1992

Synthesis of carbo- and heterocycles via palladium-catalyzed annulation of alkenes and alkynes

Eul Kgun Yum
Iowa State University

INFORMATION TO USERS

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

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

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

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

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

UMI

A Bell & Howell Information Company
300 North Zeeb Road. Ann Arbor, MI 48106-1346 USA
313/761-4700 800/521-0600

Synthesis of carbo- and heterocycles via palladium-catalyzed annulation of alkenes and alkynes

by

Eul Kgun Yum

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department : Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1992

TABLE OF CONTENTS

ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
Ar	aryl
Bu	*n*-butyl
δ	chemical shift in parts per million downfield shift from tetramethylsilane
^{13}C NMR	carbon thirteen nuclear magnetic resonance
DMA	N,N-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dba	dibenzylideneacetone
dppb	1,4-bis(diphenylphosphino)butane
Et	ethyl
GC-MS	gas chromatography-mass spectrometry
^{1}H NMR	hydrogen nuclear magnetic resonance
h	hour(s)
HRMS	high resolution mass spectrometry
IR	infrared
LDA	lithium diisopropylamide
Me	methyl
mp	melting point
Ms	methanesulfonyl
m/z	mass to charge ratio

NBS	N-bromosuccinimide
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	*n*-propyl
rt	room temperature
TBDMS	*t*-butyldimethylsilyl
TFA	trifluoroacetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
Ts	*p*-toluenesulfonyl

GENERAL INTRODUCTION

The development of new synthetic methods which utilize palladium is one of the most interesting areas in organic chemistry today. Recently, a wide variety of palladium-assisted organic reactions has been developed and applied to the synthesis of complex organic compounds. The encouraging development of organopalladium chemistry has inspired us to develop novel synthetic methods directed towards the synthesis of carbo- and heterocycles using palladium catalysis.

Recently, Larock's research group has developed some palladium-catalyzed annulation processes which exhibit remarkable versatility. To explore the scope and limitation of the annulation process, most of our research work has focused on the palladium-catalyzed annulation of alkenes and alkynes. The first part of this thesis deals with intermolecular arylation of functionally-substituted cycloalkenes. The second part deals with the synthesis of carbo- and heterocycles via palladium-catalyzed annulation of vinylic cyclopropanes, vinylic cyclobutanes, and 1,4-dienes. Finally, the third and fourth parts deal with the synthesis of carbo- and heterocycles via palladium-catalyzed annulation of internal alkynes.

Explanation of Dissertation Format

The format of this dissertation is an alternate format as described in the Thesis Manual. Each part is a paper suitable for publication, and there is a General Summary following the papers. The doctoral candidate was primarily responsible for the research and the writing of the papers.

PART I. PALLADIUM-CATALYZED INTERMOLECULAR ARYLATION OF SUBSTITUTED CYCLIC ALKENES

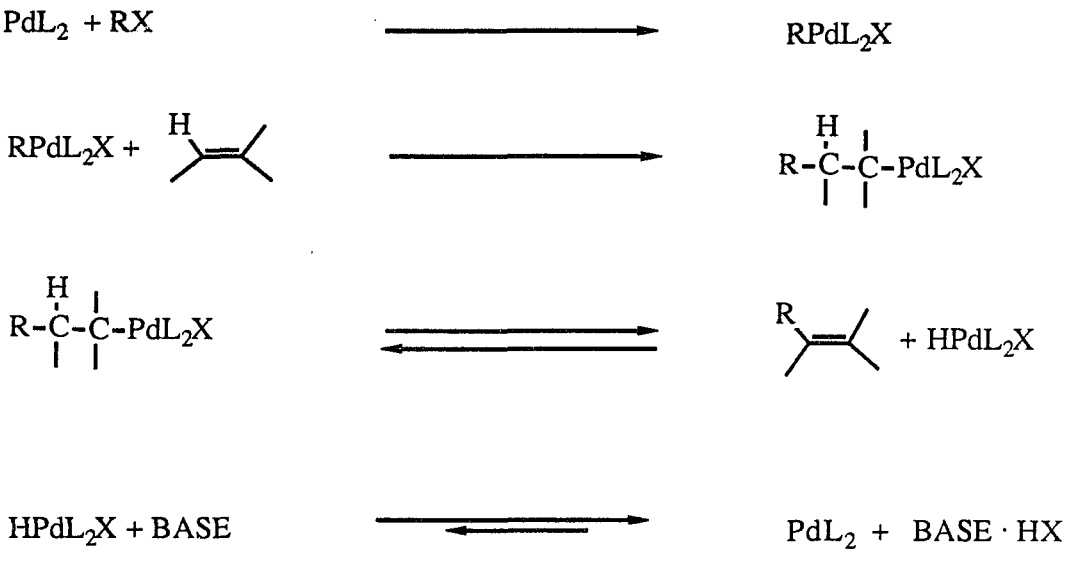
INTRODUCTION

The development of synthetic methods which utilize palladium has become an important area in organic synthesis since initial reports of its use by Heck in 1968.[1] There are basically three reasons why palladium-based methodologies have been so widely used. First, these methodologies are generally not oxygen or moisture sensitive. Secondly, they can accommodate an enormous variety of important organic functional groups. Lastly, palladium metal has the ability to catalyze a number of novel organic transformations.[2,3]

There are a number of approaches to the synthesis of the organopalladium complexes used for vinylic substitution.[2-4] Transmetallation reactions between an arylmercurial and palladium(II) salts have been used extensively, mainly because these reactions occur under very mild conditions (0 - 25 ^{o}C) to afford reactive arylpalladium intermediates. This intermediate then adds in a syn 1,2-fashion across an alkene to afford a new σ-organopalladium intermediate, followed by bond rotation so that a β-hydrogen is cis to the palladium. Subsequent syn elimination of palladium hydride yields the vinylic hydrogen substitution product. Although this method is very mild,[1] it requires a stoichiometric amount of an expensive palladium salt, and also an arylmercuric salt, which is toxic and not readily available. Another approach to organopalladium compounds involves the reaction of organic halides with catalytic amounts of zerovalent palladium, which is generated *in situ* presumably by oxidizing some of the olefin present. The detailed mechanism of the reaction has not yet been fully established, but it is thought to occur by the following pathway (Scheme 1).[5]

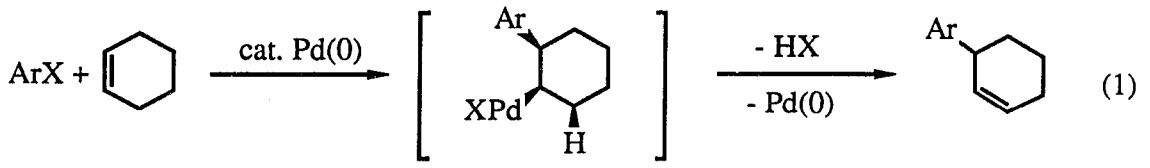
catalyst formation:

catalytic cycle:



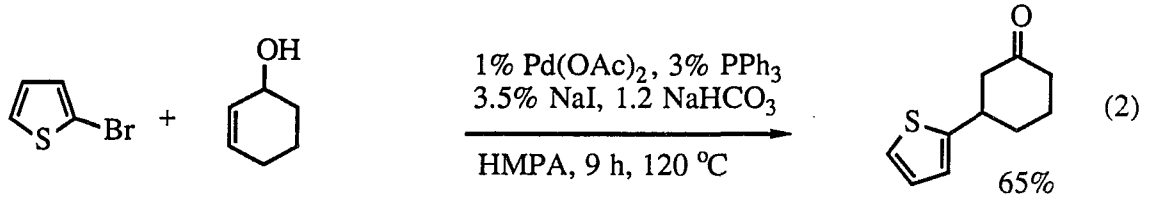
Scheme 1

The palladium-catalyzed cross-coupling of aryl halides or mercurials with acyclic alkenes has been extensively explored.[5-9] However, few examples have been reported in which cyclic olefins have been employed.[10-15] When cyclic alkenes are used, bond rotation is restricted after the 1,2- addition. Thus, there is a syn elimination of palladium hydride away from the initial addition site to afford only the allylic isomer (eq. 1).



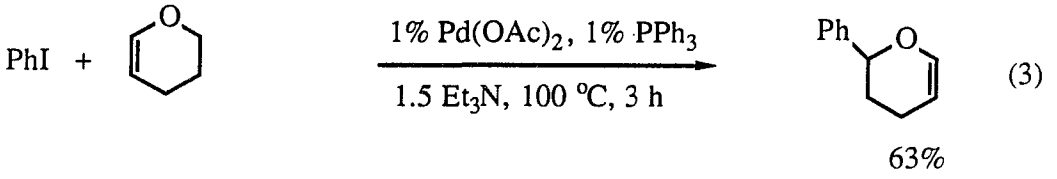
(1)

However, this reaction usually requires elevated temperatures and tends to generate a mixture of double-bond isomers. In 1978, Tamaru et al.[13] reported an approach to 3-arylcyclohexanones (eq. 2). This reaction parallels the reaction previously reported by Heck[1b]



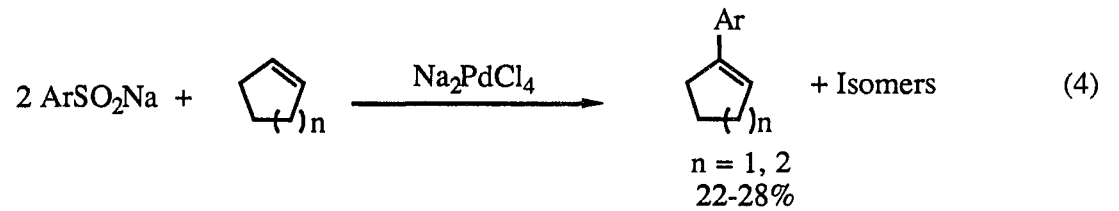
(2)

where arylmercurials were employed. Tamaru also discovered that when an acyclic allylic alcohol was employed, the regioselectivity of this process was greatly influenced by the choice of solvent. Arai and Daves[11] reported the palladium-catalyzed phenylation of 3,4-dihydro-2H-pyran (eq. 3). Migration of the double bond occurred in this reaction, probably due to additional β-hydride additions and eliminations.



(3)

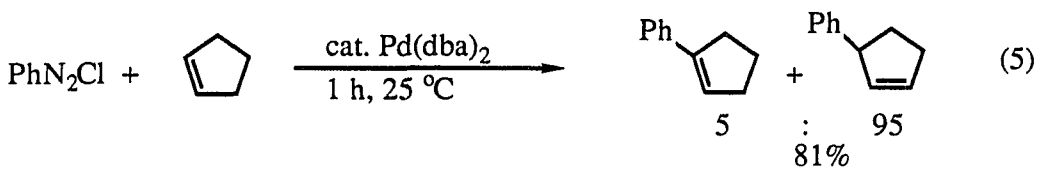
Arenesulfinate salts have also been explored as a source of organopalladium reagents.[15] However, heating arenesulfinate salts with palladium salts in the presence of cyclic olefins leads to the formation of isomeric mixtures in low overall yield (eq. 4). Furthermore, this



(4)

reaction requires a stoichiometric amount of the palladium salt.

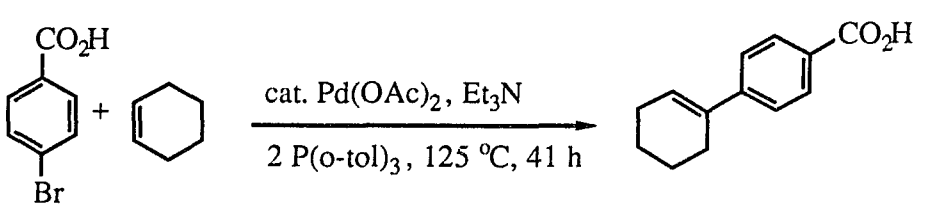
Various cyclic olefins have been arylated with arenediazonium salts in the presence of only a catalytic amount of palladium(0) (eq. 5).[16, 17] Although the yield for



(5)

phenylcyclopentene is good and the reaction conditions are mild, the product is a mixture of two isomers, with the nonconjugated product present in the greatest amount. They also observed that diazonium salts tend to be sensitive to temperatures above 25 °C, where tarry material is formed.

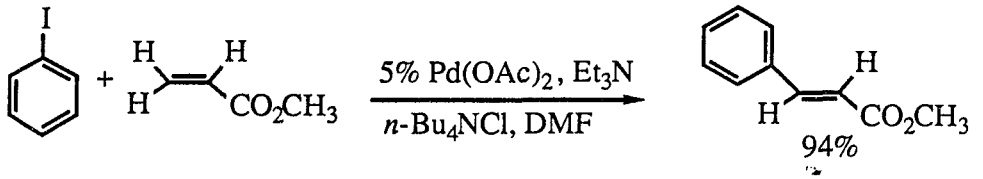
There are only a few examples of these coupling reactions using aryl or heterocyclic halides and palladium(0) as the source of the organopalladium intermediate.[11,12,18] The examples cited in the literature, which have employed only six-membered ring olefins, have required high reaction temperatures (100-125 °C), often proceed in low yield, and were frequently accompanied by double bond isomerization. For example, the reaction between 4-bromobenzoic acid and cyclohexene afforded only 16% of the conjugated product (eq. 6).[18a]



(6)

The reaction required relatively high temperatures (125 °C) and the addition of phosphines. Also, the reaction didn't produce the allylic-substituted isomer and left more than half of the starting aryl bromide unreacted.

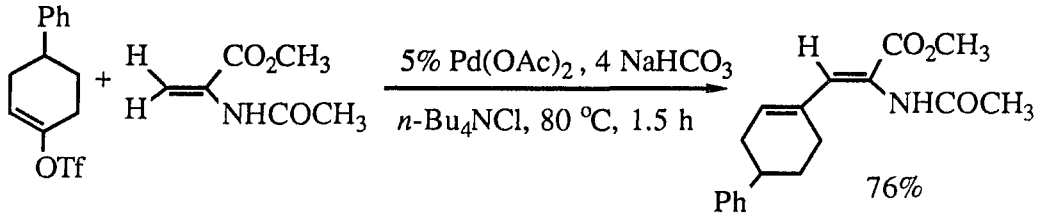
Recently, Jeffrey reported a palladium(0)-catalyzed addition reaction carried out using *n*-Bu_4NCl[19] which was based on an earlier study reported by Spencer.[20] The reaction mixture consisted of a vinylic or aryl iodide and an olefin, in the presence of a catalytic amount of palladium acetate (1-2%), a base such as KOAc or $NaHCO_3$, and *n*-Bu_4NCl in DMF at room temperature. A typical reaction done under these conditions is shown below (eq. 7).[19a]



(7)

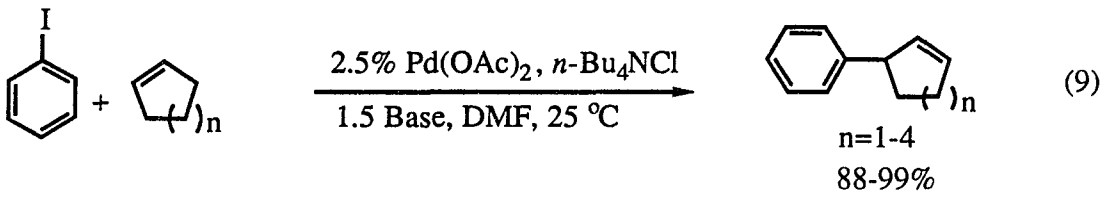
The high yield of products, mild temperatures, and small amount of palladium used make this an attractive synthetic procedure.

Aryl and vinylic halides and triflates react with methyl α-acetamidoacrylate in the presence of a catalytic amount of palladium to give β-vinyl-α,β-didehydro-α-aminoacid derivatives in good yields (eq. 8).[21] The reaction proceeds with high stereoselectivity and usually one stereoisomer was isolated as the sole or the main product.



(8)

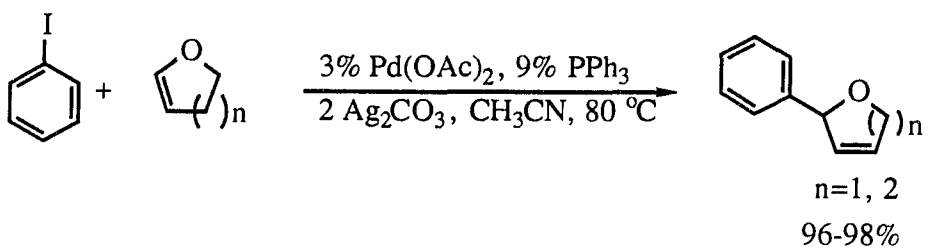
More recently, Larock and Baker[22] developed a general procedure for the arylation of a variety of cyclic alkenes (eq. 9). The authors examined various modifications of Jeffrey's



(9)

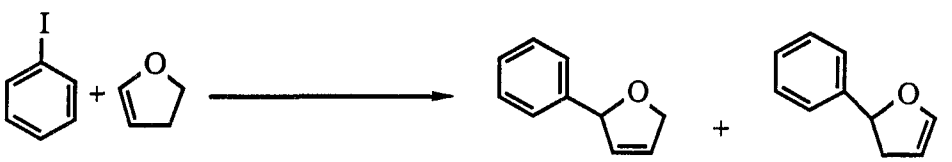
phase transfer conditions.[19] The alkali metal acetates in DMF have proven superior as bases to all others examined. Under procedure A (5% $Pd(OAc)_2$, 1 *n*-Bu_4NCl, 2 KOAc, DMF), the following relative reactivities of cycloalkenes were observed: cyclopentene > cyclooctene > cycloheptene > cyclohexene. Baker's subsequent investigation[23] revealed that aryl iodides containing a number of important organic functional groups could not be accommodated by this particular procedure. Furthermore, certain cyclic alkenes underwent double bond isomerization.

As a result of this problem, Larock et al.[24] examined an alternative procedure C (5% $Pd(OAc)_2$, 1 *n*-Bu_4NCl, 2 KOAc, 5% PPh_3, DMF). Procedure C dramatically improved the reactions of a wide variety of functionally-substituted aryl halides with cycloalkenes compared to procedure A. When procedure B[25] (3% $Pd(OAc)_2$, 9% PPh_3, 2 Ag_2CO_3 and CH_3CN at 80 °C) was employed, the arylation of 2,3-dihydrofuran or 3,4-dihydro-2-H-pyran yielded only the desired allylic isomer in high yield (eq. 10).[23,24]



(10)

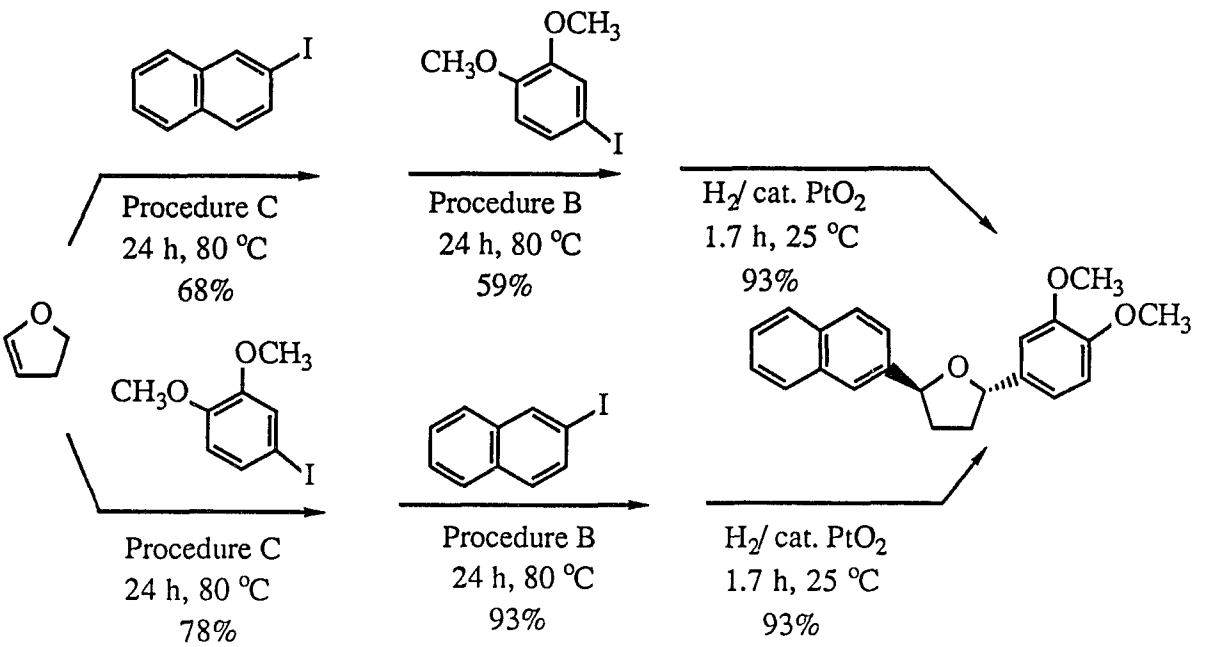
The authors concluded that procedure B inhibits isomerization, which is a major problem with procedure A. However, procedure B does not accommodate functionally- substituted aryl halides. Procedure C dramatically improved the results for a variety of functionally-substituted aryl halides, including those containing either an electron-donating or electron-withdrawing group. Unfortunately, procedure C doesn't solve the isomerization problems encountered using procedure A. The results of three different procedures for the arylation of 2,3-dihydrofuran are summarized below (eq. 11).[24]



(11)

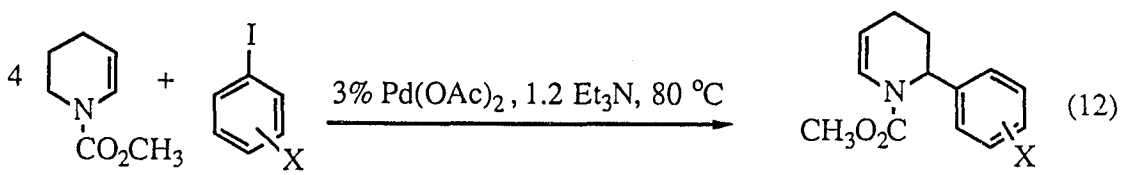
Procedure A	53%	27%
Procedure B	98%	-
Procedure C	-	76%

Larock and Gong[26] recently reported a convenient palladium-catalyzed synthesis of trans-2,5-diaryltetrahydrofurans, which are potent platelet-activating factor antagonists, using procedures B and C. The results were outlined in Scheme 2. The process exhibited excellent overall yields, and the stereochemistry of the final product from either sequence was observed to be pure trans.



Scheme 2

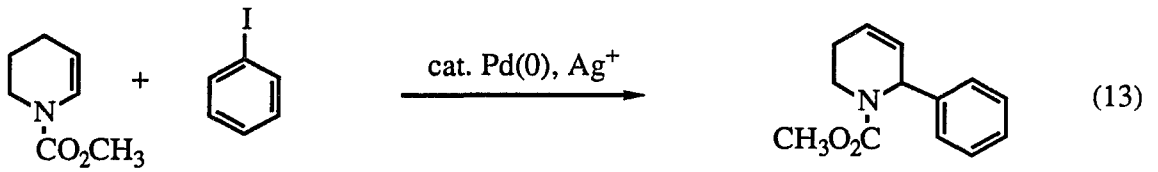
Nilson and Hallberg[27] have also reported a palladium-catalyzed tandem α-arylation / isomerization reaction of cyclic enamides (eq. 12).



(12)

(X = H, OCH_3 , CO_2CH_3 , OH) 40-60%

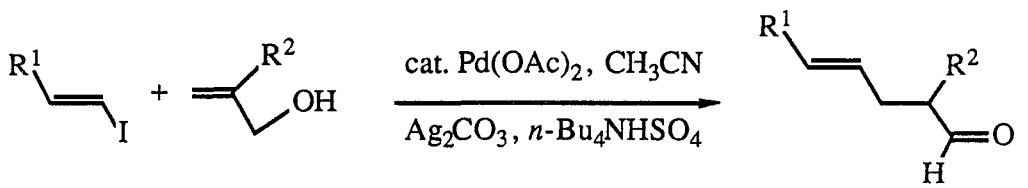
Silver ions promoted biphenyl formation, but were also effective in suppressing isomerization of the initially formed double bond, with only trace amounts of other isomers being observed (eq. 13).[28] The authors[25] believe that oxidative addition and subsequent



(13)

iodide abstraction by silver ions preceeds olefin insertion and irreversible syn elimination of a hydridopalladium species provides the product.

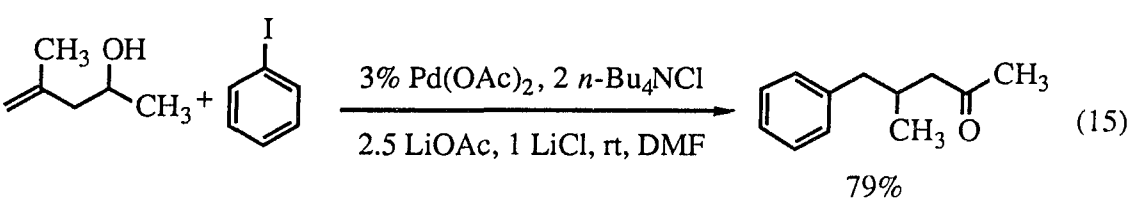
Recently Jeffery[29a] has reported the palladium-catalyzed reaction of vinylic halides with primary allylic alcohols (eq. 14). He reported that the combination of *n*-Bu_4NHSO_4 and



(14)

Ag_2CO_3 not only increased the reaction yields, but also changed the nature of the product. The use of other conditions (cat. $Pd(OAc)_2$, cat. PPh_3, AgOAc, DMF) in this reaction affords dienols instead.[29b] The enal synthesis was also highly stereospecific and proceeded with retention of stereochemistry at the double bond.

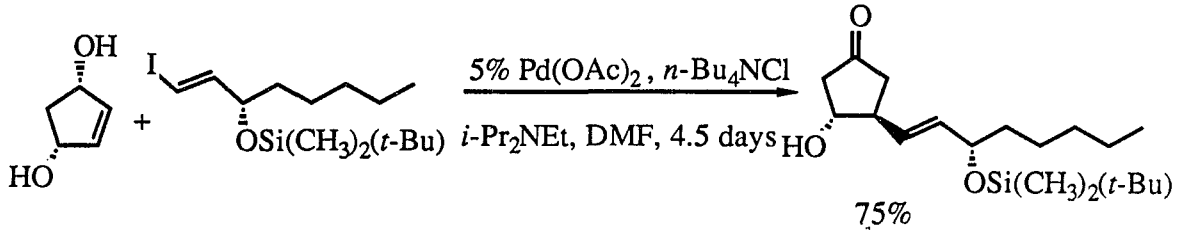
Larock et al.[30] reported the palladium-catalyzed coupling of aryl halides and non-allylic unsaturated alcohols (eq. 15). The authors observed that the reaction conditions actually gave higher yields and a decreased reaction rate with increasing chain length.

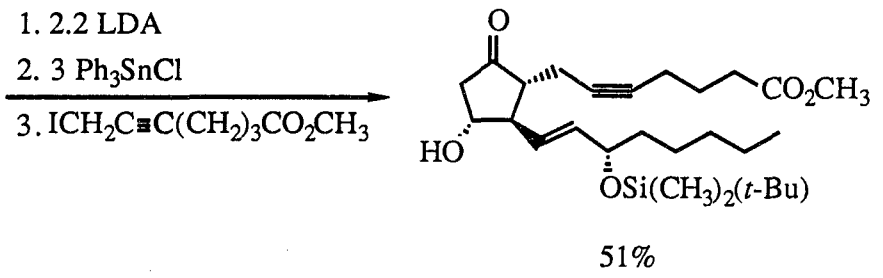


79%

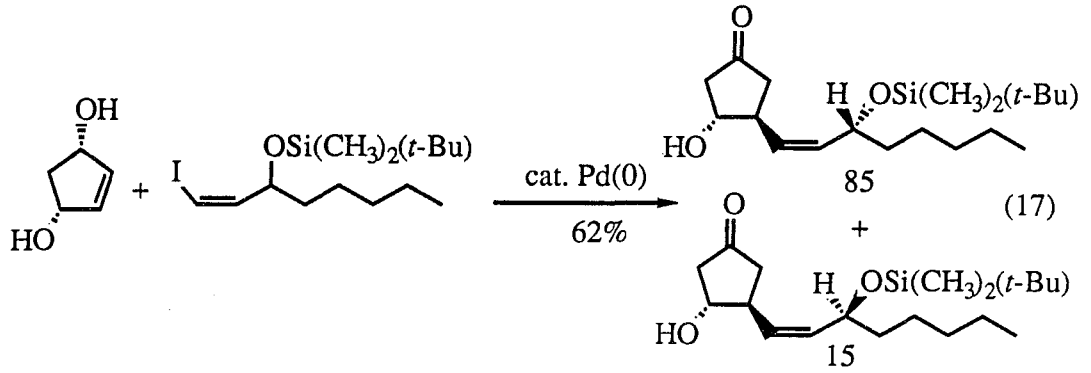
(15)

The palladium-catalyzed intermolecular vinylation has been used in the synthesis of prostaglandin analogues (eqs. 16 and 17).[31,32] In contrast to the stereoselective 1,4-addition of *cis*-alkenylcuprates,[33] this diastereoselective palladium-catalyzed reaction was remarkable with regard to simplicity of manipulation, yield, and selectivity.



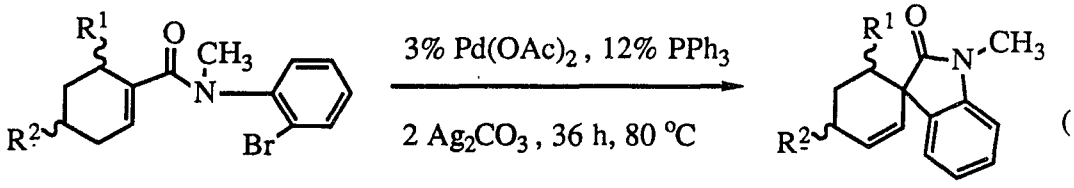


(16)



(17)

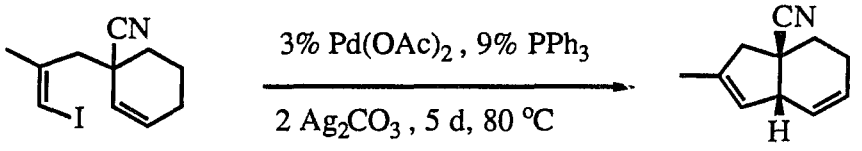
Palladium-catalyzed intramolecular arylation and vinylation are also very efficient methods to synthesize a variety of fused, bridged, and spiro carbo- and heterocyclic compounds (eqs. 18 and 19).[25a,c,34,35]



(18)

$R^1 = H$, $R^2 = t$-Bu

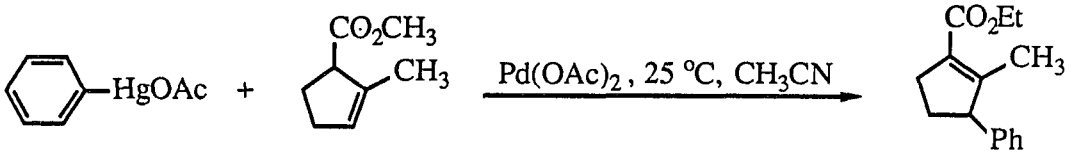
75%



(19)

77%

Until recently, few studies have been published regarding palladium-mediated arylation of substituted cyclic alkenes (eq. 20).[1b,13,36]



(20)

63%

These encouraging results prompted us to extend the palladium-catalyzed arylation to a variety of vinylic and allylically substituted cycloalkenes in order to establish the regio- and stereoselectivity. This methodology possesses vast potential for the synthesis of diverse medicinally and physiologically interesting substances.

RESULTS AND DISCUSSION

A. Palladium-catalyzed arylation of cyclic alcohols

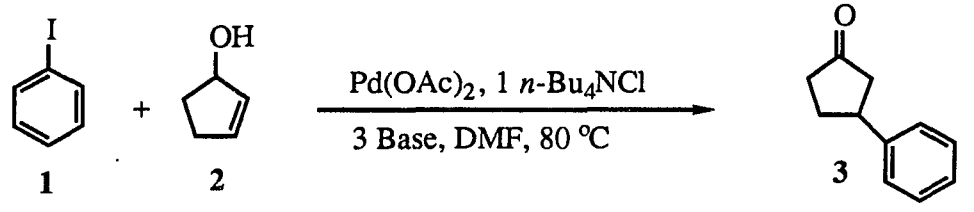
There are only a few reports of the palladium-catalyzed arylation of cyclic allylic alcohols.[1b,5,13,36] These early results prompted us to extend the palladium-catalyzed arylation to cyclic allylic alcohols in order to establish the regio- and stereoselectivity of the reaction. Hopefully, the methodology might then be applied to the synthesis of diverse medicinally and physiologically interesting substances.[37] To establish regioselectivity, 2-cyclopenten-1-ol and 2-cyclohexen-1-ol were examined as substrates. The results are summarized in Table 1.

Potassium acetate was first examined as a base for the arylation of 2-cyclopenten-1-ol (entries 1-7). Usually the reactions were complete within two days at 80 °C. Changing the amount of catalyst didn't improve the yield (entries 2 and 3). Using 2 equiv. of iodobenzene instead of 1 equiv. of iodobenzene increased the yield by 14% (entries 5 and 6). A low temperature reaction was examined to prevent formation of biphenyl. This reaction yielded 88% of the desired product without any side products in 16 hours (entry 7).

The reactions were repeated using Et_3N (entries 8-10). These reactions showed almost the same yield and reaction time as the KOAc reactions.

Reactions using NaOAc, K_2CO_3, or Na_2CO_3 as a base were also carried out at 80 °C. The results for these bases showed no desired product with sole formation of biphenyl (entries 11-13). The reactions utilizing carbonate bases with PPh_3 produced about a 50% yield (entries 14 and 15). These reactions showed that PPh_3 slowed down the formation of biphenyl, but increased the overall reaction time. The same yields were obtained for 15 and 5% PPh_3 (entries 14 and 15). From the above results, the formation of biphenyl could be avoided by

Table 1. Palladium-catalyzed phenylation of 2-cyclopenten-1-ol



Entry[a]	Equiv. of **2**	Equiv. of **1**	% $Pd(OAc)_2$	Base	Reaction time	% Isolated yield
1	1.5	1	3	KOAc	3 d	40
2	2	1	3	KOAc	3 d	55
3	2	1	5	KOAc	2 d	56
4	1	1.5	5	KOAc	2 d	36
5[b]	1	1	5	KOAc	2 d	47
6[b]	1	2	5	KOAc	2 d	61
7[c]	1	2	5	KOAc	16 h	88
8	1.5	1	3	Et_3N	3 d	40
9[b]	2	1	5	Et_3N	1.5 d	55
10[b]	1	1	5	Et_3N	3 d	47
11	2	1	3	NaOAc	3 d	0
12	2	1	3	K_2CO_3	3 d	0
13	2	1	3	Na_2CO_3	3 d	0
14[b]	2	1	5	Na_2CO_3	6 d	52
15[d]	2	1	5	Na_2CO_3	6 d	50

[a]All reactions were run on a 0.5 mmol scale.

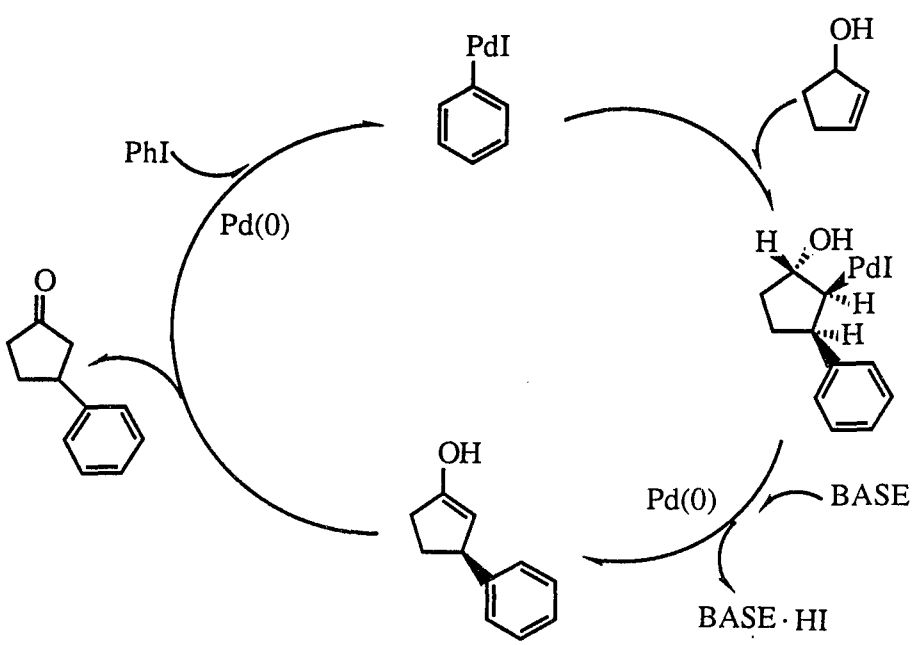
[b]5% PPh_3 added.

[c]The reaction was run at 60 °C.

[d]15% PPh_3 added.

using lower temperatures and a small amount of PPh_3. Usually PPh_3 was helpful for the carbonate reactions, but it did not give good results for the acetate reactions.

The 3-phenylcyclopentanone was formed by the following mechanism (Scheme 3). The $Pd(OAc)_2$ is reduced to palladium(0) in the presence of the olefin. The palladium(0) complex reacts with the aryl halide via oxidative addition. The aryl palladium complex next adds across the double bond of the cyclic allylic alcohol in a syn fashion. Subsequent elimination of a syn β-hydrogen provides 3-phenyl-1-cyclopenten-1-ol and a hydridopalladium halide which dissociates in the presence of base to regenerate the palladium(0) catalyst, which repeats the cycle. Subsequent tautomerization of 3-phenyl-1-cyclopenten-1-ol provides 3-phenylcyclopentanone (**3**).



Scheme 3

The arylation of 2-cyclohexen-1-ol afforded two isomeric products. The major product was 3-phenylcyclohexanone and the minor product was 2-phenylcyclohexanone. Many variations were tried to improve the isomer ratio and yield. The reaction conditions and results are summarized in Table 2.

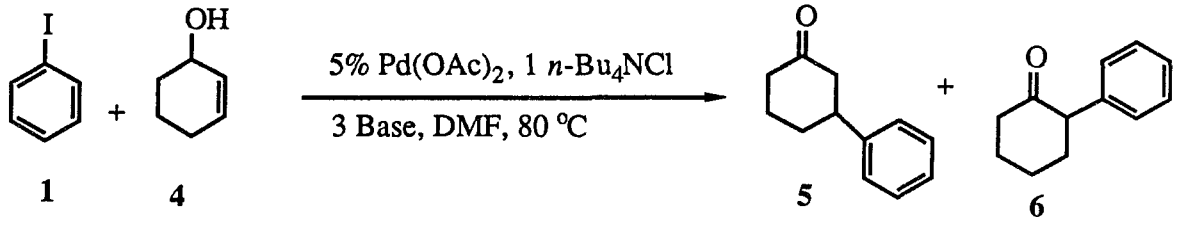
The arylation of 2-cyclohexen-1-ol with KOAc as a base was examined under several different conditions. The reaction provided two isomers in a ratio of 5 : 1 regardless of the different conditions used (entries 1 - 6). The reactions were also examined at room temperature, 60 °C and 80 °C. It was determined that a temperature of at least 80 °C was necessary to complete the reaction. The biggest problem in these reactions was the formation of biphenyl at higher temperatures.

Triethylamine was also tried as a base to improve the yield and isomeric ratio, but the reaction was very fast and similar in yield to the KOAc reactions and the isomer ratio was worse (entry 7).

Sodium carbonate was examined as a base under the same conditions as KOAc. The results showed no desired product and only the formation of biphenyl; however, the reactions with Na_2CO_3 and PPh_3 showed 55% of the desired products in a 7.5 : 1 isomeric ratio (entry 10). A $Pd(dba)_2$-catalyzed arylation was tried under these same conditions, but almost the same yield and isomeric ratio was obtained (entry 11).

The bases $KHCO_3$, K_2CO_3 and $NaHCO_3$ were also employed with PPh_3 in this reaction. These bases gave low yields, but the product obtained was solely 3-

Table 2. Palladium-catalyzed phenylation of 2-cyclohexen-1-ol



1 4 5 6

Entry[a]	Equiv. of **4**	Equiv. of **1**	Base	Reaction time	% Isolated yield	Isomer ratio (**5**:**6**)[b]
1	1	2	KOAc	3 d	56	5:1
2[c]	1	2	KOAc	6 d	0	-
3[d]	1	2	KOAc	4 d	39	5:1
4	1.5	1	KOAc	3 d	40	5:1
5	2	1	KOAc	3 d	42	5:1
6[d]	2	1	KOAc	3 d	20	5:1
7	1	2	Et_3N	1 d	40	1:1
8	1	2	Na_2CO_3	6 d	0	-
9	2	1	Na_2CO_3	6 d	0	-
10[d]	2	1	Na_2CO_3	6 d	55	7.5:1
11[d,e]	2	1	Na_2CO_3	3 d	49	7:1
12[d]	2	1	$NaHCO_3$	3 d	25	only **5**
13[d]	1	2	$KHCO_3$	6 d	33	only **5**
14[d]	1	2	K_2CO_3	6 d	33	only **5**
15	1	2	$KHCO_3$	6 d	60	only **5**
16	1	2	K_2CO_3	6 d	56	only **5**

[a]All reactions were run on a 0.5 mmol scale.

[b]The isomer ratio was determined by GC and NMR spectroscopy.

[c]Reaction run at 60 °C.

