using 5 equiv of 1,5-hexadiene.

Careful examination of the results in Table 14 shows that the lithium cation appears to be a more important component than the tetra-n-butylammonium cation in the reaction system, because the desired coupling product 15 can be obtained in good yields in the absence of

n -Bu$_4$N$^+$ (entries 1-3, 14, 17-19, 23), but when this reaction was run in the absence of the lithium cation, none of the expected product **15** was observed (entries 4 - 6).
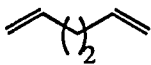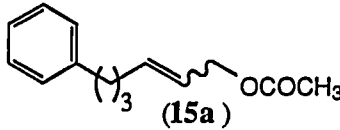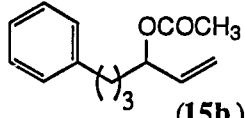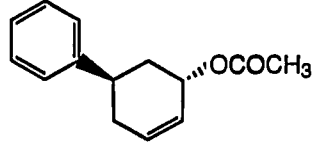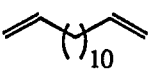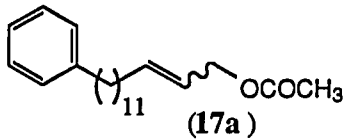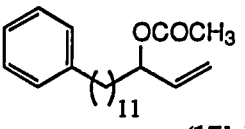
It should be pointed out that the use of acetate nucleophile in these reactions provided an inseparable mixture of both regioisomers and stereoisomers. This is not observed in the coupling of iodobenzene and 1,5-hexadiene with carbon or nitrogen nucleophiles. The ^{1}H NMR spectrum suggested the existence of a regioisomer which was formed by attack of the acetate anion on the more substituted carbon of the π-allyl unit. Careful examination of the ^{1}H NMR spectrum revealed that the primary acetate product was a mixture of E and Z isomers in a ratio of 5 : 1. In summary, the reaction of iodobenzene, 1,5-hexadiene, and lithium acetate in the presence of a catalytic amount of palladium(0) proceeds pretty well and affords the corresponding allylic acetate derivatives in moderate to good yields, unfortunately, with a low degree of regio- and stereoselectivity.

Having gained an understanding of the factors that influence the reaction, the scope and limitations of the coupling process were explored with several other dienes and aryl iodides to determine if the corresponding allylic acetates could be formed. The results of this work are summarized in Table 15. In each case, the coupling reaction has been attempted using either procedure A or procedure B.

As discussed earlier, all of the coupling products were found to be a mixture of stereoisomers with the E-isomer predominating (E/Z = ~5). Regioisomers formed by attack of acetate anions at the more substituted carbon of the π-allyl unit were also detected in the product mixture when acyclic nonconjugated dienes were employed. The ratio of terminal attack to internal attack is about 4-5 : 1, based on integration of the pertinent peaks in the ^{1}H NMR spectrum of the product mixture.

However, when 1,4-cyclohexadiene was used as the nonconjugated diene, a single isomer was observed by GC analysis and ^{1}H NMR spectroscopic data, because the π-allylpalladium intermediate now possesses a symmetrical structure.

Table 15. Palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and
acetate.[a]

Entry	Ar-I	Diene	Product (s)	Time (h)	% Yield[b] (Procedure)
1	C_6H_5I		(15a) (77 : 23 E/Z) + (15b) (15a : 15b = 82 : 18)	48	56 (A)
2	C_6H_5I		(16)	24	57 (A) 57 (B)
3[c]	C_6H_5I		(17a) (75 : 25 E/Z) + (17b) (17a : 17b = 78 : 22)	48	23 (A)

[a] Reaction was run in the presence of 5% Pd(dba)$_2$ at 100 °C in DMSO using 5 equiv of diene.

[b] Isolated yield.

[c] 2.5 Equiv of diene were used.

Table 15. Continued
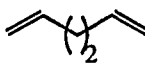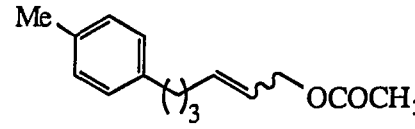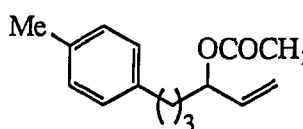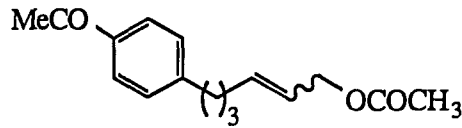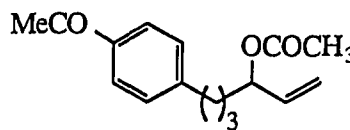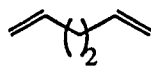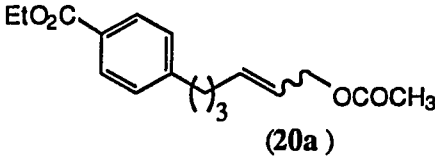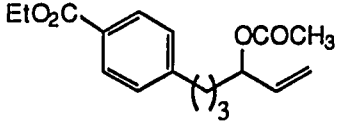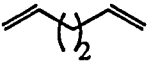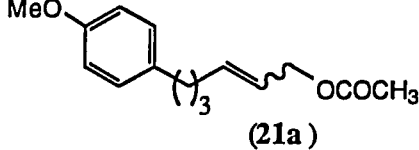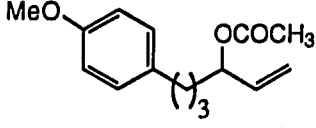
Entry	Ar-I	Diene	Product (s)	Time (h)	% Yield[b] (Procedure)
4	p-MeC$_6$H$_5$I		(18a) (83 : 17 E/Z) + (18b) (18a : 18b = 85 : 15)	60	37 (A) 38 (B)
5	p-MeCOC$_6$H$_5$I		(19a) (88 : 12 E/Z) + (19b) (19a : 19b = 80 : 20)	24	35 (B)

Table 15. Continued

Entry	Ar-I	Diene	Product (s)	Time (h)	% Yield[b] (Procedure)
6	p-EtO$_2$CC$_6$H$_5$I		(20a) (81 : 19 E/Z) + (20b) (20a : 20b = 90 : 10)	24	58 (B)
7	p-MeOC$_6$H$_5$I		(21a) (75 : 25 E/Z) + (21b) (21a : 21b = 89 : 11)	72	47 (B)

Various aryl iodides were allowed to react with 1,5-hexadiene and acetate using Pd(dba)$_2$

as the catalyst to furnish the corresponding allylic acetate derivatives in decent yields. The

effect of the substitutuent on the aryl iodide was studied. It was found that electron-donating

substituents attached to the aryl ring slow the coupling reactions, changing the reaction from a one day process to a three day process, but decent yields are still attainable (entries 4 and 7). Electron-withdrawing substituents seem to increase the reaction rate, but have no profound effect on the yield of product (entries 5 and 6).

As mentioned in the introductory section of this section, thus far, no generally useful synthetic method to prepare aryl allylic ethers from phenols and π-allylpalladium compounds has appeared. Since allylic aryl ethers are very important in organic synthesis as starting materials for thermal[44] and Lewis acid-catalyzed[45] Claisen rearrangements, phenol has been examined as an oxygen nucleophile in the palladium-catalyzed coupling of aryl iodides and nonconjugated dienes.

Iodobenzene was allowed to couple with 1,5-hexadiene and phenol under the same conditions as used for carbon nucleophiles to afford a 4:1 ratio of regioisomers **22a** and **22b** (eq 44) in a combined yield of 63%. Apparently compound **22b** is formed by attack of
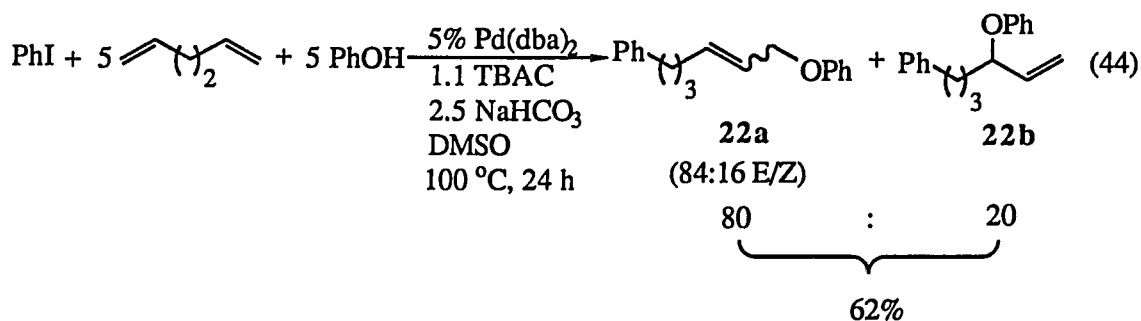
the phenoxide anion at the more substituted carbon of the π-allyl unit. It was also observed that compound **22a** was a stereoisomeric mixture with the E isomer predominating ($E:Z = \sim 5$), which was evident from the ^{1}H NMR spectrum.

The use of oxygen nucleophiles, such as acetate and phenol, results in dramatically reduced regioselectivity and stereoselectivity. This phenomenon has also been observed by Larock and Stolz-Dunn[11] (see eq 9) and Larock and Lee[46] (eq 45).
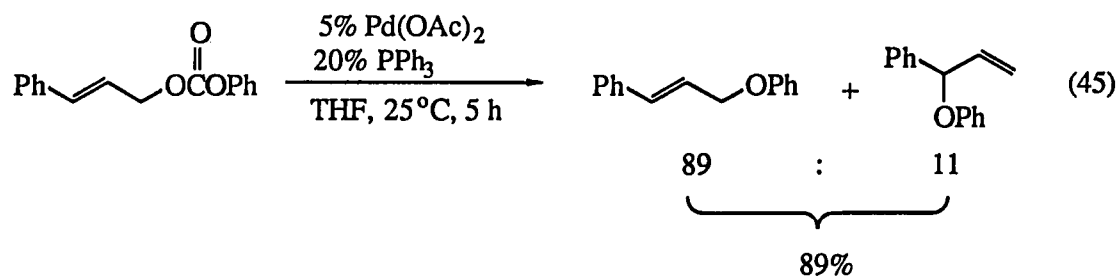
$$Ph\diagdown\diagup\diagdown OCOPh \xrightarrow[\text{THF, 25°C, 5 h}]{\substack{5\% \text{ Pd(OAc)}_2 \\ 20\% \text{ PPh}_3}} Ph\diagdown\diagup\diagdown OPh + \underset{OPh}{Ph\diagdown\diagup\diagup} \qquad (45)$$

89 : 11

89%

CONCLUSION

The results presented in this section of the dissertation provide a unique synthetic methodology in which a new carbon-carbon bond and a new carbon-nitrogen or carbon-oxygen bond are generated in a single one pot process. The process involves the palladium-catalyzed coupling of aromatic iodides and nonconjugated dienes with nitrogen and oxygen nucleophiles.

A variety of amines and azide anion has been used as representative nitrogen nucleophiles in this coupling process, and the reaction works well for both acyclic and cyclic nonconjugated dienes with a high degree of regio- and stereoselectivity; however, when oxygen nucleophiles, such as acetate anion and phenoxide anion, were employed in this coupling process, an inseparable mixture of regio- and stereoisomers was isolated. This process is remarkably versatile, giving good yields for a wide variety of heteroatom-containing nucleophiles. A considerable number of functional groups can also be accommodated.

Further work has been considered to apply this novel palladium-catalyzed cross coupling methodology to the synthesis of some naturally occurring products with unique structures. Some efforts have been made on the preparation of some pyridine alkaloid analogues and several promising results have been achieved, which will be discussed in the next section of this dissertation.

EXPERIMENTAL SECTION

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz, respectively. All infrared spectra were recorded either on an IBM IR/98 FT-IR spectrometer or a Beckmann 4250 spectrometer. GC-MS data were recorded on a Finnigan MS-50 mass spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Gas chromatographic analyses were conducted on an HP 5890 gas chromatograph equipped with an HP-1 Megabore column. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O]. Flash chromatography was carried out on 230 - 400 mesh silica gel or aluminum oxide (activated neutral, Brockman I).

Reagents

All aryl iodides, nonconjugated dienes and nitrogen nucleophiles were used as purchased from Aldrich, Fluka and Wiley without prior purification. Tetra-n-butylammonium chloride (TBAC) was purchased from Lancaster Co., Chemical Dynamics Co. or Aldrich. Tetra-n-butylammonium acetate was purchased from Aldrich and kept dry in a desiccator. Sodium bicarbonate, lithium chloride and lithium acetate were available from Fisher Inc. The solvent dimethylsulfoxide (DMSO) and others were purchased from Fisher and used without further purification. $Pd(dba)_2$ and $Pd(OAc)_2$ were generously provided by Johnson Matthey, Inc.

General procedure for the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and amine nucleophiles

To a culture tube (16 x 125 mm) with a micromagnetic stirring bar was added tetra-*n*-butylammonium chloride (TBAC) (0.306 g, 1.10 mmol) and bis(dibenzylideneacetone)palladium(0) (0.014 g, 0.025 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 2 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then the aryl iodide (0.50 mmol) was added, followed by the nonconjugated diene (1.25-2.50 mmol) and the amine (1.25-2.50 mmol). The culture tube was sealed with a cap lined with Teflon after the addition of all reagents and the reaction mixture was stirred at 100 °C for the period of time which is indicated in Tables 4 and 5. The reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous sodium chloride solution (10 mL), and extracted with diethyl ether three times (10 mL x 3). The ether layer was backwashed with brine (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to remove the solvent. Finally, the product was isolated by flash chromatography on a silica gel column.

Spectral data for coupling products prepared by the above general procedure

(E)- $C_6H_5(CH_2)_3CH=CHCH_2-N$ (ring) (1)
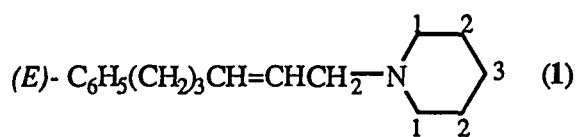
Compound **1** was isolated in 72% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of piperidine in the presence of 5% Pd(dba)$_2$ and 2.2 equivalents of *n*-Bu$_4$NCl in DMSO at 100 °C for 12 h. ^{1}H NMR (CDCl$_3$) δ 1.42 (quintet, J = 5.4 Hz, 2 H, 3-H$_2$), 1.58 (quintet, J = 5.4 Hz, 4 H, 2-H$_4$), 1.70 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$), 2.07 (q, J = 7.5 Hz, CH$_2$C=), 2.37 (br s, 4 H, 1-H$_4$), 2.60 (t, J = 7.5 Hz, 2 H, PhCH$_2$), 2.91 (d, J = 5.1

Hz, 2 H, =CCH$_2$N), 5.52 (dt, J = 15.3 Hz, J = 5.1 Hz, 1 H, vinyl), 5.57 (dt, J = 15.3 Hz, J = 7.5 Hz, 1 H, vinyl), 7.14 - 7.28 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 24.29, 25.82, 30.31, 31.81, 35.28, 54.24, 61.58, 125.53, 126.99, 128.12, 128.28, 133.66, 142.27; IR (neat) 3064, 2934, 1642 (C=C), 1495, 1119, 989 (E-CH=CH), 750, 700 cm^{-1}; mass spectrum m/z 243.19859 (calcd for C$_{17}$H$_{25}$N, 243.19870). Anal. Calcd for C$_{17}$H$_{25}$N: C, 83.89; H, 10.15. Found: C, 83.70; H, 9.99.