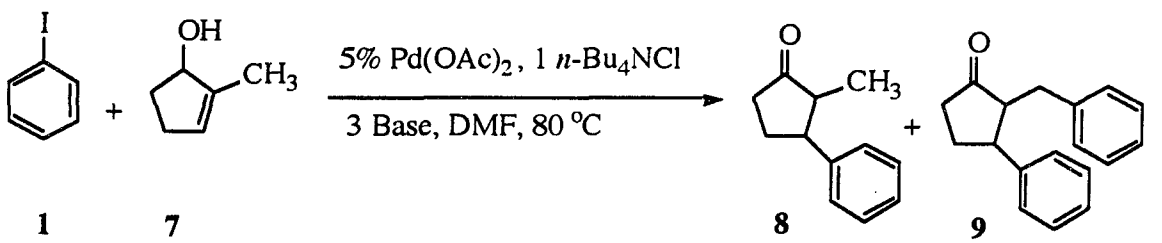
[d]5% PPh_3 added.

[e]$Pd(dba)_2$ used instead of $Pd(OAc)_2$.

phenylcyclohexanone (entries 12-14). The reactions using K_2CO_3 and $KHCO_3$ as bases, but no PPh_3, provided 56 -60% yields of 3-phenylcyclohexanone as a single product (entries 15 and 16). From the above results, the arylation of 2-cyclohexen-1-ol showed a variety of isomeric ratios and yields. The formation of biphenyl could be prevented by using lower temperatures and PPh_3 with carbonate bases.

The arylation of 2-methyl-2-cyclopenten-1-ol was examined with several bases at 60 °C and 80 °C. The results are summarized in Table 3. The arylation of 2-methyl-

Table 3. Palladium-catalyzed phenylation of 2-methyl-2-cyclopenten-1-ol



1 **7** **8** **9**

Entry[a]	Equiv. of **7**	Equiv. of **1**	Base	Reaction conditions	% Yield[b]	Product ratio(**8**:**9**)[b]
1	1	2	KOAc	80 °C, 2 d	82	3:1
2	1	2	KOAc	60 °C, 2 d	82	3:1
3[c]	1	1	KOAc	60 °C, 3 d	66	3:1
4	2	1	KOAc	60 °C, 2 d	48	3:1
5[c]	1	2	KOAc	60 °C, 3 d	24	3:1
6[c]	1	2	Na_2CO_3	80 °C, 2 d	86	1:1
7[c]	1	2	Na_2CO_3	60 °C, 2 d	80	1:1
8[c]	2	1	Na_2CO_3	60 °C, 2 d	50	1:1
9[c]	1	2	K_2CO_3	60 °C, 2 d	72	1:1

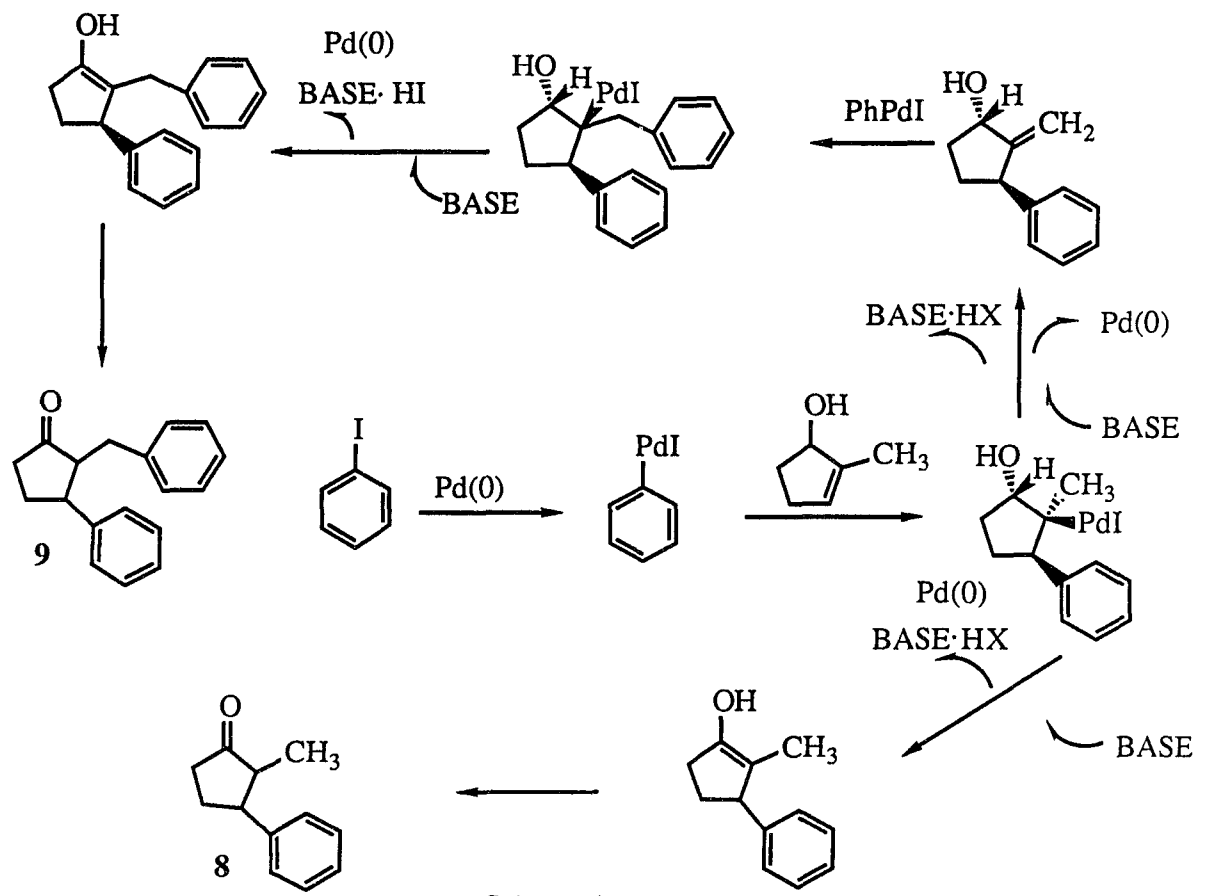
[a]All reactions were run on a 0.5 mmol scale.

[b]The yield and product ratio was determined by GC with dodecane as an internal standard.

[c]5% PPh_3 added.

2-cyclopenten-1-ol using KOAc and Na_2CO_3 was complete within two days at 80 °C. Unfortunately, single arylation and double arylation products were observed by GC-MS and ^1H NMR spectroscopy. It was impossible to assign chemical shifts, because the ^1H NMR spectra were too complicated. The reactions utilizing KOAc were complete at 60 °C or 80 °C within 2 days, but single and double arylation products were obtained in an isomer ratio of 3:1 (entries 1 and 2). The arylation of 2-methyl-2-cyclopenten-1-ol was also examined using 2 equiv. of 2-methyl-2-cyclopenten-1-ol and 1 equiv. of iodobenzene. This change didn't improve the single and double arylation isomer ratio (entry 4). Another reaction utilizing KOAc with PPh_3 didn't change the isomer ratio, but decreased the yield significantly (entry 5). Reactions using Na_2CO_3 and K_2CO_3 were also examined. These bases showed no improvement in the single and double arylation ratios.

From the above results, the single arylated intermediate is more reactive than the starting material. Table 3 also shows that single and double arylation product ratios change with different bases. Compounds **8** and **9** were formed by the following mechanism (Scheme 4). After forming the single arylated palladium intermediate, there are two possible hydrogens which can undergo elimination. Elimination of the hydrogen on the hydroxyl-substituted carbon provides 3-phenyl-1-cyclopenten-1-ol, which after tautomerization affords compound **8**. Elimination of a hydrogen on the methyl group provides the exocyclic allylic alcohol. The alcohol rapidly reacts further with another arylpalladium intermediate, eventually providing 2-benzyl-3-phenyl-1-cyclopenten-1-ol, which after tautomerization affords compound **9**.

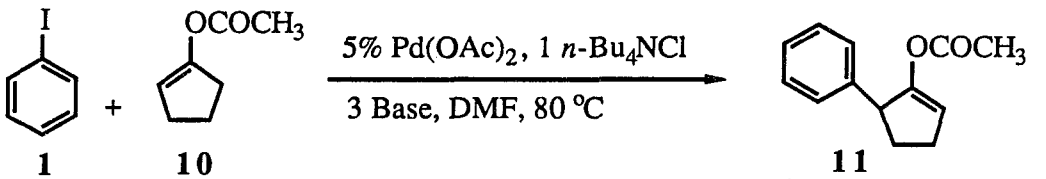


Scheme 4

B. The palladium-catalyzed arylation of enol ester, ether and cyano compounds

The palladium-catalyzed arylation of 1-acetoxy-1-cyclopentene was examined and the results are summarized in Table 4. The arylation of 1-acetoxy-1-cyclopentene was first examined using KOAc at 50 °C to 80 °C (entries 1 - 11). These reactions provided low to good yields of the single arylation product. Significant amounts of biphenyl were also formed as the main side product. The amounts of 1-acetoxy-1-cyclopenten and iodobenzene were

Table 4. Palladium-catalyzed phenylation of 1-acetoxy-1-cyclopentene



1 **10** **11**

Entry[a]	Equiv. of **10**	Equiv. of **1**	Base	Reaction conditions	% Yield[b]
1	3	1	KOAc	80 °C, 3 d	30
2	5	1	KOAc	80 °C, 3 d	36
3[c]	1	2	KOAc	80 °C, 3 d	29
4[c]	1	3	KOAc	80 °C, 3 d	29
5	1	3	KOAc	80 °C, 3 d	55
6	5	1	KOAc	80 °C, 3 d	60
7	1	2	KOAc	80 °C, 3 d	30
8	1	2	KOAc	70 °C, 5 d	43
9	3	1	KOAc	70 °C, 5 d	70
10	3	1	KOAc	60 °C, 6 d	78
11	3	1	KOAc	50 °C, 6 d	60
12	3	1	Na_2CO_3	80 °C, 3 d	23
13[c]	3	1	Na_2CO_3	80 °C, 3 d	43
14[c]	1	2	Na_2CO_3	80 °C, 2 d	34
15	3	1	K_2CO_3	80 °C, 3 d	13
16[c]	1	2	KOAc	60 °C, 6 d	57

[a]All reactions were run on a 0.5 mmol scale.

[b]The yield was determined by GC using dodecane as an internal standard.

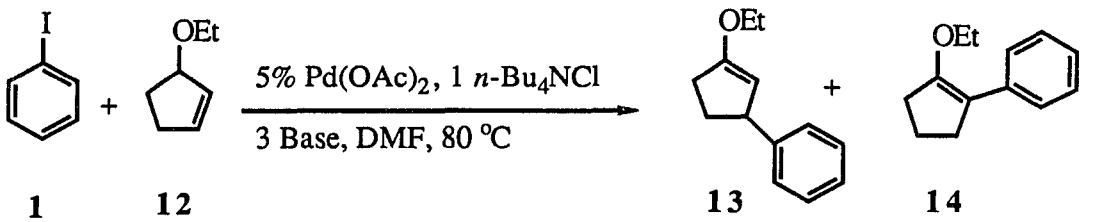
[c]5% PPh_3 added.

varied to improve the reaction yield, but significant changes were not observed. The same reaction conditions at several different temperatures were repeated in order to reduce the amount of biphenyl. The iodobenzene was consumed completely at 70 °C, resulting in a 70% yield of product (entry 9). Since 1-acetoxy-1-cyclopentene has a relatively low boiling point, there was a strong possibility that a significant amount of it might have evaporated at either 70 °C or 80 °C, before it could react with the iodobenzene. Hence, two additional reactions were run at 60 °C (entries 10 and 16). They afforded only the desired product in 78% and 57% yields respectively. Reactions using Na_2CO_3 were examined at 80 °C (entries 12-14). These reactions provided 30-40% of the desired product with formation of biphenyl.

The arylation of 3-ethoxy-1-cyclopentene was examined using several different bases at 60 °C to 80 °C. The results are summarized in Table 5.

Unfortunately, GC-MS indicated that two isomeric products were obtained in a 2:1 ratio in one of the KOAc reactions (entry 5). The major isomer was compound **13** based on the presence of a vinylic proton in the ^1H NMR spectrum. The reactions using KOAc and Na_2CO_3 were examined at 80 °C. The reaction provided only biphenyl without any of the desired product. The reaction using Na_2CO_3 and PPh_3 was completed at 60 °C after two days, resulting in a 60% yield of arylated products (entry 3). It was impossible to assign isomeric ratios by normal OV-101 column GC, because the two isomers had the same retention time . The ^1H NMR spectrum of the two isomers overlapped in the aliphatic region, so it was also impossible to obtain the exact isomeric ratio in this manner. The reaction using K_2CO_3 with PPh_3 was also examined at 60 °C (entry 4). These conditions provided 70% of the desired product. The reactions using Na_2CO_3 and K_2CO_3 without PPh_3 were also examined at 60 °C, resulting in none of the desired product (entries 7 and 8).

Table 5. Palladium-catalyzed phenylation of 3-ethoxy-1-cyclopentene



1 **12** **13** **14**

Entry[a]	Equiv. of **12**	Equiv. of **1**	Base	Reaction conditions	% Yield[b]
1	3	1	KOAc	80 °C, 2 d	0
2[c]	3	1	Na_2CO_3	80 °C, 2 d	0
3[c]	1	2	Na_2CO_3	60 °C, 2 d	60
4[c]	1	2	K_2CO_3	60 °C, 2 d	70
5[d]	1	2	KOAc	60 °C, 3 d	65
6[c]	1	2	$KHCO_3$	60 °C, 3 d	0
7	1	2	K_2CO_3	60 °C, 3 d	0
8	1	2	Na_2CO_3	60 °C, 3 d	0

[a]All reactions were run on a 0.5 mmol scale.

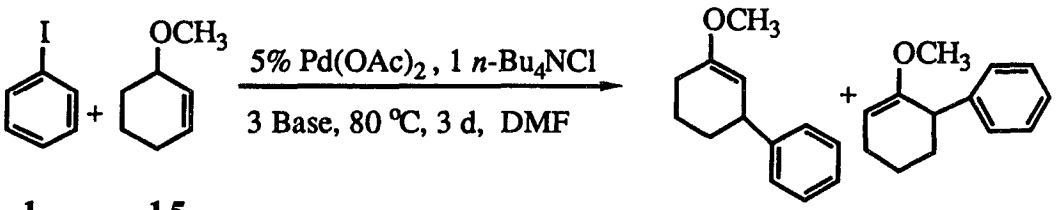
[b]Isolated yield of mixture of **13** and **14**.

[c]5% PPh_3 added.

[d]The isomer ratio (2:1) was determined by GC-MS.

The arylation of 3-methoxy-l-cyclohexene was examined, and the results are summarized in Table 6. The reaction using Na_2CO_3 with PPh_3 provided a 46-47% yield of single arylation products with an isomeric ratio of 2:1:1 (entries 1 and 2). The three isomers had the same molecular weight by GC-MS analysis. Another reaction was run using K_2CO_3 with PPh_3. The reaction was complete at 80 °C with a 60% yield of single arylated products being

Table 6. Palladium-catalyzed phenylation of 3-methoxy-1-cyclohexene



1 **15** **16** **17**

Entry[a]	Equiv. of **15**	Equiv. of **1**	Base	% PPh_3	% Yield[b]	Isomer ratio (**16**:**17**:unknown)[c]
1	3	1	Na_2CO_3	15	47	2:1:1
2	3	1	Na_2CO_3	5	46	2:1:1
3	1	2	Na_2CO_3	-	0	-
4	1	2	Na_2CO_3	5	45	2:1:1
5	3	1	K_2CO_3	15	0	-
6	1	2	K_2CO_3	5	60	2:1:1
7	1	2	K_2CO_3	-	0	-
8	3	1	KOAc	15	15	3:1:1
9	1	2	KOAc	5	20	3:1:1
10	1	2	KOAc	-	0	-
11	3	1	NaOAc	15	66	1:1:3
12	1	2	NaOAc	5	45	1:1:3
13	3	1	CsOAc	-	0	-
14	3	1	CsOAc	15	47	1:1:0
15[d]	3	1	Ag_2CO_3	9	0	-

[a]All reactions were run on a 0.5 mmol scale.

[b]The yield was determined by GC using dodecane as an internal standard.

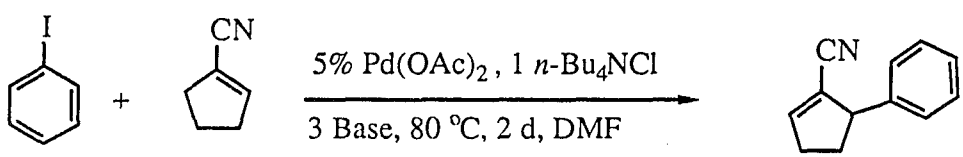
[c]The isomer ratio was determined by GC and NMR spectroscopy.

[d]3% $Pd(OAc)_2$, 5 ml CH_3CN, 2 Ag_2CO_3, no *n*-Bu_4NCl.

formed in an isomer ratio of 2:1:1 (entry 6). The reactions employing KOAc with PPh_3 gave only a 15-20% yield of products in an isomer ratio of 3:1:1. These conditions improved the isomer ratio, but the yield was decreased significantly (entries 8 and 9). Reactions using NaOAc with PPh_3 were also examined. These conditions provided 45-66% of the single addition products in an isomer ratio of 1:1:3 (entries 11 and 12). Reactions using Na_2CO_3, K_2CO_3, KOAc, and CsOAc as bases with no PPh_3 present provided only biphenyl as the product (entries 3, 7, 10 and 13). It was impossible to assign structures to each of the isomers because they were not easily separated and their ^1H NMR spectra overlapped significantly. The structure of the compounds **16** and **17** were assigned based on the chemical shift of the benzylic protons of each compound.

The arylation of 1-cyanocyclopentene was examined. The results are summarized in Table 7. The reactions using KOAc provided 75-78% of the single arylation product without any side products. Another reaction using Na_2CO_3 with PPh_3 gave only a single arylation product, but the rate of the reaction was much slower.

Table 7. Palladium-catalyzed phenylation of 1-cyanocyclopentene



1 **18** **19**

Entry	Equiv. of **18**	Equiv. of **1**	Base	% PPh_3	% Isolated yield
1	2	1	KOAc	-	75
2	1	2	KOAc	-	78
3	2	1	Na_2CO_3	5	0

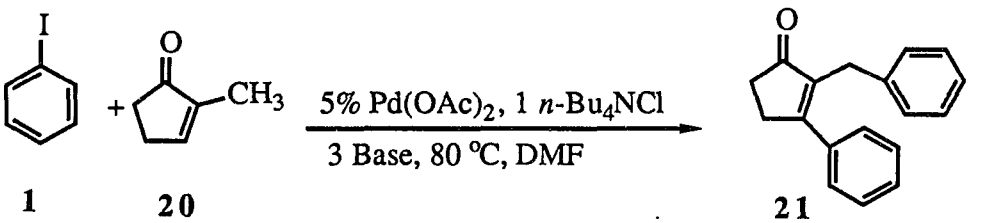
From the above results, the phenylation of 1-acetoxy, and 1-cyanocyclopentene gave good regioselectivity and yields at lower temperatures, but the phenylation of 3-methoxy-1-cyclopentene and 3-ethoxy-1-cyclohexene provided mixtures of regioisomers and low yields with formation of biphenyl as a major side product.

C. Palladium-catalyzed arylation of substituted enones

The arylation of 2-methyl-2-cyclopenten-1-one was examined. The results are summarized in Table 8. Several different bases were examined in an attempt to produce the single arylation product, but all reaction conditions provided only the double arylation product. The ratio of 2-methyl-2-cyclopenten-1-one and iodobenzene was varied in an attempt to produce the single arylation product, but the single substitution product is apparently more reactive than the starting material and only product **21** has been observed. Reactions utilizing KOAc and Na_2CO_3 were examined at 80 °C and 100 °C. At those temperatures, the reactions result in 42-48% yields of the double arylation product **21** (entries 1-4). A reaction using K_2CO_3 also resulted in a 32% yield of the double arylation product at 80 °C (entry 8). From the above results, the mono-arylation product is more reactive than the 2-methyl-2-cyclopenten-1-one.

The arylation of 2-methyl-2-cyclohexen-1-one was also examined. The results are summarized in Table 9. The arylation of 2-methyl-2-cyclohexen-1-one was attempted at 80 °C. However, after three days almost all of the starting materials remained in each case. The reactions were repeated at 100 °C to improve the reaction rate. These conditions provided 16-23% of the double arylation product and some polymer.

Table 8. Palladium-catalyzed phenylation of 2-methyl-2-cyclopenten-1-one



1 **20** **21**

Entry[a]	Equiv. of **20**	Equiv. of **1**	Base	Reaction time (d)	% Yield[b]
1[c]	1	2	KOAc	3	42
2	1	2	KOAc	3	42
3[c,d]	1	2	Na_2CO_3	3	48
4	1	2	Na_2CO_3	5	48
5	2	1	KOAc	5	16
6[d]	2	1	Na_2CO_3	5	24
7	1	2	Na_2CO_3	5	0
8[d]	1	2	K_2CO_3	5	32

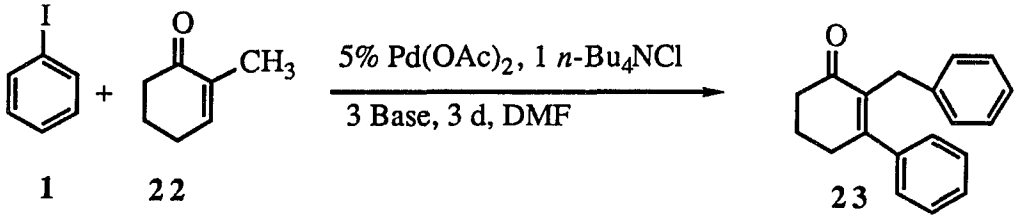
[a]All reactions were run on a 0.5 mmol scale and provided some polymer.

[b]The yield was determined by GC using dodecane as an internal standard.

[c]The reaction was run at 100 °C.

[d]5% PPh_3 added.

Table 9. Palladium-catalyzed phenylation of 2-methyl-2-cyclohexen-1-one



1 22 23

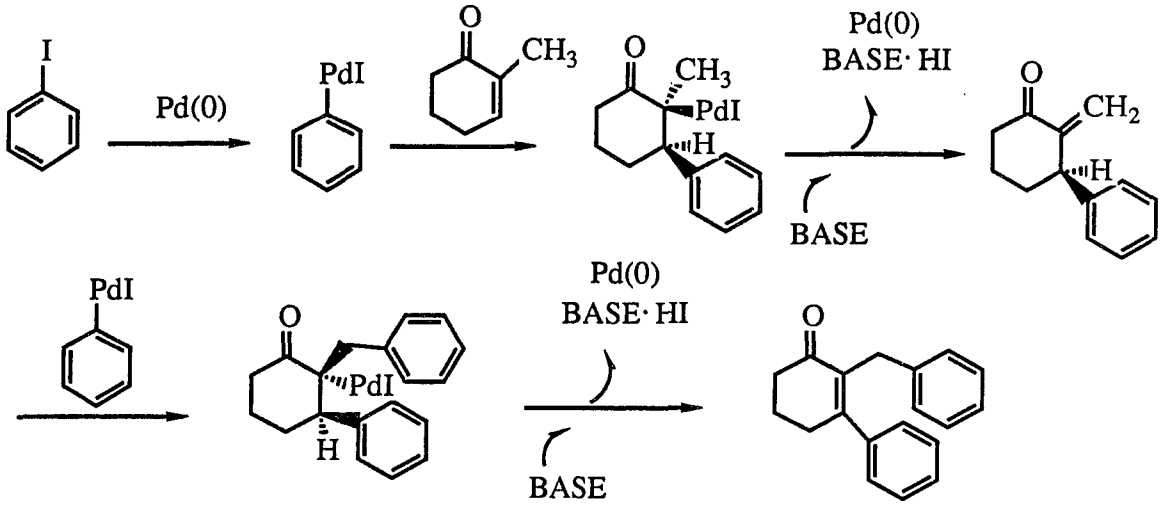
Entry[a]	Base	Temperature (°C)	% Yield[b]	Comments
1	KOAc	100	16	-
2[c]	Na_2CO_3	100	23	-
3	Na_2CO_3	80	0	slow reaction
4[c]	Na_2CO_3	100	0	biphenyl formation

[a]All reactions were run on a 0.5 mmol scale.

[b]The yield was determined by GC using dodecane as an internal standard.

[c]5% PPh_3 added.

The mechanism of formation of double arylated α,β-unsaturated ketone is described in Scheme 5. After formation of the single arylated palladium intermediate, the intermediate undergoes β-hydride elimination to provide the phenyl-substituted exocyclic α,β-unsaturated ketone. The exocyclic ketone reacts further with the arylpalladium halide, eventually providing the double arylated product.

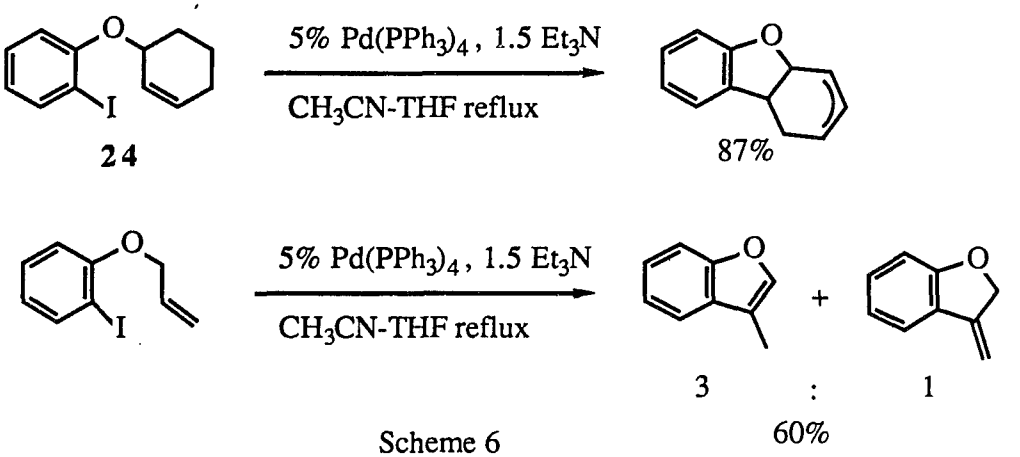


Scheme 5

From the above results, the phenylation of 2-methyl-2-cyclopenten-1-one and 2-methyl-2-cyclopenten-1-one only provided double arylation products. The single arylation intermediate is apparently more reactive than the starting α,β-unsaturated ketone.

D. Intramolecular palladium-catalyzed cyclization

The intramolecular palladium-catalyzed cyclization of olefins containing aryl and alkenyl halides, followed by dehydropalladation, has been widely applied to the synthesis of nitrogen heterocycles.[38] However, little attention has been paid to the synthesis of oxygen heterocycles by this methodology. Recently, Negishi et al.[39] reported that treatment of a variety of alkenyl ethers derived from *o*-iodophenol and *o*-iodobenzyl alcohol with a catalytic amount of palladium(0) in the presence of Et_3N in refluxing CH_3CN gave the corresponding cyclic ether in good yield. However, the following reactions gave a mixture of isomeric products (Scheme 6). These same reactions were examined to try to establish conditions for the formation of a

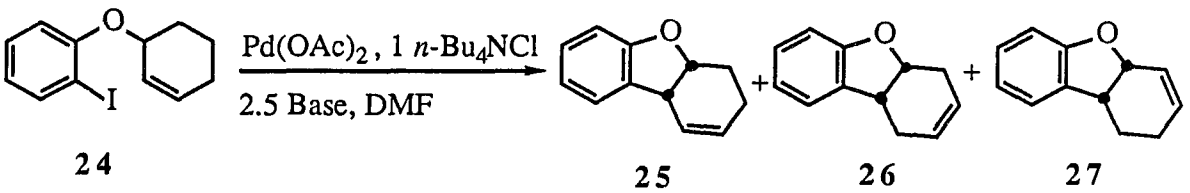


Scheme 6

single product. The results are summarized in Table 10.

The reactions of ether **24** with NaOAc, KOAc , and Na_2CO_3 provided three isomeric products according to analysis by GC and NMR spectroscopy. The reaction utilizing Na_2CO_3 was complete within two days at 100 °C, but resulted in only a 45% yield. A similar reaction run at 80 °C was much slower than that run at 100 °C (compare entries 1 and 5), but gave a substantially higher yield of all three isomers. The reaction utilizing NaOAc was complete in two days at 100 °C and resulted in a 94% yield of products formed in an isomeric ratio of 1:3:1 (entry 2). Using KOAc, the reaction was complete in one day at 100 °C and provided a 91% yield of a 3:5:1 ratio of isomers (entry 3). The reaction using KOAc proceeded much faster than that of NaOAc with almost the same isolated yield. Finally, the reaction using procedure B (4% $Pd(OAc)_2$, 2 Ag_2CO_3, 12% PPh_3, CH_3CN) was complete in two days at 80 °C and provided an 89% isolated yield of a single isomeric product **25**. In general, the reaction using KOAc gave more isomerized products than those using Ag_2CO_3 (compare entries 3 and 4). From the above results, the reactions using procedure A provided more isomerized products compared to the reaction using procedure B. Only procedure B gives a good yield of a single product.

Table 10. Palladium-catalyzed intramolecular cyclization of 2-cyclohexenyl *o*-iodophenyl ether



24 25 26 27

Entry[a]	% $Pd(OAc)_2$	Base	Reaction conditions	% Isolated yield	Isomer ratio (**25**:**26**:**27**)[b]
1	5	Na_2CO_3	100 °C, 2 d	45	5:1:1
2	5	NaOAc	100 °C, 2 d	94	1:3:1
3	5	KOAc	100 °C, 1 d	91	3:5:1
4[c]	4	Ag_2CO_3	80 °C, 2 d	89	only **25**
5	2	Na_2CO_3	80 °C, 4 d	96	1:2:1

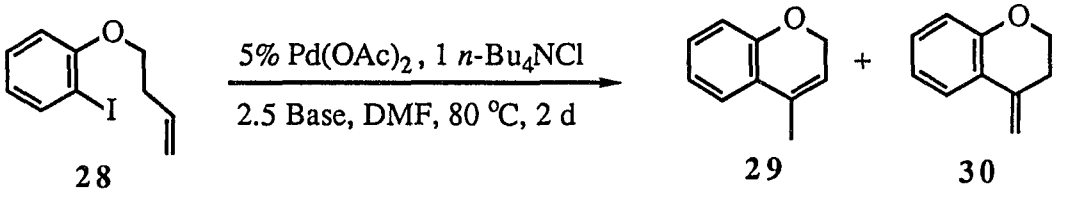
[a]All reactions were run on a 0.5 mmol scale.

[b]The isomer ratio was determined by GC and NMR spectroscopy.

[c]12% PPh_3 and 8 ml CH_3CN, no *n*-Bu_4NCl.

The cyclization of 3-butenyl *o*-iodophenyl ether was also examined under the usual palladium-catalyzed conditions. The results are summarized in Table 11. The cyclization was generally complete in two days at 80 °C. From the experimental results, there seem to be little or no difference (in terms of overall yield and isomer ratio) between the use of $Pd(OAc)_2$ or $Pd(dba)_2$ as the catalyst. For instance, the reaction using NaOAc with $Pd(OAc)_2$ afforded two isomeric products in a 52% overall yield and an isomer ratio of 1:1 (entry 4). Using $Pd(dba)_2$ as the catalyst, the analogous reaction provided almost the same yield and isomer ratio

Table 11. Palladium-catalyzed intramolecular cyclization of 3-butenyl *o*-iodophenyl ether



28 **29** **30**

Entry[a]	Palladium source	Base	% Isolated yield	Isomer ratio (**29**: **30**)[b]
1	$Pd(OAc)_2$	KOAc	61	1:1
2	$Pd(dba)_2$	KOAc	52	1.5:1
3[c]	$Pd(OAc)_2$	KOAc	0	-
4	$Pd(OAc)_2$	NaOAc	52	1:1
5	$Pd(dba)_2$	NaOAc	53	1.1:1
6	$Pd(OAc)_2$	CsOAc	5	1:1
7	$Pd(OAc)_2$	Et_3N	67	2.3:1
8	$Pd(dba)_2$	Et_3N	56	4:1
9	$Pd(OAc)_2$	*i*-Pr_2NEt	63	3:1
10	$Pd(OAc)_2$	Na_2CO_3	51	1:1
11[d]	$Pd(OAc)_2$	Na_2CO_3	52	2:1
12[d]	$Pd(OAc)_2$	K_2CO_3	58	2:1
13	$Pd(dba)_2$	$(PhCH_2)_3N$	0	-
14[c]	$Pd(OAc)_2$	Ag_2CO_3	54	1:4

[a]All reactions were run on a 0.5 mmol scale.

[b]Isomer ratio was determined by gas chromatography and NMR spectroscopy.

[c]DMF:C_2H_5OH = 9:1.

[d]5% PPh_3 added.

[e]Procedure B (4% $Pd(OAc)_2$, 2 Ag_2CO_3, 12% PPh_3, 2 ml CH_3CN).

of products (entry 5). On the other hand, the arylation process appeared to be sensitive to the different acetate bases used. Replacing KOAc with NaOAc led to a 9% decrease in overall yield decrease in overall yield of the desired products (entries 1 and 4); moreover, when CsOAc was employed instead of KOAc, a dramatic drop in yield was observed (entries 1 and 6). The reaction using Et_3N as the base provided an improved isomeric ratio when using $Pd(dba)_2$, but the product yield decreased compared to the reaction using $Pd(OAc)_2$ (entries 7 and 8). To improve the yield and the isomer ratio, a reaction using *i*-Pr_2NEt was examined. This reaction gave a better isomer ratio (entries 7 and 9). A reaction utilizing Na_2CO_3 provided two isomeric products in a ratio of 1:1 with a 51% overall yield (entry 10). To improve the isomer ratio, 5% PPh_3 was added under the same reaction conditions (entry 11). The isomer ratio was improved from 1:1 to 2:1. Procedure B was also tried. These conditions result in a 54% yield with an isomer ratio of 1:4 (entry 14). From the above results, procedure A (5% $Pd(OAc)_2$, 1 *n*-Bu_4NCl, 2.5 base, DMF) gave more of the isomerized product; on the other hand, procedure B (4% $Pd(OAc)_2$, 2 Ag_2CO_3, 12% PPh_3, CH_3CN) provided the non-isomerized product predominantly.

CONCLUSION

The palladium-catalyzed intermolecular arylation of cyclic alkenes bearing a variety of functional groups provides a valuable route to aryl-substituted cyclic alkenes.

The phenylation of 2-cyclopenten-1-ol and 2-cyclohexen-1-ol was achieved highly regioselectively providing 3-phenyl cycloalkanones in good yield, but a reaction using 2-methyl-2-cyclopenten-1-ol provided a mixture of single and double arylated cyclic ketones.

The phenylation of 1-acetoxy-1-cyclopentene and 1-cyanocyclopentene each provided a single phenylation product without any side products, but the phenylation of 3-ethoxycyclopentene and 3-methoxycyclohexene gave mixtures of isomeric singly arylated products.

The arylation of 2-methyl-2-cyclopenten-1-one and 2-methyl-2-cyclohexen-1-one provided only double arylation products without any single arylation product being observed.

The intramolecular cyclization of alkenyl *o*-iodophenyl ethers provided isomeric cyclized products; however, procedure B (3-4% $Pd(OAc)_2$, 2 Ag_2CO_3, 9-12% PPh_3, CH_3CN) minimizes isomerization of the double bond.

The phenylation of hydroxy, cyano and acetoxy-substituted five-membered cyclic olefins shows regioselectivity, but the arylation of ethoxy and methoxy-substituted five and six-membered cyclic olefins provides mixtures of regioisomers. The regioselectivity depends not only on the functional group present, but also the base employed. Another problem in the arylation of cyclic olefins is the formation of biphenyl and isomerization of the double bond. The formation of biphenyl can be avoided by using lower temperatures (below 60 ^{o}C) and Na_2CO_3 or K_2CO_3 with PPh_3, but the arylation of cyclic olefins often requires higher temperatures.

EXPERIMENTAL SECTION

A. Equipment

The infrared spectra were obtained on an IBM IR/98 FT spectrophotometer, and the ^{1}H NMR and ^{13}C NMR spectra on a Nicolet NT-300 NMR spectrometer. The GC-MS spectral data were obtained on a Finnegan 4023 GC/MS and on a Kratos MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with an OV-101 packed column.

B. Reagents

All chemicals were used directly as obtained commercially unless otherwise indicated. 4-Bromo-1-butene, 2-methyl-2-cyclohexen-1-one, iodobenzene, 2- cyclopenten-1-one, 2-cyclohexen-1-ol, PPh_3, and Ag_2CO_3 were all purchased from Aldrich Chemical Company. *o*-Iodophenol, 3-bromocyclohexene and *n*-Bu_4NCl were purchased from Lancaster Chemical Company. All inorganic bases used were purchased from Fisher Scientific. 1-Acetoxy-1-cyclopentene and 1-cyano-1-cyclopentene were prepared by Dr. Baker.[23]

Preparation of 2-cyclopenten-1-ol (**2**)[40]

2-Cyclopenten-1-one (10 mmol) was dissolved in 25 ml of methanol containing $CeCl_3 \cdot 7H_2O$ (40 mmol), and $NaBH_4$ (10 mmol) was slowly added with stirring. The mixture was allowed to react for 1 hour at room temperature, followed by hydrolysis. The mixture was extracted with two 50 ml portions of diethyl ether. The ether was dried with $MgSO_4$. The

resultant product, colorless 2-cyclopenten-1-ol (**2**) was obtained in an 85% isolated yield after column chromatography. ^{1}H NMR ($CDCl_3$) δ 2.05 (br s, 1H, OH), 2.29 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 3.34 (m, 1H, CH-O), 6.14 (m, 1H, =CH), 7.67 (m, 1H, =CH).

Preparation of 2-methyl-2-cyclopenten-1-ol (**7**)

2-Methyl-2-cyclopenten-1-ol was obtained in a 90% isolated yield using the above procedure.[40] ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H, CH_3), 2.0 (br s, 1H, OH), 2.26 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 4.56 (m, 1H, CH-O), 5.50 (t, 1H, J = 6.0 Hz, =CH).

General procedure for the palladium-catalyzed arylation of substituted cycloalkenes

To a 1 dram vial containing a magnetic stirring bar was added the following reagents; $Pd(OAc)_2$ (0.025 mmol, 3 mg), base (1-3 equivalents) and *n*-Bu_4NCl (0.5 mmol, 140 mg). The vial was sealed with a septum and purged with nitrogen. The following reagents were then added: 1 ml DMF, cycloalkene (0.5 mmol), and iodobenzene (1.0 mmol, 204 mg). The mixture was stirred at the desired temperature for the time indicated. The reaction mixture was diluted with diethyl ether (10 ml) and washed with saturated aqueous NH_4Cl (2 x 10 ml), and the combined aqueous layers were backwashed with diethyl ether, The combined ether fractions were dried over anhydrous $MgSO_4$. The reaction mixture was filtered, concentrated, and purified via flash column chromatography with hexane-ethyl acetate as the solvent. The following compounds were prepared using the above general procedure.

Preparation of compound **3**

Obtained in an 88% isolated yield from iodobenzene and 2-cyclopenten-1-ol as a yellow oil using KOAc as a base and stirring for 16 hours at 60 °C (Table 1, entry 7). IR(neat) 3061, 3028, 2982, 1740, 1495, 1404, 1151, 762, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 1H,

CH_2), 2.17-2.45 (m, 4H, CH_2 and CH_2CO), 2.6 (dd, 1H, J = 7.5 Hz, J = 1.5 Hz, CH_2CO), 3.29-3.39 (m, 1H, ArCH), 7.16-7.31 (m, 5H, ArH) ; ^{13}C NMR($CDCl_3$) δ 31.24, 38.90, 42.35, 45.82, 126.67, 128.34, 128.58, 143.15, 218.10; HRMS calculated for $C_{11}H_{12}O$: 160.0888. Found: 160.0886.

Preparation of compound **5**

Obtained in a 60% isolated yield from iodobenzene and 2-cyclohexen-1-ol as a yellow oil using $KHCO_3$ as a base and stirring for six days at 80 °C (Table 2, entry 15). IR (neat) 3063, 3030, 2937, 1711, 1497, 1450, 1250, 1225, 1030, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70-1.84 (m, 2H, CH_2), 2.00-2.13 (m, 2H, CH_2), 2.30-2.60 (m, 4H, CH_2CO), 2.95 (m, 1H, ArCH), 7.0-7.25 (m, 5H, ArH), ^{13}C NMR ($CDCl_3$) δ 25.58, 32.86, 41.21, 44.80, 48.98, 126.59, 128.53, 128.87, 144.39, 210.81; HRMS calculated for $C_{12}H_{14}O$: 174.10447. Found: 174.10451.

Preparation of compounds **8** and **9**

Obtained in an 86% isolated yield from iodobenzene and 2-methyl-2-cyclopenten-1-ol as a 1:1 mixture of two products (determined by GC and ^1H NMR spectroscopy) using Na_2CO_3 as a base and stirring for two days at 80 °C (Table 3, entry 6). IR (neat, 1:1 mixture) 3063, 2932, 1740, 1603, 1495, 1454, 1406, 1142, 910, 758, 733 cm^{-1}. Compound **8**: GC-MS m/z (rel. int.) 175.1 (13.5, M+1), 174.1 (100, M^+) , 159.1 (14.3), 145.1 (23.4), 132.1 (17.7), 130.1 (12.6), 118.1 (49.4), 117 (96.5), 115 (34.2), 105 (24.7), 104 (39.7), 91 (42.1), 77 (12.7), 65 (8.4), 57.1 (14.0), 51 (11.8), 41.0 (6.4). Compound **9**: GC-MS m/z (rel. int.) 251.1 (2.5, M+1), 250.1 (12.2, M^+), 159.1 (12.1), 146.1 (100), 131.1 (7.8), 115.1 (13.5), 104.1 (8.4), 91 (31.5), 77.0 (5.6), 65 (5.3), 51 (3.3). The ^1H NMR and ^{13}C NMR spectra were too complicated to assign chemical shifts.

Preparation of compound **11**

Obtained in a 78% GC yield from iodobenzene and 1-acetoxy-1-cyclopentene as a yellow oil using KOAc as a base and stirring for six days at 60 °C (Table 4, entry 10). IR (neat) 3063, 3028, 2956, 1759, 1664, 1493, 1454, 1369, 1240, 1043, 760, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.70 (m, 4H, CH_2's), 4.25 (m, 1H, ArCH), 5.85 (dd, 1H, J = 7.8 Hz, J = 4.2 Hz, =CH-), 7.35-7.50 (m, 5H, ArH); HRMS calculated for $C_{13}H_{14}O_2$: 202.09938. Found: 202.09934.

Preparation of compounds **13** and **14**

Obtained in a 70% isolated yield from iodobenzene and 3-ethoxycyclopentene as a 2:1 mixture of regioisomers (determined by GC-MS and ^1H NMR spectroscopy) using K_2CO_3 as a base and stirring for two days at 60 °C (Table 5, entry 4). IR (neat, 2:1 isomeric mixture) 3063, 3030, 2934, 1742, 1495, 1404, 1254, 1136, 910, 733, 648 cm^{-1}. Compound **13**: GC-MS m/z (rel. int.) 189 (12.7, M+1), 188 (100, M^+), 159 (80.7), 144 (25.5), 143 (76.4), 141 (10.8), 131 (23.9), 117 (39.1), 115 (25.9), 111 (31.3), 103 (29.5), 91 (35.5), 83 (53.6), 77 (26.8), 65 (6.7), 55 (20.7), 51 (15.1), 43 (13.5). Compound **14**: GC-MS m/z (rel. int.) 189 (8.2, M+1), 188 (53.5, M^+), 159 (13.2), 142 (12.2), 129 (13.8), 117 (15.1), 105 (13.9), 104 (12.4), 91 (16.8), 83 (8.9), 77.0 (8.7), 55 (100), 43 (16). The ^1H NMR and ^{13}C NMR spectra were too complicated to assign chemical shifts.

Preparation of compounds **16** and **17**

Compounds **16**, **17** and an unknown were obtained in approximately a 66% GC yield from iodobenzene, 3-methoxycyclohexene and 15% PPh_3 as a 1:1:3 mixture of three isomers respectively using NaOAc as a base and stirring for three days at 80 °C (Table 6, entry 11). IR (neat, 1:1:3 isomeric mixture) 3063, 3023, 2934, 1668, 1603, 1495, 1452, 1377, 1271, 1213,

1163, 1018, 910, 756, 700 cm^{-1}; GC-MS m/z (rel. int.) compound **16**: 189 (14.3, M+1), 188 (100, M^+) ; compound **17**: 189 (11.4, M+1), 188 (100, M^+); unknown compound; 189 (9.2, M+1), 188 (73.2, M^+), 84 (100). The ^1H NMR and ^{13}C NMR spectra were too complicated to assign chemical shifts.

Preparation of compound **19**

Obtained in a 78% isolated yield from iodobenzene and 1-cyanocyclopentene as a yellow oil using KOAc as a base and stirring for two days at 80 °C (Table 7, entry 2). IR (neat) 3063, 3028, 2845, 2220, 1612, 1603, 1495, 1454, 789, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (m, 1H, CH_2), 2.45-2.80 (m, 3H, CH_2's), 4.10 (m, 1H, ArCH), 6.84 (dd, 1H, J = 8.4 Hz, J = 2.7 Hz, =CH-), 7.2-7.4 (m, 5H, ArH); ^{13}C NMR (CDCl3) δ 33.21, 33.58, 52.81, 116.34, 118.81, 127.23, 127.28, 128.92, 141.48, 148.83; HRMS calculated for $C_{12}H_{11}N$: 169.08915. Found: 169.08869.

Preparation of compound **21**

Obtained in a 42% GC yield from iodobenzene and 2-methyl-2-cyclopenten-1-one as a yellow oil using KOAc as a base and stirring for three days at 80 °C (Table 8, entry 2). IR (neat) 3061, 3028, 2924, 1695, 1622, 1495, 1445, 1358, 1333, 1178, 1032, 762, 696, 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (t, 2H, J = 9.6 Hz, CH_2), 3.00 (t, 2H, J = 9.6 Hz, CH_2), 3.75 (s, 2H, $ArCH_2$), 7.10-7.50 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 30.41, 30.70, 34.93, 126.72, 127.99, 128.99, 129.15, 129.36, 130.34, 136.85, 139.86, 139.91, 169.67, 209.85; HRMS calculated for $C_{18}H_{16}O$: 248.12019. Found: 248.12020.

Preparation of compound **23**

Obtained in a 23% GC yield from iodobenzene and 2-methyl-2-cyclohexene-1-one as a yellow oil using Na_2CO_3 with PPh_3 and stirring for three days at 100 °C (Table 9, entry 2). IR ($CDCl_3$) 3061, 3028, 2932, 1724, 1668, 1599, 1495, 1452, 1427, 1358, 1180, 1130, 1072, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (m, 2H, CH_2), 2.55 (t, 2H, J = 7.2 Hz, CH_2), 2.68 (t, 2H, J = 6.3 Hz, CH_2), 3.57 (s, 2H, $ArCH_2$), 6.95-7.50 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.14, 32.13, 33.78, 38.21, 125.77, 126.77, 126.99, 128.01, 128.30, 128.48, 128.73, 135.28, 141.06, 158.60, 199.23; HRMS calculated for $C_{19}H_{18}O$: 262.13577. Found: 262.13565.

Preparation of compound **24**

In a round-bottom flask was placed K_2CO_3 (2.2 mmol, 0.304 g), *o*-iodophenol (2 mmol, 0.44 g), 3-bromocyclohexene (3 mmol, 0.48 g), and acetone (5 ml). The reaction mixture was refluxed for 24 hours under nitrogen. After cooling, the reaction mixture was poured into water (30 ml) and extracted with ether. The ether layer was dried with $MgSO_4$, filtered, concentrated, and the residue was purified by column chromatography (10:1 hexanes/EtOAc). Compound **24** was obtained in a 40% yield. ^1H NMR ($CDCl_3$) δ 1.66-2.19 (m, 6H, CH_2's), 4.77 (m, 1H, CH-O), 5.87 (m, 1H, =CH), 5.99 (dd, 1H, J = 10.2 Hz, J = 6.6 Hz, =CH), 6.67-7.70 (m, 4H, ArH).

Preparation of compound **25**

Obtained in an 89% isolated yield from the intramolecular cyclization of 3-cyclohexenyl *o*-iodophenyl ether (**24**) by procedure B (4% $Pd(OAc)_2$, 12 PPh_3, 2 Ag_2CO_3, 8 ml CH_3CN) at 80 °C for 2 days (Table 10, entry 4). IR (neat) 3005, 2935, 1715, 1479, 1364, 1223, 789, 760 cm^{-1}; ^1H NMR (CDCl3) δ 2.00-2.50 (m, 4H, CH_2's), 3.80 (dd, 1H, J = 7.8 H, J = 3.6

Hz, ArCH), 5.00 (m, 1H, -CH-O), 5.70-6.02 (m, 2H, HC=CH), 7.00-7.20 (m, 2H, ArH), 7.25-7.40 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) 19.70, 25.14, 41.25, 81.27, 109.84, 120.39, 124.21, 126.25, 127.87, 127.99, 131.50, 159.24; HRMS calculated for $C_{12}H_{12}O$: 172.0882. Found: 172.08893.

Preparation of compound **28**

In a round-bottom flask was placed K_2CO_3 (2.2 mmol, 0.304 g), *o*-iodophenol (2 mmol, 0.44 g), 4-bromo-1-butene (3 mmol, 0.4 g), and acetone (5 ml). The reaction mixture was refluxed for 24 hours under nitrogen. After cooling, the reaction mixture was poured into water (30 ml) and extracted with diethyl ether. The ether was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using 10:1 hexanes/EtOAc . Compound **28** was obtained in a 55% isolated yield. ^1H NMR ($CDCl_3$) δ 2.82 (q, 2H, J = 6.6 Hz, $-CH_2-C=$), 4.25 (t, 2H, J = 6.6 Hz, OCH_2), 5.32 (d, 1H, J = 10.2 Hz, trans to the side chain, =CH), 5.40 (d, 1H, J = 17.1 Hz, cis to the side chain, =CH), 6.10-6.22 (m, 1H, -CH=), 6.89 (dt, 1H, J = 7.5 Hz, J = 1.2 Hz, ArH), 6.99 (dd, 1H, J = 7.2 Hz, J = 1.5 Hz, ArH), 7.44-7.50 (m, 1H, ArH), 7.96 (dd, 1H, J = 7.8 Hz, J = 1.5 Hz, ArH); HRMS calculated for $C_{10}H_{11}OI$: 273.98547. Found: 273.98505.

Preparation of compounds **29** and **30**

Obtained in a 56% isolated yield from the intramolecular cyclization of 3-butenyl *o*-iodophenyl ether (**28**) as a 4:1 mixture of isomers (determined by GC and ^1H NMR spectroscopy) using Et_3N as a base (Table 11, entry 8). IR (neat, 4:1 mixture of isomers) 3067, 3030, 2937, 1728, 1607, 1489, 1452, 1047, 754, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 4:1 isomeric mixture) δ 2.03 (s, 3H, CH_3), 2.69 (t, 2H, J = 5.4 Hz, allylic hydrogen of isomer **30**), 4.25 (t, 2H, J = 5.7 Hz, OCH_2 of isomer **30**), 4.75 (m, 2H, OCH_2 of isomer **29**), 4.90

(br s, 1H, vinylic hydrogen of isomer **30**), 5.52 (br s, 1H, vinylic hydrogen of isomer **30**), 5.58 (m, 1H, vinylic hydrogen of isomer **29**), 6.79-7.59 (m, 8H, ArH). GC-MS m/z (rel. int.) compound **29**: 146 (M+, 100); compound **30**: 146 (M+), 131(100).

REFERENCES

1. (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518. (b) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5526. (c) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5535. (d) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5538. (e) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90* , 5542. (f) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5546.

2. (a) Tsuji, J. *Organic Synthesis with Palladium Compounds* , Springer Verlag, New York, **1980**. (b) Heck. R. F. *Palladium Reagents in Organic Synthesis*, Academic Press, New York, **1985**.

3. Maitlis, P. M. *The Organic Chemistry of Palladium*, Academic Press, New York, **1971**, Vol 1, Chapter 5.

4. Larock, R. C. *Organomercury Compounds in Organic Synthesis*, Springer Verlag, New York, **1985**.

5. Heck, R. F. *Organic Reactions* **1982**, *27*, 345.

6. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

7. Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083.

8. Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

9. Heck, R. F. *Accts. Chem. Res.* **1979**, *12*, 146.

10. Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. Z.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952.

11. Arai, I.; Daves, D. G., Jr. *J. Org. Chem.* **1979**, *44*, 21.

12. Anderson, C. M.; Hallberg, A.; Daves, D. G., Jr. *J. Org. Chem.* **1987**, *52*, 3529.

13. Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron* **1979**, *35*, 329.

14. Arai, I.; Daves, D. G., Jr. *J. Org. Chem.* **1978**, *43*, 4110.

15. Graves, K. *J. Org. Chem.* **1970**, *35*, 3273.

16. Kikukawa, K.; Macmura, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31.

17. Kikukawa, K.; Macmura, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1981**, *46*, 4885.

18. (a) Cortese, N. A.; Ziegler, Jr., C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952. (b) Harrington, P. J.; Difiore, K. A. *Tetrahedron Lett.* **1987**, *28*, 495.

19. (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (c) Jeffery, T. *Synthesis*, **1987**, 70.

20. Spencer, A. *J. Organomet. Chem.* **1983**, *258*, 101.

21. Arcadi, A.; Cacchi, S.; Marinelli, F.; Morera, E.; Ortar, G. *Tetrahedron* **1990**, *46*, 7151.

22. Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.

23. Baker, B. E. Ph. D. Dissertation, Iowa State University, **1988**.

24. Larock, R. F.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603.

25. (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (c) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919. (d) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047.

26. Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1990**, *55*, 407.

27. Nilson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464.

28. (a) Grove, D. M.; Koten, G. V.; Louwen, J. N.; Noltes, J. G.; Spek, A. L.; Ubbels, J. H. C. *J. Am. Chem. Soc.* **1982**, *104*, 6609. (b) Rimml, H.; Venanzi, L. M. *J. Organomet. Chem.* **1984**, *260*, C 52.

29. (a) Jeffery, T. *Tetrahedron Lett.* **1990**, *31*, 6641. (b) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121.

30. Larock, R. C.; Leung, W. Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629.

31. Larock, R. C.; Kondo, F.; Narayanan, K.; Sydnes, L. K.; Hsu, M. H. *Tetrahedron Lett.* **1989**, *30*, 5737.

32. Torii, S.; Okumoto, H.; Akahoshi, F.; Kotani, T. *J. Am. Chem. Soc.* **1989**, *111*, 8932.

33. (a) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 9256. (b) Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755. (c) Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *J. Am. Chem. Soc.* **1974**, *96*, 6774.

34. Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915.

35. Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**. 1697.

36. (a) Heck, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 6869. (b) Heck, R. F. *Organomet. Chem. Synth.* **1972**, *1*, 455. (c). Kasahara, A.; Isumi, T.; Yodono, M.; Saito, G.; *Bull. Chem. Soc. Jpn.* **1972**, *45*, 895. (d) Outten, R. A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 5056. (e) Saito, R. I.; Isumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1776.

37. (a) Sugiura, S; Toru, T.; Tanaka, T.; Hazato, A.; Okamura, K.; Bannai, K.; Manabe, K.; Kurozumi, S.; Noyori, R.; *Chem. Pharm. Bull.* **1984**, *32*, 4658. (b) Corey, E. J.;

Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4701, 4705. (c) Corey, E. J.; Williams, D. R.; Wollenberg, R. H. *Tetrahedron Lett.* **1977**, 2243. (d) Livinghouse, T.; Stevens, R. V. *J. Chem. Soc., Chem. Commun.* **1978**, 755.

38. (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (b) Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4832. (c) Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 1037. (d) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.

39. Negishi, E.; Nguyen, T.; O'Connor, B.; Jeffery, M. E.; Augustine, S. *Heterocycles* **1989**, *28*, 54.

40. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

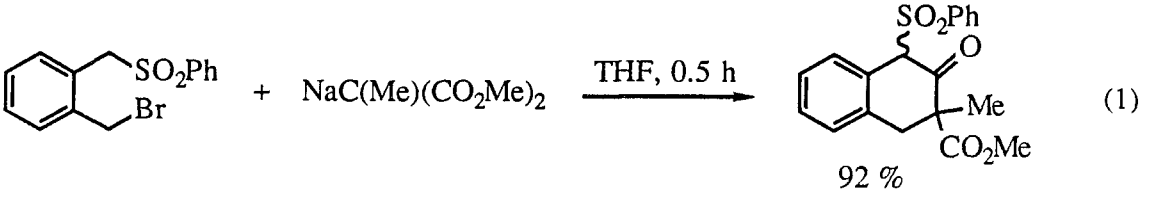
PART II. PALLADIUM-CATALYZED CARBO- AND HETERO-ANNULATION OF VINYLIC CYCLOPROPANES, VINYLIC CYCLOBUTANES AND 1,4-DIENES

INTRODUCTION

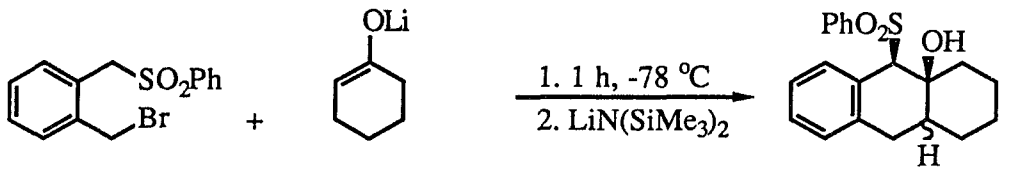
Annulation processes are among the most important reactions in organic chemistry.[1-7] The ability to form rings by adding either a heteroatom-containing unit (heteroannulation) or a carbon unit (carboannulation) to existing functionality allows for the rapid construction of heterocycles and carbocycles respectively. The most important processes are those that proceed under mild conditions, accommodate a wide variety of functionalities in the substrates, and furnish a diversity of ring sizes.

The formation of carbocycles (fused to another ring) through regioselective annulation is an area of current interest in organic chemistry. The development of new general methods for the synthesis of complex polycycles is an area of research that has experienced a tremendous growth in recent years.[8] Of particular interest are annulation processes which form more than one carbon-carbon bond in a single step. One such process is the Robinson annulation reaction,[9] one of the most widely used synthetic methods in organic synthesis. Although the Robinson annulation is very valuable and useful, it is sometimes unsuitable due to polymerization under the annulation conditions. A number of modifications to overcome this restriction have been reported.[10]

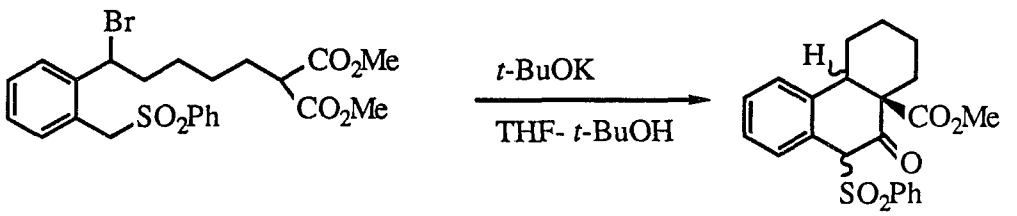
One modification of particular interest has focused primarily on using bifunctional reactants to mimic the Robinson annulation procedure.[11-14] Ghera et al. have, for example, utilized bifunctional arenes to rapidly construct derivatives of naphthalene[11] (eq. 1), anthracene[12] (eq. 2), and phenanthrene[13] (eq. 3). Although relatively high yields can be



(1)



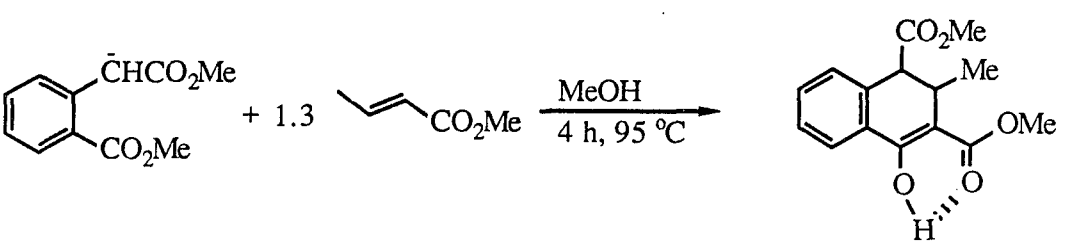
74 % (2)



89 % (3)

achieved, the diastereoselectivity of these reactions is relatively poor and Ghera's annulation procedure has limited use in the synthesis of complex natural products.

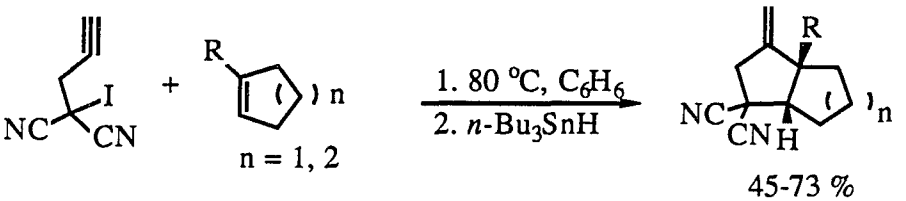
Others[14] have used Michael-induced ring closure (MIRC) reactions to annulate activated olefins. The MIRC reaction requires both a nucleophilic center and an electrophilic center on the reactant. A representive example of the MIRC reaction reported by Eisenhuth et al.[14a] utilized a preformed anion of methyl 2- (methoxycarbonyl)phenylacetate as the annulating agent for methyl crotonate (eq. 4). In general, the MIRC reaction proceeds



50% (4)

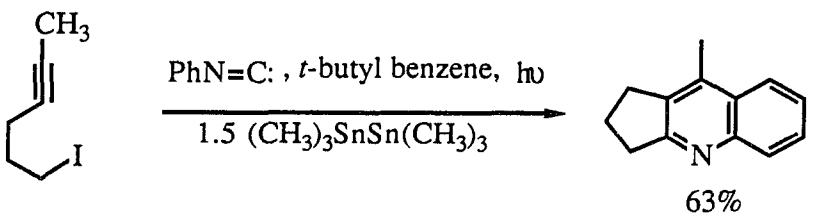
under fairly mild conditions to afford the annulated product in moderate yields. However, the MIRC reaction is intolerant of a wide variety of functionality on either the arene or the alkene moiety.

Recently, halogen atom transfer annulation (HATA) has been reported.[15-18] Functionalized, fused rings are readily prepared from unactivated di- and trisubstituted cyclopentenes and cyclohexenes (eq. 5).[16] The one-step synthesis of cyclohexa-fused



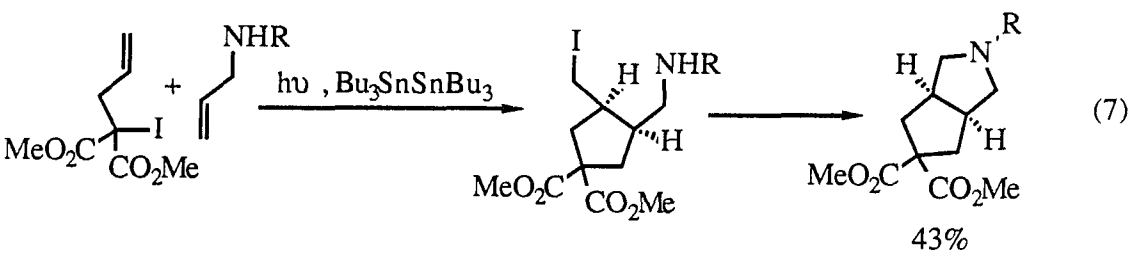
(5)

quinolines could be accomplished by the coupling of 1-substituted 5-iodo-1-pentynes with an aryl isonitrile (eq. 6).[17] Moreover, azabicycles could be synthesized from iodomalonate and



(6)

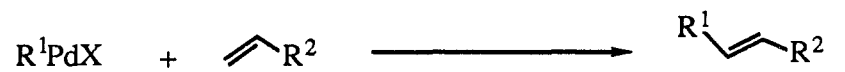
allylamine derivatives (eq. 7).[18] The HATA is particularly useful, because the halogen is



(7)

transferred to a new center in the product. The retained functionality may be useful for subsequent reactions. However, this methodology reveals at least two significant limitations of iodomalonic esters : (1) They add efficiently only to mono- and 1,1-disubstituted olefins. (2) They are not suitable for simple radical macrocyclizations.

Palladium can mediate a number of carbon-carbon bond forming processes under relatively mild conditions. One of the most common processes is the Heck reaction (eq. 8).[19]

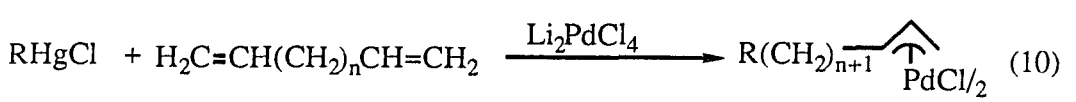


(8)

This reaction proceeds via *cis* addition of an organopalladium compound onto an alkene and subsequent cis-β hydride elimination to afford the vinylic hydrogen substitution product. When the Heck reaction is run with a 1,3-diene, instead of an simple alkene, π-allylpalladium compounds are formed which can be attacked by stabilized carbanions to form a new carbon-carbon bond under very mild conditions (eq. 9).[20]

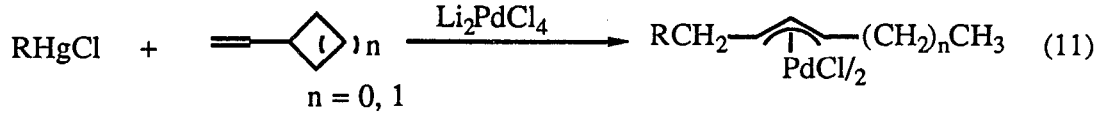
(9)

Another method of synthesizing π-allylpalladium compounds utilizes organomercurials. Heck [21] observed that π-allylpalladium compounds could be prepared by the transmetallation of organomercurials in the presence of conjugated dienes (eq. 10). While Larock and Takagi[22] observed the same for non-conjugated dienes. Also, Larock and Varaprath[23] observed that



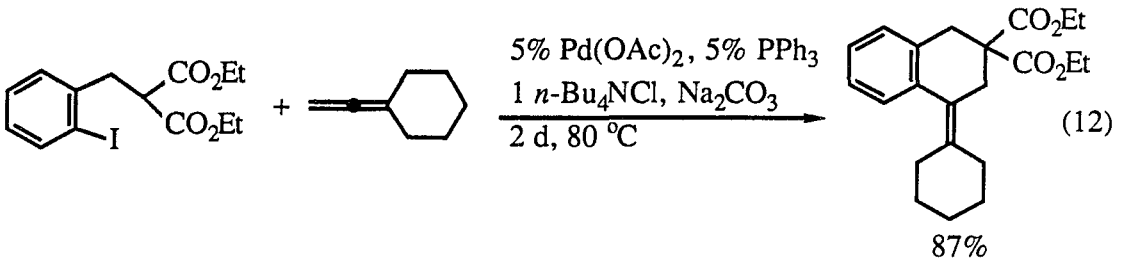
(10)

π-allylpalladium compounds could be prepared by the addition of organopalladium compounds to vinylic cyclopropanes and vinylic cyclobutanes (eq. 11).



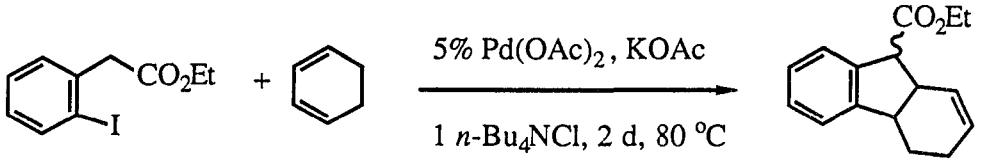
(11)

Recently, Larock and Fried[24-26] have established the feasibility of a carboannulation process employing various aryl halides and 1,2-, 1,3-, and 1,4-dienes (eqs. 12-14). Since a wide variety of unsaturated substrates could be accommodated, this annulation process could



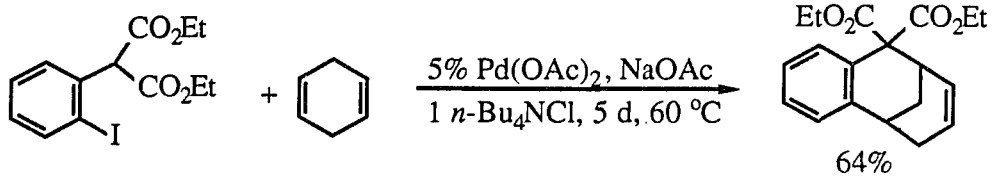
(12)

87%



(13)

85%

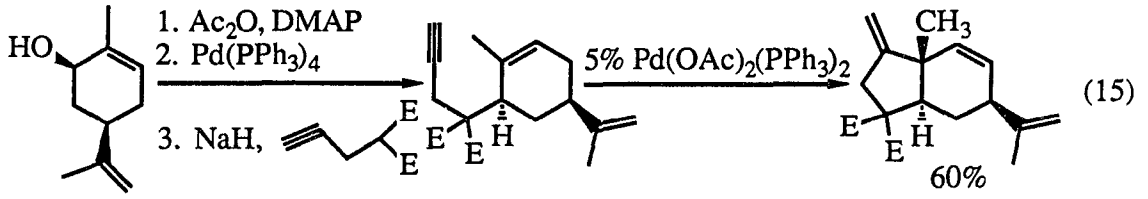


(14)

64%

prove particularly valuable in the synthesis of complex polycyclic molecules.

Trost et al.[27] demonstrated that carboannulation could be achieved via Alkylation-Alder-Ene cyclization (eq. 15). The palladium-catalyzed carbon-carbon bond formation

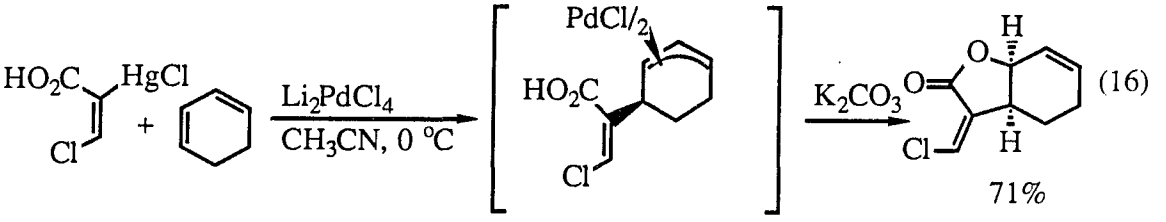


(15)

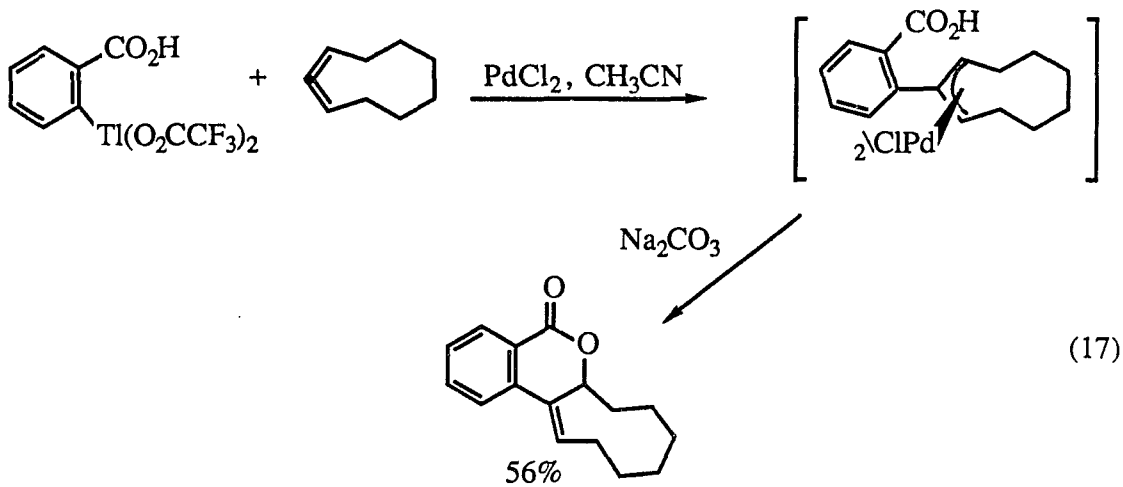
from an allylic acetate permits a facile, one-pot annulation with excellent regio- and stereoselectivity.

Heteroannulation processes provide a very valuable route to a wide variety of heterocycles. In general, heterocycles have found applications as antibiotics, anticancer agents, plant growth regulators, insecticides, fungicides, herbicides, etc. As the field of heterocycles is vast and well covered by numerous reviews, books and monographs,[28] it is my intention in this introduction to survey only that area of heteroannulation which deals with the synthesis of heterocycles from π-allylpalladium intermediates.

The generation of π-allylpalladium complexes via routes not involving ionization of an allylic leaving group permits lactone formation via carboxylate displacement. *In situ* formation of π-allylpalladium complexes by addition of σ-organopalladium intermediates, generated by transmetallations from organomercurial and organothallium compounds, to 1,3-dienes (eq. 16)[29] and allenes (eq. 17)[30] in the presence of stoichiometric amounts of palladium produces good yields of lactones.

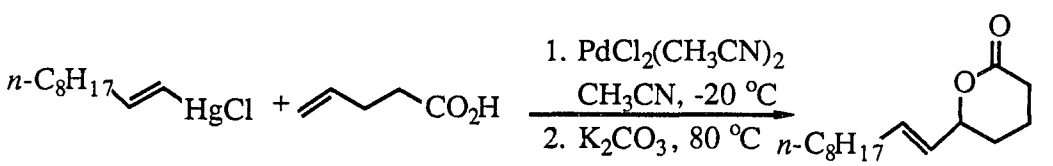


(16)



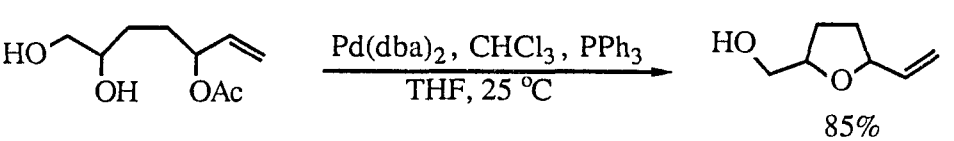
(17)

The palladium-mediated addition of alkenyl organomercurials, or vinylic halides or triflates to unsaturated acids also produces lactones via carboxylate attack on a π-allylpalladium complex that forms after rearrangement of the initial adduct (eq. 18).[31]



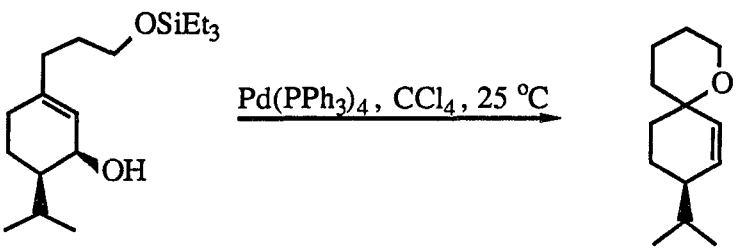
(18)

While simple alcohols are normally poor nucleophiles toward π-allylpalladium complexes in intermolecular reactions, they participate without complications in intramolecular reactions (eq. 19).[32]



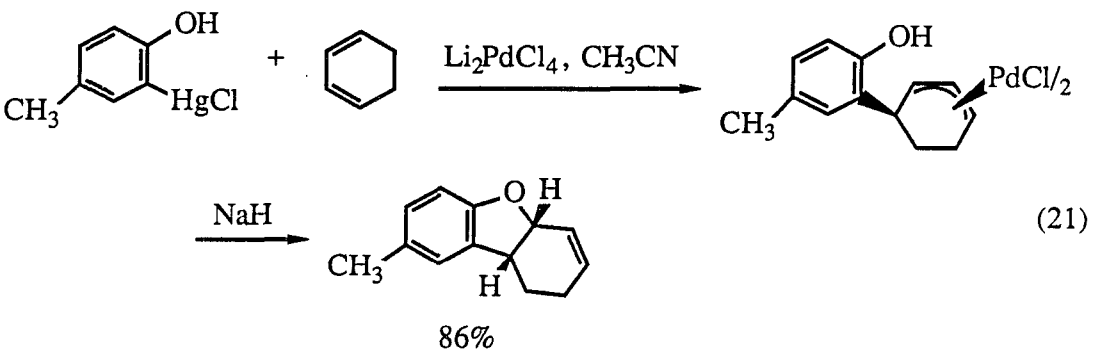
(19)

Silyl ethers can also serve as nucleophiles in the heteroannulation process. However, it is likely that desilylation occurs under the requisite reaction conditions to liberate a nucleophilic alkoxide (eq. 20).[33]



(20)

Furthermore, aryl oxides are good oxygen nucleophiles toward π-allylpalladium complexes. One synthesis of dihydrobenzofurans involves just such a step, but utilizes stoichiometric amounts of palladium (eq. 21).[29] The *cis* stereochemistry of the product

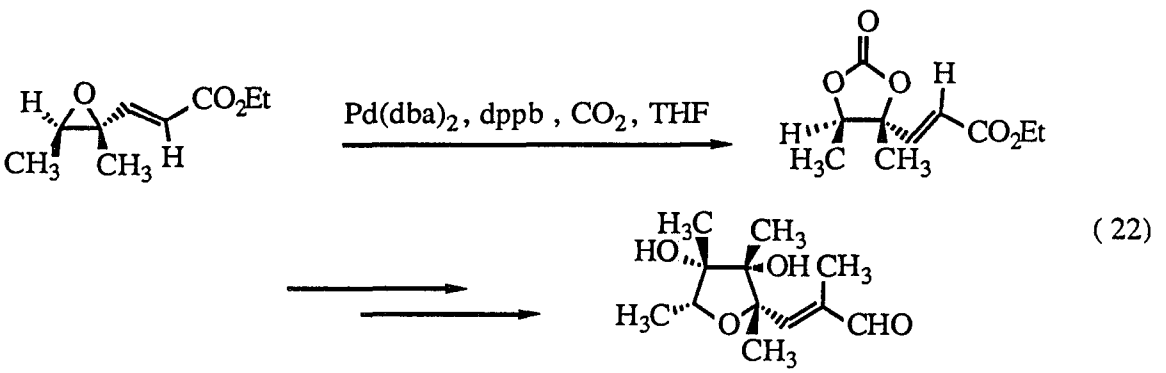


(21)

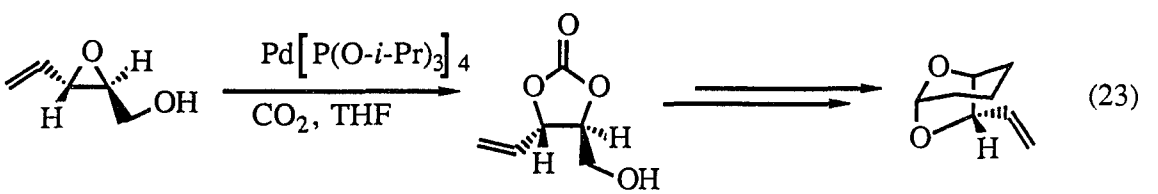
86%

demands that the oxygen attack on the same face of the π-allyl unit that is bonded to palladium.

The attack of carbon dioxide on the oxygen leaving group changes the normal 1,4-addition of nucleophiles to vinylic epoxides under palladium catalysis to the corresponding 1,2-addition. The ready availability of such epoxides in enantiomerically pure form allows for the asymmetric synthesis of vicinal diols, compounds which later proved to be useful in the synthesis of (+)-citreoviral (eq. 22)[34] and (-)-exo-brevicomin (eq. 23).[35]

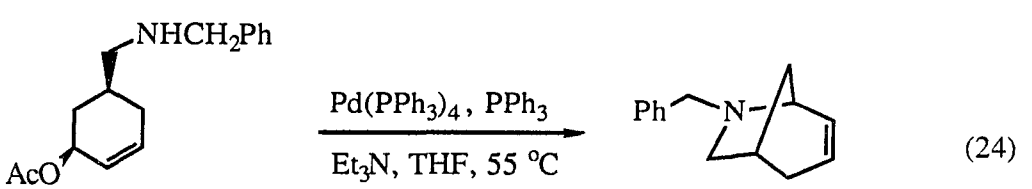


(22)



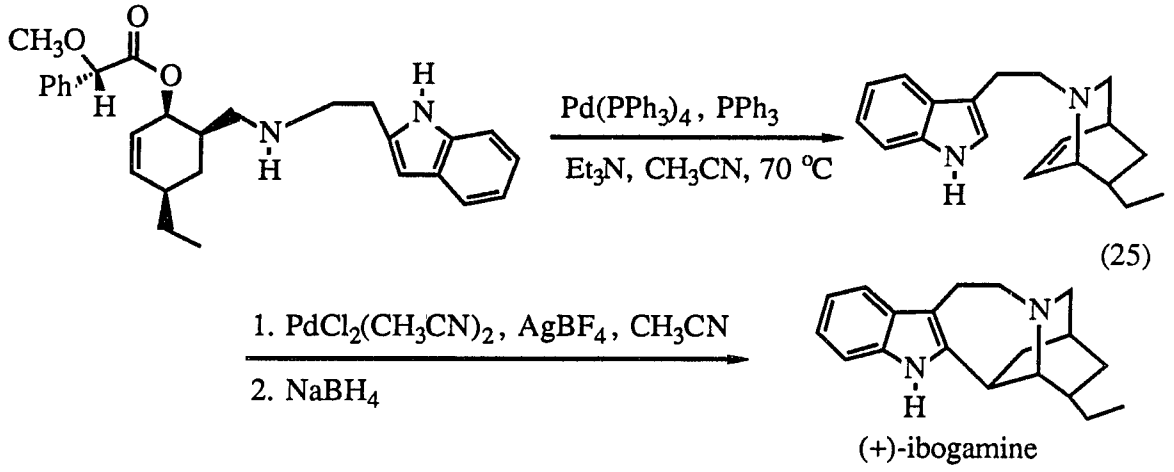
(23)

Amines are among the best nucleophiles for π-allylpalladium complexes. Their potency for intramolecular reactions was revealed by the simple construction of typical alkaloid skeletons (eq. 24).[36] The Diels-Alder reaction leads to the rapid construction of such starting



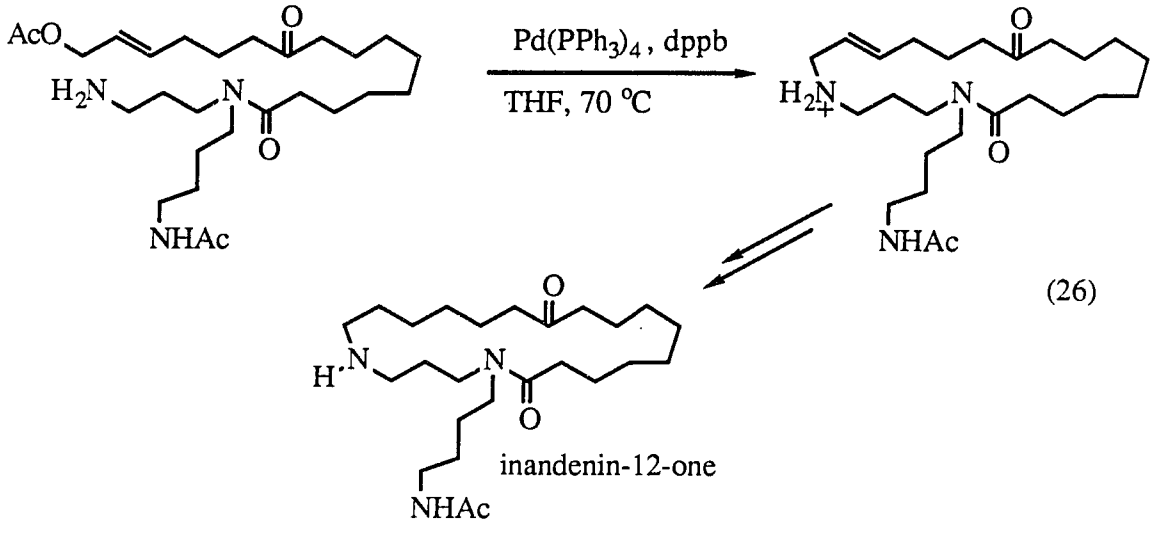
(24)

materials. An exceptionally facile synthesis of (+)-ibogamine took advantage of the asymmetric induction that was incorporated in the Diels-Alder step (eq. 25).[37]



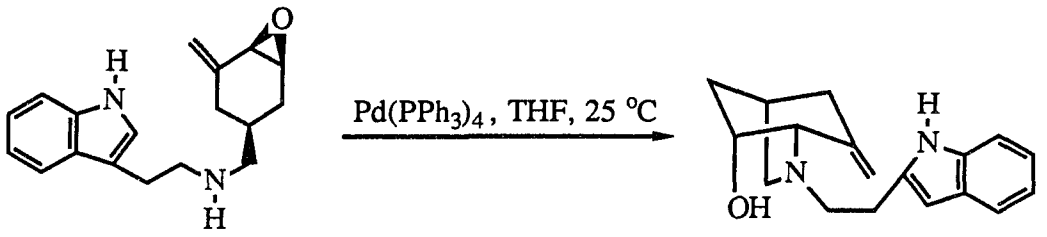
(25)

In 1982, Trost and Cossy[38] extended the allylation of amines to the synthesis of large heterocyclic rings. With their new approach, they were able to synthesize inandenin-12-one, a 21-membered ring macrolide (eq. 26).