(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$—N [ring] (3)
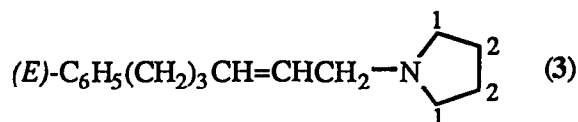
Compound 3 was isolated in 63% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of pyrrolidine in the presence of 5% Pd(dba)$_2$ and 2.2 equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 3 h. ^{1}H NMR (CDCl$_3$) δ 1.77 (m, 6 H, PhCCH$_2$, 2-H$_4$), 2.08 (q, J = 7.5 Hz, CH$_2$C=), 2.47 (br s, 4 H, 1-H$_4$), 2.62 (t, J = 7.5 Hz, 2 H, PhCH$_2$), 3.10 (d, J = 5.4 Hz, 2 H, =CCH$_2$N), 5.51 (dt, J = 15.1 Hz, J = 5.4 Hz, 1 H, vinyl), 5.56 (dt, J = 15.1 Hz, J = 7.5 Hz, 1 H, vinyl), 7.18 - 7.29 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 23.38, 30.94, 31.82, 35.30, 53.87, 58.27, 125.57, 128.00, 128.17, 128.28, 133.34, 142.39; IR (neat) 3064, 2960, 2780, 1640 (C=C), 1452, 1141, 968 (E-CH=CH), 748, 698 cm^{-1}; mass spectrum m/z 229.18195 (calcd for C$_{16}$H$_{23}$N, 229.18305). Anal. Calcd for C$_{16}$H$_{23}$N: C, 83.78; H, 10.10. Found: C, 83.39; H, 9.72.

(E)- C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$—N [ring] O (4)
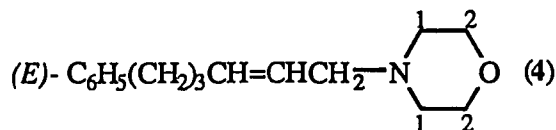
Compound 4 was isolated in 72% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 5.0 equivalents of morpholine in the presence of 5% Pd(dba)$_2$ and 2.2 equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 4 h. ^{1}H NMR (CDCl$_3$) δ 1.71 (quintet, J = 7.5 Hz, 2 H, PhCCH$_2$),

2.08 (q, J = 7.5 Hz, CH$_2$C=), 2.43 (br s, 4 H, 1-H$_4$), 2.61 (t, J = 7.5 Hz, 2 H, PhCH$_2$),

2.93 (d, J = 6.3 Hz, 2 H, =CCH$_2$N), 3.71(t, J = 4.5 Hz, 4 H, 2-H$_4$), 5.49 (dt, J = 15.3 Hz, J

= 6.3 Hz, 1 H, vinyl), 5.62 (dt, J = 15.3 Hz, J = 7.5 Hz, 1 H, vinyl), 7.14 - 7.29 (m, 5 H,

aryl); ^{13}C NMR (CDCl$_3$) δ 30.88, 31.83, 35.30, 53.44, 61.24, 66.88, 125.60, 126.15,

128.16, 128.28, 134.48, 142.19; IR (neat) 3026, 2957, 2854, 1685 (C=C), 1452, 1350 -

1285 (br), 1119, 974 (E-CH=CH), 748, 700 cm^{-1}; mass spectrum m/z 245.17805 (calcd for

C$_{16}$H$_{23}$NO, 245.17797). Anal. Calcd for C$_{16}$H$_{23}$NO: C, 78.32; H, 9.42. Found: C, 78.05;

H, 9.41.

(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$NHCH$_2$CH$_2$CH$_2$CH$_3$ (5) Compound **5** was

isolated in 50% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of

1,5-hexadiene and 2.5 equivalents of n-butylamine in the presence of 5% Pd(dba)$_2$ and 2.2

equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 8 h. ^{1}H NMR (CDCl$_3$) δ 0.93 (t, J = 7.5

Hz, 3 H, CH$_3$), 1.25 (s, 1 H, NH), 1.39 (sextet, J = 7.5 Hz, 2 H, C$\underline{H}_2$CH$_3$), 1.71(quintet, J

= 7.5 Hz, 2 H, CH$_2$), 1.81 (quintet, J = 7.2 Hz, 2 H, PhCCH$_2$), 2.12 (q, J = 7.2 Hz,

CH$_2$C=), 2.60 (t, J = 7.2 Hz, 2 H, PhCH$_2$), 2.84 (t, J = 7.5 Hz, 2 H, NCH$_2$), 3.52 (d, J =

6.9 Hz, 2 H, =CCH$_2$N), 5.69 (dt, J = 15.3 Hz, J = 6.9 Hz, 1 H, vinyl), 5.88 (dt, J = 15.3

Hz, J = 7.2 Hz, 1 H, vinyl), 7.14 - 7.29 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 13.78, 20.26,

28.85, 30.80, 31.96, 35.40, 46.12, 49.60, 123.25, 125.70, 128.26, 128.33, 137.31,

142.04; IR (neat) 3403, 3084, 2934, 1603 (C=C), 1454, 1128, 970 (E-CH=CH), 748, 698

cm^{-1}; mass spectrum m / z 231.19884 (calcd for C$_{16}$H$_{25}$N, 231.19870). Anal. Calcd for

C$_{16}$H$_{25}$N: C, 83.05; H, 10.89. Found: C, 82.84; H, 10.82.

(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$NHCH$_2$CH(CH$_3$)$_2$ (7) Compound **7** was

isolated in 60% yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of

1,5-hexadiene and 2.5 equivalents of isobutylamine in the presence of 5% Pd(dba)$_2$ and 2.2

equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 12 h. ^{1}H NMR (CDCl$_3$) δ 0.91 (d, J = 6.6 Hz, 6 H, CH$_3$'s), 1.25 (s, 1 H, NH), 1.70 (quintet, J = 7.2 Hz, 2 H, PhCCH$_2$), 1.85 (m, 1 H, CH), 2.07 (q, J = 7.2 Hz, 2 H, CH$_2$C=), 2.47 (d, J = 6.9 Hz, NCH$_2$CH), 2.60 (t, J = 7.2 Hz, 2 H, PhCH$_2$), 3.26 (d, J = 5.7 Hz, 2 H, =CCH$_2$N), , 5.62 (m, 2 H, vinyl), 7.14 - 7.29 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 20.69, 28.37, 30.94, 31.85, 35.31, 51.85, 57.39, 125.57, 128.16, 128.34, 128.83, 131.99, 142.35; IR (neat) 3301, 3084, 2955, 2804, 1603 (C=C), 1454, 1385, 1366, 1119, 970 (E-CH=CH), 733, 698 cm^{-1}; mass spectrum m/z 231.19883 (calcd for C$_{16}$H$_{25}$N, 231.19870). Anal. Calcd for C$_{16}$H$_{25}$N: C, 83.05; H, 10.89. Found: C, 82.32; H, 10.56.

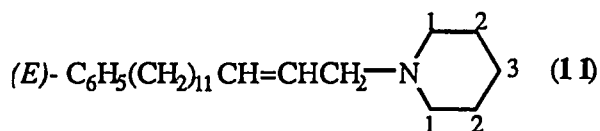**(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$NHC(CH$_3$)$_3$ (8)** Compound **8** was isolated in 60% yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 1,5-hexadiene and 2.5 equivalents of t-butylamine in the presence of 5% Pd(dba)$_2$ and 2.2 equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 24 h. ^{1}H NMR (CDCl$_3$) δ 1.13 (s, 9 H, CH$_3$'s), 1.69 (quintet, J = 7.8 Hz, 2 H, PhCCH$_2$), 2.05 (m, 3 H, CH$_2$C=, NH), 2.60 (t, J = 7.8 Hz, 2 H, PhCH$_2$), 3.16 (d J = 4.8 Hz, 2 H, =CCH$_2$N), 5.58 (m, 2 H, vinyl), 7.14 - 7.29 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 28.78, 30.86, 31.88, 35.34, 44.78, 50.73, 125.55, 128.16, 128.32, 128.83, 132.10, 142.33; IR (neat) 3360, 3024, 2966, 2804, 1603 (C=C), 1477, 1362, 1231, 978 (E-CH=CH), 746, 700 cm^{-1}; mass spectrum m/z 231.19829 (calcd for C$_{16}$H$_{25}$N, 231.19870). Anal. Calcd for C$_{16}$H$_{25}$N: C, 83.05; H, 10.89; N, 6.05. Found: C, 82.72; H, 10.26; N, 6.24.

(E)-C$_6$H$_5$(CH$_2$)$_3$CH=CHCH$_2$N(CH$_2$CH$_2$CH$_3$)$_2$ (9) Compound **9** was isolated in 65% yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 1,5-hexadiene and 2.5 equivalents of di-n-propylamine in the presence of 5% Pd(dba)$_2$ and 2.2 equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 10 h. ^{1}H NMR (CDCl$_3$) δ 0.87 (t, J = 7.5

Hz, 6 H, CH$_3$'s), 1.48 (sextet, J = 7.5 Hz, 4 H, C$\underline{H_2}$CH$_3$), 1.70 (quintet, J = 7.2 Hz, 2 H,

PhCCH$_2$), 2.08 (q, J = 7.2 Hz, 2 H, CH$_2$C=), 2.42 (t, J = 7.5 Hz, 4 H, NCH$_2$'s), 2.61 (t, J

= 7.2 Hz, 2 H, PhCH$_2$), 3.04 (d, J = 6.0 Hz, 2 H, =CCH$_2$N), 5.55 (m, 2 H, vinyl), 7.16 -

7.30 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 11.89, 19.31, 30.96, 31.93, 35.33, 54.99, 55.61,

108.90, 125.63, 128.22, 128.35, 134.70, 142.29; IR (neat) 3026, 2932, 3871, 1605 (C=C),

1497, 1454, 1078, 972 (E-CH=CH), 746, 698 cm^{-1}; mass spectrum m/z 259.22978 (calcd

for C$_{18}$H$_{29}$N, 259.23001).
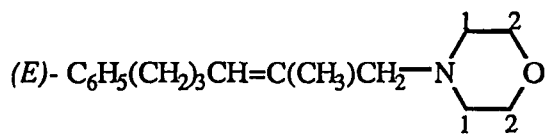
(E)- C$_6$H$_5$(CH$_2$)$_3$CH=C(CH$_3$)CH$_2$—N$\langle$O (10)   Compound **10** was isolated in 62%

yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 2-methyl-1,5-

hexadiene and 2.5 equivalents of morpholine in the presence of 5% Pd(dba)$_2$ and 2.2

equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 24 h. ^{1}H NMR (CDCl$_3$) δ 1.62 (s, 3 H,

CH$_3$), 1.67 (quintet, J = 7.2 Hz, 2 H, PhCCH$_2$), 2.06 (q, J = 7.2 Hz, CH$_2$C=), 2.34 (br s, 4

H, 1-H$_4$), 2.60 (t, J = 7.2 Hz, 2 H, PhCH$_2$), 2.82 (s, 2 H, =CCH$_2$N), 3.69 (t, J = 4.0 Hz, 4

H, 2-H$_4$), 5.33 (t, J = 7.5 Hz, 1 H, vinyl), 7.14 - 7.29 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ

15.71, 27.40, 31.39, 35.59, 58.52, 67.04, 67.84, 125.63, 126.96, 128.21, 128.33, 130.07,

142.42; IR (neat) 3026, 2957, 2854, 1452, 1346, 1329, 1267, 1119, 868, 746, 700 cm^{-1};

mass spectrum m/z 259.19390 (calcd for C$_{17}$H$_{25}$NO, 259.19361). Anal. Calcd for

C$_{17}$H$_{25}$NO: C, 78.72; H, 9.71. Found: C, 78.26; H, 9.44.

(E)- C$_6$H$_5$(CH$_2$)$_{11}$CH=CHCH$_2$—N$\langle$ (11)
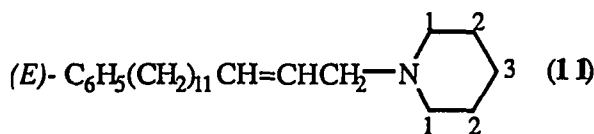
Compound **11** was isolated in 30%

yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 1,13-

1267, 1119, 868, 746, 700 cm^{-1}; mass spectrum m/z 259.19390 (calcd for $C_{17}H_{25}NO$, 259.19361). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71. Found: C, 78.26; H, 9.44.
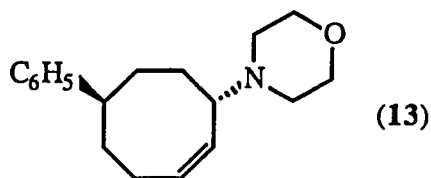
(E)- $C_6H_5(CH_2)_{11}CH=CHCH_2$—N (structure) 3 (11)

Compound **11** was isolated in 30% yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 1,13-tetradecadiene and 2.5 equivalents of piperidine in the presence of 5% $Pd(dba)_2$ and 2.2 equivalents of n-Bu_4NCl in DMSO at 100 °C for 36 h. ^1H NMR ($CDCl_3$) δ 1.25 (br m, 16 H, CH_2's), 1.60 (br m, 8 H, $PhCCH_2$, 2-H_4, 3-H_2), 2.01 (q, J = 7.5 Hz, 2 H, CH_2C=), 2.39 (br s, 4 H, 1-H_4), 2.59 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.91 (d, J = 5.7 Hz, 2 H, =CCH_2N), 5.52 (dt, J = 15.1 Hz, J = 5.7 Hz, 1 H, vinyl), 5.57 (dt, J = 15.1 Hz, J = 7.5 Hz, 1 H, vinyl), 7.15 - 7.29 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 24.29, 25.77, 29.57 (br 8 C), 31.49, 32.33, 35.95, 54.25, 61.62, 125.44, 128.09, 128.11, 128.29, 134.65, 142.84; IR (neat) 3026, 2928, 2854, 1495, 1466, 1119, 972 (E-CH=CH), 733, 698 cm^{-1}; mass spectrum m/z 355.31524 (calcd for $C_{25}H_{41}N$ 355.32390).