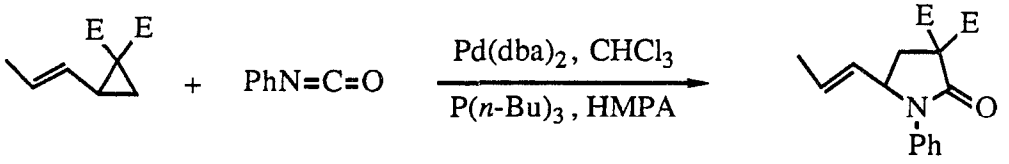
(26)

Carbon-nitrogen bond formation via vinylic epoxides also proceeds via π-allyl-palladium formation. For example, utilization of an intramolecular nucleophile ultimately led to the synthesis of enantiomerically pure isoquinuclidine (eq. 27).[39]



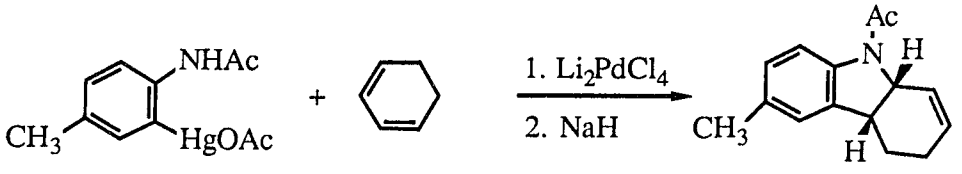
(27)

In 1987, Yamamoto, Ishida and Tsuji[40] observed that the reaction of a vinylic cyclopropane with isocyanates successfully led to the formation of heterocycles (eq. 28).



(28)

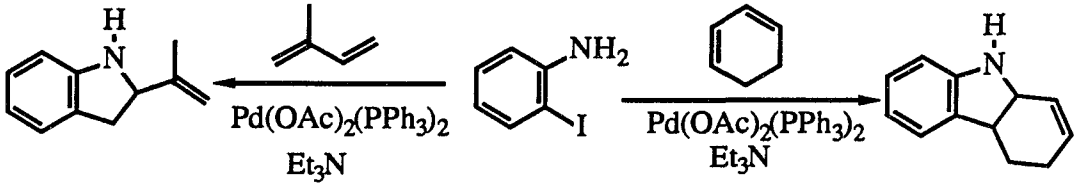
Larock et al.[29] have also reported that the reactions of conjugated or non-conjugated dienes, or vinylic cyclopropanes, with functionalized organomercurials affords a great variety of heterocyclic compounds. A wide variety of substrates, in the presence of palladium(II) salts, form an initial π-allylpalladium species that can be intramolecularly displaced by nitrogen nucleophiles (eq. 29). Unfortunately, most of these processes utilize stoichiometric amounts



(29)

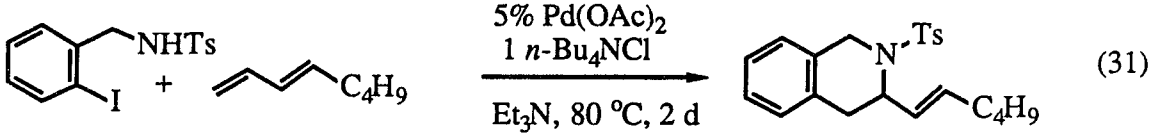
of expensive palladium salts, besides the need to prepare the requisite organomercurials which are well known for their toxic properties.

However, Dieck et al.[41] have reported that the heteroannulation of 2-iodoaniline with isoprene and 1,3-cyclohexadiene to afford the corresponding heterocyclic products can be accomplished employing only catalytic amounts of $Pd(OAc)_2$/ PPh_3 (eq. 30). Larock, Berrios-



(30)

Peña and Narayanan[42] have also reported that tosylamides react smoothly with conjugated dienes to afford the corresponding heterocyclic products in good yields (eq. 31).



(31)

With these promising earlier results in mind, we decided to investigate the possibility of synthesizing carbo- and heterocycles utilizing the palladium-catalyzed carbo- and heteroannulation of vinylic cyclopropanes, vinylic cyclobutanes, and 1,4-dienes. With this methodology, we hoped to be able to synthesize highly regioselectively a variety of carbo- and heterocycles, including biologically active substrates.

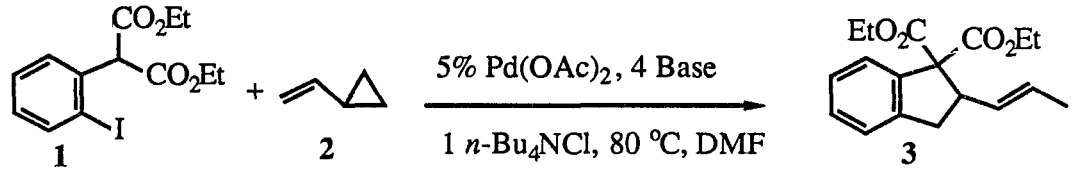
RESULTS AND DISCUSSION

Carbocycles

Initial studies were aimed at finding the best general reaction conditions for our palladium-catalyzed carboannulation process. The reaction between diethyl 2-iodophenylmalonate and vinylcyclopropane was chosen for our initial model study. In our search for a set of reaction conditions that would maximize the yield of this reaction, we explored extensively three important variables, the base, the reaction time, and the temperature, and the results are summarized in Table 1.

The reaction of diethyl 2-iodophenylmalonate with vinylcyclopropane was first attempted at 80 °C using two different bases (entries 1 and 2). These bases were chosen because they have generally performed well in the *n*-Bu_4NCl mediated, palladium-catalyzed arylation of substituted cyclic alkenes described in Part I of this dissertation. It is apparent from entries 1 and 2 that the palladium-catalyzed carbocyclization was complete at 80 °C in three days with an 80-82% isolated yield of the desired product. The effect of temperature on this reaction was also studied (entries 1-4). It was found that 80 °C was better than 60 °C and the reactions were very slow at 60 °C (entries 3 and 4). When reactions using Na_2CO_3 or K_2CO_3 were conducted, lower yields of the product were obtained (entries 5 and 6). In an attempt to further improve the reaction conditions, the reactions using several bases plus 5% PPh_3 were examined at 80 °C (entries 7-11). The addition of PPh_3 to the reaction did reduce the problem of decarboalkoxylation of the starting material, but the yield was surprisingly lowered. In addition, DMSO was examined as a solvent, but the reactions revealed increased decarboalkoxylation of the starting material without formation of any of the desired product

Table 1. Palladium-catalyzed reaction of diethyl 2-iodophenylmalonate with vinyl-cyclopropane.



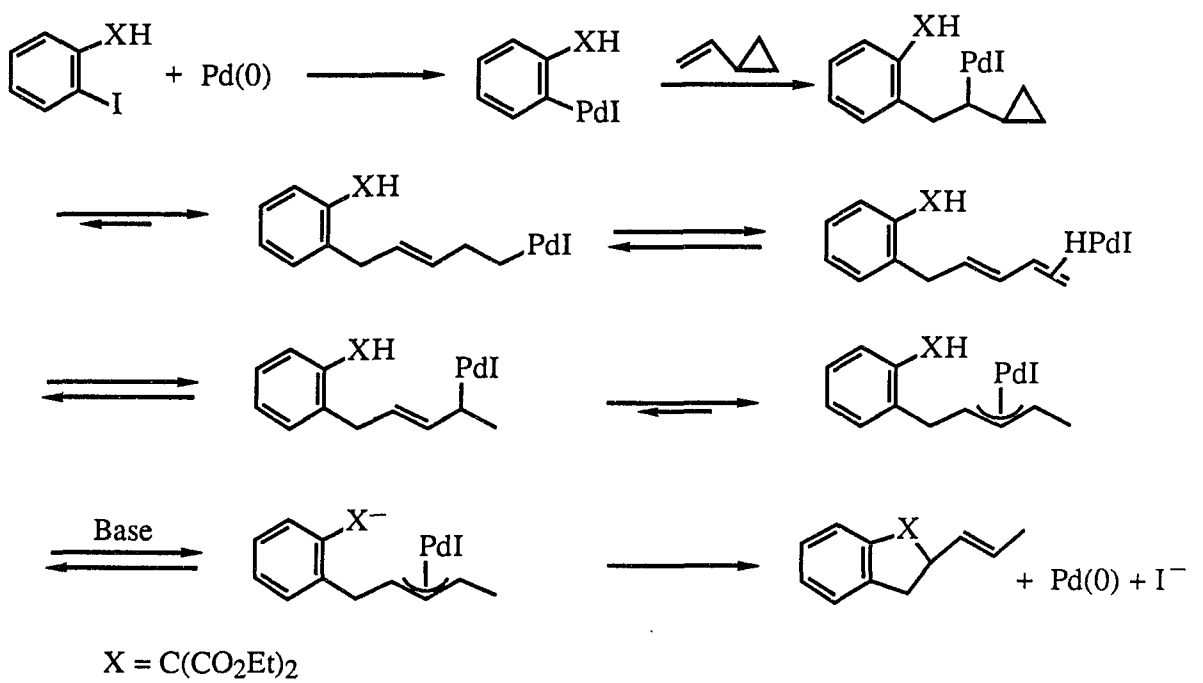
Entry	Base	5% PPh_3	Reaction time (d)	% Isolated yield
1	KOAc	–	3	80
2	NaOAc	–	3	82
3[a]	KOAc	–	4	0
4[a]	NaOAc	–	4	0
5	Na_2CO_3	–	3	61
6	K_2CO_3	–	3	26
7	KOAc	+	3	44
8	NaOAc	+	3	40
9	Na_2CO_3	+	3	52
10[a]	Na_2CO_3	+	7	0
11	K_2CO_3	+	3	51
12[b]	KOAc	–	3	0
13[b]	Na_2CO_3	–	3	0

[a]Reaction was run at 60 °C.

[b]DMSO instead of DMF.

(entries 12 and 13). Our study of the reaction between diethyl 2-iodophenylmalonate and vinylcyclopropane indicated that the best yield could be obtained with an acetate base at 80 °C. High temperatures, usually 80 °C, were also shown to be necessary for completely converting the starting aryl iodide to the desired product.

The reaction of diethyl 2-iodophenylmalonate with vinylcyclopropane most likely proceeds by the mechanism shown in Scheme 1 where added ligands on the palladium have been omitted to simplify matters.



X = $C(CO_2Et)_2$

Scheme 1

The $Pd(OAc)_2$ is most likely reduced to palladium(0) by the alkene present in the solution. Following oxidative addition of the aryl halide to the palladium(0) catalyst , an aryl-palladium intermediate is formed. The arylpalladium intermediate adds to the carbon-carbon double bond of vinylcyclopropane to generate a cyclopropylcarbinyl palladium complex, which

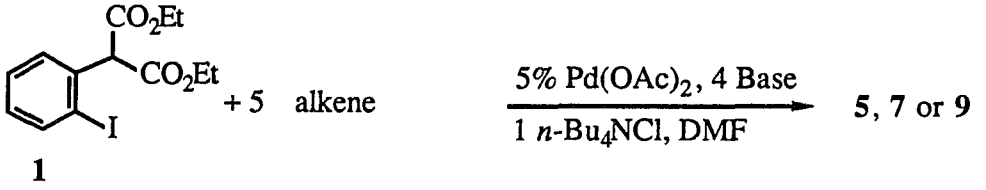
undergoes opening to form an alkylpalladium species from which palladium hydride elimination occurs to form the hydridopalladium-olefin π-complex. Re-addition of the metal hydride in the reverse direction produces a sigma allylpalladium intermediate which collapses to a very stable π-allylpalladium compound. This is followed by intramolecular displacement of the π-allylpalladium intermediate by nucleophilic attack, leading to the formation of the desired product and regeneration of the palladium(0) species.

This reaction has proven quite general. The (E)-stereochemistry of the products has been established from the NMR coupling constant between the two olefinic hydrogens (J = 15.3 - 21.9 Hz). Sometimes, it has been impossible to assign the exact structure by ^1H NMR spectroscopy. In those cases, the stereochemistry of the products has been assigned by mechanistic assumption.

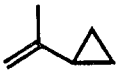
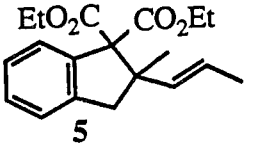
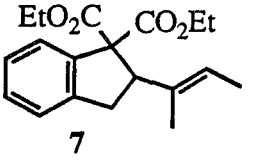
The reactions of diethyl 2-iodophenylmalonate with other vinylic cyclopropanes and vinylic cyclobutanes were also investigated, the reactions affording moderate to good yields of the desired products. The results are summarized in Table 2.

In the reaction of diethyl 2-iodophenylmalonate with isopropenylcyclopropane, several bases were explored. The reactions using KOAc, NaOAc, or Na_2CO_3 as the base were complete at 80 °C in 5-7 days; however, they all resulted in some decarboalkoxylation of the starting material. Fortunately, the reaction using Na_2CO_3 as the base was complete at 60 °C in seven days with 80% of the desired product being formed without any decarboalkoxylation of the starting material (entry 4). The reactions using NaOAc or KOAc as the base were also investigated at 60 °C, but only the starting aryl halide was recovered (entries 5 and 6). In addition, the reaction of diethyl 2-iodophenylmalonate with 1-methyl-1-ethenylcyclopropane was examined employing KOAc or Na_2CO_3 as the base. The biggest problem in these reactions was decarboalkoxylation of the starting aryl halide. In order to alleviate this difficulty, the effect of temperature on the annulation process was studied (entries 7-10).

Table 2. Palladium-catalyzed reactions of diethyl 2-iodophenylmalonate with vinylic cyclopropanes and vinylic cyclobutanes

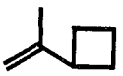
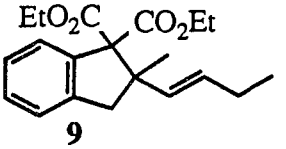


1

Entry[a]	Alkene	Base	5% PPh_3	Reaction conditions	Product	% Isolated yield
1	 4	KOAc	–	80 °C, 5 d	 5	40
2		NaOAc	–	80 °C, 5 d		56
3		Na_2CO_3	+	80 °C, 5 d		60
4		Na_2CO_3	+	60 °C, 7 d		80
5		KOAc	–	60 °C, 7 d		0
6		NaOAc	–	60 °C, 7 d		0
7	 6	KOAc	–	60 °C, 5 d	 7	30
8		KOAc	–	80 °C, 4 d		50
9		Na_2CO_3	+	60 °C, 5 d		51
10		Na_2CO_3	+	80 °C, 4 d		49

[a]Reactions were run on a 0.25 mmol scale.

Table 2. (continued)

Entry[a]	Alkene	Base	5% PPh_3	Reaction conditions	Product	% Isolated yield
11	 **8**	KOAc	–	80 °C, 3 d	 **9**	0
12		NaOAc	–	80 °C, 3 d		0
13		K_2CO_3	+	100 °C, 3 d		0
14		Na_2CO_3	+	100 °C, 4 d		20
15		Na_2CO_3	+	80 °C, 4 d		40
16		Na_2CO_3	+	60 °C, 5 d		39
17		KOAc	–	60 °C, 5 d		0
18		NaOAc	–	60 °C, 5 d		0

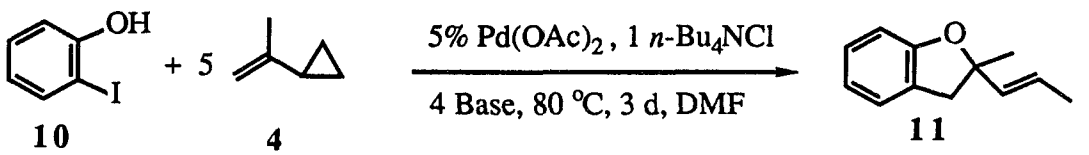
It was found that 60 °C was better than 80 °C in reducing decarboalkoxylation of the starting material when using Na_2CO_3 as the base (entries 9 and 10).

Isopropenylcyclobutane also reacted in the presence of Na_2CO_3, and only the desired annulated product was formed (entries 14-16). However, using KOAc or NaOAc as the base, the reactions failed to provide any of the desired product (entries 11, 12, 17, and 18). It was found that raising the temperature above 80 °C resulted in decarboalkoxylation of the starting aryl halide.

O- Heterocycles

We next attempted to effect the cyclization of oxygen-substituted aryl halides with vinylic cyclopropanes. In our initial model study, 2-iodophenol was chosen as the aryl halide mainly because it was commercially available. Two important variables were specifically explored, the base and the presence or absence of 5% PPh_3. The results are shown in Table 3.

Table 3. Palladium-catalyzed reaction of 2-iodophenol with isopropenylcyclopropane.



10 **4** **11**

Entry[a]	Base	5% PPh_3	% Isolated yield	Comments
1	KOAc	–	70	-
2	NaOAc	–	39	-
3	Na_2CO_3	–	70	-
4	K_2CO_3	–	70	-
5	KOAc	+	71	-
6	NaOAc	+	46	incomplete reaction[b]
7	Na_2CO_3	+	39	incomplete reaction[b]
8	K_2CO_3	+	30	incomplete reaction[b]

[a]Allreactions were run on a 0.25 mmol scale.

[b]More than 30% aryl halide was recovered.

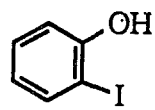
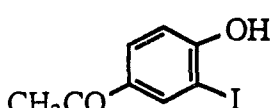
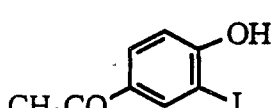
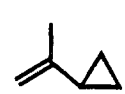
Using $Pd(OAc)_2$ as the catalyst and DMF as the solvent, we first examined the effect of different bases on the product yield. Results from our studies indicated that Na_2CO_3, K_2CO_3, and KOAc provided almost the same isolated yield, but NaOAc gave a significantly lower yield. Also, the reactions using the same four bases with 5% PPh_3 were studied. The results clearly indicate that PPh_3 had a significant deleterious effect on the product yield when carbonate bases were employed (entries 7 and 8), but little effect when the acetate bases were utilized.

With our set of optimized reaction conditions at hand, we proceeded to investigate the palladium-catalyzed heteroannulation of oxygen-containing aryl iodides with a variety of vinylic cyclopropanes and vinylic cyclobutanes. The results are summarized in Table 4.

The effect of substitution on the aryl halide was first examined using vinylcyclopropane (entries 1-8). The aryl halide containing an electron-withdrawing acetyl group provided a somewhat lower yield of the desired product, compared to the unsubstituted aryl halide, although the reaction rate was about the same. Fortunately, all of these reactions provided only one regio- and stereoisomer. The (E)-stereochemistry of the products was established from the ^1H NMR coupling constant between the two olefinic hydrogens (J = 15.3 - 21.9 Hz). Sometimes in later work, it found to be impossible to assign the exact structure by ^1H NMR spectroscopy. In those cases, the stereochemistry of the products were assigned by mechanistic assumption and analogy with our other reactions.

The results in Table 4 show that KOAc is the best base for the phenol annulation process (entries 1, 2, 6, and 7). The reactions using Na_2CO_3 or K_2CO_3 and PPh_3 were very slow compared to those using KOAc, as evident by the 30-80% yield of aryl halide recovered after 3 days of reaction (entries 3, 4, and 8).

Table 4. Palladium-catalyzed reactions of oxygen-containing aryl halides with vinylic cyclopropanes and vinylic cyclobutanes.

Entry[a]	Aryl halide	Alkyne	Base
1	 **10**	 **2**	KOAc
2			KOAc
3[b]			K_2CO_3
4[b]			K_2CO_3
5			Na_2CO_3
6	 **13**	 **2**	KOAc
7			KOAc
8[b]			K_2CO_3
9	 **13**	 **4**	KOAc
10			KOAc
11			Na_2CO_3

[a]Actual amounts of reagents used: 0.25 mmol aryl halide, 1.25 mmol alkene, 0.25 mmol *n*-Bu_4NCl, 0.0125 mmol $Pd(OAc)_2$, 1 ml DMF, 1.0 mmol base.

[b]Some aryl halide was recovered.

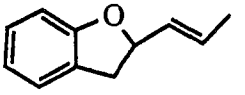
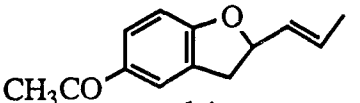
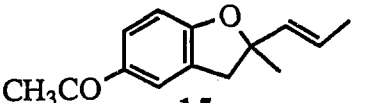
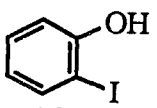
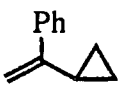
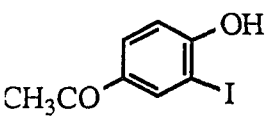
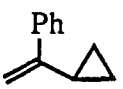
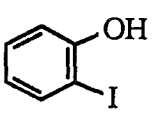
5% PPh_3	Reaction conditions	Product	% Isolated yield
–	80 °C, 3 d	 **12**	70
+	80 °C, 3 d		70
+	80 °C, 3 d		40
–	80 °C, 4 d		0
–	80 °C, 4 d		40
–	80 °C, 3 d	 **14**	54
+	80 °C, 3 d		56
+	80 °C, 3 d		32
+	80 °C, 3 d	 **15**	50
–	80 °C, 3 d		48
–	80 °C, 3 d		29

Table 4. (continued)

Entry[a]	Aryl halide	Alkene	Base
12	 **10**	 **16**	KOAc
13			KOAc
14			NaOAc
15			Na_2CO_3
16	 **13**	 **16**	KOAc
17			KOAc
18			Na_2CO_3
19[c]	 **10**	 **6**	KOAc
20[c]			KOAc
21[c]			Na_2CO_3

[c]The reaction provided 10-25% of Heck-type products.

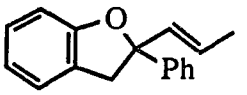
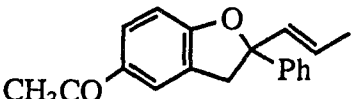
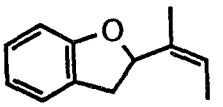
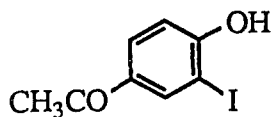
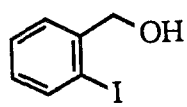
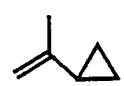
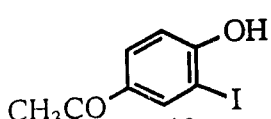
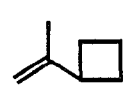
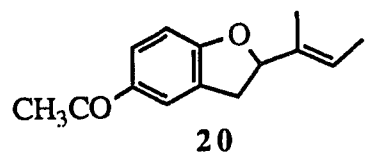
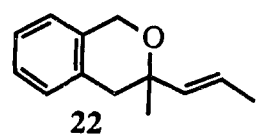
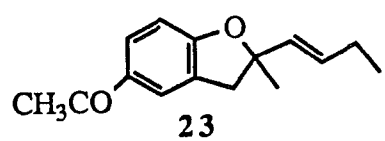
5% PPh_3	Reaction conditions	Product	% Isolated yield
–	100 °C, 3 d	 **17**	46
+	100 °C, 3 d		34
–	100 °C, 3 d		0
–	100 °C, 4 d		18
+	100 °C, 3 d	 **18**	36
–	100 °C, 3 d		43
–	100 °C, 3 d		8
–	100 °C, 3 d	 **19**	50
+	100 °C, 3 d		53
–	100 °C, 4 d		40

Table 4. (continued)

Entry[a]	Aryl halide	Alkene	Base
22[c]	 **13**	 **6**	KOAc
23[c]			KOAc
24[c]			Na_2CO_3
25	 **21**	 **4**	KOAc
26			KOAc
27			Na_2CO_3
28			Na_2CO_3
29	 **13**	 **8**	KOAc
30			KOAc
31			Na_2CO_3

5% PPh_3	Reaction conditions	Product	% Isolated yield
–	100 °C, 4 d	 **20**	41
+	100 °C, 4 d		0
–	100 °C, 5 d		18
+	100 °C, 3 d	 **22**	61
–	100 °C, 3 d		53
–	100 °C, 5 d		39
+	100 °C, 5 d		55
–	100 °C, 4 d	 **23**	38
+	100 °C, 4 d		0
–	100 °C, 5 d		17

The effect of substitution on the vinylic cyclopropane was next investigated (entries 9-24). Unsubstituted vinylcyclopropane seemed to provide a higher yield of the desired product, although isopropenylcyclopropane gave surprisingly good yields of the desired product. Using 1-cyclopropyl-1-phenylethene, the reaction required a higher temperature compared to the reactions of isopropenylcyclopropane, as conjugation with the arene appeared to slow down the reactions to a significant extent. The reactions of 1-methyl-1-ethenylcyclopropane with iodophenol were also examined (entries 19-24). They afforded 40-53% yields of the desired product, along with 10-25% yields of Heck-type products. The methyl substitution on the cyclopropane ring seemed to hinder opening of the cyclopropane ring, as indicated by the higher temperature that was required for these reactions.

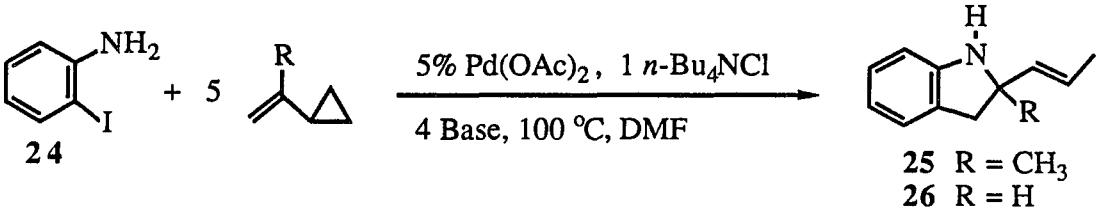
As an extension of this project, the reaction of 2-iodobenzyl alcohol with vinylcyclopropane was examined, but it didn't provide the desired product. We repeated the reaction with isopropenylcyclopropane using KOAc or Na_2CO_3 as the base, and 39-61% yields of the desired product were produced (entries 25-28).

Using isopropenylcyclobutane and KOAc or Na_2CO_3 as the base, the desired product could not be isolated cleanly because the reactions afforded several products which had approximately the same R_f value on TLC. However, the reaction of the acetyl-substituted iodophenol with isopropenylcyclobutane was investigated using KOAc or Na_2CO_3 as the base (entries 29-31). When KOAc was used, a 38% yield of the desired product was obtained without any side product (entry 29). However, when Na_2CO_3 was employed, the reaction provided only 17% of the desired product alongside a small amount of a side product (entry 31).

N-Heterocycles

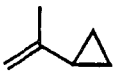
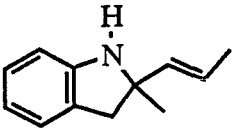
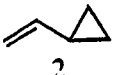
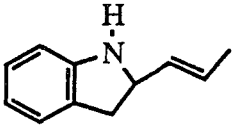
We began our study of *N*-heteroannulation by first looking at the reactions of 2-iodoaniline with vinyl- and isopropenylcyclopropanes (Table 5). Fortunately, the reactions resulted in good to excellent yields of the desired products. In our continual search for a set of reaction conditions that would maximize the yield of the product, the effects of different bases on the reaction were investigated. The reactions of 2-iodoaniline with isopropenyl-cyclopropane using Na_2CO_3 or K_2CO_3 as the base in the presence of PPh_3 provided moderate yields of the desired product. Surprisingly, without PPh_3, the reactions failed to produce any of the cyclized product (entries 2 and 4). On the other hand, much better results were obtained, when the reactions were performed in the presence of Et_3N (entries 5 and 6). Use of *i*-Pr_2NEt was not as successful. For example, when *i*-Pr_2NEt was used as the base in the presence of PPh_3, only a 33% yield of the desired product was obtained (entry 7). The preliminary results clearly indicated that Et_3N and Na_2CO_3 were the best bases for the *N*-heteroannulation process. In conjunction with our initial work, 2-iodoaniline was allowed to react with vinylcyclopropane under the same conditions and the best yield of the desired product was achieved using Et_3N with PPh_3. Throughout the course of the study, it was observed that the reactivity of isopropenylcyclopropane was somewhat lower than vinylcyclopropane, but the yield of the reaction of isopropenylcyclopropane was better than that of vinylcyclopropane. Finally, we decided to extend this method to 1-cyclopropyl-1-phenylethene and isopropenylcyclobutane. Unfortunately, we were not able to obtain any of the desired product from either of these substrates.

Table 5. Palladium-catalyzed reactions of 2-iodoaniline with vinylic cyclopropanes .



24

25 R = CH_3
26 R = H

Entry	Alkene	Base	5% PPh_3	Reaction time (d)	Product	% Isolated yield
1	 **4**	Na_2CO_3	+	2	 **25**	56
2[a]		Na_2CO_3	–	2		0
3		K_2CO_3	+	2		30
4[a]		K_2CO_3	–	2		0
5		Et_3N	+	5		69
6		Et_3N	–	5		68
7		*i*-Pr_2NEt	+	5		33
8		*i*-Pr_2NEt	–	5		16
9	 **2**	Na_2CO_3	+	5	 **26**	45
10		Et_3N	+	5		47
11		Et_3N	–	6		30

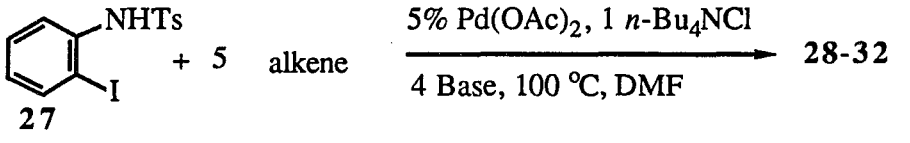
[a]2-Iodoaniline was recovered.

Based on Berrios-Peña's results,[43] it was thought that the attachment of a strong electron-withdrawing group on the nitrogen atom of 2-iodoaniline would provide a higher yield of the corresponding cyclization products. Hence, *N*-tosyl-2-iodoaniline was prepared by modification of the procedure reported by Ratcliff.[44] The reactions of *N*-tosyl-2-iodoaniline with vinylic cyclopropanes and isopropenylcyclobutane were subsequently examined, and the results are summarized in Table 6.

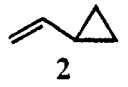
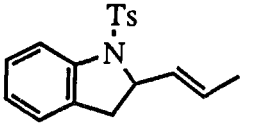
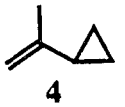
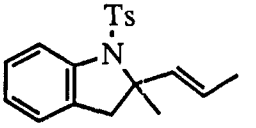
The results clearly show that the best yields were obtained when KOAc was used as the base (entries 1, 7, 12, 16 and 19). Addition of PPh_3 provided significantly lower yields of the desired products (entries 2, 8, 13 and 20). When Na_2CO_3, K_2CO_3, Et_3N, or NaOAc were used as the base , low yields of the desired products were obtained. The reactions of *N*-tosyl-2-iodoaniline with various vinylic cyclopropanes and isopropenylcyclobutane afforded no Heck-type side products. One surprising result was that the reaction of *N*-tosyl-2-iodoaniline with isopropenylcyclobutane provided almost the same yield of the desired product as that of isopropenylcyclopropane. The reactions of substituted vinylic cyclopropanes clearly showed that increased steric hindrance afforded lower yields of the desired product and required higher reaction temperatures, and longer reaction times.

Recently, Larock, Fried and Berrios-Peña [24,26,43] developed palladium-catalyzed carbo- and heteroannulation processes for 1,2-, 1,3-, and 1,4-dienes. These annulation processes provide a variety of carbocycles and heterocycles with good regioselectivity. During his study of the heteroannulation process, Berrios-Peña[43] obtained good yields of tetrahydroquinoline derivatives via heteroannulation of 1,4-dienes with *N*-tosyl-2-iodoaniline, but he did not examine the use of 2-iodoaniline itself. Hence, we decided to investigate the possibility of utilizing π-allylpalladium intermediates in the synthesis of heterocycles via the palladium-catalyzed heteroannulation of 1,4-dienes using 2-iodoaniline. The reactions of

Table 6. Palladium-catalyzed reactions of *N*-tosyl-2-iodoaniline with vinylic cyclopropanes and isopropenylcyclobutane.



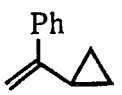
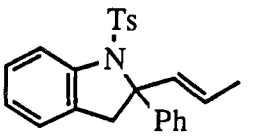
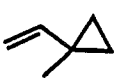
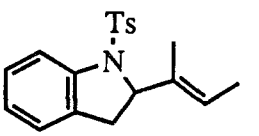
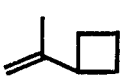
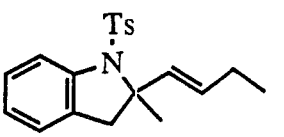
27

Entry	Alkene	Base	5% PPh_3	Reaction time (d)	Product	% Isolated yield
1[a]	 2	KOAc	–	4	 **28**	77
2[a,b]		KOAc	+	6		43
3[a]		NaOAc	–	4		30
4[a]		Na_2CO_3	+	5		25
5[a]		Na_2CO_3	–	5		18
6[a]		K_2CO_3	+	5		45
7	 **4**	KOAc	–	4	 **29**	61
8		KOAc	+	6		30
9[b]		Et_3N	–	6		9
10[b]		Et_3N	+	6		23

[a]The reaction was run at 80 °C.

[b]More than 50% aryl halide recovered.

Table 6. (continued)

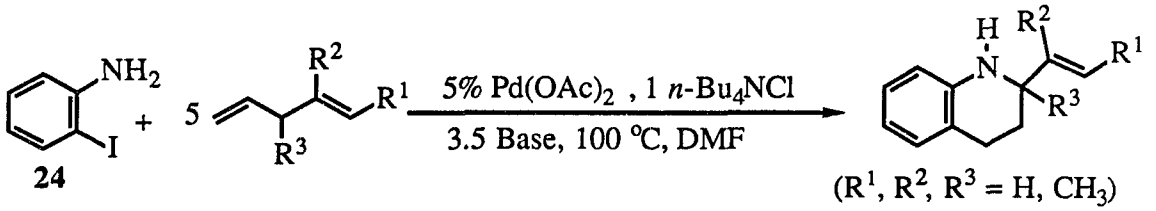
Entry	Alkene	Base	5% PPh_3	Reaction time (d)	Product	% Isolated yield
11		Na_2CO_3	–	4		21
12	 **16**	KOAc	–	6	 **30**	37
13		KOAc	+	6		8
14[b]		Et_3N	+	6		0
15[b]		Et_3N	+	5		0
16	 **6**	KOAc	–	3	 **31**	38
17		KOAc	+	6		27
18[b]		Et_3N	+	6		0
19	 **8**	KOAc	–	4	 **32**	60
20		KOAc	+	6		26
21		Na_2CO_3	+	5		19
22		K_2CO_3	+	5		16

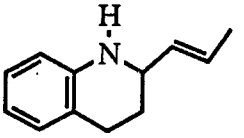
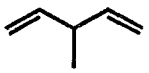
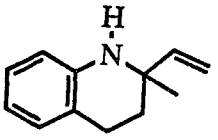
2-iodoaniline with several 1,4-dienes were thus attempted. The results are summarized in Table 7.

We began the project with the model reaction of 2-iodoaniline and *trans*-1,4-hexadiene. Fortunately, the reaction afforded a good yield of the desired product under our standard reaction conditions. The results show that the reactions using carbonate ($KHCO_3$, K_2CO_3, $NaHCO_3$, Na_2CO_3) bases give a higher yield of the desired product than those using potassium acetate. Addition of 5% PPh_3 was found to decrease the yield slightly. All of the reactions of 2-iodoaniline with *trans*-1,4-hexadiene provided three non-cyclized side products which were found to be isomeric by GC-MS analysis (entries 1-10). Unambiguous assignments for the structures of the three side products couldn't be made from the ^1H NMR spectra.

Other 1,4-dienes were examined to determine the effect on the yield of substitution on the diene. The reactions of 2-iodoaniline with 3-methyl-1,4-pentadiene using carbonate or bicarbonate bases provided 69-71% yields of the desired product with minor amounts of several non-cyclized regioisomeric side products (entries 11-14). On the other hand, the reactions of 2-iodoaniline with 2-methyl-1,4-pentadiene using Na_2CO_3 or $NaHCO_3$ as the base provided 51-52% yields of the desired product with three acyclic regioisomeric side products (entries 17 and 18). Finally, the reactions of 2-iodoaniline with 1,4-pentadiene using carbonate as the base provided 63-65% yields of the desired product with only small amounts of the acyclic side products (entries 19 and 21).

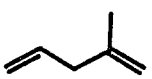
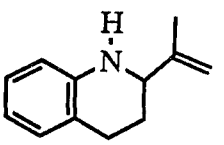
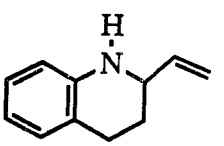
Table 7. Palladium-catalyzed reactions of 2-iodoaniline with 1,4-dienes.



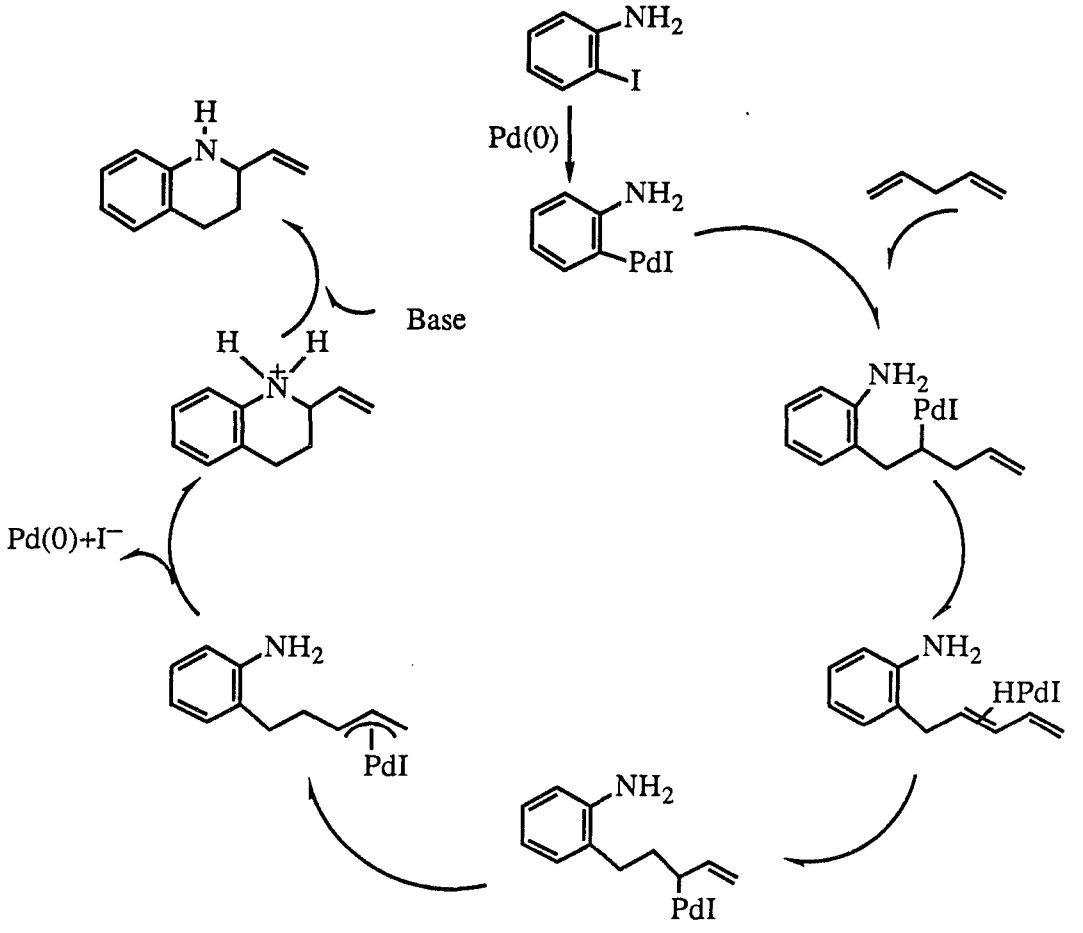
Entry[a]	Diene	Base	5% PPh_3	Reaction time (d)	Product	% Isolated yield
1		K_2CO_3	–	1.5	 **33**	69
2		K_2CO_3	+	1.5		39
3		Na_2CO_3	–	2.5		59
4		Na_2CO_3	+	1.5		57
5		KOAc	–	1.5		48
6		KOAc	+	1.5		26
7		$KHCO_3$	–	1.5		58
8		$KHCO_3$	+	1.5		56
9		$NaHCO_3$	–	1.5		57
10		$NaHCO_3$	+	1.5		49
11		K_2CO_3	–	1.5	 **34**	70
12		$KHCO_3$	–	1.5		71
13		Na_2CO_3	–	1.5		69

[a]All reactions provided small amounts of non-cyclized products

Table 7. (continued)

Entry[a]	Diene	Base	5% PPh_3	Reaction time (d)	Product	% Isolated yield
14		$NaHCO_3$	–	1.5		70
15		K_2CO_3	–	2	 **35**	35
16		$KHCO_3$	–	2		36
17		Na_2CO_3	–	2		52
18		$NaHCO_3$	–	2		51
19		K_2CO_3	–	3.5	 **36**	63
20		$KHCO_3$	–	3.5		60
21		Na_2CO_3	–	3.5		65
22		$NaHCO_3$	–	3.5		49

The mechanism of *N*-heteroannulation of 1,4-pentadiene is depicted in Scheme 2.



Scheme 2

The first step of the mechanism is oxidative addition of the aryl halide onto the metal to generate an arylpalladium intermediate which then adds in a cis manner to the carbon-carbon double bond of 1,4-pentadiene to form a σ-alkylpalladium intermediate, which subsequently undergoes β-hydride elimination and readdition to generate another σ-alkylpalladium intermediate. Subsequent π-allylpalladium formation, followed by intramolecular nucleophilic attack on the π-allylpalladium species generates the tetrahydroquinoline and regenerates Pd(0) which can be recycled.

CONCLUSION

Annulation processes are extremely important in organic synthesis for the construction of carbocycles and heterocycles. In this chapter, it has been shown that the palladium-catalyzed annulation of vinylic cyclopropanes, vinylic cyclobutanes, and 1,4-dienes by functionally- substituted aryl halides provides a novel route to a wide variety of heterocycles and carbocycles.

The reactions using carbon nucleophile-substituted aryl halides provide high yields of indanes when using KOAc as the base, but the reactions provide some decarboalkoxylation side products at higher temperatures (above 80 ^{o}C). The reactions using oxygen nucleophile-substituted aryl halides provide high yields of dihydrobenzofurans using KOAc as the base. The reactions using an iodophenol substituted with an electron-withdrawing group afford lower yields of the desired products compared to those using 2-iodophenol. With the nitrogen-substituted aryl halides, better yields were obtained when a tosyl group was attached to the nitrogen atom.

In general, in the vinylic cyclopropane and cyclobutane reactions, the best yield of the desired products are obtained using KOAc as a base. However, with 1,4-dienes, carbonate bases provided superior yields. We believe that this new annulation methodology should prove useful in the synthesis of complex natural products, which might otherwise be difficult to prepare by present synthetic methods.

EXPERIMENTAL SECTION

A. Equipment

The infrared spectra were obtained on an IBM IR/98 FT spectrophotometer, and the ^{1}H NMR and ^{13}C NMR spectra on a Nicolet NT-300 NMR spectrometer. The GC-MS spectral data were obtained on a Finnegan 4023 GC/MS and on a Kratos MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with an OV-101 packed column.

B. Reagents

All chemicals were used directly as obtained from commercial sources unless otherwise noted. Et_3N and *i*-Pr_2NEt were distilled from KOH pellets. The anhydrous form of $NaHCO_3$, Na_2CO_3, K_2CO_3, NaOAc, and KOAc were all purchased from Fisher-Scientific Co. $Pd(OAc)_2$ was provided by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. 2-Iodophenol, 2-iodoaniline, phenylacetic acid, NaH, 2-iodobenzyl alcohol and PPh_3 were purchased from Aldrich Chemical Co. Inc. *n*-Bu_4NCl was purchased from Lancaster Synthesis.

Preparation of diethyl 2-iodophenylmalonate (**1**)

Diethyl 2-iodophenylmalonate was prepared in three steps from phenylacetic acid. Phenylacetic acid (3.50 g, 26 mmol) was iodinated by the thallation/ iodination procedure of McKillop et al.[26,45] to afford 2-iodophenylacetic acid (3.60 g, 58%) as a white solid: mp 110-112 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 2H, $ArCH_2$) , 6.98 (dt, 1H, J = 7.2 Hz, J = 2.1 Hz, ArH), 7.30 (m, 2H, ArH), 7.85 (d, 1H, J = 7.8 Hz, ArH).

Ethyl 2-iodophenylacetate was prepared by the method of Harrison[46] from 2-iodophenylacetic acid (1.543 g, 5.9 mmol) to afford the ester as a white solid in 93 % yield: mp 125-126 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.2 Hz, CH_3), 3.79 (s, 2H, $ArCH_2$), 4.18 (q, 2H, J = 7.2 Hz, OCH_2), 6.99 (m, 1H, ArH), 7.35 (m, 2H, ArH), 7.83 (d, 1H, J = 7.5 Hz, ArH).

Sodium hydride (0.48 g, 20 mmol) was weighed into a flame-dried, 50 ml round-bottom flask equipped with a septum inlet and a magnetic stirring bar. The flask was flushed with nitrogen. A solution of ethyl 2-iodophenylacetate (2.78 g, 10 mmol) dissolved in diethyl carbonate (20 ml) was added via syringe. The reaction mixture was stirred under nitrogen at room temperature overnight. The solution was poured into a cold saturated aqueous solution of ammonium chroride (100 ml) and extracted with methylene chloride. The extracts were dried over $MgSO_4$. Flash column chromatography over silica gel using 5:1 hexanes : ethyl acetate afforded diethyl 2-iodophenylmalonate (3.25 g, 90%) as a yellow oil. IR (neat) 2955, 2924, 1753, 1736, 1468, 1304, 1259, 1217, 1175, 1030, 745, 648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 6H, J = 7.2 Hz, CH_3's), 4.25 (m, 4H, OCH_2's), 5.12 (s, 1H, ArCH), 7.01 (dt, 1H, J = 7.2 Hz, J = 1.5 Hz, ArH), 7.37 (m, 1H, ArH), 7.47 (m, 1H, ArH), 7.87 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.05, 29.74, 61.96, 101.63, 128.49, 129.63, 129.67, 136.41, 139.55, 167.66; HRMS calculated for $C_{13}H_{15}IO_4$: 362.00151. Found: 362.00131.

Preparation of vinylcyclopropane (**2**)

Vinylcyclopropane was prepared via 3-vinyl-1-pyrazoline using the procedure developed by Crawford and Cameron.[47] To a flask containing condensed butadiene (15 ml), a solution containing 3 g of diazomethane dissolved in 15 ml of ethyl ether prepared from 21.5 g of diazald (Aldrich) was added at -78 °C. The reaction was run 2 hours at -78 °C. After the reaction mixture stood overnight at ice bath temperature, the ether was distilled out at

atmospheric pressure. The remaining concentrate was distilled at 62 °C / 25 mm Hg to provide 4.23 g (44 mmol, 61%) of 3-vinyl-1-pyrazoline. ^{1}H NMR ($CDCl_3$) δ 1.31–1.38 (m, 1H, CH), 1.86-1.95 (m, 1H, CH), 4.23-4.35 (m, 1H, N-CH), 4.59-4.70 (m, 1H, N-CH), 4.89-4.92 (m, 1H, N-CH), 5.30 (dd, H, J = 10.4 Hz, J = 1.2 Hz, $=CH_2$), 5.36 (dd, 1H, J = 17.4 Hz, J = 1.2 Hz, =CH-), 5.40 (m, 1H, =CH-).

3-Vinyl-1-pyrazoline was placed in a flask equipped with a magnetic stirring bar and distillation apparatus and heated in an oil bath kept at 135 °C. Vinylcyclopropane was trapped in a flask kept at -78 °C; vinylcyclopropane was obtained in 69% yield: bp 45 °C; ^{1}H NMR ($CDCl_3$) δ 0.36–0.41(m, 2H, CH-CH, trans), 0.68–0.74 (m, 2H, CH-CH, cis), 1.37-1.44 (m, 1H, -CH-), 4.85 (dd, 1H, J = 10.5 Hz, J = 1.8 Hz, $=CH_2$), 5.07 (dd, 1H, J = 17.3 Hz, J = 1.8 Hz, $=CH_2$), 5.34 (ddd, 1H, J = 17.1 Hz, J = 10.5 Hz, J = 1.8 Hz, =CH-).

Preparation of isopropenylcyclopropane (**4**)

Isopropenylcyclopropane was prepared by the procedure developed by Corey et al.[48] Sodium hydride (0.1 mol) was placed in a 250 ml three-neck flask and washed several times with hexane. After the system was purged, 25 ml of DMSO was added via syringe, and the mixture was heated at 75-80 °C until the evolution of hydrogen ceased. The resulting solution of methylsulfinyl carbanion was cooled in an ice bath, and 17.9 g (0.05 mol) of methyltriphenylphosphonium bromide (Aldrich) dissolved in 50 ml of DMSO was added slowly to the methylsulfinyl anion solution. The color turned from green to brown upon completion of the addition, and the reaction mixture was then stirred for 15 minutes at a temperature of 0-10 °C. Methyl cyclopropyl ketone (4.62 g, 55 mmol, Aldrich) was added slowly and the mixture was warmed to room temperature and stirred for an additional 1 hour at that temperature. Distillation of the mixture provided 2.6 g (0.013 mol, 62 %) of isopropenylcyclopropane in a fraction boiling between 70-80 °C; ^{1}H NMR ($CDCl_3$) δ 0.50

(m, 2H, CH-CH), 0.60 (m, 2H, CH-CH), 1.42 (m, 1H, -CH-), 1.65 (s, 3H, CH_3), 4.70-4.80 (overlapping d, 2H, J = 1.2 Hz, $=CH_2$).

Preparation of 1-methyl-1-ethenylcyclopropane (**6**)

1-Methylcyclopropanecarboxaldehyde was prepared by the oxidation of 1-methylcyclopropanemethanol (Aldrich) using a modification of the procedure reported by Corey et al.[48] To a flask containing 5.06 g (22.5 mmol) of pyridinium chlorochromate in 30 ml of methylene chloride at room temperature was added 1.28 g (15.0 mmol) of 1-methylcyclopropanemethanol under nitrogen. The reaction mixture was stirred at room temperature for 2 hours and filtered through a florisil column. 1-Methylcyclopropane-carboxaldehyde was distilled at 110 ^{o}C to afford a 43% yield (0.55 g, 6.5 mmol): ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 2H, CH-CH), 1.14 (m, 2H, CH-CH), 1.22 (s, 3H, CH_3), 8.15 (s, 1H, CHO)

1-Methyl-1-ethenylcyclopropane (**6**) was prepared in a 49% yield by olefination of 1-methylcyclopropanecarboxaldehyde using the same procedure used for the preparation of isopropenylcyclopropane (**4**): ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 2H, CH-CH), 1.14 (m, 2H, CH-CH), 1.22 (s, 3H, CH_3), 4.85 (d, 1H, J = 10.5 Hz, =CH, trans to the ring), 5.07 (d, 1H, J = 17.3 Hz, =CH, cis to the ring), 5.34 (dd, 2H, J = 17.3 Hz, J = 10.5 Hz, =CH-)

Preparation of isopropenylcyclobutane (**8**)

This compound was prepared in a 49% yield by olefination of cyclobutyl methyl ketone (Aldrich) using the same procedure used for the preparation of isopropenylcyclopropane (**4**). ^{1}H NMR ($CDCl_3$) δ 1.5-2.0 (m, 6H, CH_2's), 2.50 (s, 3H, CH_3), 2.80 (m, 1H, -CH-), 4.50 (s, 1H, =CH), 4.60 (s, 1H, =CH).

Preparation of 1-cyclopropyl-1-phenylethene (**16**)

This compound was prepared in a 50% yield by olefination of cyclopropyl phenyl ketone (Aldrich) using the same procedure used for the preparation of isopropenylcyclopropane (**4**): ^{1}H NMR ($CDCl_3$) δ 0.63 (m, 2H, CH-CH), 0.85 (m, 2H, CH-CH), 1.68 (m, 1H, CH), 4.96 (s, 1H, $=CH_2$), 5.30 (s, 1H, $=CH_2$), 7.36 (m, 4H, ArH), 7.62 (d, 1H, J = 7.2 Hz, ArH).

Preparation of 4-hydroxy-3-iodoacetophenone (**13**)

Compound **13** was prepared by a procedure reported by Berrios-Peña.[43] To a solution of *p*-hydroxy acetophenone (5.1 g, 38 mmol) (prepared as reported by Schreiber and Stevenson[49]) in concentrated ammonium hydroxide (250 ml) was added rapidly and with stirring a solution of KI (9.63 g) in water (76 ml). After stirring at room temperature overnight (color changed from black to a cloudy green), the mixture was filtered. The filtrate was then acidified with concentrated sulfuric acid to pH 1 after cooling in an ice bath. The temperature was kept below 35 °C. The heterogeneous solution formed was cooled to 0-5 °C and then filtered. The solid collected was dissolved in ether and treated with activated charcoal. Filtration, concentration, and purification via flash column chromatography (4:1 hexanes/ethyl acetate) gave 5.52 g (56%) of the desired product. Recrystallization from 1:2 CH_3OH/ H_2O afforded 4.86 g (49%) of 4-hydroxy-3-iodoacetophenone: mp 153-155 °C; IR ($CDCl_3$) 3483, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H, CH_3CO), 5.91 (s, 1H, OH), 7.02 (d, 1H, J = 8.4 Hz, ArH), 7.87 (dd, 1H, J = 8.4 Hz, J = 2.1 Hz, ArH), 8.30 (d, 1H, J = 2.1 Hz, ArH).

Preparation of *N*-tosyl-2-iodoaniline (**27**)[43]

Compound **27** was prepared by a procedure reported by Berrios-Peña.[43] 2-Iodoaniline (5.48 g, 25 mmol) was dissolved in 8 ml of pyridine and solid tosyl chloride (4.77 g, 25 mmol) was added slowly. After the addition of the tosyl chloride was completed, the reaction mixture was heated for 1 hour at 80 °C in an oil bath. The reaction mixture was then cooled, diluted with Et_2O, and washed with 5% HCl several times. The organic phase was then dried with $MgSO_4$ and activated charcoal was added. Filtration and concentration of the filtrate afforded a yellowish solid. Recrystallization of the solid obtained from EtOH afforded 4.9 g (52%) of the desired product as white crystals: mp 90-92 °C; IR ($CDCl_3$) 3327, 2980, 1339, 1167 cm^{-1}; ^1H NMR (d^6-acetone) δ 2.40 (s, 3H, CH_3), 6.95 (m, 1H, ArH), 7.34 (d, 2H, J = 7.8 Hz, ArH), 7.37 (m, 1H, ArH), 7.47 (dd, 1H, J = 8.1 Hz, J = 1.5 Hz, ArH), 7.65 (d, 2H, J = 8.1 Hz, J = 1.5 Hz, ArH), 7.79 (dd, 1H, J = 8.1 Hz, J = 1.5 Hz, ArH), 8.0 (br s, 1H, NH). Anal. calculated for $C_{13}H_{12}INO_2S$: C, 41.82; H, 3.22. Found: C, 41.77; H, 3.47.

General procedure for the palladium-catalyzed reactions of substituted aryl halides and vinylic cyclopropanes and vinylic cyclobutanes

Palladium acetate (0.0125 mmol), *n*-Bu_4NCl (0.25 mmol), the appropriate base (1.0 mmol), the aryl iodide (0.25 mmol), the alkene (1.25 mmol), DMF (1ml) and , where indicated, PPh_3 (0.0125 mmol) were added to a 1 dram vial equipped with a stirring bar and teflon-lined screw cap. After heating for the appropriate time, the reaction mixture was diluted with ether (20 ml), washed with saturated ammonium chloride (3 x 20 ml) and dried over $MgSO_4$. The reaction mixture was filtered, concentrated and purified by flash column chromatography using hexane-ethyl acetate. The following compounds were obtained using the above general procedure.

Preparation of compound **3**

Compound **3** was obtained as a pale yellow oil in 80% isolated yield from the reaction of diethyl 2-iodophenylmalonate and vinylcyclopropane using KOAc as a base, and stirring for three days at 80 °C (Table 1, entry 1): IR (neat) 2937, 1732, 1477, 1263, 1231, 1051, 735 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.14 (m, 6H, CH_3's), 1.54 (d, 3H, J = 6.0 Hz, =C-CH_3), 2.78 (dd, 1H, J = 15.3 Hz, J = 5.4 Hz, ArCH), 3.17 (dd, 1H, J = 15.6 Hz, J = 7.6 Hz, ArCH), 3.65 (m, 1H, -CH-C=), 4.10 (m, 4H, OCH_2's), 5.35 (m, 1H, =CH-), 5.45 (m, 1H, -CH=), 7.15 (m, 3H, ArH), 7.45 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.30, 18.00, 37.48, 49.77, 61.57, 61.19, 69.49, 124.67, 126.67, 126.85, 127.81, 128.54, 129.77, 138.83, 143.65, 169.74.

Preparation of compound **5**

Compound **5** was obtained as a pale yellow oil in 80% isolated yield from the reaction of diethyl 2-iodophenylmalonate and isopropenylcyclopropane using Na_2CO_3 as a base with PPh_3, and stirring for seven days at 60 °C (Table 2, entry 4): IR (neat) 3030, 2992, 1750, 1475, 1263, 1227, 1045, 912, 736 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.20 (m, 6H, CH_3's), 1.30 (s, 3H, CH_3), 1.64 (dd, 3H, J = 6.3 Hz, J = 1.5 Hz, =C-CH_3), 2.99 (d, 1H, J = 15 Hz, ArCH), 3.12 (d, 1H, J = 15 Hz, ArCH), 4.15 (m, 4H, OCH_2's), 5.55 (m, 1H, =CH-), 5.58 (d, 1H, J = 15.6 Hz, CH=), 7.10- 7.30 (m, 3H, ArH), 7.50 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.98, 18.18, 22.35, 44.94, 45.83, 60.87, 60.95, 71.72, 124.00, 124.73, 126.30, 127.47, 128.22, 135.07, 133.42, 144.36, 169.11, 169.27.

Preparation of compound **7**

Compound **7** was obtained as a yellow oil in 51% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 1-methyl-1-vinylcyclopropane using Na_2CO_3 as a base with

PPh_3, and stirring for five days at 60 °C (Table 2, entry 9). The stereochemistry of the product was assigned by mechanistic assumption: IR (neat) 2996, 2930, 1726, 1477, 1266, 1234, 1039, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, 6H, J = 7.2 Hz , CH_3's), 1.33 (s, 3H, CH_3), 1.52 (d, 3H, J = 7.5 Hz, =C-CH_3), 2.90 (dd, 1H, J = 7.8 Hz, J = 3.6 Hz, ArCH), 3.33 (dd, 1H, J = 15.9 Hz, J = 7.8 Hz, ArCH), 3.95 (dd, 1H, J = 7.8 Hz, J = 3.6 Hz, -CH-), 4.15 (m, 4H, OCH_2's), 5.45 (q, 1H, J = 7.5 Hz, =CH-), 7.15- 7.25 (m, 3H, ArH), 7.50 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.83, 14.22, 14.40, 14.60, 20.06, 36.56, 54.50, 61.65, 61.61, 122.72, 124.12, 126.57, 126.74, 128.54, 135.37, 139.22, 144.33, 169.48, 169.48.

Preparation of compound **9**

Compound **9** was obtained as a yellow oil in 40% isolated yield from the reaction of diethyl 2-iodophenylmalonate and isopropenylcyclobutane using Na_2CO_3 as a base with PPh_3, and stirring for four days at 80 °C (Table 2, entry 15): IR (neat) 3028, 2924, 1726, 1477, 1129, 1045, 910, 733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.2 Hz, CH_3), 1.19 (m, 6H, CH_3's), 1.30 (s, 3H, CH_3), 1.95 (m, 2H, =C-CH_2), 2.99 (d, 1H, J = 15 Hz, ArCH), 3.19 (d, 1H, J = 15.6 Hz, ArCH), 4.05 (m, 4H, OCH_2's), 5.56 (d, 1H, J = 15.6 Hz, =CH-), 5.75 (dt, 1H, J = 15.6 Hz, J = 1.2 Hz, CH=C-), 7.22 (m, 3H, ArH), 7.50 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.10, 25.94, 29.79, 31.00, 45.22, 51.91, 60.06, 60.33, 65.93, 71.93, 124.86, 126.43, 127.59, 130.87, 131.87, 131.23, 133.20, 139.04, 143.51, 169.21, 169.45.

Preparation of compound **11**

Compound **11** was obtained as a yellow oil in 71% isolated yield from the reaction of 2-iodophenol and isopropenylcyclopropane using KOAc as a base with PPh_3, and stirring for three days at 80 °C (Table 3, entry 5): IR (neat) 3034, 2928, 2856, 1627, 1597, 1491, 1246,

916, 755 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.53 (s, 3H, CH_3), 1.70 (d, 3H, J = 5.1Hz, =C-CH_3), 3.01 (d, 1H, J = 15.3 Hz, ArCH), 3.32 (d, 1H, J = 15.3 Hz, ArCH), 5.65-5.85 (m, 2H, CH=CH-) , 6.75-6.85 (m, 2H, ArH), 7.10 (t, 2H, J = 7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 17.85, 26.49, 42.49, 87.46, 109.82, 120.21, 124.20, 125.18, 126.89, 128.09, 134.69, 158.93; HRMS calculated for $C_{12}H_{14}O$: 174.10447. Found 174.10439.

Preparation of compound **12**

Compound **12** was obtained as a yellow oil in 70% isolated yield from the reaction of 2-iodophenol and vinylcyclopropane using KOAc as a base, and stirring for three days at 80 °C (Table 4, entry 1): The IR, ^1H and ^{13}C NMR spectral data for compound **12** were identical with those previously reported for this compound by Berrios-Peña:[43] IR (neat) 3015, 2928, 2856, 1675, 1615, 1510, 1490, 1260, 1246, 916, 755 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.75 (dd, 3H, J = 6.6 Hz, J = 1.5 Hz, =C-CH_3), 2.97 (dd, 1H, J = 15.6 Hz, J = 8.1 Hz, ArCH), 3.32 (dd, 1H, J = 15.6 Hz, J = 9.3 Hz, ArCH), 5.05 (m, 1H, O-CH), 5.60-5.75 (m, 1H, HC=), 5.75-5.95 (dq, 1H, J = 15.3 Hz, J = 6.3 Hz, =CH-), 6.70-6.90 (m, 2H, ArH), 7.0-7.20 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.85, 36.21, 83.91, 104.47, 120.43, 124.93, 126.70, 128.12, 130.66, 133.50, 159.48; HRMS calculated for $C_{11}H_{12}O$: 160.08882. Found: 160.08853.

Preparation of compound **14**

Compound **14** was obtained as a yellow oil in 54% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and vinylcyclopropane using KOAc as a base, and stirring for three days at 80 °C (Table 4, entry 6): IR (neat) 2924, 1678, 1605, 1596, 1498, 1368, 1236, 912, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (dd, 3H, J = 6.6 Hz, J = 0.9 Hz, =C-CH_3), 2.52 (s, 3H, $COCH_3$), 3.00 (dd, 1H, J = 15.9 Hz, J = 7.8 Hz, ArCH), 3.35 (dd, 1H, J = 15.6 Hz,

J = 9.0 Hz, ArCH), 5.22 (dd, 1H, J = 8.1 Hz, J = 7.8 Hz, O-CH), 5.63 (dd, 1H, J = 21.9 Hz , J = 7.8 Hz, -CH=), 5.84 (m, 1H, =CH-), 6.65 (d, 1H, J = 8.1 Hz, ArH), 7.79 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.69, 26.36, 35.28, 85.15, 108.85, 124.01, 125.40, 127.60, 129.76, 130.27, 130.45, 163.61, 196.49.

Preparation of compound **15**

Compound **15** was obtained as a yellow oil in 50% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and isopropenylcyclopropane using KOAc as a base with PPh_3, and stirring for three days at 80 °C (Table 4, entry 9): IR (neat) 2928, 2856, 1754, 1674, 1607, 1498, 1375, 1266, 910, 753 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3H, CH_3), 1.87 (d, 3H, J = 5.1 Hz, =C-CH_3), 2.69 (s, 3H, $COCH_3$), 3.20 (d, 1H, J = 15.6 Hz, ArCH), 3.35 (d, 1H, J = 15.6 Hz, ArCH), 5.87 (m, 2H, CH=CH), 6.94 (d, 1H, J = 7.8 Hz, ArH), 7.96 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.78, 26.44, 29.79, 41.65, 89.49, 109.02, 109.13, 124.86, 125.79, 127.61, 130.52, 134.15, 163.13, 196.67 ; HRMS calculated for $C_{14}H_{16}O_2$: 216.11503. Found: 216.11527.

Preparation of compound **17**

Compound **17** was obtained as a yellow oil in 46% isolated yield from the reaction of 2-iodophenol and 1-cyclopropyl-1-phenylethene using KOAc as a base, and stirring for three days at 100 °C (Table 4, entry 12): IR (neat) 3030, 2928, 2856, 1752, 1627, 1470, 1364, 1268, 1107, 912, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (dd, 3H, J = 6.6 Hz, J = 1.5 Hz, =C-CH_3), 3.48 (two doublets, 2H, J = 15.6 Hz, $ArCH_2$), 5.67 (m, 2H, =CH-), 5.90 (d, 1H, J = 15.6 Hz, CH=), 6.80-6.95 (m, 2H, ArH), 7.10-7.50 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.86, 43.49, 90.82, 109.60, 120.65, 124.94, 125.62, 126.02, 126.36, 127.34, 128.19, 128.32, 134.66, 144.82, 158.77.

Preparation of compound **18**

Compound **18** was obtained as a yellow oil in 43% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and 1-cyclopropyl-1-phenylethene using KOAc as a base, and stirring for three days at 100 °C (Table 4, entry 17): IR (neat) 3030, 2928, 2856, 1754, 1674, 1607, 1498, 1375, 1266, 910, 753 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.62 (dd, 3H, J = 6.3 Hz, J = 1.5 Hz, =C-CH_3), 2.45 (s, 3H, $COCH_3$), 3.43 (two doublets, 2H, J = 15.6 Hz, $ArCH_2$), 5.59 (m, 1H, =CH-), 5.80 (d, 1H, J = 16.5 Hz, -CH=), 6.84 (d, 1H, J = 9.6 Hz, ArH), 7.15-7.41 (m, 6H, ArH), 7.75 (t, 1H, J = 9.6 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 17.81, 26.47, 42.61, 92.63, 109.20, 125.45, 125.62, 126.16, 126.54, 127.23, 127.53, 130.60, 130.97, 133.98, 143.92, 162.94, 196.58.

Preparation of compound **19**

Compound **19** was obtained as a yellow oil in 53% isolated yield from the reaction of 2-iodophenol and 1-methyl-1-vinylcyclopropane using KOAc as a base with PPh_3, and stirring for three days at 100 °C (Table 4, entry 20). The stereochemistry of the product was assigned by mechanistic assumption: IR (neat) 2968, 2920, 1697, 1491, 1462, 1232, 916, 735 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.64 (s, 3H, CH_3), 1.65 (d, 3H, J = 6.6 Hz, =C-CH_3), 3.04 (dd, 1H, J = 15.9 Hz, J = 7.2 Hz, ArCH), 3.24 (dd, 1H, J = 15.9 Hz, J = 9.3 Hz, ArCH), 5.12 (two overlapping doublets), 1H, J = 9.0 Hz, O-CH-), 5.64 (q, 1H, J = 4.2 Hz, =CH-), 6.75-6.90 (m, 2H, ArH), 7.0- 7.20 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 10.83, 13.27, 34.33, 88.07, 109.19, 120.22, 122.73, 124.82, 127.13, 128.01, 134.61, 159.95 ; HRMS calculated for $C_{12}H_{14}O$: 174.10447. Found 174.10451.

Preparation of compound **20**

Compound **20** was obtained as a yellow oil in 41% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and 1-methyl-1-vinylcyclopropane using KOAc as a base, and stirring for 4 days at 100 °C (Table 4, entry 22). The stereochemistry of the product was assigned by mechanistic assumption: IR (neat) 2924, 1678, 1605, 1498, 1368, 1236, 916, 736 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.64 (s, 3H, CH_3), 1.65 (d, 3H, J = 6.6 Hz, =C-CH_3), 2.26 (s, 3H, $COCH_3$), 3.04 (dd, 1H, J = 15.9 Hz, J = 7.2 Hz, ArCH), 3.24 (dd, 1H, J = 15.9 Hz, J = 9.3 Hz, ArCH), 5.12 (two overlapping doublets, 1H, J = 9.0 Hz, O-CH-), 5.64 (q, 1H, J = 4.2 Hz, =CH-), 6.75-6.90 (m, 2H, ArH), 7.03 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.15, 13.95, 26.40, 33.45, 89.42, 108.65, 115.05, 123.40, 125.30, 127.83, 130.47, 133.88, 164.17, 196.64.

Preparation of compound **22**

Compound **22** was obtained as a yellow oil in 61% isolated yield from the reaction of 2-iodobenzyl alcohol and isopropenylcyclopropane using KOAc as a base with PPh_3, and stirring for three days at 100 °C (Table 4, entry 25): IR (neat) 3026, 2923, 2856, 1454, 1376, 1259, 1078, 910, 735 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.64 (d, 3H, J = 4.8 Hz, =C-CH_3), 2.80 (d, 1H, J = 16.5 Hz, ArCH), 2.90 (d, 1H, J = 16.5 Hz, ArCH), 4.75 (s, 2H, $ArCH_2O$), 5.50 (m, 2H, -CH=CH-), 7.00-7.15 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.03, 27.41, 29.82, 37.70, 68.48, 123.92, 125.77, 125.92, 126.31, 128.70, 133.04, 134.37, 134.30 ; HRMS calculated for $C_{13}H_{16}O$: 188.12012. Found: 188.12035.

Preparation of compound **23**

Compound **23** was obtained as a yellow oil in 38% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and isopropenylcyclobutane using KOAc as a base, and

stirring for four days at 100 °C (Table 4, entry 29): IR (neat) 2932, 1670, 1605, 1498, 1273, 916, 733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J = 7.5 Hz, CH_3), 1.51 (s, 3H, CH_3), 2.00 (m, 2H, =C-CH_2), 2.50 (s, 3H, $COCH_3$), 3.00 (d, 1H, J = 15.6 Hz, ArCH), 3.15 (d, 1H, J = 15.6 Hz, ArCH), 5.60-5.80 (m, 2H, -CH=CH-), 6.74 (d, 1H, J = 9.0 Hz, ArH), 7.75 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.43, 25.28, 26.51, 26.69, 41.81, 89.60, 109.17, 125.80, 127.65, 130.51, 130.52, 131.65, 131.94, 163.13, 196.71; HRMS calculated for $C_{15}H_{18}O_2$: 230.13068. Found: 230.13068.

Preparation of compound **25**

Compound **25** was obtained as a yellow oil in 69% isolated yield from the reaction of 2-iodoaniline and isopropenylcyclopropane using Et_3N as a base with PPh_3, and stirring for five days at 100 °C (Table 5, entry 5): IR (neat) 3376, 3028, 2963, 1601, 1485, 1464, 1268, 972, 910, 756 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H, CH_3), 1.70 (d, 3H, J = 7.2 Hz, =C-CH_3), 2.87 (d, 1H, J = 15.6 Hz, ArCH), 2.98 (d, 1H, J = 15.6 Hz, ArCH), 3.71 (br s, 1H, NH), 5.60-5.75 (m, 2H, CH=CH), 6.58-6.73 (m, 2H, ArH), 7.70-7.85 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.86, 26.88, 43.68, 64.14, 109.17, 118.46, 122.34, 124.93, 127.34, 128.09, 137.69, 150.15; HRMS calculated for $C_{12}H_{15}N$: 173.12044. Found: 173.12040.

Preparation of compound **26**

Compound **26** was obtained as a yellow oil in 47% isolated yield from the reaction of 2-iodoaniline and vinylcyclopropane using Et_3N as a base with PPh_3, and stirring for five days at 100 °C (Table 5, entry 10): IR (neat) 3376, 3028, 2963, 1601, 1485, 1268, 972, 910, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (d, 3H, J = 4.8 Hz, =C-CH_3), 2.75 (dd, 1H, J = 15.3 Hz, J = 7.8 Hz, ArCH), 3.14 (dd, 1H, J = 15.3 Hz, J = 7.8 Hz, ArCH), 3.25 (br s, 1H, NH), 4.25 (m, 1H, N-CH), 5.60-5.75 (m, 2H, CH=CH), 6.58-6.73 (m, 2H, ArH), 6.90-7.08 (m, 2H,

ArH) ; ^{13}C NMR ($CDCl_3$) δ 17.85, 36.21, 64.25, 107.47, 120.43, 124.93, 126.70, 128.12, 130.66, 133.50, 145.48; HRMS calculated for $C_{11}H_{13}N$: 159.10480. Found: 159.10510.

Preparation of compound **28**

Compound **28** was obtained as a yellow oil in 77% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and vinylcyclopropane using KOAc as a base, and stirring for four days at 80 °C (Table 6, entry 1): IR (neat) 3032, 2957, 1598, 1493, 1477, 1354, 1186, 910, 758, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (d, 3H, J = 6.3 Hz, =C-CH_3), 2.37 (s, 3H, ArCH_3), 2.62 (dd, 1H, J = 15.9 Hz, J = 9.6 Hz, ArCH), 2.96 (dd, 1H, J = 15.9 Hz, J = 9.6 Hz, ArCH), 4.75 (m, 1H, N-CH), 5.80-5.85 (m, 2H, CH=CH), 7.04 (m, 2H, ArH), 7.22 (m, 3H, ArH), 7.62 (q, 3H, J = 8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 17.72, 21.63, 35.47, 63.78, 116.78, 124.45, 125.18, 127.16, 127.25, 129.56, 129.72, 130.82, 131.58, 135.72, 141.46, 143.81; HRMS calculated for $C_{18}H_{19}NO_2S$: 313.1136. Found 313.1132.

Preparation of compound **29**

Compound **29** was obtained as a yellow oil in 61% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and isopropenylcyclopropane using KOAc as a base, and stirring for four days at 100 °C (Table 6, entry 7): IR (neat) 3032, 2957, 2871, 1599, 1479, 1360, 1230, 1100, 910, 733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.72 (dd, 3H, J = 6.3 Hz, J = 1.2 Hz, =C-CH_3), 1.83 (s, 3H, CH_3), 2.44 (s, 3H, ArCH_3), 3.01 (d, 1H, J = 15.9 Hz, ArCH), 3.15 (d, 1H, J = 15.9 Hz, ArCH), 5.60- 5.80 (m, 2H, CH=CH), 7.00 (t, 1H, J = 7.2 Hz, ArH), 7.12-7.32 (m, 4H, ArH), 7.65 (d, 1H, J = 8.4 Hz, ArH), 7.80 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 17.88, 21.59, 26.26, 45.17, 71.61, 114.19, 122.75, 124.95, 125.05,

127.15, 127.73, 128.42, 129.31, 134.27, 139.12, 142.00, 143.30; HRMS calculated for $C_{20}H_{23}NO_2S$: 341.14496. Found 341.14536.

Preparation of compound **30**

Compound **30** was obtained as a yellow oil in 37% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 1-cyclopropyl-1-phenylethene using KOAc as a base, and stirring for six days at 100 °C (Table 6, entry 12): IR (neat) 3032, 2926, 1599, 1478, 1356, 1168, 910, 733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.86 (dd, 3H, J = 7.8 Hz, J = 1.5 Hz, =C-CH_3), 2.35 (s, 3H, ArCH_3), 3.34 (d, 1H, J = 16.2 Hz, ArCH), 3.65 (d, 1H, J = 16.2 Hz, ArCH), 5.82 (m, 1H, =CH-), 6.30 (d, 1H, J = 15.6 Hz, -CH=), 7.00-7.80 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.88, 21.55, 34.33, 68.59, 109.88, 115.92, 121.44, 123.99, 124.75, 126.80, 127.13, 127.28, 127.61, 129.41, 129.53, 131.52, 134.92, 135.40, 142.26, 143.62.

Preparation of compound **31**

Compound **31** was obtained as a yellow oil in 38% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 1-methyl-1-vinylcyclopropane using KOAc as a base, and stirring for three days at 100 °C (Table 6, entry 16): IR (neat) 3030, 2926, 1600, 1478, 1462, 1354, 1180, 910, 733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3H, CH_3), 1.59 (d, 3H, J = 6.6 Hz, =C-CH_3), 2.35 (s, 3H, ArCH_3), 2.65 (dd, 1H, J = 16.2 Hz, J = 9.9 Hz, ArCH), 3.00 (dd, 1H, J = 16.2 Hz, J = 9.9 Hz, ArCH), 5.60 (q, 1H, J = 5.7 Hz, =CH-), 7.00 (m, 2H, ArH), 7.19 (t, 3H, J = 8.1 Hz, ArH), 7.60 (d, 2H, J = 8.4 Hz, ArH), 7.65 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 11.33, 13.19, 21.53, 34.33, 68.59, 115.93, 121.45, 123.99, 124.75, 127.14, 127.62, 129.42, 131.52, 134.92, 135.41, 142.26, 143.62; HRMS calculated for $C_{19}H_{21}NO_2S$: 327.12970. Found: 327.12931.

Preparation of compound **32**

Compound **32** was obtained as a yellow oil in 60% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and isopropenylcyclobutane using KOAc as a base, and stirring for four days at 100 °C (Table 6, entry 19): IR (neat) 3028, 2968, 1601, 1478, 1462, 1360, 1216, 1186, 1032, 760 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H, J = 7.5 Hz, CH_3), 1.94 (s, 3H, CH_3), 2.10-2.20 (m, 2H, =C-CH_2-), 2.54 (s, 3H, $ArCH_3$), 3.12 (d, 1H, J = 15.6 Hz, ArCH), 3.27 (d, 1H, J = 15.6 Hz, ArCH), 5.70-5.95 (m, 2H, CH=CH), 7.10-7.43 (m, 5H, ArH), 7.74 (m, 1H, ArH), 7.91 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 13.47, 21.43, 21.59, 25.34, 43.28, 71.66, 114.19, 122.71, 124.95, 127.13, 127.74, 128.42, 129.33, 131.75, 132.03, 139.09, 142.00, 143.39; HRMS calculated for $C_{20}H_{23}NO_2S$: 341.14496. Found: 341.14482.

General procedure for the palladium-catalyzed reactions of 2-iodoaniline with 1,4-dienes

Palladium acetate (0.006 g, 0.025 mmol), the base (1.75 mmol), the aryl halide (0.5 mmol) and *n*-Bu_4NCl (0.139 g, 0.5 mmol) were weighed into a 1 dram vial equipped with a magnetic stirring bar and septum inlet, and DMF (1 ml) and the diene (2.5 mmol) were added sequentially via syringe. Stirring was continued at 100 °C for the required amount of time. The reaction mixture was diluted with ether (20 ml), washed with saturated ammonium chloride (3 x 20 ml) and dried over $MgSO_4$. The reaction mixture was filtered, concentrated and purified by flash column chromatography using hexanes-ethyl acetate. The following compounds were obtained using the above procedure.

Preparation of compound **33**

Compound **33** was obtained as the yellow oil in 69% isolated yield from the reaction of 2-iodoaniline and *trans*-1,4-hexadiene using K_2CO_3 as a base and stirring for 1.5 days at 100

°C (Table 7, entry 1): IR (neat) 3406, 3017, 2926, 2854, 1607, 1585, 1483, 1340, 1310, 1111, 966, 746 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.71 (d, 3H, J = 6.3 Hz, =C-CH_3), 1.75-1.80 (m, 1H, CH), 1.94 (m, 1H, CH), 2.77 (m, 2H, $ArCH_2$), 3.78 (m, 2H, N-CH and NH), 5.50 (ddq, 1H, J = 16.8 Hz, J = 7.2 Hz, J = 1.2 Hz, -CH=), 5.66 (m, 1H, =CH-), 6.47 (d, 1H, J = 7.8 Hz, ArH), 6.60 (td, 1H, J = 7.2 Hz, J = 0.6 Hz, ArH), 6.95 (d, 2H, J = 7.5 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 17.68, 25.98, 28.53, 53.87, 113.92, 116.86, 120.90, 126.28, 126.69, 129.12, 133.72, 144.23; HRMS calculated for $C_{12}H_{15}N$: 173.12045. Found: 173.12044.

Preparation of compound **34**

Compound **34** was obtained as the yellow oil in 70% isolated yield from the reaction of 2-iodoaniline and 3-methyl-1,4-pentadiene using K_2CO_3 as the base and stirring for 1.5 days at 100 °C (Table 7, entry 11): IR (neat) 3396, 2663, 2926, 1607, 1585, 1501, 1483, 1313, 1261, 918, 764, 716 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3H, CH_3), 1.74 (m, 2H, CH_2), 2.63 (t, 2H, J = 7.5 Hz, $ArCH_2$), 3.76 (br s, 1H, NH), 5.01 (d, 1H, J = 10.5 Hz, =CH, H trans to the ring), 5.06 (d, 1H, J = 17.1 Hz, =CH, H cis to the ring), 5.83 (dd, 1H, J = 17.1 Hz, J = 10.5 Hz, CH=), 6.49 (d, 1H, J = 7.8 Hz, ArH), 6.58 (t, 1H, J = 7.5 Hz, ArH), 6.93 (t, 2H, J = 5.7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 24.21, 28.43, 33.03, 53.61, 112.72, 113.59, 116.55, 120.16, 126.72, 129.05, 143.71, 144.43; HRMS calculated for $C_{12}H_{15}N$: 173.12045. Found: 173.12023.

Preparation of compound **35**

Compound **35** was obtained as the yellow oil in 52% isolated yield from the reaction of 2-iodoaniline and 2-methyl-1,4-pentadiene using Na_2CO_3 as the base and stirring for two days at 100 °C (Table 7, entry 17): IR (neat) 3411, 2940, 2854, 1607, 1483, 1275, 1117, 910,

733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.81 (s, 3H, CH_3), 1.87 (m, 1H, CH), 2.0 (m, 1H, CH), 2.78 (m, 2H, $ArCH_2$), 3.80 (dd, 1H, J = 8.7 Hz, J = 3.3 Hz, N-CH), 3.82 (br s, 1H, NH), 4.89 (s, 1H, =CH), 5.02 (s, 1H, =CH), 6.52 (d, 1H, J = 8.1 Hz, ArH), 6.62 (t, 1H, J = 7.2 Hz, ArH), 6.96 (t, 2H, J = 5.7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 18.77, 26.03, 26.75, 57.14, 110.97, 113.79, 116.83, 120.84, 126.73, 129.06, 144.52, 147.34; HRMS calculated for $C_{12}H_{15}N$: 173.12045. Found: 173.12030.