(structure) (12) (structure)
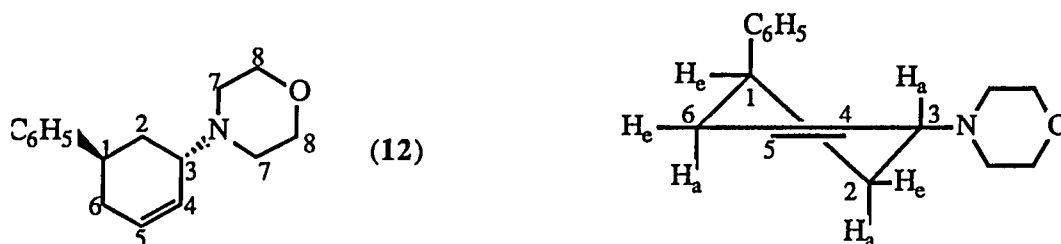
Compound **12** was isolated in 78% yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 1,4-cyclohexadiene and 2.5 equivalents of morpholine in the presence of 5% $Pd(dba)_2$ and 2.2 equivalents of n-Bu_4NCl in DMSO at 100 °C for 12 h. ^1H NMR ($CDCl_3$) δ 1.74 (ddd, J = 13.5 Hz, J = 11.1 Hz, J = 4.2 Hz, 1 H, 2-H_a), 2.12 (ddd, J = 13.5 Hz, J = 4.2 Hz, J = 2.7 Hz, 1 H, 2-H_e,), 2.16 (m, 1 H, 6-H_a), 2.37 (dt, J = 18.2 Hz, J

1600, 1488, 1452, 1119, 1033, 738, 698 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 78.16; H, 8.68.

(13)

Compound **13** was isolated in 42% yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 1,5-cyclooctadiene and 2.5 equivalents of morpholine in the presence of 5% Pd(dba)$_2$ and 2.2 equivalents of n-Bu$_4$NCl in DMSO at 100 °C for 24 h. ^{1}H NMR (CDCl$_3$) δ 1.72 (m, 2 H, CH$_2$), 1.83 - 2.12 (m, 4 H, CH$_2$'s), 2.48 (m, 2 H, CH$_2$), 2.58 (br s, 4 H, CH$_2$NCH$_2$), 2.72 (m, 1 H, PhCH), 3.36 (m, 1 H, CHN), 3.73 (t, J = 4.5 Hz, 4 H, CH$_2$OCH$_2$), 5.67 (m, 1 H, vinyl), 5.82 (m, 1 H, vinyl), 7.11 - 7.28 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 25.15, 31.79, 33.40, 37.53, 48.33, 49.85, 63.74, 67.26, 125.50, 126.82, 128.26, 128.66, 131.35, 150.02; IR (neat) 3024, 2924, 2854, 1601, 1452, 1281, 1117, 1016, 910, 733, 702 cm^{-1}; mass spectrum m/z 271.40428 (calcd for $C_{18}H_{25}NO$, 271.40487). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.29. Found: C, 79.88; H, 8.96.

Preparation of Compound (6)

(E)-**C₆H₅(CH₂)₃CH=CHCH₂NHC₆H₅**

(E)-$C_6H_5(CH_2)_3CH{=}CHCH_2NHC_6H_5$

To a culture tube (20 x 150 mm) with a micromagnetic stirring bar was added sodium bicarbonate (0.205 g, 2.50 mmol), tetra-n-butylammonium chloride (TBAC) (0.612 g, 2.20 mmol) and bis(dibenzylideneacetone)palladium(0) (0.028 g, 0.050 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 4 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then iodobenzene (0.204 g, 1.00 mmol) was added, followed by 1,5-hexadiene (0.213 g, 2.50 mmol) and aniline (0.242 g, 2.50

mmol). The culture tube was sealed with a screw cap lined with Teflon after the addition of all reagents and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous sodium chloride solution (20 mL), and extracted with diethyl ether three times (20 mL x 3). The ether layer was backwashed with brine (40 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to remove the solvent. The crude product was purified by flash chromatography on a silica gel column using 1:4 EtOAc/hexane to give compound 6 (0.136 g, 66% yield). ^1H NMR ($CDCl_3$) δ 1.70 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.08 (q, J = 7.5 Hz, 2 H, CH_2C=), 2.60 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 3.68 (d, J = 6.0 Hz, 2 H, =CCH_2N), 5.57 (dt, J = 15.2 Hz, J = 6.0 Hz, 1 H, vinyl), 5.66 (dt, J = 15.2 Hz, J = 7.5 Hz, 1 H, vinyl), 6.60 (m, 2 H, aryl), 7.14 -7.28 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.84, 31.79, 35.28, 45.95, 112.92, 117.31, 125.61, 127.22, 128.19, 128.34, 129.06, 132.62, 142.23, 148.06; IR (neat) 3414, 3053, 3026, 2932, 1603, 1504, 1452, 1310, 1252, 970 (E-CH=CH), 748, 694 cm^{-1}; mass spectrum m/z 251.16688 (calcd for $C_{18}H_{21}N$, 251.16740). Anal. Calcd for $C_{18}H_{21}N$: C, 86.01 ; H, 8.42. Found: C, 85.06; H, 8.48.

Preparation of compound (14)

(E)-$C_6H_5(CH_2)_3CH=CHCH_2N_3$

To a culture tube (16 x 125 mm) with a micromagnetic stirring bar was added sodium azide (0.048 g, 0.75 mmol) and bis(dibenzylideneacetone)palladium(0) (0.014 g, 0.025 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 2 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then iodobenzene (0.102 g, 0.50 mmol) and 1,5-hexadiene (0.205 g, 2.50 mmol) was added into the culture tube, which was sealed with a screw cap lined with Teflon. The reaction mixture was stirred at 100 °C for 12 hours. The reaction mixture was allowed to cool to room temperature, diluted

with saturated aqueous sodium chloride solution (10 mL), and extracted with diethyl ether three times (10 mL x 3). The ether layer was backwashed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to remove the solvent. The crude product was purified by flash chromatography on a silica gel column using 1: 20 EtOAc/hexane to give compound **14** (0.047 g, 47% yield). ^1H NMR (CDCl$_3$) δ 1.74 (quintet, J = 7.2 Hz, 2 H, PhCCH$_2$), 2.13 (q, J = 7.2 Hz, 2 H, CH$_2$C=), 2.63 (t, J = 7.2 Hz, 2 H, PhCH$_2$), 3.70 (d, J = 6.9 Hz, 2 H, CH$_2$N$_3$), 5.54 (dt, J = 15.2 Hz, J = 6.9 Hz, 1 H, vinyl), 5.76 (dt, J = 15.2 Hz, J = 7.2 Hz, 1 H, vinyl), 7.16 - 7.33 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 30.89, 31.68, 35.21, 52.81, 123.23, 125.72, 128.29, 128.37, 136.50, 142.06; IR (neat) 3065, 2934, 2097 (N=N=N), 1452, 1240, 970 (*E*-CH=CH), 748, 700 cm^{-1}; mass spectrum m/z 201.12640 (calcd for C$_{12}$H$_{15}$N$_3$, 201.12660). Anal. Calcd for C$_{12}$H$_{15}$N$_3$: C, 71.61; H, 7.51. Found: C, 72.10; H, 7.44.

General procedure for the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and lithium acetate.

Procedure A   To a culture tube (16 x 125 mm) with a micromagnetic stirring bar was added tetra-*n*-butylammonium chloride (TBAC, 0.138 g, 0.50 mmol), lithium chloride (0.031 g, 0.75 mmol), lithium acetate (0.10 g, 1.5 mmol), and bis(dibenzylideneacetone)palladium(0) (0.014 g, 0.025 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 2 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then the aryl iodide (0.50 mmol) was added, followed by the nonconjugated diene (2.50 mmol). The culture tube was sealed with a screw cap lined with Teflon after the addition of all reagents, and the reaction mixture was stirred at 100 °C for the period of time required. The reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous sodium chloride solution (10 mL), and extracted with diethyl ether three times (10 mL x 3). The ether layer was backwashed with brine (20 mL), dried over anhydrous Na_2SO_4 and

evaporated under reduced pressure to remove the solvent. Finally, the product was isolated by flash chromatography on a silica gel column.

Procedure B   These procedure is the same as procedure A, except that 3.0 - 4.0 equivalents of lithium chloride are used instead of 1.5 equivalents of lithium chloride and 1.0 equivalent of tetra-*n*-butylammonium chloride (TBAC).

Spectral data for coupling products prepared by the above general procedure

Compounds 15a and 15b   These compounds were obtained as an inseparable 82:18 mixture of regioisomers 15a : 15b in 56% combined yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,5-hexadiene and 3.0 equivalents of lithium acetate using the general procedure A. The ratio of regioisomers, as well as the *E*- and *Z*-isomer ratio of compound 15a, was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic and allylic hydrogens. ^{1}H NMR (CDCl$_3$) δ 1.71 (m, 2 H, PhCCH$_2$), 2.05 (s, 0.66 H, CH$_3$ in 15b), 2.06 (s, 3 H, CH$_3$ in 15a), 2.08 (m, 2 H, CH$_2$C= in 15a, CH$_2$CHO in 15b), 2.62 (t, J = 7.5 Hz, 2 H, PhCH$_2$), 4.52 (d, J = 6.3 Hz, 2 H, =CCH$_2$O, *E*-15a), 4.60 (d, J = 6.3 Hz, 0.56 H, =CCH$_2$O, *Z*-15a), 5.14 (dd, J = 9.6 Hz, J = ~1 Hz, 0.22 H, C=CH in 15b) 5.16 (dd, J = 15.9 Hz, J = ~1 Hz, 0.22 H, C=CH in 15b), 5.25 (m, 0.44 H, C=CH, CHO in 15b), 5.58 (m, 1 H, C=CH in 15a), 5.75 (m, 1 H, C=CH in 15a), 7.15 - 7.30 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 20.96, 30.47, 31.67, 35.26, 65.19, 116.63 (C=C in 15b), 124.14, 125.67, 128.32, 128.50, 136.00, 138.31 (C=C in 15b), 142.07, 170.08 (C=O in 15b), 170.87 (C=O in 15a) (small peaks corresponding to compound 15b were not always evident);   IR (neat) 3084, 2934, 1740 (C=O), 1497, 1376, 1234, 1026, 968, 748, 700 cm^{-1};   ·mass spectrum m/z 218.13119 (calcd for C$_{14}$H$_{18}$O$_2$, 218.13068).

(16)
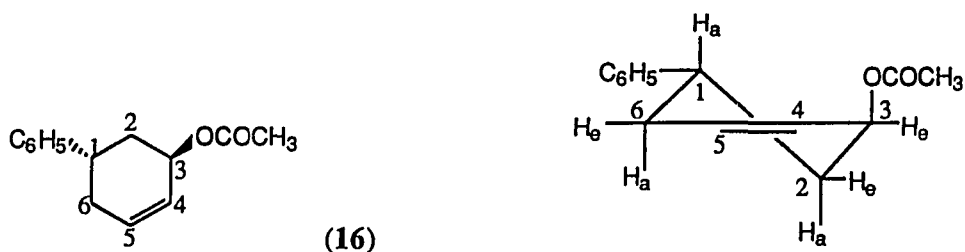
Compound **16** was isolated in 57% yield from the coupling of 1.0 equivalent of iodobenzene, 5.0 equivalents of 1,4-cyclohexadiene and 3.0 equivalents of lithium acetate using the general procedures A or B. ^{1}H NMR (CDCl₃) δ 1.94 (ddd, J = 14.5 Hz, J = 11.4 Hz, J = 4.8 Hz, 1 H, 2-Hₐ), 2.06 (s, 3 H, CH₃), 2.07 - 2.17 (m, 2 H, 2-Hₑ, 6-Hₐ), 2.39 (dt, J = 16.2 Hz, J = 4.8 Hz, 1 H, 6-Hₑ), 3.04 (tt, J = 11.4 Hz, J = 4.8 Hz, 1 H, 1-Hₐ), 5.35 (br m, 1 H, 3-Hₑ), 5.88 (m, 1 H, 4-H), 6.11 (m, 1 H, 5-H), 7.21 - 7.33 (m, 5 H, aryl); ^{13}C NMR (CDCl₃) δ 21.34, 33.51, 35.09, 35.11, 67.17, 124.27, 126.28, 126.83, 128.42, 133.13, 145.49, 170.47 (C=O); IR (neat) 3030, 2916, 1730 (C=O), 1371, 1236, 1043 - 1016 (br), 760, 751, 700 cm⁻¹; mass spectrum m / z 216.11536 (calcd for C₁₄H₁₆O₂, 216.11503).

Compounds **17a** and **17b** These compounds ware obtained as an inseparable 78:22 mixture of regioisomers **17a** : **17b** in 23% combined yield from the coupling of 1.0 equivalent of iodobenzene, 2.5 equivalents of 1,13-tetradecadiene and 3.0 equivalents of lithium acetate using the general procedure A. The ratio of regioisomers and the *E / Z* ratio of compound **17a** was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic and allylic hydrogens. ^{1}H NMR (CDCl₃) δ 1.26 (m, 16 H, CH₂'s), 1.63 (m, 2 H, PhCCH₂), 2.02 (m, 2 H, CH₂C= in **17a**, CH₂CHO in **17b**), 2.05 (s, 3 H, CH₃) , 2.59 (t, J = 7.5 Hz, 2 H, PhCH₂), 4.50 (d, J = 6.6 Hz, 2 H, =CCH₂O, *E*-**17a**), 4.61 (d, J = 6.9 Hz, 0.66 H, =CCH₂O, *Z*-**17a**), 5.15 (dd, J = 10.6 Hz, J = ~1 Hz, 0.28 H, C=CH in **17b**), 5.18 (dd, J = 16.9 Hz, J = ~1 Hz, 0.28 H, C=CH in **17b**), 5.24 (m, 0.28 H, CHO in **17b**), 5.38 (m, 0.28 H, C=CH in **17b**), 5.55 (m, 1 H, C=CH in **17a**), 5.75 (m, 1 H, C=CH in **17a**), 7.14 - 7.29 (m, 5 H, aryl); ^{13}C NMR (CDCl₃) δ 21.12, 29.56 (br 8 C),

31.52, 35.28, 35.98, 65.33, 116.44 (C=C in **17b**), 123.60, 125.49, 128.16, 128.33, 136.72, 138.31 (C=C in **17b**), 142.87, 170.06 (C=O in **17b**), 170.83 (C=O in 17a) (small peaks corresponding to compound **17b** were not always evident); IR (neat) 3063, 2924, 1742 (C=O), 1495, 1369, 1236, 1024, 968, 746, 700 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.94; H, 10.36. Found: C, 79.02; H, 9.77.

Compounds 18a and 18b   These compounds were obtained as an inseparable 85:15 mixture of regioisomers **18a : 18b** in 37-38% yields from the coupling of 1.0 equivalent of *p*-tolyl iodide, 5.0 equivalents of 1,5-hexadiene and 3.0 equivalents of lithium acetate using the general procedure A or B. The ratio of regioisomers and the *E / Z* ratio of compound **18a** were determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic and allylic hydrogens. ^{1}H NMR (CDCl$_3$) δ 1.69 (m, 2 H, ArCCH$_2$), 2.04 (s, 0.54 H, CH$_3$CO in **18b**), 2.05 (s, 3 H, CH$_3$CO in **18a**), 2.08 (m, 2 H, CH$_2$C= in **18a**, CH$_2$CHO in **18b**), 2.31 (s, 3 H, CH$_3$), 2.57 (t, J = 7.5 Hz, 2 H, ArCH$_2$), 4.50 (d, J = 6.3 Hz, 2 H, =CCH$_2$O, *E*-**18a**), 4.60 (d, J = 6.3 Hz, 0.64 H, =CCH$_2$O, *Z*-**18a**), 5.14 (dd, J = 9.6 Hz, J = ~1 Hz, 0.18 H, C=CH in **18b**), 5.16 (dd, J = 15.9 Hz, J = ~1 Hz, 0.18 H, C=CH in **18b**), 5.24 (m, 0.36 H, C=CH, CHO in **18b**), 5.58 (m, 1 H, C=CH in **18a**), 5.75 (m, 1 H, C=CH in **18a**), 7.03 - 7.10 (m, 4 H, aryl); ^{13}C NMR (CDCl$_3$) δ 21.01, 21.03, 30.65, 31.73, 34.86, 65.23, 116.63 (C=C in **18b**), 124.12, 126.75, 128.24, 128.94, 135.11, 136.07, 136.41 (C=C in **18b**), 170.07 (C=O in **18b**), 170.80 (C=O in **18a**) (small peaks corresponding to compound **18b** were not always evident); IR (neat) 3020, 2924, 2860, 1740 (C=O), 1456, 1371, 1232, 1022, 968, 806 cm^{-1}; mass spectrum m/z 232.14584 (calcd for $C_{15}H_{20}O_2$, 232.14633).

Compounds 19a and 19b   These compounds were obtained as an inseparable 80:20 mixture of regioisomers **19a : 19b** in 35% combined yield from the coupling of 1.0

equivalent of *p*-iodoacetophenone, 5.0 equivalents of 1,5-hexadiene, and 3.0 equivalents of lithium acetate using the general procedure B. The ratio of regioisomers and the E/Z ratio of compound **19a** were determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic and allylic hydrogens. ^{1}H NMR (CDCl$_3$) δ 1.66 (m, 0.40 H, ArCCH$_2$ in **19b**), 1.74 (quintet, J = 7.5 Hz, 2 H, ArCCH$_2$ in **19a**), 2.06 (s, 3 H, CH$_3$CO$_2$), 2.09 (m, 2 H, CH$_2$C= in **19a**, CH$_2$CHO in **19b**), 2.58 (s, 3 H, CH$_3$CO), 2.68 (t, J = 7.5 Hz, 2 H, ArCH$_2$), 4.51 (d, J = 6.3 Hz, 2 H, =CCH$_2$O, *E*-**19a**), 4.58 (d, J = 6.3 Hz, 0.28 H, =CCH$_2$O, *Z*-**19a**), 5.16 (dd, J = 10.5 Hz, J = ~1 Hz, 0.20 H, C=CH in **19b**), 5.16 (dd, J = 16.2 Hz, J = ~1 Hz, 0.20 H, C=CH in **19b**), 5.24 (m, 0.40 H, C=CH, CHO in **19b**), 5.58 (m, 1 H, C=CH in **19a**), 5.75 (m, 1 H, C=CH in **19a**), 7.15 (d, J = 8.4 Hz, 2 H, aryl), 7.87 (d, J = 8.4 Hz, 2 H, aryl); ^{13}C NMR (CDCl$_3$) δ 20.94, 28.49, 30.07, 31.59, 35.21, 65.06, 116.18 (C=C in **19b**), 124.46, 128.53, 128.54, 134.94, 135.62, 136.14 (C=C in **19b**), 147.9, 170.04 (C=O in **19b**), 170.73 (C=O in **19a**), 197.71 (C=O) (small peaks corresponding to compound **19b** were not always evident); IR (neat) 3003, 2935, 2862, 1738 (C=O), 1682 (C=O), 1687, 1414, 1450, 1238 (br), 1024, 960, 834 cm^{-1}; mass spectrum m/z 260.14130 (calcd for C$_{16}$H$_{20}$O$_3$, 260.14124).

Compounds **20a** and **20b**   These compounds were obtained as an inseparable 90:10 mixture of regioisomers **20a** : **20b** in 58% yield from the coupling of 1.0 equivalent of ethyl *p*-iodobenzoate, 5.0 equivalents of 1,5-hexadiene, and 3.0 equivalents of lithium acetate using the general procedure B. The ratio of regioisomers and the E/Z ratio of compound **20a** were determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic and allylic hydrogens. ^{1}H NMR (CDCl$_3$) δ 1.38 (t, J = 7.2 Hz, 3 H, CH$_2$CH$_3$), 1.64 (m, 0.22 H, ArCCH$_2$ in **20b**), 1.74 (quintet, J = 7.5 Hz, 2 H, ArCCH$_2$ in **20a**), 2.06 (s, 3 H, CH$_3$CO), 2.08 (m, 2 H, CH$_2$C= in **20a**, CH$_2$CHO in **20b**), 2.67 (t, J = 7.5 Hz, 2 H, ArCH$_2$), 4.36 (q, J = 7.2 Hz, 2 H, CO$_2$CH$_2$), 4.51 (d, J = 6.3 Hz, 2 H, =CCH$_2$O in *E*-**20a**),

4.58 (d, J = 6.3 Hz, 0.22 H, =CCH$_2$O in Z-**20a**), 5.15 (dd, J = 10.5 Hz, J = ~1 Hz, 0.11 H,

C=CH in **20b**), 5.17 (dd, J = 15.0 Hz, J = ~1 Hz, 0.11 H, C=CH in **20b**), 5.24 (m, 0.22 H,

C=CH, CHO in **20b**), 5.59 (m, 1 H, C=CH in **20a**), 5.75 (m, 1 H, C=CH in **20a**), 7.22 (d,

J = 7.8 Hz, 2 H, aryl), 7.95 (d, J = 7.8 Hz, 2 H, aryl); ^{13}C NMR (CDCl$_3$) δ 14.24, 20.87,

30.06, 31.52, 35.17, 60.63, 64.97, 116.18 (C=C in **20b**), 124.24, 128.24, 128.80, 129.51,

135.39, 136.15 (C=C in **20b**), 147.42, 166.42 (C=O), 170.08 (C=O in **20b**), 170.61 (C=O

in **20a**) (small peaks corresponding to compound **20b** were not always evident); IR (neat)

2982, 2937, 2862, 1744 (br C=O), 1610, 1448, 1367, 1310 (br C-O), 1007, 1024, 970, 766,

704 cm^{-1}; mass spectrum m/z 290.15218 (calcd for C$_{17}$H$_{22}$O$_4$, 290.15181).

Compounds **21a** and **21b**   These compounds were obtained as an inseparable 89:11

mixture of regioisomers **21a** : **21b** in 47% yield from the coupling of 1.0 equivalent of *p*-

anisyl iodide, 5.0 equivalents of 1,5-hexadiene and 3.0 equivalents of lithium acetate using the

general procedure B. The ratio of regioisomers and the *E* / *Z* ratio of compound **21a** were

determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic

and allylic hydrogens. ^{1}H NMR (CDCl$_3$) δ 1.67 (m, 2 H, ArCCH$_2$), 2.03 (s, 0.54 H,

CH$_3$CO in **21b**), 2.05 (s, 3 H, CH$_3$CO in **21a**), 2.06 (m, 2 H, CH$_2$C= in **21a**, CH$_2$CHO in

21b), 2.55 (t, J = 7.5 Hz, 2 H, ArCH$_2$), 3.77 (s, 3 H, CH$_3$O), 4.50 (d, J = 6.3 Hz, 2 H,

=CCH$_2$O in *E*-**21a**), 4.59 (d, J = 6.3 Hz, 0.35 H, =CCH$_2$O in Z-**21a**), 5.14 (dd, J = 10.5

Hz, J = ~1 Hz, 0.18 H, C=CH in **21b**), 5.16 (dd, J = 18.0 Hz, J = ~1 Hz, 0.18 H, C=CH in

21b), 5.24 (m, 0.36 H, C=CH, CHO in **21b**), 5.59 (m, 1 H, C=CH in **21a**), 5.75 (m, 1 H,

C=CH in **21a**), 6.81 (d, J = 8.7 Hz, 2 H, aryl), 7.08 (d, J = 8.7 Hz, 2 H, aryl); ^{13}C NMR

(CDCl$_3$) δ 20.78, 30.31, 31.22, 33.94, 54.76, 64.97, 113.24, 116.18 (C=C in **21b**),

123.68, 128.78, 133.77, 135.62, 135.97 (C=C in **21b**), 157.23, 169.09 (C=O in **21b**),

170.36 (C=O in **21a**) (small peaks corresponding to compound **21b** were not always evident);

IR (neat) 2999, 2934, 2856, 1732 (C=O), 1612, 1512, 1450, 1300 -1229 (br C-O), 1034, 970, 831, 700 cm^{-1}; mass spectrum m/z 248.14120 (calcd for $C_{15}H_{20}O_3$, 248.14124).

Preparation of compounds 22a and 22b

To a culture tube (20 x 150 mm) with a micromagnetic stirring bar was added sodium bicarbonate (0.205 g, 2.5 mmol), tetra-n-butylammonium chloride (TBAC, 0.306 g, 1.1 mmol), phenol (0.282 g, 3.0 mmol), and bis(dibenzylideneacetone)palladium(0) (0.028 g, 0.05 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 4 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then the iodobenzene (0.204 g, 1.0 mmol) was added, followed by the 1,5-hexadiene (0.213 g, 2.5 mmol). The culture tube was sealed with a screw cap lined with Teflon after the addition of all reagents and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous sodium chloride solution (20 mL), and extracted with diethyl ether three times (20 mL x 3). The ether layer was backwashed with brine (40 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to remove the solvent. The crude product was purified by flash chromatography on a silica gel column using 1:10 EtOAc/hexane to give a 80:20 mixture of the regioisomers 22a and 22b (0.160 g, 62% yield).

The ratio of regioisomers and the E / Z ratio of compound 22a was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic and allylic hydrogens. ^{1}H NMR (CDCl$_3$) δ 1.71 (m, 2 H, PhCCH$_2$, 0.50 H, C$\underline{H}_2$CHO in 22b), 2.10 (q, J = 7.2 Hz, 2 H, CH$_2$C= in 22a), 2.60 (t, J = 7.2 Hz, 2 H, PhCH$_2$ in 22a), 2.63 (t, J = 7.2 Hz, 0.5 H, PhCH$_2$ in 22b), 4.44 (d, J = 5.7 Hz, 2 H, =CCH$_2$O in E-22), 4.49 (d, J = 5.7 Hz, 0.38 H, =CCH$_2$O in Z-22), 4.47 (m, 1 H, CHO in 22b), 5.15 (dd, J = 10.5 Hz, J = ~1 Hz, C=CH in 22b), 5.22 (dd, J = 18.1 Hz, J = ~1 Hz, 1 H, C=CH in 22b), 5.70 (m, 1 H, C=CH in 22a, 0.25 H, C=CH in 22b), 5.80 (m, 1 H, C=CH in 22a), 6.90 (m, 2 H,

aryl), 7.12 -7.27 (m, 8 H, aryl); ^{13}C NMR (CDCl$_3$) δ 30.60, 31.80, 35.30, 68.53, 114.68, 116.01 (C=C in **22b**), 120.62, 125.28, 125.66, 128.24, 128.37, 129.33, 134.88, 137.93 (C=C in **22b**), 142.16, 158.24 (aryl C-O in **22b**), 158.60 (aryl C-O); IR (neat) 3063, 3026, 2932, 1598, 1454, 1240, 1030, 1011, 752, 694 cm^{-1}. Anal. Calcd for C$_{18}$H$_{20}$O: C, 85.67 ; H, 7.98. Found: C, 85.59; H, 8.06.

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SECTION III. SYNTHESIS OF PYRIDINE ALKALOID ANALOGUES

VIA PALLADIUM(0)-CATALYZED COUPLING OF ARYL IODIDES,

NONCONJUGATED DIENES, AND NITROGEN NUCLEOPHILES

INTRODUCTION

Our study of the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes, and nucleophiles via palladium migration provides a general and very useful methodology that allows for the generation of more than one carbon-carbon or carbon-heteroatom bond at a time. Considerable functionality can be accommodated in this reaction and the palladium can migrate along a carbon chain as far as ten carbon atoms. In order to demonstrate the unique ability of this methodology to rapidly increase molecular complexity, we have examined its application to the synthesis of several naturally occurring, biologically active products, which might be synthesized in a few steps through the use of this palladium-catalyzed coupling-migration methodology.