Preparation of compound **36**

Compound **36** was obtained as a yellow oil in 63% isolated yield from the reaction of 2-iodoaniline and 1,4-pentadiene using K_2CO_3 as the base and stirring for 3.5 days at 100 °C (Table 7, entry 19): IR (neat) 3408, 3011, 2930, 2854, 1605, 1587, 1502, 1403, 1312, 1275, 1217, 926, 754 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.78 (m, 1H, CH), 1.99 (m, 1H, CH), 2.76 (m, 2H, $ArCH_2$), 3.85 (m, 2H, N-CH and NH), 5.12 (d, 1H, J = 10.2 Hz, -CH=, H trans to the ring), 5.24 (d, 1H, J = 16.8 Hz, =CH, H cis to the ring), 5.90 (ddd, 1H, J = 16.8 Hz, J = 10.2 Hz, J = 6.6 Hz, -CH=, H cis to the ring), 6.51 (d, 1H, J = 7.5 Hz, ArH), 6.62 (t, 1H, J = 7.2 Hz, ArH), 6.97 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 25.88, 28.08, 54.23, 113.99, 114.94, 117.03, 120.87, 128.79, 129.15, 140.70, 144.02; HRMS calculated for $C_{11}H_{13}N$: 159.10480. Found: 159.10509.

REFERENCES

1. Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

2. Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 14.

3. Posner, G. M. *Chem. Rev.* **1986**, *86*, 831.

4. Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1989**, *111*, 7285.

5. Piers, E. *Pure. Appl. Chem.* **1988**, *60*, 107.

6. Trost, B. M.; Mignani, S.; Seoane, P.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, *111*, 7489.

7. Zhang, Y.; O'Connor, B.; Neigishi, E. *J. Org. Chem.* **1988**, *53*, 5590.

8. (a) Ciganek, E. *Organic Reactions* **1984**, *32*, 1. (b) Paquette, L. A. *Topics in Current Chem.* **1984**, *119*, 1. (c) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855.

9. Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.

10. (a) Stork, G.; Borch, R. *J. Am. Chem. Soc.* **1964**, *86*, 935. (b) Stork, G.; Rosen, P.; Goldman, R. V.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275. (c) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (d) Stork, G.; Angelo, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 7114. (e) Kametani, J.; Nemoto, H. *Heterocycles* **1978**, *10*, 349.

11. Ghera, E.; Ben-David, Y. *J. Org. Chem.* **1985**, *50*, 3355.

12. Ghera, E.; Maurya, R.; Ben-David, Y. *J. Org. Chem.* **1988**, *53*, 1912.

13. Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1985**, *26*, 6253.

14. For representative papers; (a) Eisenhuth, W.; Renfroe, H. B.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 375. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 179. (c) Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162. (d) Kraus, G.; Dodd, J. H.; Weinrub, S. M. *Tetrahedron Lett.* **1979**, 3593.

15. Curran, D. P.; Chen, M. H.; Spletzer, E.; Seong, C.; Chang, C. *J. Am. Chem. Soc.* **1989**, *111*, 8872.

16. Curran, D. P.; Seong, C. *J. Am. Chem. Soc.* **1990**, *112*, 9401.

17. Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127.

18. Flynn, D. F.; Zabrowski, D. L. *J. Org. Chem.* **1990**, *55*, 3673.

19. Heck, R. F. *Palladium Reagents in Organic Synthesis*, Academic Press, London, **1985**.

20. Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4837.

21. Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5542.

22. Larock, R. C.; Takagi, K. *J. Org. Chem.* **1984**, *49*, 2701.

23. Larock, R. C.; Varaprath, S. *J. Org. Chem.* **1984**, *49*, 3432.

24. Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882.

25. Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615.

26. Fried, C. A. Ph. D. Dissertation, Iowa State University, **1989**.

27. Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636.

28. *Comprehensive Heterocyclic Chemistry*, Pergamon Press, New York, **1984**, Vol 1-8.

29. Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274.

30. Larock, R. C.; Harrison, L. W.; Hsu, M. H. *J. Org. Chem.* **1984**, *49*, 3662.

31. (a) Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1987**, *28*, 4977. (b) Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1988**, *29*, 6399.

32. (a) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, 29, 2927. (b) Stork, G.; Poirier, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 1073.

33. Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964.

34. Trost, B. M.; Lynch, J. K.; Angle, S. R. *Tetrahedron Lett.* **1987**, *28*, 37.

35. Wershofen, S.; Scharf, H. D. *Synthesis* **1988**, 854.

36. Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516.

37. Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930.

38. Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881.

39. Trost, B. M.; Romero, G. A. *J. Org. Chem.* **1986**, *51*, 2332.

40. Yamamoto, K.; Ishida, J.; Tsuji, J. *Chem Lett.* **1987**, 1157.

42. Larock, R. C. ; Berrios-Peña, N. G.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447.

43. Berrios-Peña, N. G., Ph. D. Dissertation, Iowa State University, **1989**.

44. Ratcliff, J. *J. Chem. Soc.* **1951**, 1140.

45. McKillop, A; Hunt, J. D.; Zelesko, M. J.; Fowler, J. S.; Taylor, E. C.; McGillvaray, G.; Klenzle, F. *J. Am. Chem. Soc.* **1976**, *93*, 4841.

46. Harrison, L. W. Ph. D. Dissertation, Iowa State University, **1984**.

47. Crawford, R. J.; Cameron, D. M. *Can. J. Chem.* **1967**, *45*, 691.

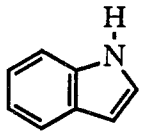
48. Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

49. Schreiber, F. G.; Stevenson, R. *J. Chem. Soc., Perkin Trans. I* **1977**, 90.

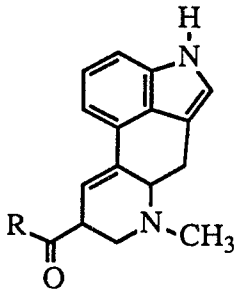
PART III. INDOLE SYNTHESIS VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

INTRODUCTION

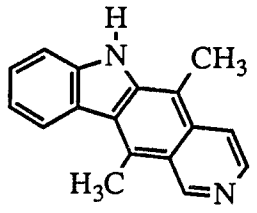
The indole nucleus is prevalent in a wide variety of biologically active natural and unnatural compounds.[1] The synthesis and functionalization of indoles have been the objects of research for over one hundred years. Among the most recent synthetic targets have been the pharmacologically active ergot alkaloids,[2] the antitumor agents ellipticine[3] and mitomycin C,[4] and the considerably more complex "dimeric" indole alkaloids, such as vincristine and vinblastine.



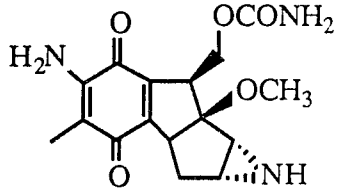
Indole



Ergot alkaloids



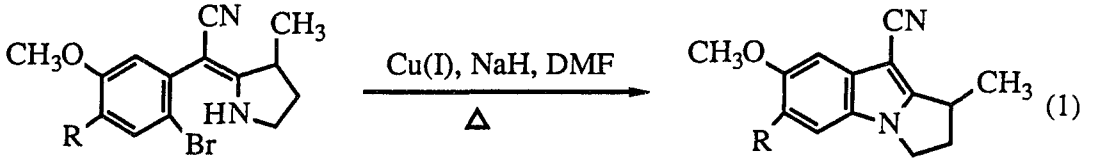
Ellipticine



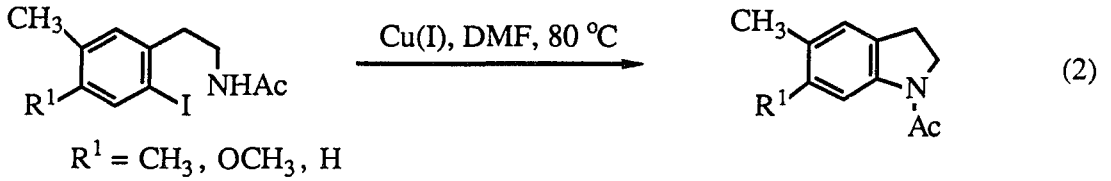
Mitomycin C

Until very recently, indole syntheses relied primarily on well-established methods such as the Fischer indole synthesis, the Madelung cyclization of *N*-acyl-*o*-toluidines, the reductive cyclization of *o*-nitrobenzyl ketones, the Batcho-Leimgruber synthesis of indoles from *o*-nitrotoluenes and dimethylformamide acetal, and the Gassman synthesis of indoles from *N*-haloanilines.[5] All of these approaches involve "classic" organic synthetic methodology and display typical "organic" reactivity patterns and selectivities. With the advent and continuing refinement of transition metal-mediated organic synthetic methodology,[6] a number of new and potentially versatile methods for both the synthesis and functionalization of indoles have been developed. In this review, a discussion pertaining to organometallic approaches to the indole ring system will be covered in detail.

The use of organotransition metal complexes in the synthesis of heterocyclic compounds has become prevalent in recent years. Copper(I) salts have been used in the cyclization of *o*-haloarylenamines which affords indoles in excellent yields (eq. 1).[7,8] Under similar conditions, *o*-haloacetamides also can be cyclized to the corresponding indole derivatives (eq. 2).[9]



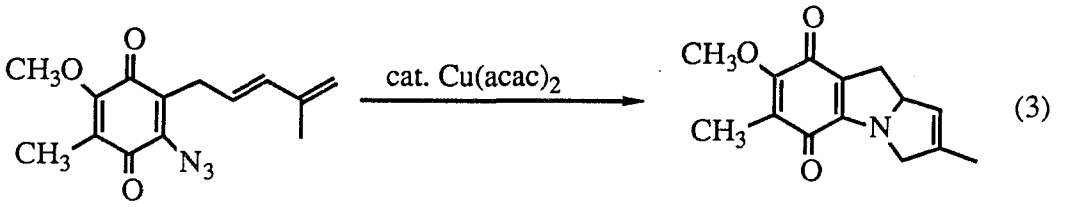
(1)



(2)

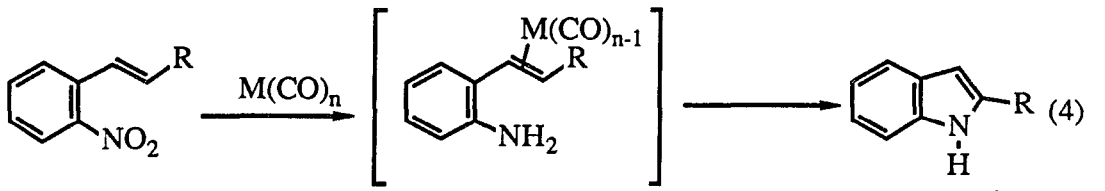
$R^1 = CH_3, OCH_3, H$

The copper-catalyzed decomposition of aryl azides to produce nitrenes has been used to synthesize a number of pyrroloindolequinones (eq. 3).[10]



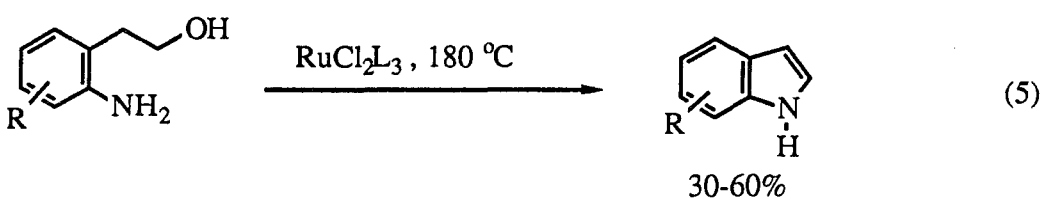
(3)

A number of indole syntheses utilize low-valent transition metals to reduce aromatic nitro groups to amines, which can then be cyclized with electrophilic groups in the ortho position to form indoles. Specifically, *o*-nitrostyrenes have been reductively cyclized to indoles by metal carbonyls, a process which must involve olefin activation by the metal, as well as nitro group reduction (eq. 4).[11]

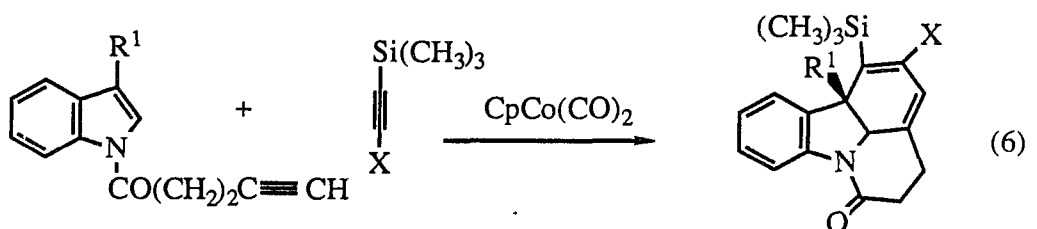


R = H, CH_3, Ph, CO_2CH_3
$M(CO)_n$ = $Fe(CO)_5$, $Ru_3(CO)_{12}$, $Rh_6(CO)_{16}$

Ruthenium(II) chloride has also been used to cyclize *o*-amino-β-phenylethanols to form indoles in modest yield, although the conditions are somewhat severe (eq. 5).[12]

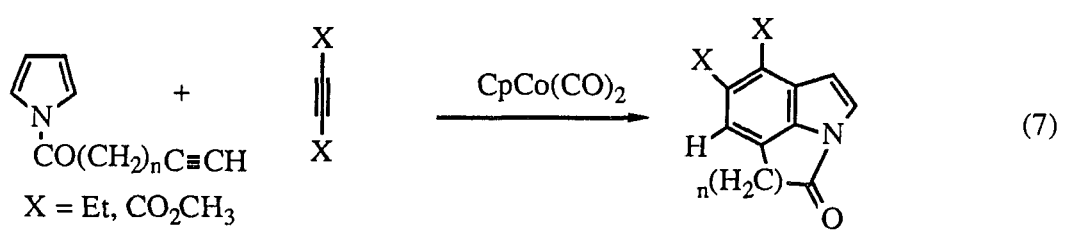


The cobalt(I)-catalyzed cyclotrimerization of alkynes and alkenes has been extensively developed for the synthesis of indoles (eqs. 6 and 7).[13,14] Arenes readily form



R^1 = H, CH_3, $(CH_2)_2NHAc$, $(CH_2)_2Si(CH_3)_3$
X = CO_2CH_3, OCH_3

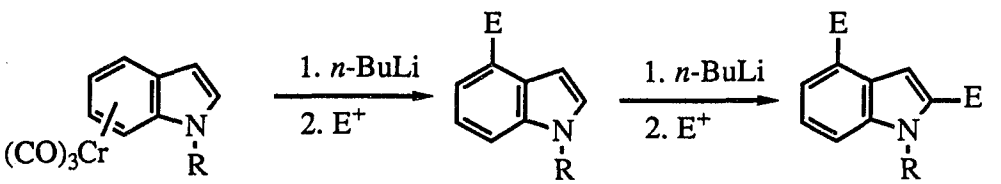
30-60%



X = Et, CO_2CH_3

η^6-complexes with chromium hexacarbonyl usually by simply heating the two reagents together. Once complexed to the chromium tricarbonyl fragment, the arene becomes reactive

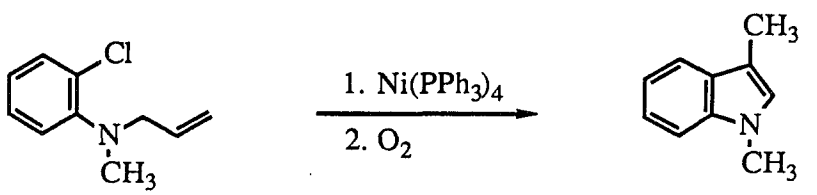
towards nucleophilic attack. This feature has been used to introduce functionality at normally unreactive positions of the indole ring system (eq. 8).[15,16]



(8)

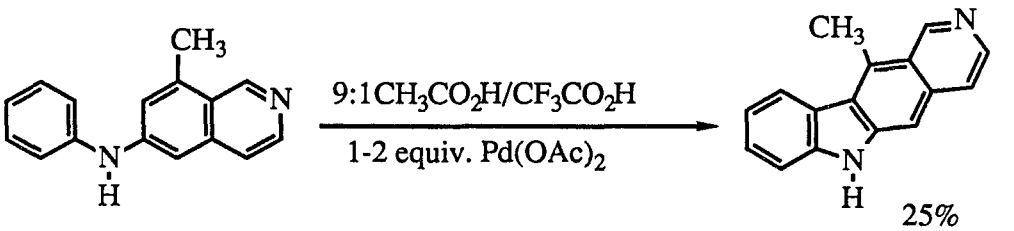
R = CH_3, $Si(CH_3)_3$
E = $Si(CH_3)_3$, CO_2Et

Nickel(0) complexes have been used to cyclize *N*-methyl-*N*-allyl-2-chloroaniline to 1,3-dimethylindole (eq. 9).[17,18] However, the poor yields of the desired product and the formation of side products render this approach unattractive.



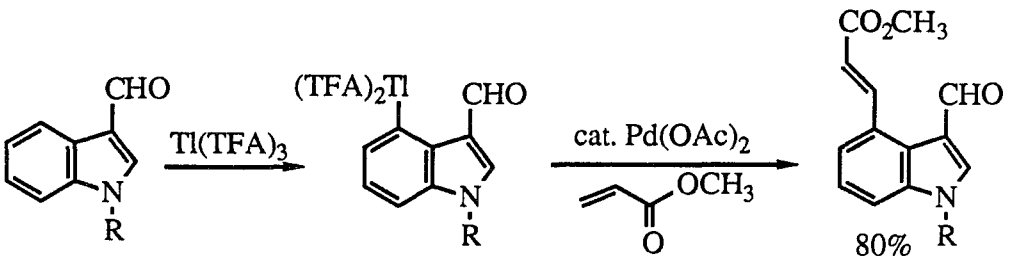
(9)

A wide variety of palladium-mediated organic reactions has been developed and applied to the synthesis of indoles. Palladium exists in two stable oxidation states, palladium(II) and palladium(0), and the chemistry thus differs substantially with regard to both substrate specificity and the types of reaction promoted. Palladium(II) salts are moderate to strong electrophiles, and they activate and complex with π-electron rich organic compounds. Arenes, for example, can be directly palladated by $Pd(OAc)_2$ or $Pd(O_2CCF_3)_2$, forming σ-arylpalladium(II) complexes. Although the coupling of arenes by direct palladation is not an efficient process, it has been used to synthesize functionalized indole ring systems (eq. 10).[19]



(10)

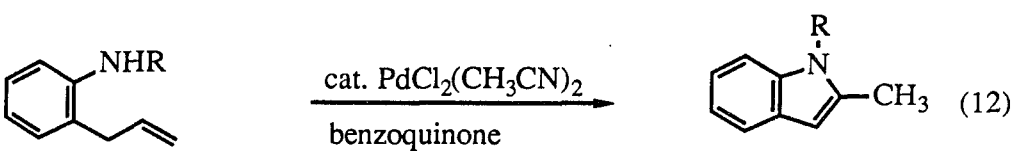
Palladium(II) is also an efficient catalyst for the olefination and alkylation of thallated indoles via a transmetallation-insertion-elimination process (eq. 11).[20] This is a synthetically



(11)

important reaction for ergot alkaloid synthesis, since these alkaloids require substitution in the normally unreactive 4-position of the indole ring system.

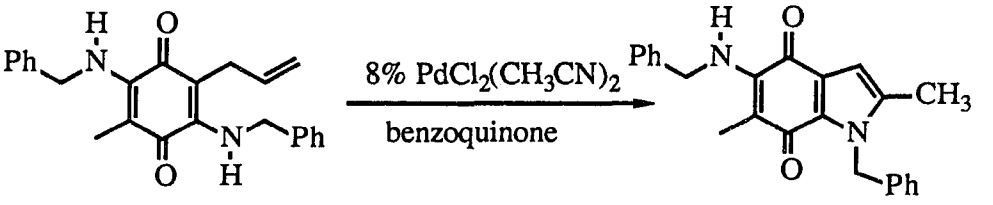
o-Allylanilines are efficiently converted into 2-methylindoles using a palladium(II) catalyst with benzoquinone as a reoxidant (eq. 12).[21] This is a typical example of the palladium-mediated intramolecular amination of an olefin. This process has been used in the



(12)

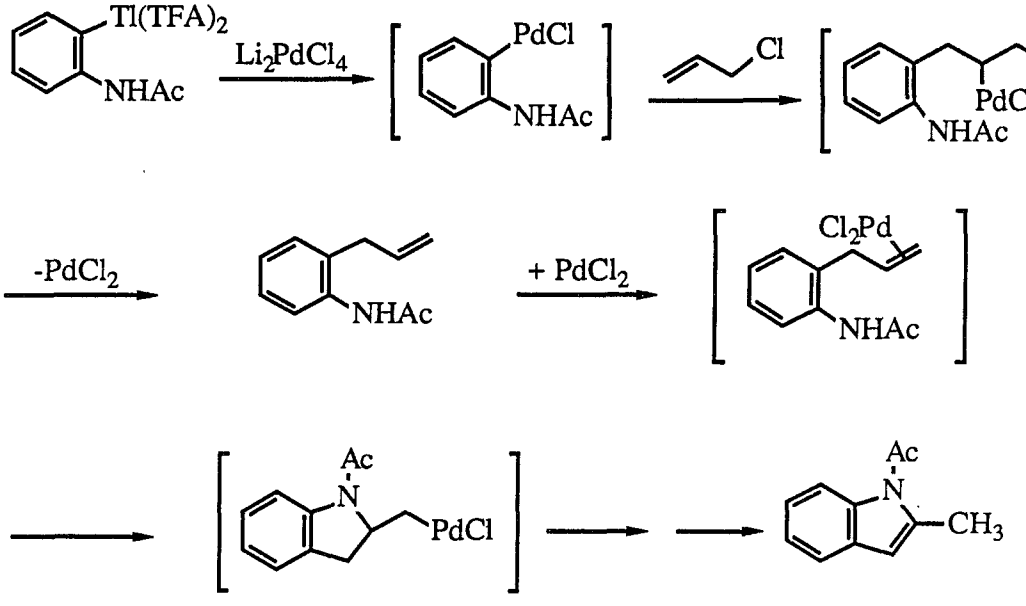
R = H, CH_3, Ac

synthesis of pyrroloindolequinones, a class of compounds which are related to mitomycin (eq. 13).[22]



(13)

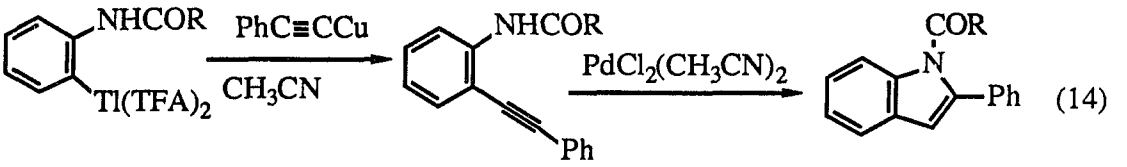
In addition, 2-methylindole derivatives are readily produced in a stoichiometric reaction involving transmetalation, insertion, elimination, and amination of olefins (Scheme 1).[23] In



Scheme 1

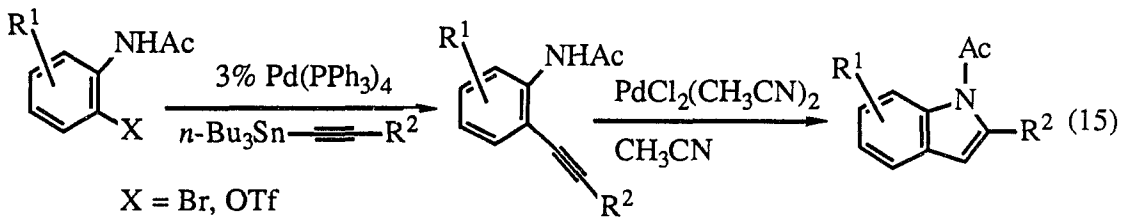
contrast to alkenes, alkyne amination mediated by palladium(II) is much less common, primarily because of the facile alkyne oligomerization reactions which tend to occur .

The palladium-catalyzed cyclization of 2-acetamido tolanes has been shown to yield 2-phenylindoles.[24] The preparation of 2-acetamido tolanes was achieved via ortho-thallation of acetanilide and coupling with alkynyl copper reagents (eq. 14).



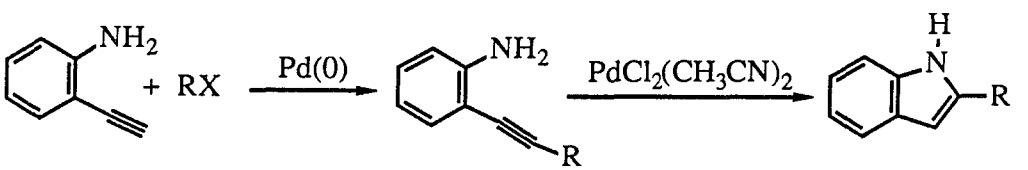
(14)

The palladium-catalyzed coupling reaction of organostannanes with aryl halides or triflates takes place under mild reaction conditions in the presence of a wide variety of functionality on either coupling partner.[25] A variety of alkynylanilines can thus be synthesized. They can be subsequently converted to the corresponding indoles by palladium dichloride (eq. 15).



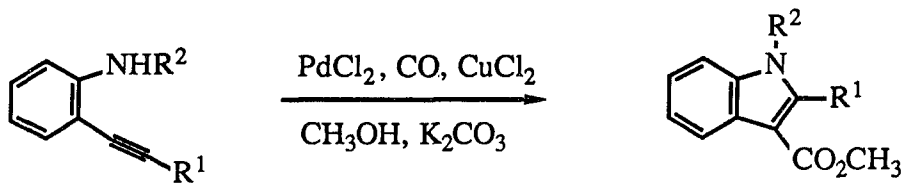
(15)

The palladium(0)-catalyzed coupling of aryl and vinylic triflates or halides with the readily available 2-ethynylaniline, followed by a palladium(II)-catalyzed cyclization step, provides another efficient and very versatile procedure for the synthesis of functionalized, 2-substituted indoles (eq. 16).[26]



(16)

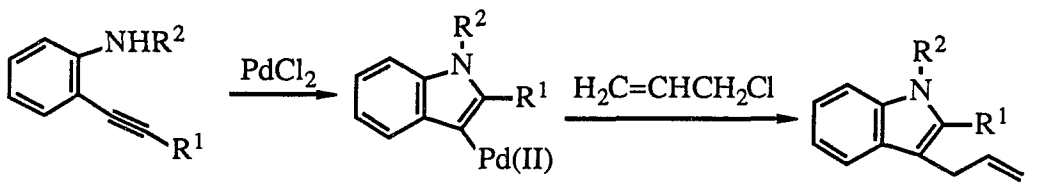
The reaction of 2-(1-hexynyl)aniline with carbon monoxide in methanol under basic conditions can be promoted by the catalytic action of palladium dichloride to give an indole ester (eq. 17).[27]



(17)

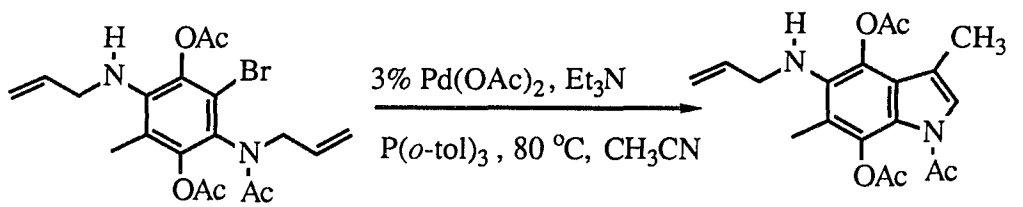
$R^1 = n\text{-Bu}$; $R^2 = SO_2CH_3$, H

The palladium(II)-catalyzed reaction of *N*-carbomethoxy-2-(1-alkynyl)anilines with allyl chloride produces *N*-carbomethoxy-2-alkyl-3-allylindoles (eq. 18).[28]



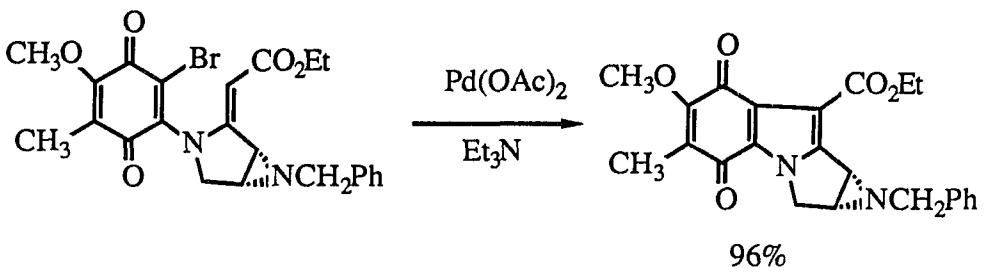
(18)

While palladium(II) salts are electrophilic reagents which react with olefins and arenes, palladium(0) complexes are strong nucleophiles and are most reactive towards organic halides. Palladium(0)-catalyzed cyclizations leading to indoles have also been very widely studied. *o*-Haloanilines are easily *N*-allylated, producing substrates ideally suited for a palladium(0)-catalyzed oxidative addition-olefin insertion approach to the indole ring system (eq. 19).[29]



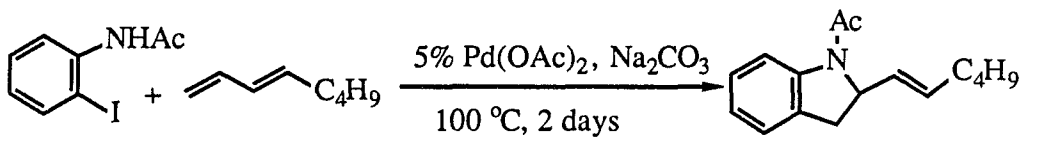
(19)

Mitomycin analogues have been prepared very efficiently by this type of palladium(0)-catalyzed intramolecular cyclization (eq. 20).[30]



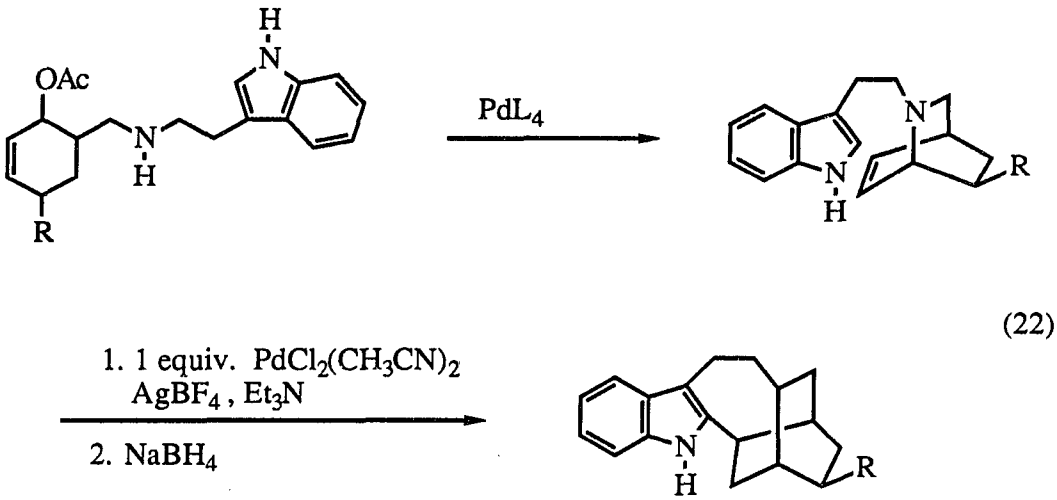
(20)

Formation of the indole ring via π-allylpalladium intermediates has been studied extensively by Larock et al. (eq. 21).[31]



(21)

π-Allylpalladium intermediates are commonly used to elaborate existing indole ring systems. For example, the isoquinuclidine ring of ibogamine has been also synthesized by palladium(0)-catalyzed allylic amination (eq. 22).[32] Because of the potent biological activity



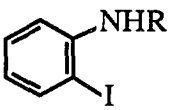
(22)

exhibited by various indole derivatives, the methods for rapid construction of the indole ring system have attracted considerable attention in recent years.

With these promising earlier results in mind, our research has been focused primarily on developing novel synthetic methodology for the synthesis of 2,3-disubstituted indoles via palladium-catalyzed heteroannulation of internal alkynes by 2-iodoaniline and its derivatives. With this methodology, we hoped to be able to synthesize a wide variety of indole derivatives, including biologically active substrates.

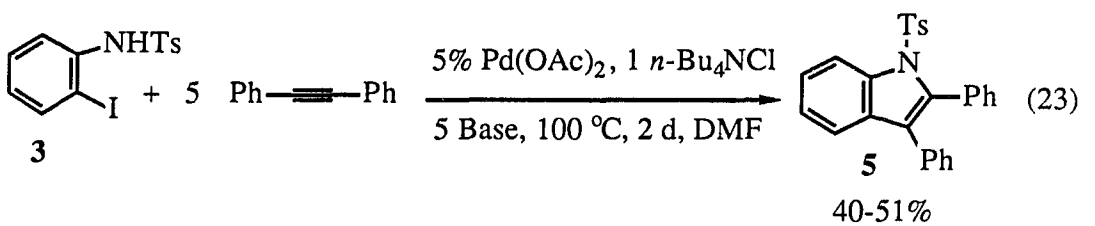
RESULTS AND DISCUSSION

2-Iodoaniline and its derivatives have been examined extensively for the annulation of internal alkynes under palladium catalysis.



R = H (**1**), Ac (**2**), Ts (**3**), Me (**4**)

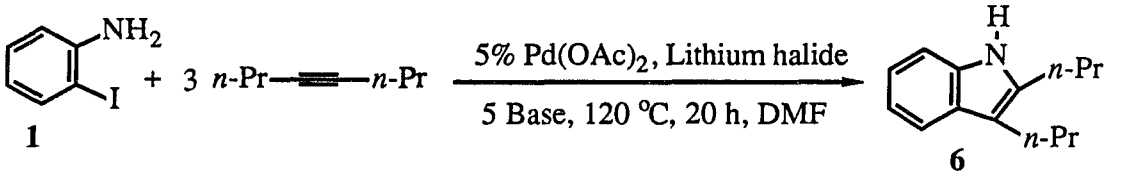
Initial studies were aimed at finding a set of general reaction conditions for our palladium-catalyzed annulation process. The reaction between *N*-tosyl-2-iodoaniline and diphenylacetylene was chosen for the initial model study (eq. 23). Results from our preliminary



3 **5** 40-51% (23)

study showed that reactions using KOAc, NaOAc, Na_2CO_3, K_2CO_3, and Et_3N as bases all gave similar yields. Also, reactions using 10 ml of DMF afforded cleaner products than those using 2 ml of DMF when the reaction was run on a 0.5 mmol scale, although a longer reaction time was needed to complete the reactions. In addition, the reactions using *n*-Bu_4NCl were very sensitive with respect to the purity of the salt. Several different companies' *n*-Bu_4NCl showed different yields and required different reaction times. To overcome this difficulty, the reactions of 2-iodoaniline with 4-octyne utilizing lithium halides were investigated with several bases. The results are summarized in Table 1.

Table 1. Palladium-catalyzed reaction of 2-iodoaniline with 4-octyne using different lithium halides.



1 6

Entry[a]	Lithium species		Base	5% PPh_3	% Isolated yield	Comments
1	2	LiCl	KOAc	–	56	-
2	2	LiCl	KOAc	+	36	-
3	1	LiCl	KOAc	–	80	-
4	3-5	LiCl	KOAc	–	0	very slow reaction
5[b]	1	LiCl	KOAc	–	0	only aryl halide recovered
6[b]	1	LiCl	KOAc	+	0	only aryl halide recovered
7	1	LiCl	KOAc	+	40	some multiple-insertion products
8	1	LiBr	KOAc	–	0	only multiple-insertion products
9	1	LiI	KOAc	–	26	some multiple-insertion products
10	-	none	KOAc	–	36	no side product
11[b]	1	LiCl	K_2CO_3	–	80	-
12	1	LiCl	K_2CO_3	–	60	some multiple-insertion products
13[b]	1	LiCl	K_2CO_3	+	0	aryl halide recovered
14	1	LiCl	K_2CO_3	+	60	some multiple-insertion products
15	2	LiCl	K_2CO_3	+	0	very slow reaction
16	2	LiCl	K_2CO_3	–	68	-
17	1	LiBr	K_2CO_3	–	60	-
18	1	LiI	K_2CO_3	–	70	-
19	-	none	K_2CO_3	–	46	some multiple-insertion products

[a]All reactions were run on a 0.25 mmol scale.

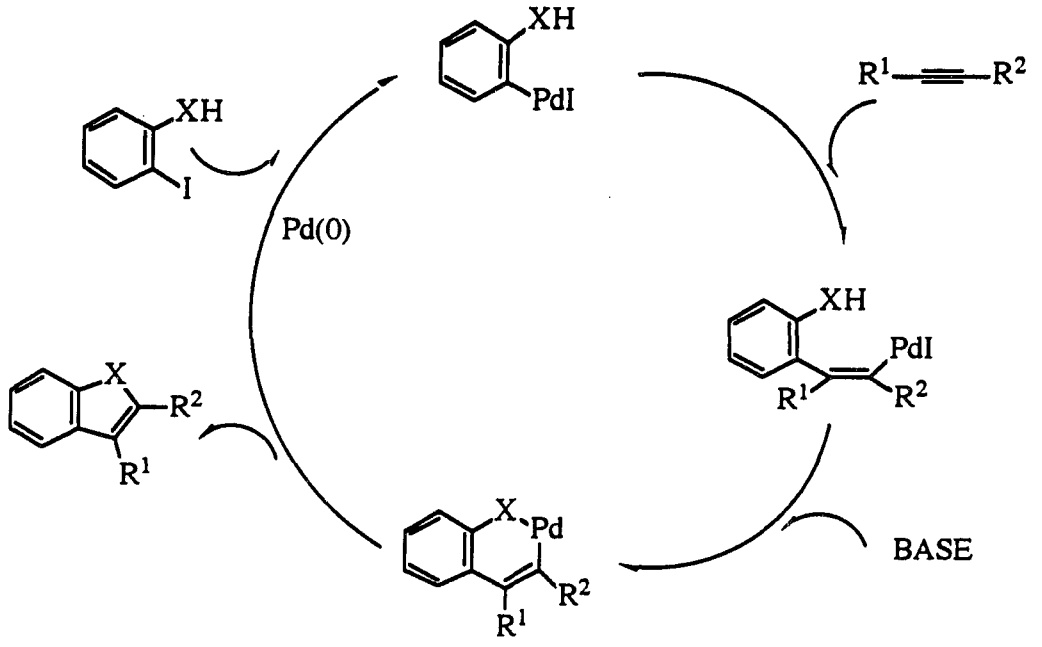
[b]The reaction was run at 100 °C.

Table 1. (continued)

Entry[a]	Lithium species		Base	5% PPh_3	% Isolated yield	Comments
20	2	LiCl	Na_2CO_3	–	50	-
21	1	LiCl	Na_2CO_3	–	46	-
22	2	LiCl	Na_2CO_3	+	44	-
23	1	LiBr	Na_2CO_3	–	0	only multiple-insertion products
24	1	LiI	Na_2CO_3	–	20	some multiple-insertion products
25	1	LiCl	NaOAc	–	38	-
26	1	LiCl	NaOAc	+	42	-
27[b]	1	LiCl	NaOAc	–	0	only multiple-insertion products
28	1	LiBr	NaOAc	–	0	only multiple-insertion products

In general, reactions employing LiCl as the chloride source were very sensitive to the number of equivalents of LiCl used. Increasing the number of equivalents of LiCl slowed down the reaction rate to a significant extent with concomitant formation of multiple-insertion products (entries 1-4). Also, addition of a catalytic amount of PPh_3 not only failed to improve the yield of the desired product, but also led to generation of multiple-insertion products (compare entries 3 and 7). In addition, it was observed that when using LiBr or LiI instead of LiCl, the reactions afforded predominantly multiple insertion products (entries 8 and 9). On the other hand, reactions employing LiBr or LiI with K_2CO_3 as the base gave only the desired product in good yields (entries 17 and 18). The reactions using Na_2CO_3 or NaOAc as the base with lithium halides provided poor yields of the desired product (entries 20-28). In conclusion, the reactions using LiCl seemed to provide higher yields of the desired product and more reproducible results than those using *n*-Bu_4NCl.

A possible mechanistic explanation for this heteroannulation process is presented in Scheme 2. The first step of the mechanism is the oxidative addition of the aryl iodide onto the palladium metal to generate an intermediate arylpalladium species . This intermediate then

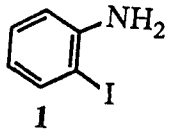
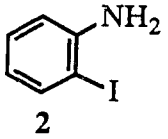
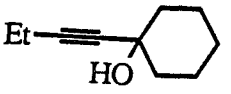
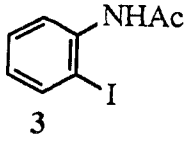
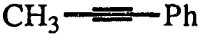


Scheme 2

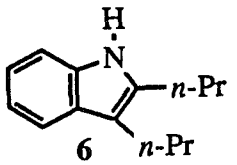
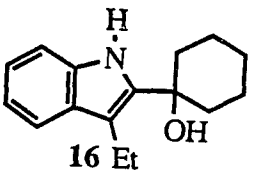
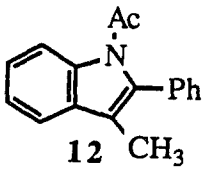
adds to the internal alkyne, generating a vinylpalladium intermediate. Intramolecular nucleophilic attack on the palladium metal leads to the formation of a six-membered ring, nitrogen-containing cyclopalladated intermediate, which subsequently undergoes reductive elimination to afford the desired product.