Several pyridine alkaloids including pulo'upone,[1] niphatynes,[2] navenones,[3] anabaseine,[4] and halitoxins,[5] have been isolated from marine organisms such as molluscs, a nemertean and sponges. Kobayashi et al.[6] have reported four new pyridine alkaloids, theonelladins A - D, that exhibit potent antineoplastic activity.
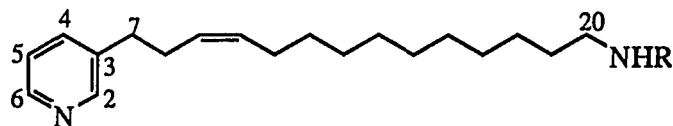

R = H   theonelladin A

R = CH$_3$ theonelladin B
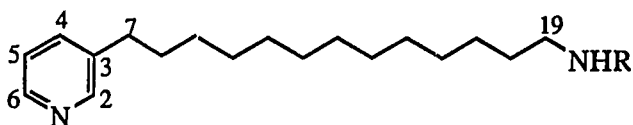
R = H   theonelladin C

R = CH$_3$ theonelladin D

During active studies on the bioactive substances from Okinawan marine organism, Kobayashi et al.[7] recently also isolated four new monosubstituted pyridine derivatives from the methanol extracts of the Okinawan sponge. These new compounds were named niphatesines A - D and shown to be antineoplastic compounds.
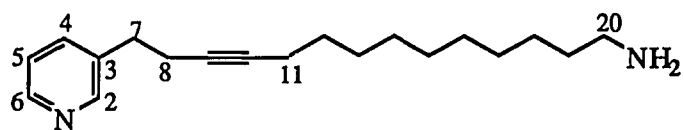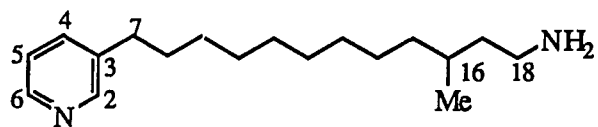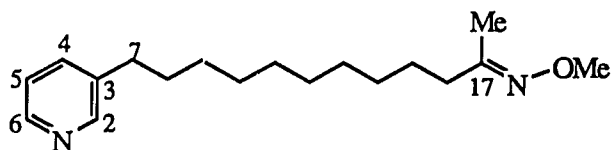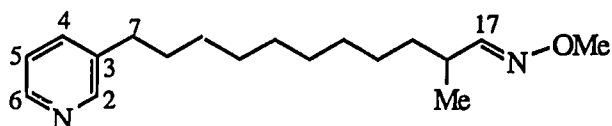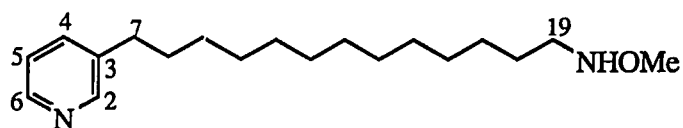
niphatesine A
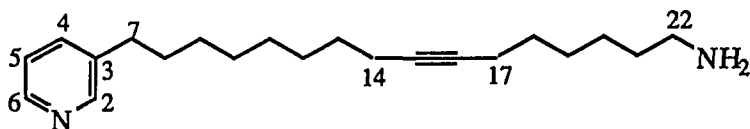
niphatesine B
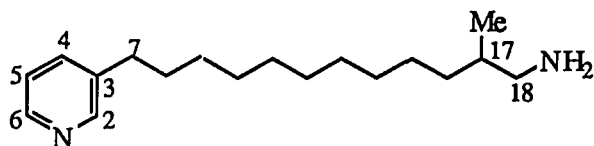
niphatesine C

niphatesine D

Four examples of sponge-derived alkylpyridines which terminate in methoxyimino or methoxyamino functions were reported by Scheuer and Carrol[8] and were named ikimine A - D.

Me
|

ikimine B

ikimine B

ikimine C
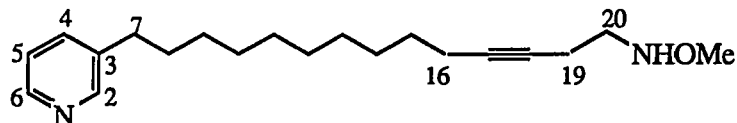
ikimine D

It is of interest to observe that theonelladin C and D, and ikimine C are long-chain saturated hydrocarbons functionalized by a pyridine group at one terminus and an amino group at the other terminus. The long-chain hydrocarbon moiety of all these pyridine alkaloids ranges from 12 to 16 carbons. These compounds would appear to be molecules which might be synthesized by our palladium-catalyzed coupling-migration methodology.

In this section, nitrogen nucleophile procedures, which were discussed in Section II of Part II of this dissertation, have been applied to the preparation of analogues of theonelladin C and D. In order to obtain the proper functionality to complete these syntheses, only one reagent, palladium on charcoal, has been used as a heterogeneous catalyst to perform several

functional group transformations. These involve hydrogenation of a carbon-carbon double bond, reduction of an alkyl azide to a primary amine, and hydrogenolysis of a benzylamine. Therefore, the synthesis of analogues of theonelladins C and D is featured here in a palladium-catalyzed total synthesis.

RESULTS AND DISCUSSION

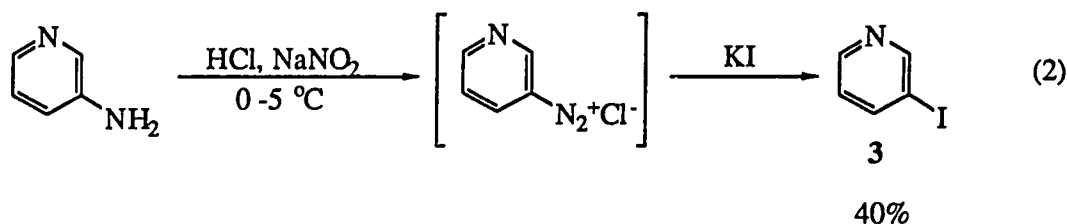The palladium-catalyzed coupling of phenyl iodide, 1,5-hexadiene and sodium azide has already been optimized as described in Section II of Part II of this thesis. This reaction was carried out in the presence of 5% bis(benzylideneacetone)palladium(0) in DMSO solvent at 100 °C without using tetra-n-butylammonium chloride (TBAC) to afford the desired allylic azide 1 in 47% yield, alongside a 24% yield of Heck product 2 (eq 1).

$$\text{PhI} + 5 \underset{}{\diagup\!\!\!\diagdown\!\!\!\diagup_2\!\!\!\diagdown} + 1.5 \text{ NaN}_3 \xrightarrow[\substack{\text{DMSO} \\ 100\,°\text{C},\ 12\ \text{h}}]{5\%\ \text{Pd(dba)}_2} \text{Ph}\underset{3}{\diagup\!\!\!\diagdown\!\!\!\diagup\!\!\!\diagdown}\text{N}_3 + \text{Ph}\underset{2}{\diagdown\!\!\!\diagup\!\!\!\diagup\!\!\!\diagdown} \quad (1)$$

$$\underset{\substack{\mathbf{1} \\ 47\%}}{} \qquad \underset{\substack{\mathbf{2} \\ 24\%}}{}$$
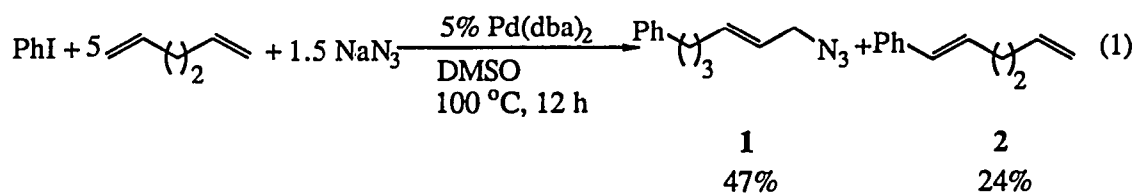
With these reaction conditions in hand, we tried to change the aryl iodide from iodobenzene to 3-iodopyridine (3) in order to fit the molecular structure of theonelladins C and D. Although 3-iodopyridine (3) is not commercially available, the procedure for the preparation of this aryl iodide is relatively simple. Based on the procedure reported by Shnaidman et al.,[9] 3-iodopyridine (3) was prepared in 40% yield by the reaction of 3-aminopyridine with concentrated hydrochloric acid and sodium nitrite at 0 - 5 °C, followed by treatment with potassium iodide (eq 2).

$$\underset{\text{NH}_2}{\overset{\text{N}}{\diagup\!\!\!\diagdown}} \xrightarrow[0\text{-}5\,°\text{C}]{\text{HCl, NaNO}_2} \left[\underset{\text{N}_2^+\text{Cl}^-}{\overset{\text{N}}{\diagup\!\!\!\diagdown}} \right] \xrightarrow{\text{KI}} \underset{\substack{\text{I} \\ \mathbf{3}}}{\overset{\text{N}}{\diagup\!\!\!\diagdown}} \quad (2)$$

$$40\%$$

Initially the coupling of 3-iodopyridine, 1,5-hexadiene and sodium azide was conducted under the same reaction conditions as those shown in equation 1. Fortunately, the presence of

the pyridine functional group did not totally inhibit the palladium-catalyzed coupling process and the desired product **4** was obtained in 36% yield, along with the Heck product **5** in 35% yield (eq 3).
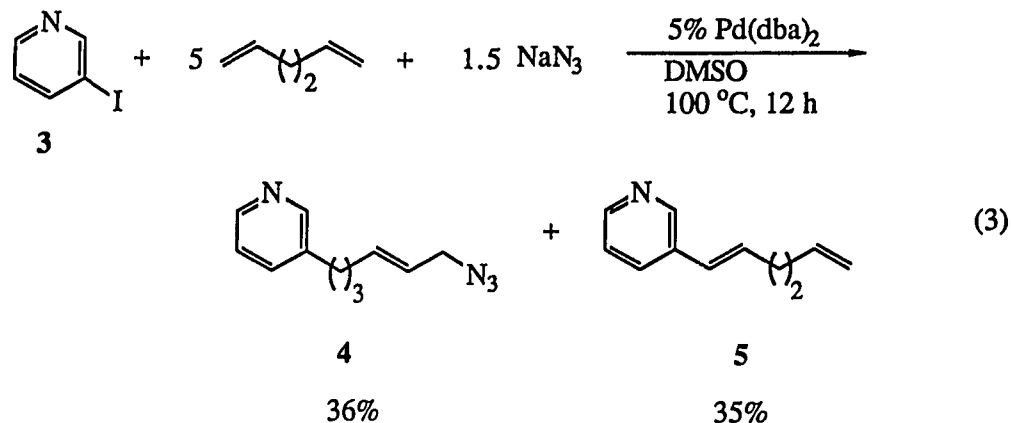
In an attempt to improve the yield of compound **4**, the palladium-catalyzed coupling (see eq 3) was investigated under various conditions. The results are summarized in Table 1.

Table 1. Reaction conditions for the palladium-catalyzed coupling of **3**, 1,5-hexadiene, and NaN$_3$.[a]

Entry	NaN$_3$ (equiv)	Additive (equiv) LiCl	TBAC	Temp (°C)	Time (h)	% Isolated Yield 4	5
1	1.5	---	---	100	12	36	35
2	1.5	1.0	---	100	24	46	25
3	1.5	1.5	---	100	24	40	26
4	1.5	2.0	---	100	48	31	49
5	1.5	1.0	1.0	100	12	41	30
6	1.5	3.0	1.0	100	24	42	32
7	3.0	1.0	---	100	12	31	21
8	1.5	1.0	---	80	36	43	33

[a] Reaction was run in the presence of 5% Pd(dba)$_2$ in DMSO using 5 equiv of 1,5-hexadiene.

The best result is presented in entry 2 in which 1.5 equivalents of sodium azide is used as the nucleophile in the presence of 1 equivalent of lithium chloride. The addition of lithium chloride (1.0 - 1.5 equiv) favors the formation of coupling product **4**; however, the addition of more LiCl decreased the reaction rate dramatically without any improvement in the selectivity (entry 4). The effect of TBAC was examined, but no significant improvement was observed (entries 5 and 6). When the reaction was conducted at a lower temperature (80 °C), the reaction required much more time (36 h) and resulted in a yield of **4** similar to that in entry 2.

Since the addition of lithium chloride appears to favor the formation of the desired product **4** and lithium azide shows greater solubility than sodium azide in the solvent DMSO , lithium azide (commercially available) was chosen as an alternative azide anion source to participate in the coupling reaction. The results are summarized in Table 2.

Table 2. Reaction conditions for the palladium-catalyzed coupling of **3**, 1,5-hexadiene, and LiN$_3$.[a]

Entry	LiN$_3$ (equiv)	Additive (equiv)		% Isolated Yield	
		LiCl	TBAC	4	5
1	1.1	1.0	---	30	32
2	1.5	1.0	---	55	14
3	3.0	1.0	---	44	32
4	5.0	1.0	---	32	30
5	1.5	2.0	---	36	33
6	1.5	3.0	---	40	31
7	1.5	1.0	1.0	35	28

[a] Reaction was run in the presence of 5% Pd(dba)$_2$ in DMSO at 100 °C for 12 h using 5 equiv of 1,5-hexadiene.

It is noteworthy that the yield of migration compound **4** can be increased to 55%, when 1.5

equivalents of lithium azide instead of sodium azide was used as the nucleophile (entry 2) (eq

4). The application of lithium azide keeps the reaction system totally homogeneous even at

$$\text{(4)}$$
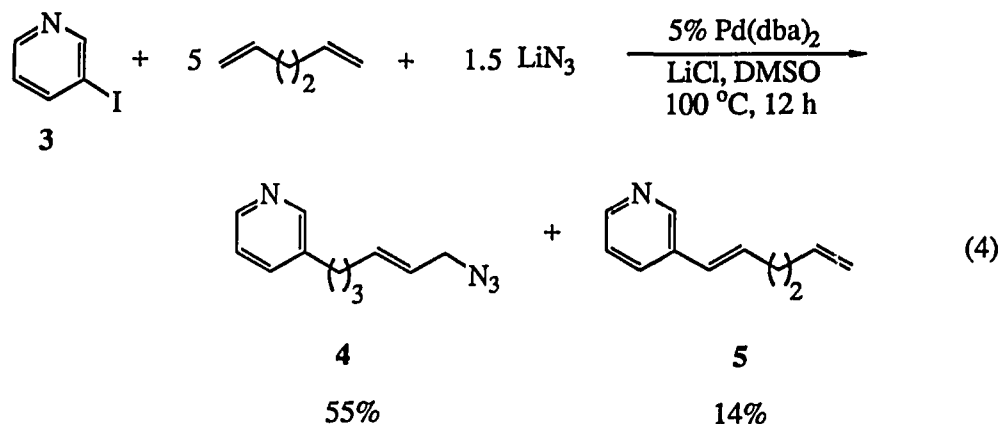
room temperature. The use of additional lithium azide promotes the generation of Heck

product **5** (entries 3 and 4). The best yield of **4** was obtained when using 1.0 equivalent of

LiCl. The addition of TBAC sharply reduced the yield of the desired product (entry 7).