Since the annulation of internal alkynes was very sensitive to the alkyne concentration, we examined the effect of the number of equivalents of the internal alkyne in the heteroannulation process with several different internal alkynes in the presence of LiCl at 100 ^{o}C. The results are summarized in Table 2. Using 3 or 5 equivalents of the alkyne, the reactions of 2-iodoaniline with 4-octyne provided 80% of the desired product (entries 1 and 2).

Table 2. The effect of equivalents of alkyne used in the heteroannulation process.

Entry[a]	Aryl halide	Equiv. of alkyne	Alkyne	Halide source	Base
1	 1	5		LiCl	K_2CO_3
2		3		LiCl	K_2CO_3
3		2		LiCl	K_2CO_3
4		1		LiCl	K_2CO_3
5	 2	2		LiCl	KOAc
6		1		LiCl	KOAc
7	 3	2	2 	LiCl	KOAc
8		1		LiCl	KOAc

[a]All reactions were run at 100 °C for 1 day.

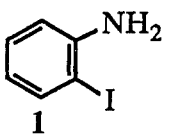
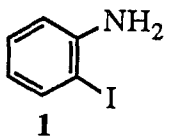
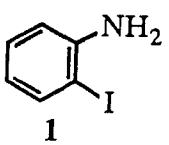
Product	% Isolated yield
 **6**	80
	80
	64
	50
 **16**	85
	51
 **12**	75
	70

However, the identical reactions using 1 and 2 equivalents of 4-octyne afforded only 50 and 64% of the desired product respectively (entries 3 and 4). The reactions of 2-iodoaniline with 1-(1-butynyl)cyclohexanol using 1 and 2 equivalents of the alkyne afforded 51 and 85% isolated yields of the desired product respectively (entries 5 and 6). Finally, the reaction of 2-iodoacetanilide with 1-phenyl-1-propyne using 1 and 2 equivalents of the alkyne provided 70 and 75% yields of the desired product respectively (entries 7 and 8).

From the above results, it can be deduced that the annulation of internal alkynes using more equivalents of the alkyne generally provides higher yields of the desired product, but also increases the chance of forming multiple-insertion products. In addition, it was observed that when using LiBr or LiI instead of LiCl, the reactions afforded predominantly multiple insertion products.

Having gained an understanding of the factors that were influencing the heteroannulation process, a wide variety of alkynes ranging from those bearing alkyl, aryl, and alkenyl groups, to those bearing hydroxyalkyl and silyl groups, were examined. In general, carbonate or acetate bases in the presence or absence of 5% PPh_3 were employed. All of the work was carried out using 5 mol % $Pd(OAc)_2$, 1 equivalent of LiCl or *n*-Bu_4NCl (Lancaster) at 100 ^oC. Only later in this project was the significant difference in yields between *n*-Bu_4NCl and LiCl observed. So not all reactions were run under optimal conditions. The effect of PPh_3 was also not realized during some of the early work. The more volatile the alkyne was, the greater the amount of the alkyne used. In cases where multiple-insertion products were apparently produced, their structures and yields were not determined, primarily because the ^1H and ^{13}C NMR spectra of these compounds were usually very complicated. The results are summarized in Table 3.

Table 3. Palladium-catalyzed reactions of 2-iodoaniline derivatives with internal alkynes

Entry	Aryl halide	Alkyne	Halide source	Base
1[a]	 **1**	2 Ph—≡—Ph	*n*-Bu_4NCl	KOAc
2[a]			*n*-Bu_4NCl	Na_2CO_3
3	 **1**	5 *n*-Pr—≡—*n*-Pr	*n*-Bu_4NCl	K_2CO_3
4[b]			*n*-Bu_4NCl	Na_2CO_3
5[b]			*n*-Bu_4NCl	KOAc
6[c]			LiCl	KOAc
7			LiCl	K_2CO_3
8	 **1**	5 CH_3—≡—$C(CH_3)_3$	*n*-Bu_4NCl	Na_2CO_3
9[d]			LiCl	Et_3N

[a]The reaction provided many products as indicated by TLC and GC analysis.

[b]The reaction provided small amounts of multi-insertion products.

[c]The reaction was run at 120 °C.

[d]The reaction provided multi-insertion product as the major product.

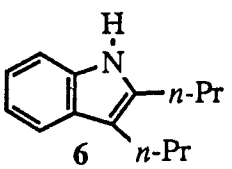
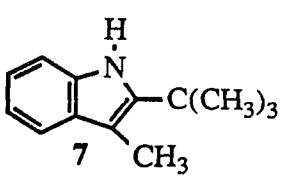
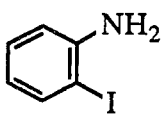
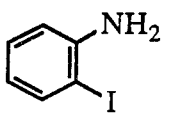
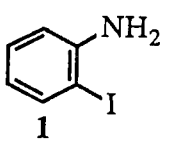
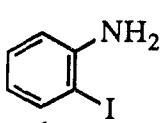
5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	48	-------	0
–	48	--------	0
+	16	 **6**	70
–	16		35
–	16		36
–	20		80
–	20		80
+	24	 **7**	82
+	24		0

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
10[a]	 **1**	2 CH_3—≡—Ph	*n*-Bu_4NCl	KOAc
11[a]			*n*-Bu_4NCl	Na_2CO_3
12[b]	 **1**	5 CH_3—≡— 	*n*-Bu_4NCl	KOAc
13[b]			*n*-Bu_4NCl	K_2CO_3
14[b]			*n*-Bu_4NCl	Na_2CO_3
15[b]			*n*-Bu_4NCl	NaOAc
16[b]			LiCl	K_2CO_3
17[e]	 **1**	5 CH_3—≡—$CH(CH_3)_2$	*n*-Bu_4NCl	K_2CO_3
18[e]			*n*-Bu_4NCl	K_2CO_3
19[e]			LiCl	K_2CO_3
20[e]			LiCl	K_2CO_3
21[e]	 **1**	5 CH_3—≡—CH_2CH_3	*n*-Bu_4NCl	K_2CO_3

[e]The isomer ratio is the actual yield of each isolated produc .

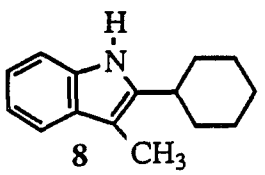
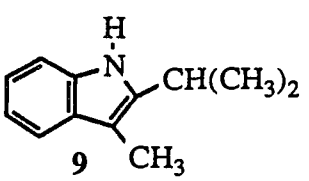
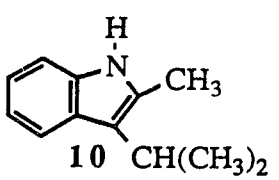
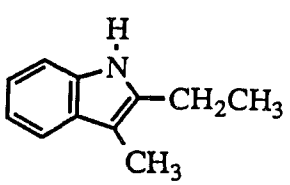
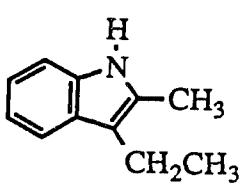
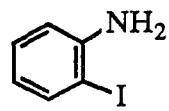
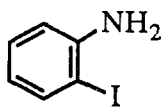
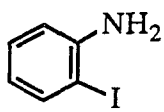
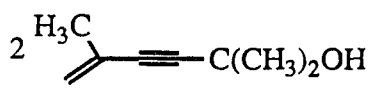
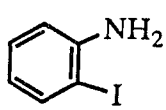
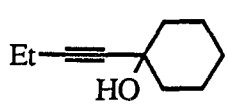
5% PPh_3	Reaction time (h)	Product	% Isolated yield (isomer ratio)
–	24	-----	0
+	24	----	0
–	24	 **8**	57
+	24		30
+	24		55
–	24		40
+	24		56
+	24	 **9**  **10**	87 (62:25)
–	24		84 (59:25)
+	24		85 (62:23)
–	24		76 (60:16)
–	24	 **11**  **12**	63 (1:1)

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
22[f]			*n*-Bu$_4$NCl	K_2CO_3
23[f]			LiCl	K_2CO_3
24[f]			LiCl	K_2CO_3
25	 **1**	2 $CH_3-C\equiv C-C(CH_3)_2OH$	*n*-Bu$_4$NCl	Na_2CO_3
26	 **1**	2 $HO(CH_3)_2C-C\equiv C-C(CH_3)_2OH$	*n*-Bu$_4$NCl	Na_2CO_3
27			*n*-Bu$_4$NCl	KOAc
28	 **1**	2 	*n*-Bu$_4$NCl	Na_2CO_3
29			*n*-Bu$_4$NCl	KOAc
30	 **1**	2 	*n*-Bu$_4$NCl	Na_2CO_3

[f]The isomer ratio was determined by GC and ^{1}H NMR spectroscopy.

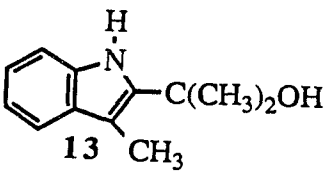
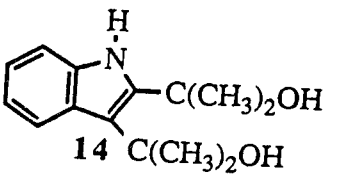
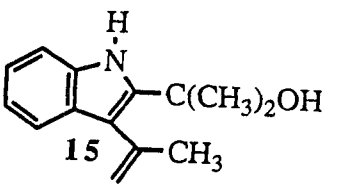
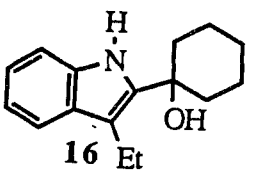
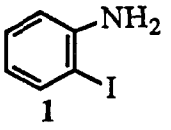
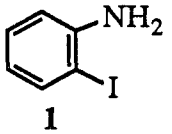
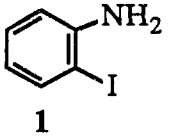
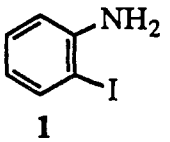
5% PPh_3	Reaction time (d)	Product	% Isolated yield(isomer ratio)
+	24		62 (1.5:1)
+	24		44 (1.5:1)
–	24		30 (1:1)
+	12	 **13**	52
+	72	 **14**	54
–	48		42
+	24	 **15**	67
–	24		70
+	24	 **16**	78

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
31[a]	 1	2 $CH_3-C\equiv C-CH_2CH(CH_3)OH$	*n*-Bu_4NCl	KOAc
32[a]			*n*-Bu_4NCl	Na_2CO_3
33	 1	5 $CH_3-C\equiv C-Si(CH_3)_3$	*n*-Bu_4NCl	Na_2CO_3
34[a]			*n*-Bu_4NCl	NaOAc
35	 1	5 *n*-$Bu-C\equiv C-Si(CH_3)_3$	*n*-Bu_4NCl	Na_2CO_3
36			*n*-Bu_4NCl	NaOAc
37	 1	5 $Ph-C\equiv C-Si(CH_3)_3$	*n*-Bu_4NCl	NaOAc
38[g]			*n*-Bu_4NCl	KOAc
39[g]			*n*-Bu_4NCl	KOAc
40[g]			*n*-Bu_4NCl	Na_2CO_3
41[g]			LiCl	K_2CO_3

[g]The reaction provided 20-30% desilylated coupling product.

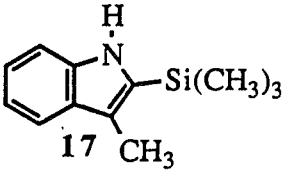
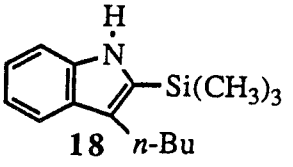
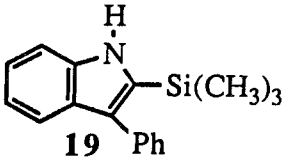
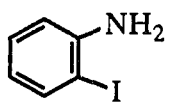
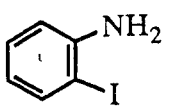
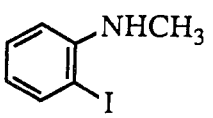
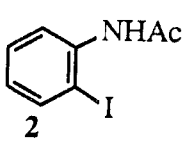
5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	24	-----	0
–	24	------	0
+	24	 **17**	98
–	24	-------	?
–	12	 **18**	81
–	12		81
–	16	 **19**	68
–	16		32
+	16		18
+	16		40
–	16		32

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
42	 **1**	2 $HOCH_2$—≡—$Si(CH_3)_3$	*n*-Bu_4NCl	KOAc
43			*n*-Bu_4NCl	NaOAc
44[d]			*n*-Bu_4NCl	Na_2CO_3
45			*n*-Bu_4NCl	Et_3N
46[b,h]	 **1**	2 $(CH_3)_3Si$—≡—$Si(CH_3)_3$	*n*-Bu_4NCl	Na_2CO_3
47			*n*-Bu_4NCl	NaOAc
48	 **4**	3 *n*-Pr—≡—*n*-Pr	*n*-Bu_4NCl	K_2CO_3
49[b]			*n*-Bu_4NCl	Na_2CO_3
50[d]			*n*-Bu_4NCl	KOAc
51[d]			*n*-Bu_4NCl	NaOAc
52	 **2**	3 *n*-Pr—≡—*n*-Pr	*n*-Bu_4NCl	KOAc

[h]The reaction provided two regioisomers.

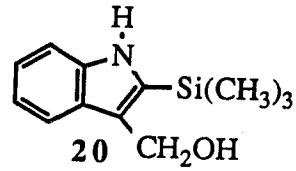
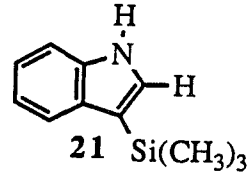
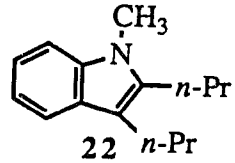
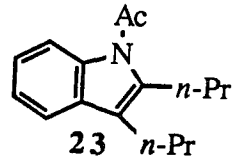
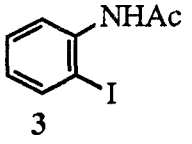
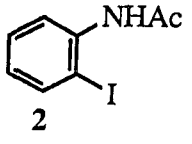
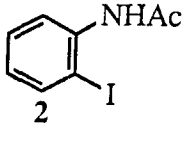
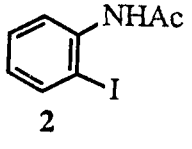
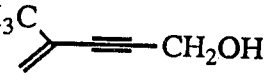
5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	24	 **20**	19
–	24		45
+	24		60
+	24		0
+	20	 **21**	60 [h]
–	20		54
+	24	 **22**	71
+	24		47
–	24		0
–	24		0
–	24	 **23**	91

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
53			*n*-Bu_4NCl	Na_2CO_3
54			*n*-Bu_4NCl	Na_2CO_3
55			*n*-Bu_4NCl	NaOAc
56	 3	2 $CH_3-\equiv-Ph$	*n*-Bu_4NCl	KOAc
57			*n*-Bu_4NCl	NaOAc
58			LiCl	KOAc
59[e]	 2	2 $CH_3-\equiv-CH(CH_3)_2$	*n*-Bu_4NCl	KOAc
60[e]			*n*-Bu_4NCl	NaOAc
61[e]			*n*-Bu_4NCl	Na_2CO_3
62[e]	 2	5 $CH_3-\equiv-CH_2CH_3$	LiCl	K_2CO_3
63[e]			LiCl	K_2CO_3
64	 2	2 	*n*-Bu_4NCl	Na_2CO_3

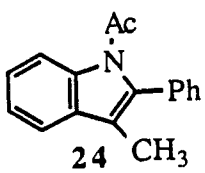
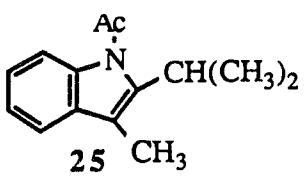
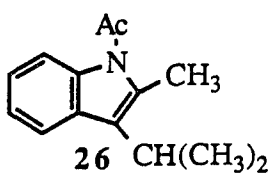
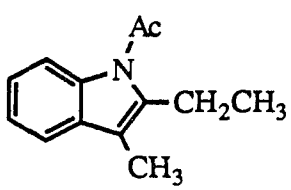
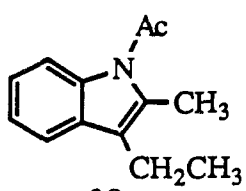
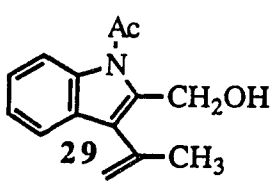
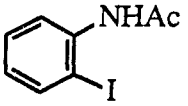
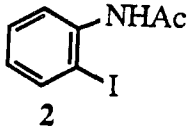
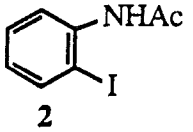
5% PPh_3	Reaction time (d)	Product	% Isolated yield
+	24		91
–	24		43
–	24		91
–	24	 **24**	56
–	24		56
–	24		75
–	12	 **25**  **26**	78 (52:26)
–	24		91 (65:26)
–	24		93 (67:26)
–	24	 **27**  **28**	58 (30:28)
+	24		56 (31:25)
+	24	 **29**	26

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
65			*n*-Bu_4NCl	NaOAc
66[e]	 **2**	2 $CH_3-C\equiv C-CH_2CH(CH_3)OH$	*n*-Bu_4NCl	Na_2CO_3
67[e]			*n*-Bu_4NCl	K_2CO_3
68[e]			*n*-Bu_4NCl	KOAc
69[e]			*n*-Bu_4NCl	NaOAc
70[i]	 **2**	2 $CH_3-C\equiv C-CH_2OH$	*n*-Bu_4NCl	Na_2CO_3
71[i]			*n*-Bu_4NCl	KOAc
72[i]			*n*-Bu_4NCl	NaOAc
73[i]			*n*-Bu_4NCl	K_2CO_3
74[i]			LiCl	K_2CO_3
75[i]	 **2**	2 $CH_3-C\equiv C-CH_2CH_2OH$	*n*-Bu_4NCl	KOAc
76[i]			*n*-Bu_4NCl	Na_2CO_3

[i]Acetyl group was transferred.

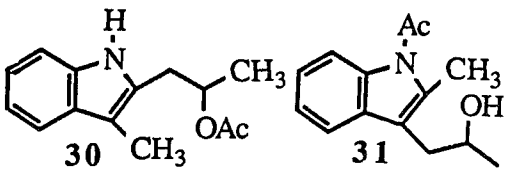
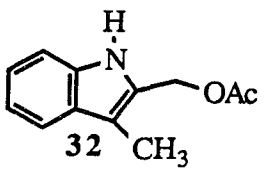
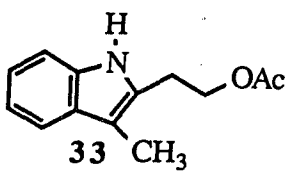
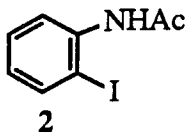
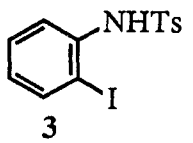
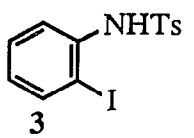
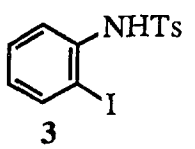
5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	24		27
+	12	 **30** **31**	76 (60:16)
+	12		41(28:13)
–	12		73 (46:27)
–	12		61 (41:20)
–	24	 **32**	33
–	24		30
–	24		26
+	24		60
+	24		60
–	24	 **33**	43
–	24		44

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
77[b]	 **2**	5 $CH_3-C\equiv C-Si(CH_3)_3$	LiCl	K_2CO_3
78[b]			LiCl	KOAc
79	 **3**	2 $Ph-C\equiv C-Ph$	*n*-Bu_4NCl	KOAc
80			*n*-Bu_4NCl	KOAc
81			*n*-Bu_4NCl	Na_2CO_3
82			LiCl	K_2CO_3
83	 **3**	3 *n*-Pr—C≡C—*n*-Pr	*n*-Bu_4NCl	KOAc
84			*n*-Bu_4NCl	Na_2CO_3
85	 **3**	5 $CH_3-C\equiv C-C(CH_3)_3$	*n*-Bu_4NCl	Na_2CO_3
86			*n*-Bu_4NCl	KOAc

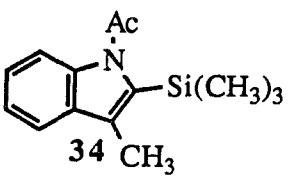
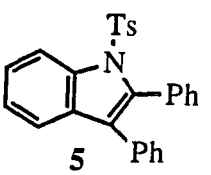
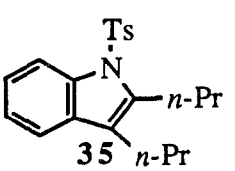
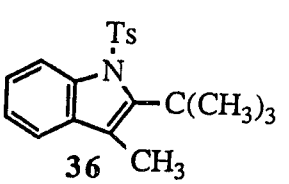
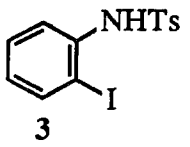
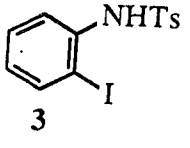
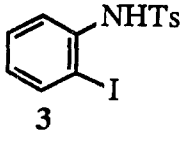
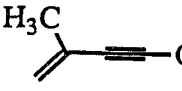
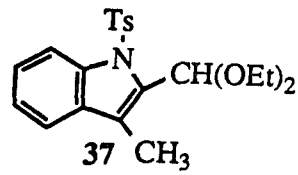
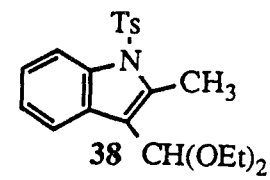
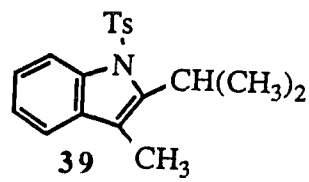
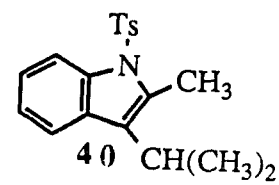
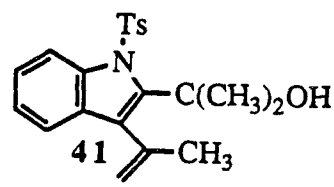
5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	12	 **34**	70
–	12		55
–	48	 **5**	51
+	48		45
+	48		40
–	48		60
–	24	 **35**	86
+	24		84
+	24	 **36**	86
–	24		86

Table 3. (continued)

Entry	Aryl halide	Alkyne	Halide source	Base
87[e]	 **3**	5 $CH_3-C\equiv C-CH(OEt)_2$	*n*-Bu_4NCl	NaOAc
88[e]			*n*-Bu_4NCl	Na_2CO_3
89[e]			*n*-Bu_4NCl	KOAc
90[f]	 **3**	2 $CH_3-C\equiv C-CH(CH_3)_2$	LiCl	K_2CO_3
91	 **3**	2 H_3C  $C(CH_3)_2OH$	*n*-Bu_4NCl	KOAc

5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	24	 **37**  **38**	56 (28:28)
–	24		56 (28:28)
–	24		32 (16:16)
–	36	 **39**  **40**	60 (1:1)
–	24	 **41**	45

As an inital study, the reactions of 2-iodoaniline with diphenylacetylene were examined in the absence of PPh_3. The reaction provided many products as indicated by GC and TLC analysis (entries 1 and 2).

The reaction of 2-iodoaniline with 4-octyne was examined using a number of different reaction conditions. Reactions using *n*-Bu_4NCl or LiCl in the presence of K_2CO_3 afforded respectively 70% and 80% isolated yields of the desired product along with small amounts of multiple-insertion products (entries 3 and 7), although it should be noted that the *n*-Bu_4NCl reaction also contained 5% PPh_3. The reaction using KOAc in the presence of LiCl provided a much higher yield compared with that using *n*-Bu_4NCl (entries 5 and 6).

The reaction of 2-iodoaniline with 4,4-dimethyl-2-pentyne using *n*-Bu_4NCl and Na_2CO_3 in the presence of PPh_3 gave an 82% yield of a single isomeric product (entry 8). However, using Et_3N as the base, the same substrate provided only multiple-insertion products (entry 9). This was probably due to the fact that the vinylpalladium intermediate coordinated with Et_3N, thereby preventing nucleophilic attack on palladium.

The reaction of 2-iodoaniline with 1-phenyl-1-propyne was only examined using *n*-Bu_4NCl and afforded none of the desired product (entries 10 and 11).

In order to further examine the regioselectivity of the heteroannulation process, the reactions of 2-iodoaniline with several different unsymmetrical internal alkynes were attempted. Specifically, the reactions of 2-iodoaniline with 1-cyclohexyl-1-propyne using KOAc, NaOAc, K_2CO_3, or Na_2CO_3 as the base, in the presence of *n*-Bu_4NCl provided 30 to 57% isolated yields of a single product, along with small amounts of multiple-insertion products (entries 12-15). When the reaction was conducted using a combination of LiCl and K_2CO_3, a 56% yield of the single, regioisomeric, desired product was obtained, in addition to small amounts of multiple-insertion products (entry 16).

The reaction of 4-methyl-2-pentyne with 2-iodoaniline was also investigated. These reactions afforded moderate to good yields of two regioisomeric 2,3-disubstituted indoles. In the reactions of 2-iodoaniline with 4-methyl-2-pentyne using K_2CO_3 as the base in the presence of *n*-Bu_4NCl , an isomeric ratio of approximately 2.5:1 was formed whether or not PPh_3 was included (entries 17 and 18). The analogous reaction using LiCl also provided a high yield of the desired products in an isomeric ratio of 3-4:1 (entries 19 and 20).

The reactions of 2-iodoaniline with 2-pentyne using K_2CO_3 as the base were also examined. Specifically, the reactions of 2-iodoaniline in the presence of *n*-Bu_4NCl afforded a good yield of a mixture of two isomeric products. GC-MS analysis showed that both products have the same molecular weight. The ^1H NMR spectrum of the major product was identical with that of 3-methyl-2-ethylindole previously reported in the literature[33] (entries 21-24).

The reactions of 2-iodoaniline with hydroxy group substituted internal alkynes were also examined. Specifically, alkynes bearing a tertiary propargylic hydroxy group were employed as substrates. This was to prevent the formation of an α,β-unsaturated ketone, a potential side product that could be generated upon addition of the aryl iodide to the alkyne followed by palladium hydride elimination to an allenic alcohol and subsequent tautomerization. The reaction of 2-iodoaniline with 2-methyl-3-pentyn-2-ol using Na_2CO_3 as the base in the presence of PPh_3 provided a 52% isolated yield of a single product (entry 25). In addition, the reaction of 2-iodoaniline with 2,5-dimethyl-3-hexyne-2,5-diol using Na_2CO_3 in the presence of PPh_3 gave a 54% yield of the desired product after three days (entry 26). Moreover, the reactions of 2-iodoaniline with 2,5-dimethyl-5-hexen-3-yn-2-ol using Na_2CO_3 (plus PPh_3) or KOAc (no PPh_3) afforded 67-70% isolated yields of a single product (entries 28 and 29). Finally, the reaction of 2-iodoaniline with 1-(1-butynyl)cyclohexanol using Na_2CO_3 as the base in the presence of PPh_3 provided a 78% yield of the desired product, with a small amount of an unknown side product (entry 30).

The regioselectivity of the reactions of 2-iodoaniline with tertiary propargylic alcohols was consistent with Cacchi's report.[34] The reactions of 2-iodoaniline with 4-hexyn-2-ol using *n*-Bu_4NCl and KOAc or Na_2CO_3 in the absence of PPh_3 provided only unknown products based on TLC and GC analyses (entries 31 and 32).

The reactions of 2-iodoaniline with trimethylsilyl-substituted internal alkynes were examined using several different bases under our standard conditions. The reactions of 2-iodoaniline with 1-trimethylsilyl-1-propyne were first examined using *n*-Bu_4NCl and NaOAc or Na_2CO_3. The reaction using Na_2CO_3 as the base in the presence of PPh_3 provided a 98% isolated yield of the desired product (entry 33). However, the reaction using NaOAc afforded the desired product with many side products (entry 34). The yield of the desired product was not determined. The regiochemistry of the product was determined by desilylation of the product with $AlCl_3$ in the presence of methylene chloride (see the later discussion). The ^1H NMR spectrum and melting point of the desilylated product were identical with those reported for 3-methylindole.[35]

The reactions of 2-iodoaniline with 1-trimethylsilyl-1-hexyne and *n*-Bu_4NCl using Na_2CO_3 or NaOAc as the base provided an 81% yield of the desired product and a small amount of side products (entries 35 and 36).

In order to examine the directing effect of a trimethylsilyl group versus a phenyl group, the reaction of 2-iodoaniline with 1-phenyl-2-trimethylsilylacetylene was examined using several different bases (entries 37-41). Specifically, the reaction using *n*-Bu_4NCl and NaOAc as the base and no PPh_3 afforded a 68% yield of the desired product, but the reactions using KOAc, K_2CO_3, or Na_2CO_3 with or without PPh_3 and *n*-Bu_4NCl or LiCl gave 18-40 % yields of the desired product and a significant amount of the *o*-aminotolane. Again, the regio-chemistry of the product was determined by desilylation of the product with $AlCl_3$ in the presence of methylene chloride. The ^1H NMR spectrum and melting point of the desilylated product were found to be consistent with those of the literature reported for 3-phenylindole.[36]

The reactions of 2-iodoaniline with 3-trimethylsilyl-2-propyn-1-ol were investigated using several different bases (entries 42-45). The reaction using *n*-Bu_4NCl and Na_2CO_3 in the presence of PPh_3 provided a 60% yield of the desired product (entry 44). Surprisingly, the reaction using Et_3N afforded only multiple-insertion products (entry 45).

The reaction of 2-iodoaniline with bis(trimethylsilyl)acetylene using *n*-Bu_4NCl, PPh_3 and Na_2CO_3 as the base provided a mixture of two monodesilylated indoles with a small amount of a side product (entries 46). Using NaOAc as the base and no PPh_3, the reaction afforded 54% of only one single regioisomer with a small amount of a side product (entry 47). The ^1H NMR spectrum of this product was identical with existing literature data[37] for 3-(trimethylsilyl)-indole.

N-Substituted indoles have also been examined in the annulation process. The reaction of *N*-methyl-2-iodoaniline with 4-octyne was attempted employing *n*-Bu_4NCl and several different bases. Using K_2CO_3 as the base in the presence of PPh_3, the reaction provided a 71% isolated yield of the desired product without formation of any side product (entry 48). In contrast, the reactions using acetate bases, but no PPh_3, provided only multiple-insertion products (entries 50 and 51). On the other hand, using Na_2CO_3 in the presence of 5 % PPh_3, the reaction gave a 47% yield of the desired product along with a small amount of multiple-insertion products (entry 49).

The reaction of 2-iodoacetanilide with 4-octyne was conducted using *n*-Bu_4NCl and KOAc, NaOAc, or Na_2CO_3 without PPh_3 and Na_2CO_3 with PPh_3. Without PPh_3, the Na_2CO_3 reaction gave a substantially reduced yield (entry 54). The other reactions afforded a 91% isolated yield of the desired product (entries 52, 53, and 55).

The reaction of 2-iodoacetanilide with 1-phenyl-1-propyne using KOAc as the base in the presence of *n*-Bu_4NCl provided a lower yield compared with that using LiCl (compare entries 56 and 58). The regiochemistry is observed to place the phenyl group near the nitrogen of the indole.[38]

The reactions of 2-iodoacetanilide with 4-methyl-2-pentyne afforded 78-93% isolated yields of two regioisomeric products in a ratio of approximately 2-2.5:1 (entries 59-61). The regioisomers were assigned based on the steric hindrance of the two different substitutents on the alkyne.

The reaction of 2-iodoacetanilide and 2-pentyne using LiCl and K_2CO_3 with or without PPh_3 provided a moderate yield of two isomeric products in an isomeric ratio of close to 1:1 (entries 62 and 63).

The reaction of 2-iodoacetanilide with 4-methyl-4-penten-2-yn-1-ol using Na_2CO_3 with PPh_3 or NaOAc without PPh_3 gave 26 and 27% isolated yields of the desired product respectively, along with a small amount of a side product (entries 64 and 65). The regiochemistry of the product is not clear at this point, but the structure was assumed based on the result of *N*-acetyl-2-iodobenzylamine with 2-methyl-1-hexen-3-yne in the next part of this thesis.

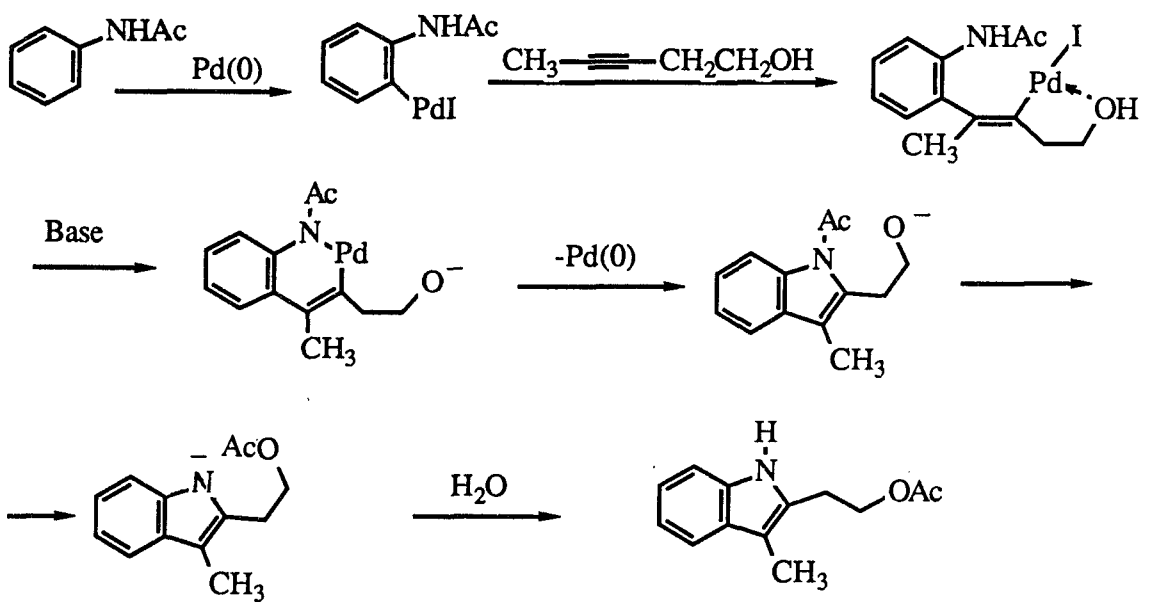
The reactions of 2-iodoacetanilide with hydroxy group-substituted internal alkynes were also examined. The reactions of 2-iodoacetanilide with 4-hexyn-2-ol using *n*-Bu_4NCl and several bases provided two products (entries 66-69). The best yield and isomer ratio was obtained using Na_2CO_3 as the base in the presence of PPh_3. The structures of both products were assigned based on the ^1H NMR spectra (chemical shift for **30**: δ 2.28 (CH_3), 8.10 (NH); chemical shift for **31**: δ 1.75 (OH), 2.60 (CH_3) and GC-MS fragmentation patterns (the base peak for **30**: M-59, the base peak for **31**: M-43) of the two products. The chemical shift of the methyl peak in 2-methylindole comes at higher value compared with that of 3-methylindole.

The reactions of 2-butyn-1-ol with 2-iodoacetanilide using acetate and carbonate bases afforded exclusively one regioisomeric product in which the acetyl group has transferred to the hydroxy group (entries 70-74).[39] These reactions using several different companys' *n*-Bu_4NCl (Aldrich, Chemical Air Co., and Lancaster) were very sensitive to the purity of the salts. To overcome this difficulty, a reaction using K_2CO_3 as the base in the presence of LiCl

and 5% PPh_3 was examined (entry 74). The reaction provided a 60% yield (similar to that using *n*-Bu_4NCl) of a single product in which the acetyl group has migrated.

The reaction of 2-iodoacetanilide with 3-pentyn-1-ol using *n*-Bu_4NCl and KOAc or Na_2CO_3 without PPh_3 provided 43-44% yields of a single product alongside small amounts of side products (entries 75 and 76). Again, the acetyl group appears to have migrated based on the ^1H NMR spectrum (NH and no OH).

A possible mechanism for this reaction is described in Scheme 3. Probably, the hydroxy group coordinates to the intitial vinylpalladium intermediate, which stabilizes the intermediate. After cyclization and reductive elimination, the *N*-acetyl indole derivative is formed. The



Scheme 3

acetyl group of the indole is then transferred by alkoxide anion attack on the acetyl group.

The reactions of 2-iodoacetanilide with 1-trimethylsilyl-1-propyne were examined using K_2CO_3 or KOAc as the base in the presence of LiCl (entries 77 and 78). The reactions provided 70 and 55% yields respectively of the desired product, along with a small amount of

the desilylated product. Usually, the reactions of 2-iodoacetanilide with trimethylsilyl-substituted internal alkynes provided more desilylation product compared with those of 2-iodoaniline.

The use of *N*-tosyl derivatives has also been examined in these annulation reactions. The reactions of *N*-tosyl-2-iodoaniline with diphenylacetylene, in the presence or absence of PPh_3, were successful, affording the desired product in yields ranging from 40 to 60% (entries 79-82).

The reactions of *N*-tosyl-2-iodoaniline with 4-octyne in the presence of *n*-Bu_4NCl and two different bases (KOAc, Na_2CO_3) provided 86% and 84% isolated yields respectively of the desired product, without formation of any multiple-insertion product (entries 83 and 84).

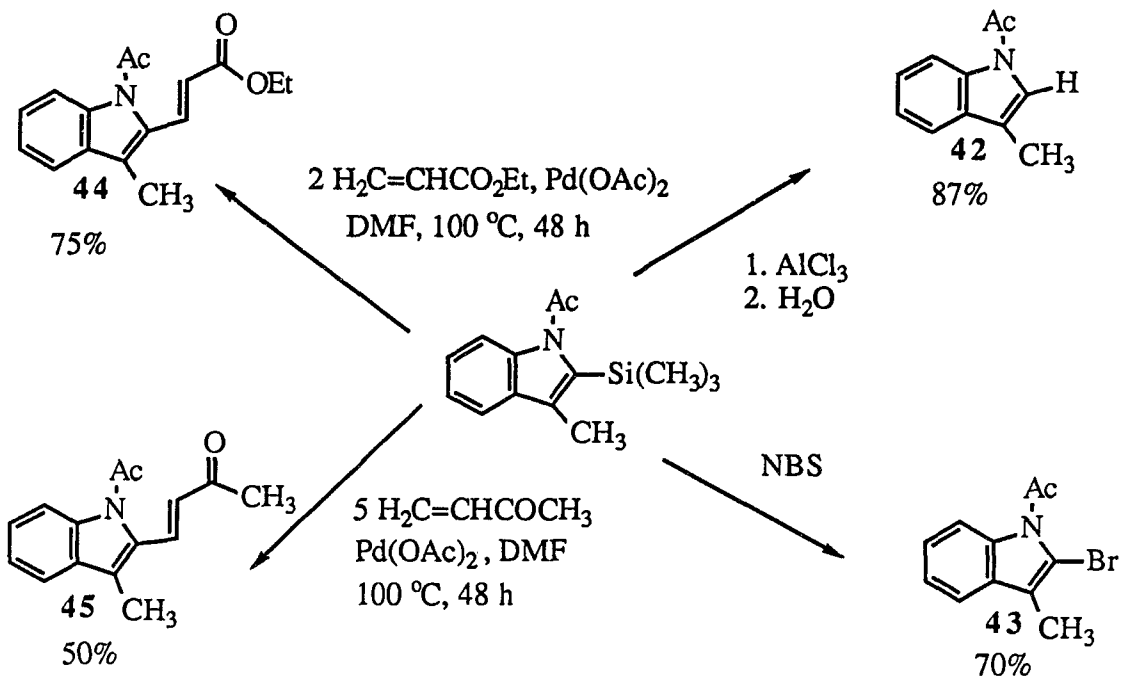
With *N*-tosyl-2-iodoaniline as the starting aryl iodide, the reaction with 4,4-dimethyl-2-pentyne using Na_2CO_3 (plus PPh_3) or KOAc (no PPh_3) in the presence of *n*-Bu_4NCl provided an 86% isolated yield of the desired product, without formation of any side product (entries 85 and 86).

The reactions of *N*-tosyl-2-iodoaniline with 2-butynal diethyl acetal provided two isomeric products in a ratio of 1:1 along with a small amount of multiple-insertion products (entries 87-89). Again, the structure assignment of these isomers was based on the ^1H NMR spectra of the two isolated products. The chemical shift of the methyl group in the 2-methyl-substituted indole appeared at higher value compared with the 3-methyl-substituted indole.

The reaction of *N*-tosyl-2-iodoaniline and 2-pentyne using LiCl, K_2CO_3 and no PPh_3 provided a 60% isolated yield of a 1:1 mixture of two regioisomers (entry 90). Once again, no regioselectivity is observed with this alkyne.

The reaction of *N*-tosyl-2-iodoaniline with 2,5-dimethyl-5-hexen-3-yn-2-ol using *n*-Bu_4NCl with KOAc as the base provided a 45% yield of the desired product (entry 91).

Finally, the facile functionalization of 1-acetyl-3-methyl-2-(trimethylsilyl)indole was examined (Scheme 4). First, the desilylation of 1-acetyl-3-methyl-2-(trimethylsilyl)indole was



Scheme 4

investigated under several reaction conditions. Using *n*-Bu_4NF in THF-methanol (9:1) at reflux temperature, the reaction did not provide any of the desilylated product. However, using aqueous HF in CH_3CN provided an 80% isolated yield of 1-acetyl-3-methylindole.[41] Using $AlCl_3$ with methylene chloride as the solvent, and running the reaction for 1 hour at 0 °C provided an 87% isolated yield of the desilylated indole after aqueous workup. 1-Acetyl-2-bromo-3-methylindole[42] could be readily prepared by the bromination of the corresponding 2-(trimethylsilyl)indole with NBS.