The coupling of 3-iodopyridine, 1,11-dodecadiene and lithium azide proceeded smoothly

under the reaction conditions shown in equation 4; however, an inseparable 1 : 1 mixture of the

desired coupling product and Heck product was obtained in a combined yield of 75%.

The studies on the palladium-catalyzed coupling of 3-iodopyridine, 1,5-hexadiene and

azide indicate that the pyridine functional group does not poison the palladium catalyst system

or interfere with the palladium migration mechanism, even though pyridine is a good ligand for

transition metals over a range of oxidation states.[10]

As described in Section II of Part II of this dissertation, organic azides are extremely

readily reduced to form primary amines.[11] A variety of reducing agents can be used in this

reduction process. We decided to examine a supported palladium heterogeneous catalyst first, because such catalysts are generally used in the hydrogenation of carbon-carbon double bonds.

If the reduction of the azide to a primary amine and the hydrogenation of the carbon-carbon double bond were performed simultaneously, we could effect the conversion of the pyridine substituted allylic azide 4 to a theonelladin C analogue in a one pot reaction. The overall process is represented by equation 5.

$$\text{4} + \text{H}_2 \xrightarrow[\text{solvent}]{\text{Pd/C}} \text{6} \tag{5}$$
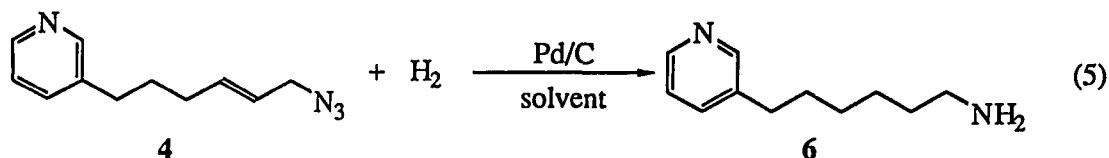
An efficient, one-pot procedure for the reductive hydrogenation of compound 4 was conducted under various conditions. The results are summarized in Table 3.

As can be seen from Table 3, both 5% Pd/C and 5% Pd/CaCO$_3$ (Lindlar Catalyst) are effective catalysts in the one-pot reductive hydrogenation of allylic azide 4 (entries 3 -5) to 6. The only disadvantage of the 5% Pd/C procedure lies in the fact that it requires a mixture of

Table 3. Reductive-hydrogenation of compound 4 (eq 5).

Entry	Catalyst (Pd%)[b]	Solvent	Temp (^{o}C)	Time (h)	% Yield[a] of 6
1	5% Pd/C (2.5)	MeOH	25	12	40
2	5% Pd/C (1.0)	EtOH	25	8	44
3	5% Pd/C (2.5)	EtOH (1% CHCl$_3$)	0	18	56
4	5% Pd/C (2.5)	EtOH (10% CHCl$_3$)	25	1.5	68
5	5% Pd/CaCO$_3$ (1.0)	EtOH	25	1	60
6	5% Pd/CaCO$_3$ (1.0)	EtOH	0	5	---
7	5% Pd/C (2.5)	DMSO	25	24	54[c]

[a] Isolated yield.
[b] Percent of palladium metal relative to compound 4.
[c] Only side product alkyl pyridine formed.

ethanol and chloroform as the solvent, as reported previously by Logue and Secrist III.[12]

Only a 44% yield of the desired product was observed in the absence of chloroform.

Ethanol appears to be a better solvent than methanol or DMSO, and is the solvent of choice in this reduction process. The only side product observed in this reaction was 3-n-hexylpyridine, which was formed by cleavage of the carbon-nitrogen bond of 4, followed by hydrogenation of the unsaturated intermediate.

The theonelladin D molecule has a methylamino group attached to one end of the carbon chain. Unfortunately, our earlier attempt at the preparation of an aryl-substituted, long carbon-chain secondary methylamine was unsuccessful (see Section II of Part II). Neither methylamine gas nor 40% aqueous methylamine solution was a successful nucleophile in the three-component coupling reaction. Recently, Murahashi et al.[13] reported that allylic hydroxylamines could be prepared by palladium-catalyzed reactions and the subsequent reduction of these intermediates leads to the formation of secondary allylic amines. Hence, N-methylhydroxylamine was investigated as an alternative to methylamine in the cross-coupling of iodobenzene and 1,5-hexadiene under conditions described in equation 6. Unfortunately,

$$\text{Ph-I} \;+\; 5 \;\text{(1,5-hexadiene)}_2 \;+\; 5\; HN(OH)CH_3 \cdot HCl \quad \xrightarrow[\substack{2.2\ \text{TBAC} \\ 5.0\ \text{base} \\ \text{DMSO, 100 °C}}]{5\%\ \text{Pd(dba)}_2}$$

base = NaHCO_3
       LiOH
       NaOH

$$\text{Ph}\text{(}\text{)}_3\text{NH(CH}_3\text{)} \quad + \quad \text{Ph}\text{(}\text{)}_2 \quad \mathbf{2}$$

  0%   50-60%

(6)

the reaction failed to give any of the desired allylic methylamine product and only Heck product 2 was isolated in 50 - 60% yield. The addition of 5 equivalents of base is to remove the hydrochloric acid which is involved in the starting ammonium salt.

In our studies on amine nucleophiles in Section II of Part II of this dissertation, it has been shown that most secondary amines can be used as nucleophiles in the palladium-catalyzed coupling of aryl iodides and nonconjugated dienes. We decided to use benzylmethylamine to make a pyridine substituted benzylmethyl tertiary amine by this procedure. Thereby, a theonelladin D analogue might be prepared by debenzylation of the tertiary amine formed (Scheme I).

Scheme I

First of all, the palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and benzylmethylamine was investigated. This reaction was conducted in the presence of 2.2 equivalents of TBAC in DMSO at 100 °C for 8 hours to afford the desired allylic benzylmethylamine 7 in 51% yield and a 25% yield of Heck product 2 (eq 7).

(7)

Upon successful application of benzylmethylamine in the palladium-catalyzed coupling reaction, 3-iodopyridine was used as the aryl iodide and allowed to react with 1,5-hexadiene and benzylmethylamine under the same conditions as those shown in equation 7. Unfortunately, no desired coupling product was detected and only Heck product 2 was isolated in 69% yield (eq 8).

$$\text{(8)}$$
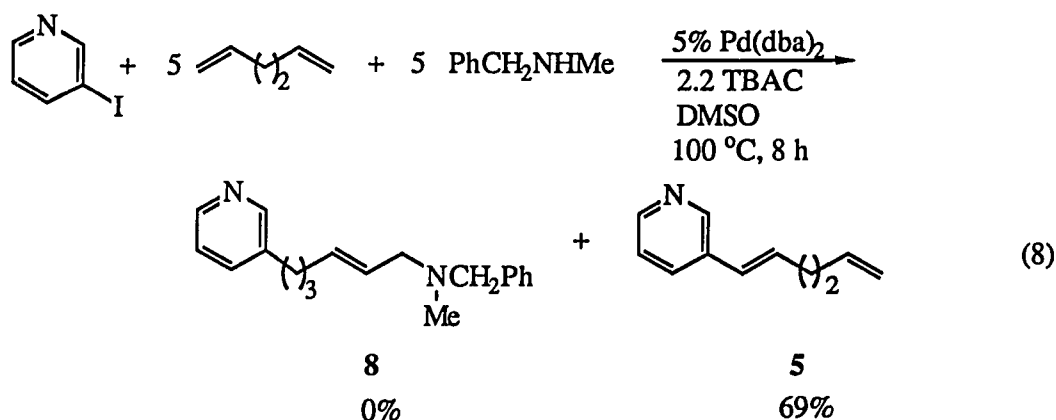
It was thought that the loss of the reaction selectivity might be caused by the strong coordinating ability of pyridine, which might promote dissociation of the intermediate palladium-diene π-complex (see Scheme III in Section II of Part II) and facilitate formation of the Heck product. Therefore, lithium chloride was examined as an additive to stabilize the palladium complex.

The palladium-catalyzed coupling of 3-iodopyridine, 1,5-hexadiene, and benzylmethylamine was carried out in the presence of 1 equivalent of LiCl, instead of 2.2 equivalents of TBAC, in DMSO at 100 °C for 12 hours to give the desired allylic amine 8 in 52% yield and a 36% yield of Heck product 5 (eq 9). The important role that lithium chloride plays in suppressing the formation of the Heck product can be verified by comparing the results shown in equations 8 and 9.

$$(9)$$

8
52%

5
36%
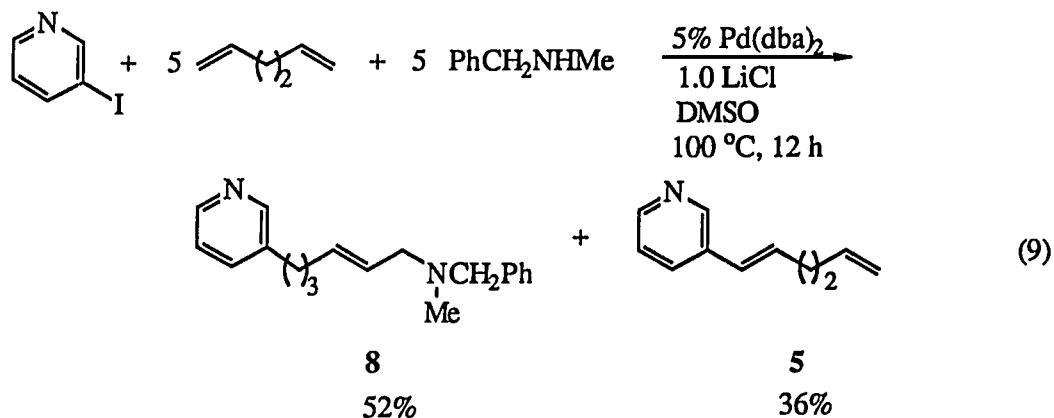
When 2 equivalents of 1,13-tetradecadiene were used as the nonconjugated diene with 1 equivalent of 3-iodopyridine and 2 equivalents of benzylmethylamine, the reaction proceeded smoothly under the same conditions as those shown in equation 9. The desired long carbon-chain product **9** was isolated in 20% yield, alongside a 40% yield of Heck product (eq 10).
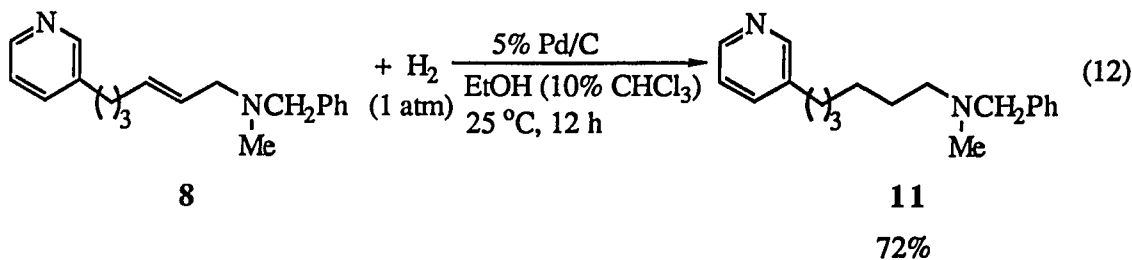

$$(10)$$

9
20%

40%
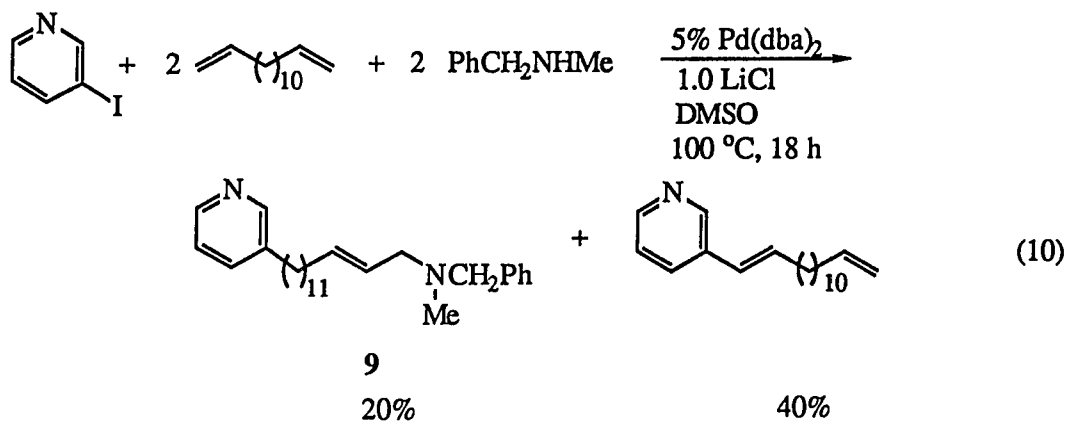
Hydrogenation of the double bond and debenzylation of compound **8** constitute the second challenging step in the synthesis of theonelladin D analogues. It was hoped that these two reactions would proceed simultaneously or in sequence under identical reaction conditions.

In our earlier work (see entry 4 in Table 3) on the one-pot reductive hydrogenation of 6-(3-pyridyl)-2-hexenyl azide (**4**), palladium on charcoal as the catalyst and ethanol blended with chloroform as the solvent offered the highest yield of **6**. These conditions were applied to the hydrogenation-debenzylation of compound **7**. At first, 10% chloroform by volume was employed as an additive in the ethanol solvent, but only the hydrogenation product **10** was obtained in an 83% yield when benzylmethylallylic amine **7** was hydrogenated under one atmosphere of hydrogen at room temperature (eq 11). When the same procedure was used

$$7 \quad + \quad H_2 \ (1 \text{ atm}) \quad \xrightarrow[\substack{\text{EtOH (10\% CHCl}_3) \\ 25\,^\circ\text{C, 12 h}}]{\text{5\% Pd/C}} \quad 10 \quad (11)$$

7

10
83%
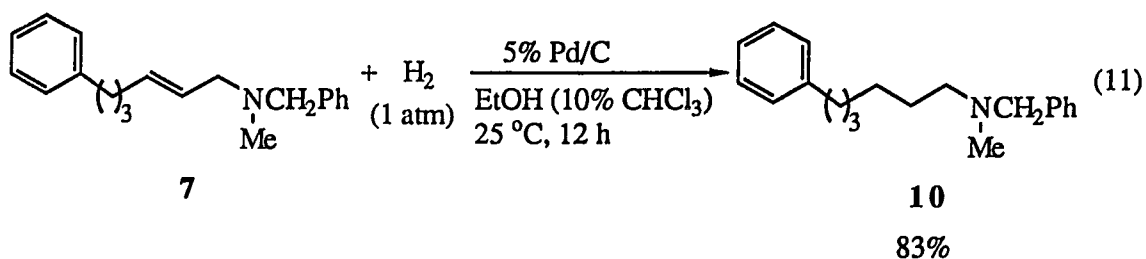
in the hydrogenation and debenzylation of the pyridine substituted benzylallylic amine **8**, again, only the hydrogenation product was isolated (72% yield) (eq 12).

$$8 \quad + \quad H_2 \ (1 \text{ atm}) \quad \xrightarrow[\substack{\text{EtOH (10\% CHCl}_3) \\ 25\,^\circ\text{C, 12 h}}]{\text{5\% Pd/C}} \quad 11 \quad (12)$$

8

11
72%

In order to perform the debenzylation reaction, several literature procedures[14] were examined. The hydrogenation and hydrogenolysis of compound **7** in ethanol (10% CHCl$_3$) using 5% PtO$_2$ as the catalyst did produce the desired debenzylated saturated methyl amine **12**, but only in 23% yield (eq 13).

$$\text{(13)}$$
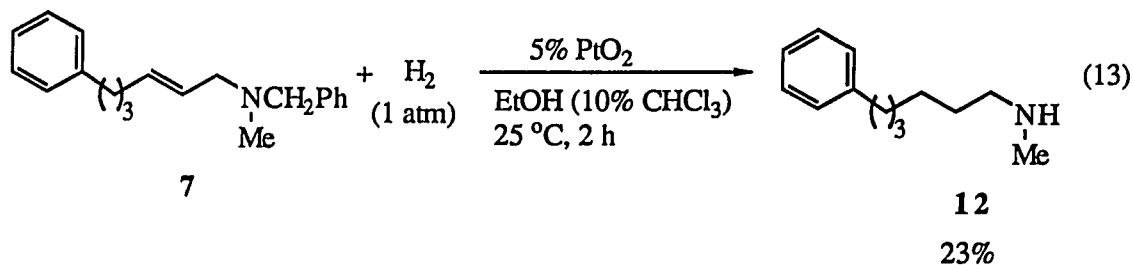
At this point, we wondered if chloroform is still the essential additive in the debenzylation operation. The hydrogenation and debenzylation of **7** was performed under the same conditions as those described in equation 11, except that pure ethanol was used as the solvent. Beyond expectation, an excellent 90% yield of debenzylation product **12** was isolated (eq 14).

$$\text{(14)}$$
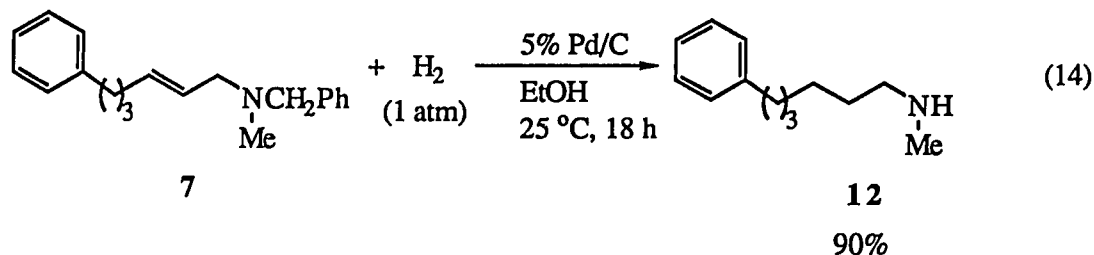
However, during the hydrogenation and hydrogenolysis of compound **9** under the same conditions as those of equation 14, the only product isolated was the hydrogenation product **11** (72%) (eq 15).

$$\text{(15)}$$
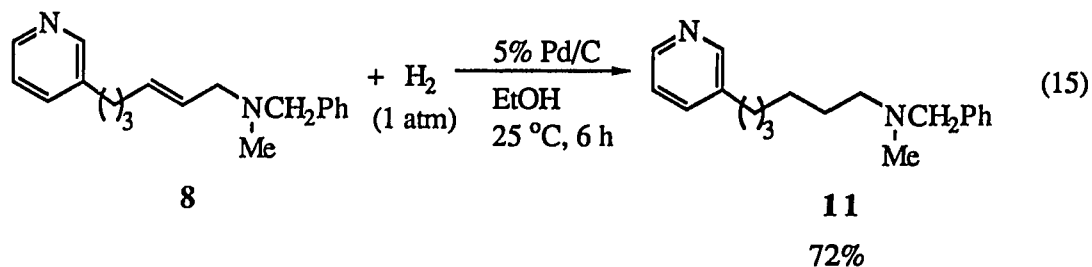
It appears that the presence of the pyridine ring in the reaction system inhibits the debenzylation process. In an attempt to neutralize the basic pyridine ring, several acids, such

as hydrochloric acid, *p*-toluenesulfonic acid and benzenesulfonic acid were added to the

reaction system prior to hydrogenation; however, no improvement was observed. Another

effort to promote the hydrogenolysis process was conducted by raising the reaction temperature

to 60 - 70 °C in ethanol for 3 days; again, no debenzylation product was detected.

According to a literature report,[15] good yields have been obtained with the Pearlman[16]

catalyst, 20% palladium hydroxide-on-carbon, even where other palladium catalysts have

failed. When the Pearlman catalyst was used in the hydrogenation-debenzylation of compound

8 in methanol at room temperature, only starting material 8 was recovered. It seemed likely

that the catalyst was either totally poisoned by something or was totally inactive.

Based on the above suspicions, we decided to activate the Pearlman catalyst with

hydrogen at room temperature for about six hours prior to the addition of the amine substrate.

After the activation process, compound 8 was added to the reaction mixture which was

allowed to stir for another 24 hours at 60 °C. To our delight, the desired product, a six carbon

theonelladin D analogue 13, was isolated in 90% yield (eq 16).

$$ \text{8} \quad + \quad H_2 \ (1 \text{ atm}) \xrightarrow[\substack{\text{MeOH} \\ 60\,°C,\,24\,h}]{20\%\ Pd(OH)_2/C} \quad \text{13} \qquad (16) $$

90%
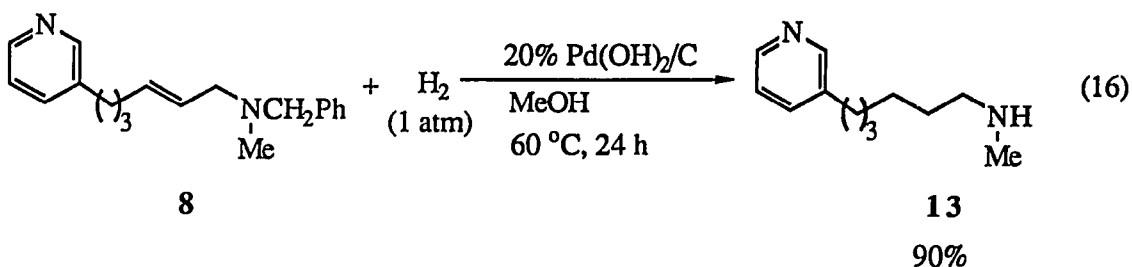
CONCLUSION

The formal synthesis of theonelladin C analogue **6** and D analogue **13** in which a pyridine ring and an amino or methylamino group is tethered by a saturated six carbon-chain has been accomplished from 3-iodopyridine, 1,5-hexadiene, and sodium azide or benzylmethylamine in only two synthetic steps. The palladium-catalyzed coupling-migration approach to the molecular skeletons of **6** and **13** was employed as the key step.

A supported palladium catalyst (5% Pd/C or 20% Pd(OH)$_2$/C) was effectively used in the hydrogenation of the carbon-carbon double bond and reduction of the azide moiety, or hydrogenolysis of the benzylamine. The synthetic approach to compound **6** and **13** is a very general and useful procedure, through which a series of theonelladin C and D analogues can be prepared by simply changing the carbon number of the nonconjugated diene.

EXPERIMENTAL SECTION

<u>Spectral data and analysis</u>

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz, respectively. All infrared spectra were recorded either on an IBM IR/98 FT-IR spectrometer or a Beckmann 4250 spectrometer. GC-MS data were recorded on a Finnigan MS-50 mass spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Gas chromatographic analyses were carried out on an HP 5890 gas chromatograph equipped with an HP-1 Megabore column. Thin-layer chromatography (TLC) was conducted using commercially prepared 60 mesh silica gel plates (Whatman K6F), and the visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O]. Flash chromatography was carried out on 230 - 400 mesh silica gel.

<u>Reagents</u>

All nonconjugated dienes was used as purchased from Wiley, and all amines were purchased from Aldrich and used without prior purification. 3-Aminopyridine was used as purchased from Aldrich. Tetra-*n*-butylammonium chloride (TBAC) was purchased from Lancaster or Aldrich. Sodium azide, potassium iodide and sodium nitrite were available from Fisher, lithium azide from Kodak, and lithium chloride from Mallinckrodt. The solvent dimethylsulfoxide (DMSO) and others were purchased from Fisher and used without further purification. 5% Pd/C and 5% $Pd/CaCO_3$ (Lindlar) was purchased from Kawaken Fine Chemicals; 20%$Pd(OH)_2$/C (Pearlman) was bought from Aldrich, and $Pd(dba)_2$ was generously provided by Johnson Matthey Inc.

Preparation of 3-Iodopyridine (3)

3-Iodopyridine was prepared by the procedure reported by Shnaidman et al.[9] To a solution of 3-aminopyridine (10 g, 0.106 mol) in 36 mL of concentrated hydrochloric acid and 36 mL of water was added sodium nitrite (8 g, 0.115 mol) in 12 mL of water over 10 min at 0 - 5 °C. Then a solution of potassium iodide (20 g, 0.120 mol) in 46 mL of water was dropped into the reaction mixture over another 10 min with stirring. After stirring for 30 min at 0 - 5 °C and 40 min at 70 - 75 °C, 42% NaOH solution was added dropwise until the pH of the mixture reached 8.5. The mixture was then cooled and the product precipitated. The mixture was extracted with diethyl ether three times (50 mL x 3) and the aqueous phase was continuously extracted overnight with diethyl ether in a liquid-liquid extractor. The combined ether phase was dried over anhydrous Na_2SO_4, followed by removal of the solvent under reduced pressure, to afford 14.0 g of 3-iodopyridine as a brown solid (64%): mp. 50-51 °C (lit. mp.[9] 52.5 °C); ^{1}H NMR ($CDCl_3$) δ 7.09 (dd, J = 7.8 Hz, J = 5.2 Hz, 1 H, Py), 8.02 (d, J = 7.8 Hz, 1 H, Py), 8.56 (d, J = 5.2 Hz, 1 H, Py), 8.85 (s, 1 H, Py); IR (neat) 3069, 3048, 1562, 1458, 1404, 1317, 1188, 1090, 1020, 791, 700 cm^{-1}.

Preparation of 6-(3-Pyridyl)-2-hexenyl azide (4)

To a culture tube (20 x 150 mm) with a micromagnetic stirring bar was added lithium azide (0.367 g, 1.5 mmol), lithium chloride (0.423 g, 1.0 mmol), 3-iodopyridine (0.205 g, 1.0 mmol), and bis(dibenzylideneacetone)palladium(0) (0.028 g, 0.05 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 4 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then the 1,5-hexadiene (0.410 g, 5.0 mmol) was added and the culture tube was sealed with a screw cap lined with Teflon. The reaction mixture was stirred at 100 °C for 12 hours and then allowed to cool to room temperature, diluted with saturated aqueous sodium chloride solution (20 mL), and extracted

with diethyl ether three times (20 mL x 3). The ether layer was backwashed with brine (40 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to remove the solvent. The crude product was purified by flash chromatography on a silica gel column using 1:4 EtOAc/hexane to give compound 4 (0.112 g, 55% yield): ^1H NMR ($CDCl_3$) δ 1.74 (quintet, J = 7.5 Hz, 2 H, PyCCH$_2$), 2.14 (q, J = 7.5 Hz, 2 H, CH$_2$C=), 2.63 (t, J = 7.5 Hz, 2 H, PyCH$_2$), 3.71(d, J = 6.6 Hz, 1 H, CH$_2$N$_3$), 5.54 (dt, J = 15.0 Hz, J = 7.2 Hz, 1 H, vinyl), 5.76 (dt, J = 15.0 Hz, J = 6.6 Hz, 1 H, vinyl), 7.21 (dd, J = 7.8 Hz, J = 5.1 Hz, 1 H, Py), 7.49 (dt, J = 7.8 Hz, J = 1.5 Hz, 1 H, Py), 8.44 (br d, J = 5.1 Hz, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 30.27, 31.48, 32.19, 52.67, 123.20, 123.60, 135.38, 135.69, 137.15, 147.43, 149.83; IR (neat) 3030, 2995, 2860, 2089 (N$_3$), 1576, 1244, 972 (E-CH=CH), 716, cm^{-1}; mass spectrum m / z 201.11452 (calcd for $C_{11}H_{13}N_4$, 201.11402). Anal. Calcd for $C_{11}H_{13}N_4$: C, 65.32 ; H, 7.04; N, 27.70. Found: C, 65.59; H, 7.04; N, 26.60.

Preparation of 6-(3-Pyridyl)-1-hexylamine (6)

To a thick wall pyrex glass reaction tube (20 x 100 mm) was added 5% Pd/C (10 mg), compound 4 (46 mg, 0.23 mmol), 5 mL of ethanol and 0.5 mL of chloroform. The tube was then flushed with hydrogen gas and capped with a Teflon cap which has an outlet to connect the hydrogen source. The reaction mixture was stirred under one atmosphere of hydrogen at 25 °C for 1.5 hours. After removal of the catalyst by filtration with Celite, the reaction mixture was evaporated under reduced pressure. The residue was isolated on a silica gel column using pure methanol with 2% NH$_4$OH to give compound 6 (28 mg, 68%): ^1H NMR ($CDCl_3$) δ 1.34 (br m, 4 H, CH$_2$'s), 1.44 (br m, 2 H, PyCCH$_2$), 1.63 (br m, 2 H, CH$_2$CH$_2$N), 2.22 (br s, 2 H, CH$_2$N), 2.60 (t, J = 7.5 Hz, 2 H, PyCH$_2$), 2.68 (br s, 2 H, NH$_2$), 7.18 (dd, J = 5.1 Hz, J = 7.8 Hz, 1 H, Py), 7.48 (d, J = 7.8 Hz, 1 H, Py), 3.42 (br d, J = 5.1 Hz, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 17.78, 30.87, 31.42, 32.67, 35.66, 44.68, 123.57, 135.49, 135.74, 147.66, 149.98; IR (neat) 3298 (N-H), 3282 (N-H), 3026, 2930, 2856, 1576, 1479, 1464,

1319, 1043, 798, 716 cm^{-1}; mass spectrum m / z 177.13917 (M$^+$-1) (calcd for C$_{11}$H$_{17}$N$_2$, 177.13916).

Preparation of Benzylmethyl(6-phenyl-2-hexenyl)amine (7)

To a culture tube (20 x 150 mm) with a micromagnetic stirring bar was added TBAC (0.610 g, 2.2 mmol), and Pd(dba)$_2$ (0.028 g, 0.05 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 4 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then the iodobenzene (0.204 g, 1.0 mmol) was added, followed by 1,5-hexadiene (0.410 g, 5.0 mmol) and benzylmethylamine (0.605 g, 5.0 mmol). The culture tube was sealed with a screw cap lined with Teflon. The reaction mixture was stirred at 100 °C for 8 hours and then cooled to room temperature, diluted with saturated aqueous sodium chloride solution (20 mL), and extracted with diethyl ether three times (20 mL x 3). The ether layer was backwashed with brine (40 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure to remove the solvent. The crude product was purified by flash chromatography on a silica gel column using 1:4 EtOAc/hexane to give compound 7 (0.145 g, 55% yield): ^{1}H NMR (CDCl$_3$) δ 1.70 (quintet, J = 7.8 Hz, 2 H, PhCCH$_2$), 2.08 (q, J = 7.8 Hz, 2 H, CH$_2$C=), 2.17 (s, 3 H, CH$_3$), 2.61 (t, J = 7.8 Hz, 2 H, PhCH$_2$), 2.97 (d, J = 5.4 Hz, 2 H, CH$_2$N), 3.47 (s, 2 H, NCH$_2$Ph), 5.57 (m, 2 H, vinyl), 7.14 - 7.17 (m, 10 H, aryl); ^{13}C NMR (CDCl$_3$) δ 31.02, 31.91, 35.34, 41.97, 59.66, 61.57, 125.61, 126.84, 127.57, 128.13, 128.19, 128.36, 129.04, 133.65, 139.00, 142.84; IR (neat) 3063, 2930, 2856, 1603, 1495, 1452, 1366, 1022, 972 (E-CH=CH), 739, 698 cm^{-1}. Anal. Calcd for C$_{20}$H$_{25}$N: C, 85.97; H, 9.02. Found: C, 85.31; H, 9.04.

Preparation of Benzylmethyl[6-(3-pyridyl)-2-hexenyl]amine (8)

To a culture tube (16 x 125 mm) with a micromagnetic stirring bar was added lithium chloride (0.021 g, 0.5 mmol), 3-iodopyridine (0.103 g, 0.5 mmol), and Pd(dba)$_2$ (0.014 g,

0.025 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 2 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then 1,5-hexadiene (0.205 g, 2.5 mmol) and benzylmethylamine (0.303 g, 2.5 mmol) were added and the culture tube was sealed with a screw cap lined with Teflon. The reaction mixture was stirred at 100 °C for 12 hours and then cooled to room temperature, diluted with saturated aqueous sodium chloride solution (10 mL), and extracted with diethyl ether three times (10 mL x 3). The ether layer was backwashed with brine (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to remove the solvent. The crude product was purified by flash chromatography on a silica gel column using 1:4 EtOAc/hexane to give compound **8** (0.075 g, 52% yield): ^1H NMR ($CDCl_3$) δ 1.71 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 2.01 (q, J = 7.5 Hz, 2 H, $CH_2C=$), 2.18 (s, 3 H, CH_3), 2.61 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.98 (d, J = 5.1 Hz, 2 H, CH_2N), 3.48 (s, 2 H, NCH_2Ph), 5.58 (m, 2 H, vinyl), 7.16 - 7.31 (m, 6 H, Py, aryl), 7.46 (d, J = 7.8 Hz, 1 H, Py), 8.43 (br s, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 30.62, 31.72, 32.38, 41.96, 59.54, 61.57, 123.16, 126.86, 127.97, 128.12, 129.00, 133.10, 135.69, 137.42, 138.99, 147.22, 149.92; IR (neat) 3028, 2928, 2785, 1576, 1479, 1423, 1366, 1128, 1026, 972 (E-CH=CH), 740, 714 cm^{-1}. Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63. Found: C, 80.99; H, 8.33.

Preparation of Benzylmethyl[14-(3-pyridyl)-2-tetradecenyl]amine (9)

To a culture tube (20 x 150 mm) with a micromagnetic stirring bar was added lithium chloride (0.042 g, 1.0 mmol), 3-iodopyridine (0.205 g, 1.0 mmol), and Pd(dba)$_2$ (0.028 g, 0.05 mmol). After flushing with nitrogen for several minutes, the tube was sealed by a septum and 4 mL of dimethyl sulfoxide (DMSO) was injected into the tube through a septum. Then 1,13-tetradecadiene (0.388 g, 2.5 mmol) and benzylmethylamine (0.243 g, 2.0 mmol) was added and the culture tube was sealed with a screw cap lined with Teflon. The reaction mixture was stirred at 100 °C for 18 hours and then cooled to room temperature, diluted with saturated

aqueous sodium chloride solution (20 mL), and extracted with diethyl ether three times (20 mL x 3). The ether layer was backwashed with brine (40 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to remove the solvent. The crude product was purified by flash chromatography on a silica gel column using 1:4 EtOAc/hexane to give compound 9 (0.071 g, 20% yield): ^1H NMR ($CDCl_3$) δ 1.25 (br m, 16 H, CH_2's), 1.60 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 2.01 (q, J = 7.5 Hz, 2 H, CH_2C=), 2.17 (s, 3 H, CH_3), 2.58 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.96 (d, J = 5.7 Hz, 2 H, CH_2N), 3.47 (s, 2 H, NCH_2Ph), 5.55 (m, 2 H, vinyl), 7.16 - 7.31 (m, 6 H, Py, aryl), 7.46 (d, J = 7.8 Hz, 1 H, Py), 8.43 (br s, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 29.55 (br s, 8 C), 31.12, 32.38, 33.00, 41.91, 59.66, 61.50, 123.14, 123.47, 126.85, 128.12, 129.08, 134.50, 135.67, 137.10, 138.93, 147.10, 149.90; IR (neat) 3026, 2986, 2854, 1576, 1477, 1421, 1366, 1128, 1024, 970 (E-CH=CH), 908, 793, 735 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2$: C, 82.48; H, 10.12. Found: C, 81.99; H, 10.31.

Preparation of Benzylmethyl(6-phenyl-1-hexyl)amine (10)

To a thick wall pyrex glass reaction tube (20 x 100 mm) was added 5% Pd/C (7 mg), compound 7 (47 mg, 0.17 mmol), 5 mL of ethanol and 0.5 mL of chloroform. The tube was then flushed with hydrogen gas and capped with a Teflon cap which has an outlet to connect a hydrogen source. The reaction mixture was stirred under one atmosphere of hydrogen at 25 °C for 12 hour. After removal of the catalyst by filtration with Celite, the reaction mixture was evaporated under reduced pressure. The residue was isolated on a silica gel column using 1:1 EtOAc/hexane to give compound 10 (39 mg, 83%): ^1H NMR ($CDCl_3$) δ 1.33 (br m, 4 H, CH_2's), 1.58 (br m, 4 H, $PhCCH_2$, CH_2CN), 2.24 (s, 3 H, CH_3), 2.42 (t, J = 7.5 Hz, 2 H, CH_2N), 2.59 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 3.56 (s, 2 H, NCH_2Ph), 7.15 - 7.34 (m, 10 H, aryl); ^{13}C NMR ($CDCl_3$) δ 27.15, 29.11, 29.78, 31.36, 35.40, 41.25, 52.08, 61.78, 125.67, 126.90, 128.12, 128.34, 128.87, 129.07, 139.02, 142.36; IR (neat) 3085, 2936,

2856, 1485, 1380, 1134, 1076, 1011, 970, 736, 697 cm^{-1}; mass spectrum m/z 281.44310 (calcd for $C_{20}H_{27}N$, 281.44302).

Preparation of Benzylmethyl[6-(3-pyridyl)-1-hexyl]amine (11)

To a thick wall pyrex glass reaction tube (20 x 100 mm) was added 5% Pd/C (16 mg), compound 8 (45 mg, 0.16 mmol), 5 mL of ethanol and 0.5 mL of chloroform. The tube was then flushed with hydrogen gas and capped with a Teflon cap which has an outlet to connect the hydrogen source. The reaction mixture was stirred under one atmosphere of hydrogen at 25 °C for 6 hours. After removal of the catalyst by filtration with Celite, the reaction mixture was evaporated under reduced pressure. The residue was isolated on a silica gel column using a solvent gradient: hexane-EtOAc-MeOH to give compound 11 (32 mg, 72%): ^{1}H NMR (CDCl$_3$) δ 1.33 (br m, 4 H, CH$_2$'s), 1.52 (br m, 2 H, PyCCH$_2$), 1.61 (br m, 2 H, CH$_2$CN), 2.19 (s, 3 H, CH$_3$), 2.36 (t, J = 7.2 Hz, 2 H, CH$_2$N), 2.59 (t, J = 7.5 Hz, 2 H, PyCH$_2$), 3.48 (s, 2 H, NCH$_2$Ph), 7.18 - 7.31 (m, 6 H, aryl, Py), 7.47 (d, J = 7.8 Hz, 1 H, Py), (8.43 (br s, 2 H, Py); ^{13}C NMR (CDCl$_3$) δ 27.34, 29.15, 29.81, 31.37, 35.28, 41.90, 52.54, 61.67, 123.25, 125.89, 128.80, 129.00, 135.88, 137.42, 138.90, 147.22, 149.90; IR (neat) 3029, 2929, 2786, 1488, 1389, 1130, 1026, 1011, 970, 739, 700 cm^{-1}; mass spectrum m/z 282.43206 (calcd for $C_{19}H_{26}N_2$, 282.43256).

Preparation of Methyl(6-phenyl-1-hexyl)amine (12)

To a thick wall pyrex glass reaction tube (20 x 100 mm) was added 5% Pd/C (22 mg), compound 7 (156 mg, 0.56 mmol) and 5 mL of ethanol. The tube was then flushed with hydrogen gas and capped with a Teflon cap which has an outlet to connect a hydrogen source. The reaction mixture was stirred under one atmosphere of hydrogen at 25 °C for 18 hours. After removal of the catalyst by filtration with Celite, the reaction mixture was evaporated under reduced pressure. The residue was isolated on a silica gel column using 1:4 MeOH/EtOAc to

give compound **12** (96 mg, 90%): ^{1}H NMR (CDCl$_3$) δ 1.37 (br m, 4 H, CH$_2$'s), 1.47 (br m, 2 H, PhCCH$_2$), 1.62 (br m, 2 H, C**H$_2$**CH$_2$N), 2.41 (s, 3 H, CH$_3$), 2.52 -2.62 (m, 4 H, CH$_2$N, PhCH$_2$), 7.14 -7.28 (m, 5 H, aryl); ^{13}C NMR (CDCl$_3$) δ 27.14, 29.16, 29.76, 31.38, 35.84, 36.43, 52.06, 125.46, 128.11, 128.26, 142.65; IR (neat) 3300 (br N-H), 3063, 2928, 2854, 1605, 1495, 1454, 1381, 1310, 1124, 746, 698 cm^{-1}.

Preparation of Methyl[6-(3-pyridyl)-1-hexyl]amine (13)

To a thick wall pyrex glass reaction tube (20 x 100 mm) was added 20% Pd(OH)$_2$/C (40 mg) and 2 mL of methanol. The tube was then flushed with hydrogen gas and capped with a Teflon cap which has an outlet to connect the hydrogen source. The catalyst suspension was stirred under an atmosphere of hydrogen at 25 °C for 6 hours, then compound **8** (84 mg, 0.30 mmol) was added to the reaction tube which was flushed with hydrogen again. The stirring was continued for another 24 hours. After removal of the catalyst by filtration with Celite, the reaction mixture was evaporated under reduced pressure. The residue was isolated on a silica gel column using a solvent gradient: hexane-EtOAc-MeOH to give compound **13** (52 mg, 90%): ^{1}H NMR (CDCl$_3$) δ 1.39 (br m, 4 H, CH$_2$'s), 1.62 (br m, 2 H, C**H$_2$**CH$_2$N), 1.86 (br m, 2 H, PyCCH$_2$), 2.59 (t, J = 7.5 Hz, 2 H, PyCH$_2$), 2.65 (s, 3 H, CH$_3$), 2.91 (t, J = 7.2 Hz, 2 H, CH$_2$N), 7.22 (dd, J = 7.8 Hz, J = 5.1 Hz, 1 H, Py), 7.42 (d, J = 7.8 Hz, 1 H, Py), 8.45 (br s, 2 H, Py); ^{13}C NMR (CDCl$_3$) δ 27.12, 29.16, 29.82, 31.80, 35.91, 36.49, 52.23, 123.55, 135.80, 135.98, 147.60, 149.76; IR (neat) 3303 (br N-H), 2932, 2854, 1738, 1661, 1576, 1479, 1425, 1375, 1244, 1049, 716, 636 cm^{-1}.

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GENERAL SUMMARY

This dissertation describes the first observed examples of aluminum chloride promoted acylation of allylic mercurials by acyl chlorides. A variety of allylic mercurials and acyl chlorides, including aliphatic, aromatic, and α, β-unsaturated acyl chlorides can be employed successfully in this reaction. This reaction provides a convenient new synthetic route to allylic ketones. A modified, good yielding procedure to prepare allylic mercuric iodides from the corresponding allylic halides and metallic mercury is presented and a considerable amount of functionality can be tolerated in this procedure.

Synthetic methodology, which allows for a rapid increase in molecular complexity, is extremely valuable in modern synthetic organic chemistry, particularly when it generates more than one carbon-carbon and carbon-heteroatom bond at a time, accommodates considerable functionality, and is broad in scope. This dissertation reports just such methodology involving the palladium-catalyzed coupling of aromatic iodides, nonconjugated dienes, and nucleophiles via palladium migration.

This process is remarkably versatile, giving good yields for a wide variety of carbon and nitrogen nucleophiles with a high degree of regio- and stereoselectivity; however, when oxygen nucleophiles, such as acetate anion and phenoxide anion, are employed in this coupling process, an inseparable mixture of regio- and stereoisomers is isolated.

The palladium-catalyzed coupling-migration approach has been successfully employed as the key step in the formal synthesis of theonelladin C and D analogues. The overall synthesis has been accomplished in only two synthetic steps.

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