The Heck reaction provided a convenient entry into variously substituted indoles using an alkene and 1 equivalent of $Pd(OAc)_2$ in DMF. For example, the reaction of methyl vinyl ketone with the 2-(trimethylsilyl)indole provided a 30% yield of 1-acetyl-3-methylindole and a 50% yield of the Heck product was isolated. On the other hand, the reaction of ethyl acrylate

with the 2-(trimethylsilyl)indole provided a 75% isolated yield of the desired product without any side product.

CONCLUSION

In the third part of this dissertation, the synthesis of 2,3-disubstituted indoles has been accomplished by the reaction of iodoanilines with internal alkynes in the presence of a base and catalytic amounts of palladium. The reactions of 2-iodoaniline derivatives with a variety of internal alkynes bearing alkyl, aryl, alkenyl, hydroxyalkyl, and silyl groups provides high regioselectivity and high yields. The more sterically bulky group present on the alkyne ends up near the nitrogen atom in the indole product. The facile annulation of silylalkynes broadens tremendously the scope of this synthetic process. Desilylation by protonolysis, halogenation, or Heck-substitution provide variously substituted indoles.

EXPERIMENTAL SECTION

A. Equipment

The infrared spectra were obtained on an IBM IR/98 FT spectrophotometer, and the ^{1}H NMR and ^{13}C NMR spectra on a Nicolet NT-300 NMR spectrometer. The GC-MS spectral data were obtained on a Finnegan 4023 GC/MS and on a Kratos MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with an OV-101 packed column. Melting points were determined on a Thomas-Hoover melting point apparatus and elemental analyses were performed by Galbraith Laboratories, Inc.

B. Reagents

All chemicals were used directly as obtained from commercial sources unless otherwise noted. Et_3N and *i*-Pr_2NEt were distilled from KOH pellets. Anhydrous forms of $NaHCO_3$, Na_2CO_3, K_2CO_3, NaOAc, and KOAc were purchased from Fisher-Scientific. DMF and LiCl were also obtained from Fisher-Scientific. *n*-Bu_4NCl was purchased from Lancaster Synthesis. $Pd(OAc)_2$ was provided by Johnson Matthey, Inc, and Kawaken Fine Chemicals Co., Inc. 2-Iodoaniline and PPh_3 were purchased from Aldrich Chemical Co., Inc. 4,4-Dimethyl-2-pentyne, 1-trimethylsilyl-1-propyne, 4-octyne, 1-phenylpropyne, 1-cyclohexyl-1-propyne, 4-methyl-2-pentyne, 2-pentyne, 2-methyl-3-pentyn-2-ol, 2,5-dimethyl-3-hexyne-2,5-diol, 2,5-dimethyl-5-hexene-3-yn-2-ol, 1-(1-butynyl)cyclohexanol, 3-(trimethylsilyl)-2-propyn-1-ol, 1,2-bis(trimethylsilyl)acetylene, 4-hexyn-2-ol and 2-butyn-1-ol were purchased from Farchan Scientific Co.

Preparation of 2-iodoacetanilide (**2**)

Compound **2** was prepared by a procedure reported by Berrios-Peña.[43] 2-Iodoaniline (5.48 g, 25 mmol) was dissolved in 150 ml of Et_2O; Et_3N (3.51 ml) was added and the solution cooled to 0 °C. Acetyl chloride (2.55 g, 25.2 mmol) dissolved in 15 ml of Et_2O was added dropwise. After stirring at 0 °C for 1 hour, the reaction mixture was allowed to reach room temperature and then it was stirred overnight. Filtration (to remove $Et_3N{\cdot}HCl$), followed by concentration of the filtrate, afforded 5.25 g (80%) of a white solid. Recrystallization from Et_2O afforded 4.9 g (75%) of colorless needles: mp 109-111 °C; IR ($CDCl_3$) 3407, 3026, 1697, 1585, 1431, 1318 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H, CH_3CO), 6.48 (dd, 1H, J = 7.5 Hz, J = 1.5 Hz, ArH), 7.34 (m, 1H, ArH), 7.41 (br s, 1H, NH), 7.78 (d, 1H, J = 7.5 Hz, ArH), 8.21 (d, 1H, J = 8.3 Hz, ArH).

Preparation of *N*-methyl-2-iodoaniline (**4**)

Compound **4** was prepared by a procedure reported by Harrison.[44] In a flame-dried 100 ml round-bottom flask, 2-iodoaniline (2.25 g, 10.3 mmol) was dissolved in 30 ml of dry THF. The resulting solution was cooled to -78 °C under a nitrogen atmosphere and 1.6 M methyl lithium (6.25 ml, 10 mmol) was added dropwise, and the resulting solution was stirred at -78 °C for 30 minutes. .To the solution was added dimethyl sulfate (1.90 g, 15.1 mmol) and stirring was continued for 10 minutes at -78 °C. The solution was then warmed to room temperature and stirred for 2 hours, followed by acidification with 10% HCl solution. The reaction mixture was diluted with ether and the aqueous layer was removed. The ether extract was stirred with 30 ml of concentrated ammonium hydroxide for 30 minutes. The aqueous layer was removed and the organic phase was washed with 20 ml of water and 30 ml of brine, dried with $MgSO_4$, and concentrated. Distillation at 101-105 °C (2.0 mm Hg) yielded 2.03 g (8.7 mmol, 87%) of *N*-methyl-2-iodoaniline: IR (neat) 3410 (NH), 1590 cm^{-1}; ^1H NMR

($CDCl_3$) δ 2.80 (s, 3H, NCH_3), 4.0 (br s, 1H, NH), 6.20-6.80 (m, 4H, ArH); HRMS calculated for C_7H_8IN: 232.97015. Found: 232.97023.

Preparation of 1-(trimethylsilyl)-2-phenylethyne

Under a nitrogen atmosphere, *n*-BuLi (1.5 M in hexane, 10.5 ml, 15.8 mmol) was added to a solution of phenylacetylene (1.45 g, 14.3 mmol) in dried THF (10 ml) at 0 °C over 10 minutes. The mixture was stirred for 1.5 hours and hexamethylphosphoric triamide (2.8 ml, Aldrich) containing trimethylsilylchloride (3 g, 28 mmol) was slowly added. The mixture was stirred overnight at room temperature. The reaction mixture was poured into a mixture of ice and pentane (20 ml). The organic layer was separated, and the aqueous layer was extracted with pentane (20 ml). The combined organic layer was washed with brine (10 ml), dried, and concentrated. The crude product was distilled in vacuum to give 1.9 g (65%) of 1-(trimethylsilyl)-2-phenylethyne: bp 63 °C/ 2 mm Hg; ^1H NMR ($CDCl_3$) δ 0.22 (s, 9H, $Si(CH_3)_3$), 7.27 (m, 2H, ArH), 7.45 (m, 2H, ArH).

Preparation of 1-(trimethylsilyl)-1-hexyne

This compound was prepared by the same procedure used for the synthesis of 1-(trimethylsilyl)-2-phenylethyne. A 70% yield of the desired product was obtained: ^1H NMR ($CDCl_3$) δ 0.11 (s, 9H, $Si(CH_3)_3$), 0.85 (t, 3H, J = 5.1 Hz, CH_3), 1.46 (m, 4H, CH_2), 2.18 (t, 2H, J = 6.3 Hz, propargylic).

General procedure for the palladium-catalyzed heteroannulation of alkynes

Palladium acetate (0.0125 mmol), LiCl (0.5 mmol) or *n*-Bu_4NCl (0.5 mmol), the appropriate base (2.50 mmol), the aryl iodide (0.50 mmol), the alkyne (0.50-2.50 mmol), DMF (10 ml) and, where indicated, PPh_3 (0.025 mmol) were added to a 4 dram vial equipped

with a stirring bar and teflon-lined screwcap. After being heated for the appropriate time at 100 °C, the reaction mixture was diluted with ether and washed with saturated aqueous ammonium chloride and water. The organic layer was dried over anhydrous $MgSO_4$. The reaction mixture was filtered, concentrated, and the product was purified by flash column chromatography using hexane-ethyl acetate. The following compounds were prepared using the above general procedure.

Preparation of 2,3-diphenyl-1-tosylindole (**5**)

Compound **5** was obtained as yellow crystals in 51% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and diphenylacetylene using KOAc and *n*-Bu_4NCl, and stirring for 48 hours at 100 °C (Table 3, entry 79): mp 173-174 °C; IR (neat) 3070, 3040, 2930, 1600, 1450, 1387, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3), 7.0-7.5 (m, 17H, ArH), 8.41 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 21.44, 116.10, 119.86, 124.07, 124.65, 124.65, 125.04, 126.78, 127.14, 128.06, 128.34, 129.17, 129.70, 130.32, 130.77, 131.95, 132.50, 135.20, 136.72, 137.15, 144.46. Anal. calculated for $C_{27}H_{21}NO_2S$: C, 76.57, H, 5.00. Found: C, 76.57 ; H, 5.05.

Preparation of 2,3-di-*n*-propylindole (**6**)

Compound **6** was obtained as a slightly yellow oil in 80% isolated yield from the reaction of 2-iodoaniline and 4-octyne using K_2CO_3 and LiCl, and stirring for 20 hours at 100 °C (Table 3, entry 7): IR (neat) 3412, 2961, 2931, 1462, 903, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (m, 6H, CH_3's), 1.72 (m, 4H, CH_2's), 2.73 (m, 4H, CH_2's), 7.15 (m, 2H, ArH), 7.29 (m, 1H, ArH), 7.56 (m, 1H, ArH), 7.70 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 14.21, 14.45, 23.37, 24.33, 26.45, 28.30, 110.37, 112.21, 118.52, 118.97, 120.87, 128.97, 135.34, 135.40; HRMS calculated for $C_{14}H_{19}N$: 201.15178. Found: 201.15118. Anal. calculated for $C_{14}H_{19}N$: C, 83.58; H, 9.45. Found: C, 81.44 ; H, 9.11.

Preparation of 2-*t*-butyl-3-methylindole (**7**)[37]

Compound **7** was obtained as a slightly yellow oil in 82% isolated yield from the reaction of 2-iodoaniline and 4,4-dimethyl-2-pentyne using Na_2CO_3, *n*-Bu_4NCl and PPh_3, and stirring for 24 hours at 100 °C (Table 3, entry 8): IR (neat) 3441, 3054, 2966, 2870, 1462, 1243, 1009, 908, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H, $C(CH_3)_3$), 2.48 (s, 3H, CH_3), 7.18 (m, 2H, ArH), 7.34 (d, 1H, J = 7.3 Hz, ArH), 7.57 (d, 1H, J = 7.3 Hz, ArH), 7.88 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 10.23, 29.34, 32.05, 105.15, 110.12, 117.70, 118.89, 120.81, 130.35, 133.67, 141.55; HRMS calculated for $C_{13}H_{17}N$: 187.13610. Found: 187.13614. Anal. calculated for $C_{13}H_{17}N$: C, 83.42; H, 9.09. Found: C, 82.53 ; H, 9.23.

Preparation of 2-cyclohexyl-3-methylindole (**8**)

Compound **8** was obtained as a slightly yellow oil in 57% isolated yield from the reaction of 2-iodoaniline and 1-cyclohexyl-1-propyne using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 12): IR (neat) 3425, 3059, 2920, 2854, 1610, 1464, 910, 733, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-2.0 (m, 10H, CH_2's), 2.30 (s, 3H, CH_3), 2.95 (m, 1H, CH), 7.10 (m, 2H, ArH), 7.25 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.80 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 8.44, 26.08, 26.68, 32.83, 35.82, 105.31, 110.16, 117.96, 118.90, 120.74, 129.32, 134.78, 139.67. This compound decomposes fairly rapidly. So no further data was obtained.

Preparation of 2-isopropyl-3-methylindole (**9**) and 3-isopropyl-2-methylindole (**10**)

Compound (**9**) was obtained in a 62% isolated yield and compound (**10**) in a 25% isolated yield from the reaction of 2-iodoaniline and 4-methyl-2-pentyne using K_2CO_3, PPh_3 and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 17).

2-Isopropyl-3-methylindole (**9**): Rf 0.70 (6:1 hexanes/ethyl acetate); IR (neat) 3422, 3057, 2963, 2926, 1610, 1469, 1296, 1007, 741 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.35 (d, 6H, J = 6.9 Hz, CH_3's), 2.29 (s, 3H, CH_3), 3.40 (m, 1H, CH), 7.14 (m, 2H, ArH), 7.30 (m, 1H, ArH), 7.51 (m, 1H, ArH), 7.75 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 22.53, 22.64, 25.86, 105.42, 110.40, 118.17, 119.14, 121.00, 129.62, 135.04, 140.36; HRMS calculated for $C_{12}H_{15}N$: 173.12045. Found: 173.12068.

3-Isopropyl-2-methylindole (**10**): Rf 0.55 (6:1 hexanes/ethyl acetate); IR (neat) 3406, 3059, 2963, 2928, 1589, 1460, 908, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, 6H, J = 6.9 Hz, CH_3's), 2.36 (s, 3H, CH_3), 3.16 (m, 1H, CH), 7.06 (m, 2H, ArH), 7.22 (m, 1H, ArH), 7.55 (br s, 1H, NH), 7.64 (d, 1H, J = 8.1 Hz, ArH) ; ^{13}C NMR ($CDCl_3$) δ 12.10, 23.00, 25.86, 110.24, 114.70, 118.60, 119.89, 120.42, 129.50, 135.30, 138.90; HRMS calculated for $C_{12}H_{15}N$: 173.12045. Found: 173.12060.

Preparation of 2-ethyl-3-methylindole (**11**) and 3-ethyl-2-methylindole (**12**)

Compounds **11** and **12** were obtained as a pale yellow oil in 62% isolated yield as a 1.5:1 mixture of isomers from the reaction of 2-iodoaniline with 2-pentyne using K_2CO_3, PPh_3 and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 22): IR (neat, 1.5:1 mixture) 3401, 3057, 2968, 2932, 1690, 1610, 1464, 1335, 1153, 1009, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 1.5:1 mixture) δ 1.30 (m, 6H, CH_3's), 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.80 (q, 4H, CH_2's), 7.15 (m, 4H, ArH), 7.28 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.60-7.70 (br s, 2H, NH) ; ^{13}C NMR ($CDCl_3$, 1.5:1 mixture) δ 8.29, 11.29, 13.99, 15.39, 15.48, 17.30, 19.28, 105.90, 110.14, 113.62, 117.91, 118.83, 120.57, 120.71, 124.13, 128.30, 129.28, 129.33, 129.53, 134.08, 135.10, 136.48; HRMS calculated for $C_{11}H_{13}N$: 159.10480. Found: 159.10510.

Preparation of 2-(1-hydroxy-1-methylethyl)-3-methylindole (**13**)

Compound **13** was obtained as a slightly yellow oil in 52% isolated yield from the reaction of 2-iodoaniline and 2-methyl-3-pentyn-2-ol using Na_2CO_3, *n*-Bu_4NCl and PPh_3, and stirring for 12 hours at 100 °C (Table 3, entry 25): IR (neat) 3431, 3352, 2966, 2928, 1707, 1622, 1454, 1364, 910, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 6H, CH_3's), 2.03 (br s, 1H, OH), 2.33 (s, 3H, CH_3), 7.10 (m, 2H, ArH), 7.38 (d, IH, J = 6.0 Hz, ArH), 7.49 (d, 1H, J = 7.5 Hz, ArH), 8.45 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 9.50, 30.03, 70.68, 103.67, 110.55, 118.86, 121.16, 127.05, 130.02, 133.49, 139.96. HRMS calculated for $C_{12}H_{15}NO$: 189.11543. Found: 189.11531.

Preparation of 2,3-bis(1-hydroxy-1-methylethyl)indole (**14**)

Compound **14** was obtained as a slightly yellow oil in 54% isolated yield from the reaction of 2-iodoaniline and 2,5-dimethyl-3-hexyne-2,5-diol using Na_2CO_3, *n*-Bu_4NCl and PPh_3, and stirring for 72 hours at 100 °C (Table 3, entry 26): IR (neat) 3450, 3416, 3061, 2990, 1730, 1456, 1375, 1252, 910, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (s, 12H, CH_3's), 2.03 (br s, 2H, OH), 7.30 (m, 2H, ArH), 7.49 (d, 1H, J = 8.1 Hz, ArH), 7.74 (d, 1H, J = 7.5 Hz, ArH), 8.80 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 30.65 (overlapped), 69.72 (overlapped), 97.15, 111.07, 119.81, 120.47, 121.76, 128.37, 135.76, 145.76; HRMS calculated for $C_{14}H_{19}NO$: 233.14166. Found: 233.14170.

Preparation of 3-isopropenyl-2-(1-hydroxy-1-methylethyl)indole (**15**)

Compound **15** was obtained as a slightly yellow solid in 70% isolated yield from the reaction of 2-iodoaniline and 2,5-dimethyl-5-hexen-3-yn-2-ol using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 29): mp 122-123 °C; IR ($CDCl_3$) 3543, 3362, 2996, 2963, 1641, 1458, 1437, 1333, 1205, 1169, 865, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 6H, CH_3's), 2.03 (s, 3H, CH_3), 2.35 (br s, 1H, OH), 4.90 (d, 1H, J = 1.2 Hz, C=CH),

5.25 (d, 1H, J = 1.2 Hz, C=CH), 7.02 (m, 2H, ArH), 7.16 (d, 1H, J = 8.1 Hz, ArH), 7.36 (d, 1H, J = 7.8 Hz, ArH), 8.45 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 25.62, 31.19, 71.30, 110.80, 113.69, 117.42, 119.23, 119.58, 121.81, 128.86, 133.77, 139.33, 140.54; HRMS calculated for $C_{14}H_{17}NO$: 215.13101. Found: 215.13103.

Preparation of 3-ethyl-2-(1-hydroxycyclohexyl)indole (**16**)

Compound **16** was obtained as a white solid in 78% isolated yield from the reaction of 2-iodoaniline and 1-(1-butynyl)cyclohexanol using Na_2CO_3, PPh_3 and *n*-Bu_4NCl, and stirring for one day at 100 °C (Table 3, entry 30): mp 89-90 °C; IR (neat) 3487, 3315, 2963, 2928, 1462, 1447, 1157, 957, 908, 727 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.5 Hz, CH_3), 1.65-1.86 (m, 6H, CH_2's), 2.27 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 2.85 (q, 2H, J = 7.5 Hz, CH_2), 6.05 (br s, 1H, OH), 7.14 (m, 2H, ArH), 7.28 (t, 1H, J = 8.1 Hz, ArH), 7.59 (d, 1H, J = 6.9 Hz, ArH), 7.77 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 16.22, 21.72, 21.89, 24.46, 37.96, 72.19, 110.84, 111.21, 118.56, 119.00, 121.33, 129.58, 133.91, 140.10; HRMS calculated for $C_{14}H_{15}NO_2$: 243.16231. Found: 243.16203.

Preparation of 3-methyl-2-(trimethylsilyl)indole (**17**)

Compound **17** was obtained as a slightly yellow oil in 98% isolated yield from the reaction of 2-iodoaniline and 1-trimethylsilyl-1-propyne using Na_2CO_3, PPh_3 and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 33): IR (neat) 3439, 2955, 1250, 1159, 1092, 841, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H, $Si(CH_3)_3$), 2.32 (s, 3H, CH_3), 7.05 (m, 2H, ArH), 7.23 (d, 1H, J = 7.8 Hz, ArH), 7.48 (d, 1H, J = 7.8 Hz, ArH), 7.76 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ –0.65, 10.65, 110.87, 118.78, 119.15, 120.39, 122.36, 130.65, 133.04, 138.16; HRMS calculated for $C_{12}H_{17}NSi$: 203.11303. Found: 203.11245. Anal. calculated for $C_{12}H_{17}NSi$: C, 70.93; H, 8.37. Found: C, 70.24; H, 8.38.

Preparation of 3-*n*-butyl-2-(trimethylsilyl)indole (**18**)

Compound **18** was obtained as a slightly yellow oil in 81% isolated yield from the reaction of 2-iodoaniline and 1-trimethylsilyl-1-hexyne using Na_2CO_3 and *n*-Bu_4NCl, and stirring for 12 hours at 100 °C (Table 3, entry 35): IR ($CDCl_3$) 3439, 2957, 2932, 1458, 1337, 1250, 1155, 1094, 908, 841, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.26 (s, 9H, $Si(CH_3)_3$), 0.87 (t, 3H, J = 7.2 Hz, CH_3), 1.36 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 2.72 (t, 2H, J = 7.8 Hz, CH_2), 6.96 (t, 1H, J = 5.1 Hz, ArH), 7.05 (t, 1H, J = 4.2 Hz, ArH), 7.19 (d, 1H, J = 8.1 Hz, ArH), 7.50 (d, 1H, J = 7.5 Hz, ArH), 7.69 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ –0.31, 14.33, 29.39, 28.28, 34.56, 110.97, 119.09, 119.24, 122.30, 126.31, 129.00, 132.65, 138.41; HRMS calculated for $C_{15}H_{23}NSi$: 245.15998. Found: 245.15964.

Preparation of 3-phenyl-2-(trimethylsilyl)indole (**19**)

Compound **19** was obtained as a slightly yellow oil in 68% isolated yield from the reaction of 2-iodoaniline and 1-phenyl-2-(trimethylsilyl)ethyne using NaOAc and *n*-Bu_4NCl, and stirring for 16 hours at 100 °C (Table 3, entry 37): IR ($CDCl_3$) 3472, 2995, 1605, 1491, 1327, 1252, 1153, 910, 841, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.27 (s, 9H, $Si(CH_3)_3$), 7.15 (t, 1H, J = 6.6 Hz, ArH), 7.27 (t, 2H, J = 7.2 Hz, ArH), 7.45 (m, 5H, ArH), 7.62 (d, 1H, J = 7.8 Hz, ArH), 8.19 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ –0.21, 110.91, 114.58, 119.69, 120.03, 122.83, 126.70, 127.95, 128.20, 128.57, 128.74, 136.67, 138.00; HRMS calculated for $C_{17}H_{19}NSi$: 265.12868. Found: 265.12876.

Preparation of 3-(hydroxymethyl)-2-(trimethylsilyl)indole (**20**)

Compound **20** was obtained as a white solid in 60% isolated yield from the reaction of 2-iodoaniline and 3-(trimethylsilyl)-2-propyn-1-ol using Na_2CO_3, PPh_3 and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 44): mp 156-158 °C; IR ($CDCl_3$) 3474, 3382, 2953, 1616, 1493, 1452, 1302, 1252, 1086, 1047, 970, 908, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ

0.44 (s, 9H, $Si(CH_3)_3$), 1.50 (br s, 1H, OH), 4.95 (s, 2H, CH_2O), 7.15 (m, 2H, ArH), 7.40 (d, 1H, J = 7.8 Hz, ArH), 7.76 (d, 1H, J = 8.1 Hz, ArH), 8.20 (br s, 1H, NH) ; ^{13}C NMR (DMSO-d6) δ –0.23, 55.06, 111.15, 118.26, 118.75, 121.31, 124.34, 128.12, 134.88, 138.38; HRMS calculated for $C_{12}H_{17}NOSi$: 219.10794. Found: 219.10813.

Preparation of 3-(trimethylsilyl)indole (**21**)[37]

Compound **21** was obtained as a yellow oil in 54% isolated yield from the reaction of 2-iodoaniline and 1,2-bis(trimethylsilyl)acetylene using NaOAc and *n*-Bu_4NCl, and stirring for 20 hours at 100 °C (Table 3, entry 47): IR ($CDCl_3$) 3423, 2959, 2899, 1499, 1445, 1342, 1250, 1117, 949, 841, 797, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 9H, $Si(CH_3)_3$), 6.46 (s, 1H, 2-indole-H), 6.89 (m, 2H, ArH), 7.10 (d, 1H, J = 8.4 Hz, ArH), 7.36 (d, 1H, J = 7.8 Hz, ArH), 7.90 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ –0.76, 118.08, 115.57, 119.92, 120.81, 122.52, 128.93, 138.48, 138.90 ; HRMS calculated for $C_{11}H_{15}NSi$: 189.09738. Found: 189.09705.

Preparation of 1-methyl-2,3-di-*n*-propylindole (**22**)

Compound **22** was obtained as a slightly yellow oil in 71% isolated yield from the reaction of *N*-methyl-2-iodoaniline and 4-octyne using K_2CO_3, *n*-Bu_4NCl and PPh_3, and stirring for 24 hours at 100 °C (Table 3, entry 48): IR (neat) 2959, 2932, 1472, 1369, 910, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (m, 6H, CH_3's), 1.85 (m, 4H, CH_2's), 2.92 (m, 4H, CH_2's), 3.86 (s, 3H, NCH_3), 7.35 (m, 3H, ArH), 7.74 (d, 1H, J = 7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 14.29, 14.57, 23.73, 24.68, 26.76, 26.93, 29.74, 108.71, 111.81, 118. 51, 118.62, 120.56, 128.02, 136.83, 137.03; HRMS calculated for $C_{15}H_{21}N$: 215.16740. Found: 215.16737. Anal. calculated for $C_{15}H_{21}N$: C, 83.72; H, 9.77. Found: C, 82.75 ; H, 9.83.

Preparation of 1-acetyl-2,3-di-*n*-propylindole (**23**)

Compound **23** was obtained as a slightly yellow oil in 91% isolated yield from the reaction of 2-iodoacetanilide and 4-octyne using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 52): IR (neat) 2961, 2931, 1703, 1475, 1367, 1315, 1217, 910, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (m, 6H, CH_3's), 1.67 (m, 4H, CH_2's), 2.68 (t, 2H, J = 7.5 Hz, CH_2), 2.78 (s, 3H, $COCH_3$), 3.01 (t, 2H, J = 7.8 Hz, CH_2), 7.23 (m, 2H, ArH), 7.52 (m, 1H, ArH), 7.78 (m, 1H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 14.30, 14.46, 23.34, 23.75, 26.18, 27.83, 29.14, 114.59, 118.87, 120.17, 122.67, 128.45, 131.04, 135.74, 138.29, 170.14; HRMS calculated for $C_{16}H_{21}N$: 243.16231. Found: 243.16193. Anal. calculated for $C_{16}H_{21}N$: C, 79.01; H, 8.64. Found: C, 78.72 ; H, 6.70.

Preparation of 1-acetyl-3-methyl-2-phenylindole (**24**)[38]

Compound **24** was obtained as slightly yellow crystals in 75% isolated yield from the reaction of 2-iodoacetanilide and 1-phenyl-1-propyne using KOAc and LiCl, and stirring for 24 hours at 100 °C (Table 3, entry 58): mp 81-82 °C (lit.[38] mp 80-81.5 °C); IR ($CDCl_3$) 3063, 2922, 1687, 1454, 1393, 1348, 908, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (s, 3H, CH_3), 2.14 (s, 3H, $COCH_3$), 7.40 (m, 8H, ArH), 8.45 (d, 1H, J = 7.2 Hz, ArH) ; ^{13}C NMR ($CDCl_3$) δ 9.43, 27.82, 116.42, 118.25, 118.89, 123.55, 125.44, 128.56, 128.80, 130.34, 133.70, 134.99, 136.90, 171.12, one peak missing; HRMS calculated for $C_{17}H_{15}NO$: 249.11536. Found: 249.11535. Anal. calculated for $C_{17}H_{15}NO$: C, 81.92; H, 6.17. Found: C, 82.35 ; H, 6.35.

Preparation of 1-acetyl-2-isopropyl-3-methylindole (**25**) and 1-acetyl-3-isopropyl-2-methyl-indole (**26**).

Compound **25** was obtained as a pale yellow oil in 65% isolated yield and compound **26** was obtained in 26% isolated yield from the reaction of 2-iodoacetanilide and 4-methyl-2-pentyne using NaOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 60).

1-Acetyl-2-isopropyl-3-methylindole (**25**): Rf 0.75 (4:1 hexanes/ethyl acetate); IR (neat) 3059, 2963, 2928, 1701, 1460, 908, 733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.42 (d, 6H, J = 7.2 Hz, CH_3's), 2.29 (s, 3H, CH_3), 2.73 (s, 3H, $COCH_3$), 3.75 (m, 1H, CH), 7.25 (m, 2H, ArH), 7.47 (m, 1H, ArH), 7.67 (m, 1H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 9.66, 21.44, 26.98, 27.88, 113.57, 114.66, 118.03, 122.26, 123.30, 131.61, 134.78, 142.75, 170.70; HRMS calculated for $C_{14}H_{17}N$: 215.13101. Found: 215.13102.

1-Acetyl-3-isopropyl-2-methylindole (**26**): Rf 0.65 (4:1 hexanes/ethyl acetate); IR (neat) 3060, 2673, 2928, 1700, 1460, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (d, 6H, J = 7.2 Hz, CH_3's), 2.57 (s, 3H, CH_3), 2.73 (s, 3H, $COCH_3$), 3.12 (m, 1H, CH), 7.23 (m, 2H, ArH), 7.67 (m, 1H, ArH), 7.95 (m, 1H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 14.26, 21.94, 25.27, 27.68, 114.94, 119.70, 122.29, 123.12, 125.00, 129.01, 131.08, 136.96, 170.31; HRMS calculated for $C_{14}H_{17}N$: 215.13101. Found: 215.13090.

Preparation of 1-acetyl-2-ethyl-3-methylindole (**27**) and 1-acetyl-3-ethyl-2-methylindole (**28**).

Compound **27** was obtained as a yellow oil in a 30% isolated yield and compound **28** was obtained in a 28% isolated yield from the reaction of 2-iodoacetanilide and 2-pentyne using K_2CO_3 and LiCl, and stirring for 24 hours at 100 °C (Table 3, entry 62).

1-Acetyl-2-ethyl-3-methylindole (**27**): IR (neat) 2976, 1696, 1475, 1462, 1377, 1312, 1211, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H, J = 7.2 Hz, CH_3), 2.33 (s, 3H, CH_3), 2.79 (s, 3H, $COCH_3$), 3.07 (q, 2H, J = 7.2 Hz, CH_2), 7.28 (m, 2H, ArH), 7.49 (m, 1H, ArH), 7.79 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 8.33, 14.35, 21.94, 27.56, 114.37, 118.38,

120.74, 122.59, 123.43, 131.40, 135.30, 139.52, 169.79; HRMS calculated for $C_{13}H_{15}NO$: 201.11536. Found: 201.11592.

1-Acetyl-3-ethyl-2-methyl-indole (**28**): IR (neat) 2970, 1695, 1462, 1396, 1348, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.8 Hz, CH_3), 2.53 (s, 3H, CH_3), 2.67 (q, 2H, J = 7.8 Hz, CH_2), 2.69 (s, 3H, $COCH_3$), 7.23 (m, 2H, ArH), 7.45 (m, 1H, ArH), 7.95 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.16, 14.48, 17.12, 27.51, 115.05, 118.06, 120.74, 122.74, 123.53, 130.19, 132.90, 135.90, 170.18; HRMS calculated for $C_{13}H_{15}NO$: 201.11592. Found: 201.11570.

Preparation of 1-acetyl-3-isopropenyl-2-(hydroxymethyl)indole (**29**)

Compound **29** was obtained as a slightly yellow oil in 27% isolated yield from the reaction of 2-iodoacetanilide and 4-methyl-4-penten-2-yn-1-ol using NaOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 65): IR (neat) 3383, 2976, 1701, 1454, 1373, 1015, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (br s, 1H, OH), 2.10 (s, 3H, =C-CH_3), 2.68 (s, 3H, $COCH_3$), 4.77 (s, 2H, CH_2O), 5.27 (d, 1H, J = 1.5 Hz, =CH), 5.53 (d, 1H, J = 1.5 Hz, =CH), 7.32 (m, 2H, ArH), 7.71 (m, 1H, ArH), 8.21(d, 1H, J = 7.5 Hz, ArH) ; ^{13}C NMR ($CDCl_3$) δ 24.63, 26.38, 55.89, 115.96, 119.40, 119.84, 120.02, 123.70, 125.42, 129.00, 136.47, 136.92, 139.32, 170.64; HRMS calculated for $C_{14}H_{15}NO_2$: 229.11028. Found: 229.11014

Preparation of 2-(2-acetoxy-*n*-propyl)-3-methylindole (**30**) and 1-acetyl-3-(2-hydroxy-*n*-propyl)-2-methylindole (**31**)

Compound **30** was obtained as a yellow oil in a 60% isolated yield and compound **31** was obtained in 16% isolated yield from the reaction of 2-iodoacetanilide and 4-hexyn-2-ol using Na_2CO_3, PPh_3 and *n*-Bu_4NCl, and stirring for 12 hours at 100 °C (Table 3, entry 66).

2-(2-Acetoxy-*n*-propyl)-3-methylindole (**30**): IR (neat) 3401, 3059, 2980, 2932,

1718, 1462, 1246, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, 1H, J = 6.3 Hz, CH_3), 2.09 (s, 3H, $COCH_3$), 2.28 (s, 3H, CH_3), 3.00 (m, 2H, CH_2), 5.18 (m, 1H, CH-O), 7.13 (m, 2H, ArH), 7.28 (t, 1H, J = 7.2 Hz, ArH), 7.52 (d, 1H, J = 7.5 Hz, ArH), 8.10 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 8.78, 19.53, 21.58, 32.75, 70.90, 108.91, 110.50, 118.42, 119.10, 121.51, 129.12, 130.58, 135.63, 170.20; HRMS calculated for $C_{14}H_{17}NO_2$: 231.12602. Found: 231.12618.

1-Acetyl-3-(2-hydroxy-*n*-propyl)-2-methylindole (**31**): IR ($CDCl_3$) 3383, 1701, 1468, 1373, 1015, 910, 733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3H, J = 6.3 Hz, CH_3), 1.75 (br s, 1H, OH), 2.60 (s, 3H, CH_3), 2.72 (s, 3H, $COCH_3$), 2.83 (d, 2H, J = 6.6 Hz, CH_2), 3.10 (m, 1H, CH-O), 7.30 (m, 2H, ArH), 7.50 (m, 1H, ArH), 7.90 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.95, 23.31, 27.80, 34.14, 68.11, 115.12, 115.21, 118.65, 122.10, 123.18, 124.06, 130.80, 134.60, 170.41; HRMS calculated for $C_{14}H_{17}NO_2$: 231.12602. Found: 231.12625.

Preparation of 2-(acetoxymethyl)-3-methylindole (**32**)[39]

Compound **32** was obtained as a slightly yellow solid in 60% isolated yield from the reaction of 2-iodoacetanilide and 2-butyn-1-ol using K_2CO_3, PPh_3 and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 73): mp 88-89 °C (lit.[39] mp 91.0-93.5 °C); IR ($CDCl_3$) 3398, 3059, 2880, 2932, 1717, 1462, 959, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 7.20 (m, 3H, ArH), 7.53 (d, 1H, J = 7.8 Hz, ArH), 8.40 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 8.62, 21.51, 57.76, 111.11, 111.75, 119.39, 119.45, 123.02, 128.34, 128.98, 135.93, 172.36; HRMS calculated for $C_{12}H_{13}NO_2$: 203.09463. Found: 203.0943.

Preparation of 2-(2-acetoxyethyl)-3-methylindole (**33**)

Compound **33** was obtained as a slightly yellow oil in 43% isolated yield from the reaction of 2-iodoacetanilide and 3-pentyn-1-ol using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 75): IR ($CDCl_3$) 3398, 3059, 2980, 1717, 1462, 1375, 1246, 959, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H, $COCH_3$), 2.27 (s, 3H, CH_3), 3.06 (t, 2H, J = 6.9 Hz, CH_2), 4.31 (t, 2H, J = 6.9 Hz, CH_2-O), 7.13 (m, 2H, ArH), 7.27 (m, 1H, ArH), 7.51 (m, 1H, ArH), 7.97 (br s, 1H, NH) ; ^{13}C NMR ($CDCl_3$) δ 8.64, 21.24, 26.05, 63.82, 108.53, 110.53, 118.47, 119.29, 121.19, 129.19, 130.91, 135.56, 171.09; HRMS calculated for $C_{13}H_{15}NO_2$: 217.11034. Found: 217.11018 .

Preparation of 1-acetyl-3-methyl-2-(trimethylsilyl)indole (**34**)

Compound **34** was obtained as a slightly yellow solid in 70% isolated yield from the reaction of 2-iodoacetanilide and 1-(trimethylsilyl)-1-propyne using K_2CO_3 and LiCl, and stirring for 12 hours at 100 °C (Table 3, entry 77): mp 65-67 °C; IR ($CDCl_3$) 2953, 1693, 1474, 1377, 1344, 1249, 910, 756, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.35 (s, 9H, $Si(CH_3)_3$), 2.35 (s, 3H, CH_3), 2.77 (s, 3H, $COCH_3$), 7.20-7.33 (m, 2H, ArH), 7.52 (d, 1H, J = 7.5 Hz, ArH), 7.62 (d, 1H, J = 7.5 Hz, ArH) ; ^{13}C NMR ($CDCl_3$) δ 2.79, 11.30, 26.46, 113.57, 119.48, 122.52, 124.76, 129.39, 134.00, 136.59, 137.12, 168.98; HRMS calculated for $C_{14}H_{19}NOSi$: 245.12359. Found: 245.12367.

Preparation of 2,3-di-*n*-propyl-1-tosylindole (**35**)

Compound **35** was obtained as a slightly yellow oil in 86% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 4-octyne using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 83): IR (neat) 2963, 2932, 1599, 1454, 1366, 1186, 784, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J = 7.5 Hz, CH_3) 1.00 (t, 3H, J = 7.2 Hz, CH_3), 1.57 (m, 2H, CH_2), 1.76 (m, 2H, CH_2), 2.29 (s, 3H, $ArCH_3$), 2.59 (t, 2H, J = 7.8 Hz,

CH_2), 2.95 (t, 2H, J = 7.5 Hz, CH_2), 7.11 (d, 2H, J = 7.8 Hz, ArH), 7.23 (m, 2H, ArH), 7.38 (d, 1H, J = 6.9 Hz, ArH), 7.53 (d, 2H, J = 8.4 Hz, ArH), 8.17 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 13.20, 14.90, 22.30, 23.00, 24.27, 26.16, 26.73, 114.20, 117.60, 119.62, 122.73, 124.38, 124.97, 127.17, 128.38, 130.51, 131.06, 136.81, 144.21; HRMS calculated for $C_{21}H_{25}NSO$: 355.16060. Found: 355.15995. Anal. calculated for $C_{21}H_{25}NSO_2$: C, 70.98; H, 7.04. Found: C, 67.47 ; H, 6.94.

Preparation of 2-*t*-butyl-3-methyl-1-tosylindole (**36**)

Compound **36** was obtained as a slightly yellow oil in 86% isolated yield from the reaction of N-tosyl-2-iodoaniline and 4,4-dimethyl-2-pentyne using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 86): IR (neat) 2963, 2932, 1599, 1475, 1455, 1399, 1177, 936 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (s, 9H, $C(CH_3)_3$), 2.38 (s, 3H, CH_3), 2.40 (s, 3H, $ArCH_3$), 7.09 (d, 2H, J = 8.7 Hz, ArH), 7.28 (d, 2H, J = 4.2 Hz, ArH), 7.34 (m, 1H, ArH), 7.42 (d, 2H, J = 8.4 Hz, ArH), 8.18 (d, 1H, J = 4.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 12.62, 21.37, 31.84, 35.85, 117.92, 118.89, 124.34, 124.39, 124.62, 126.70, 128.29, 132.40, 135.01, 139.59, 143.55, 147.18; HRMS calculated for $C_{20}H_{23}NSO_2$: 341.14495. Found: 341.14463.

Preparation of 2-formyl-3-methyl-1-tosylindole diethyl acetal (**37**) and 3-formyl-2-methyl-1-tosylindole diethyl acetal (**38**).

Compound **37** was obtained as a pale yellow oil in 28% isolated yield and compound **38** was obtained in 28% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 2-butynal diethyl acetal using NaOAc and *n*-Bu_4NCl, and stirring for one day at 100 °C (Table 3, entry 87).

2-Formyl-3-methyl-1-tosylindole diethyl acetal (**37**) : IR (neat) 2976, 2928, 1452, 1369, 1202, 1105, 959, 912, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, 6H, J = 6.9 Hz, CH_3's)

, 2.45 (s, 3H, CH_3), 2.58 (s, 3H, $ArCH_3$), 3.80 (m, 4H, OCH_2's), 6.84 (s, 1H, CH), 7.29 (d, 2H, J = 7.8 Hz, ArH), 7.41 (m, 2H, ArH), 7.59 (d, 1H, J = 7.5 Hz, ArH), 7.92 (d, 2H, J = 8.1 Hz, ArH), 8.29 (d, 1H, J = 8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 10.1, 15.38, 21.69, 68.20, 98.43, 115.42, 119.33, 120.88, 123.61, 125.29, 127.01, 129.50, 131.65, 133.46, 135.69, 136.46, 144.50 ; HRMS calculated for $C_{21}H_{25}NSO_4$: 387.15043. Found: 387.14937.

3-Formyl-2-methyl-1-tosylindole diethyl acetal (**38**): IR (neat) 2976, 2930, 1454, 1391, 1199, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 6H, J = 6.9 Hz, CH_3's), 2.50 (s, 3H, $ArCH_3$), 2.81 (s, 3H, CH_3), 3.70 (m, 4H, OCH_2's), 5.85 (s, 1H, CH), 7.36 (m, 4H, ArH), 7.81 (d, 2H, J = 9.6 Hz, ArH), 8.01 (d, 1H, J = 7.8 Hz, ArH), 8.34 (d, 1H, J = 7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 13.26, 15.37, 21.70, 61.52, 98.65, 114.41, 118.02, 121.01, 123.70, 124.11, 126.52, 128.80, 129.78, 129.96, 135.30, 136.41, 144.83 ; HRMS calculated for $C_{21}H_{25}NSO_4$: 387.15043. Found: 387.15076.

Preparation of 2-ethyl-3-methyl-1-tosylindole (**39**) and 3-ethyl-2-methyl-1-tosylindole (**40**).

These compounds were obtained as a pale yellow oil in a 60% isolated yield as a 1:1 mixture of two regioisomers from the reaction of *N*-tosyl-2-iodoaniline with 2-pentyne using K_2CO_3 and LiCl, and stirring 36 hours at 100 °C (Table 3, entry 90): IR (neat, 1:1 mixture) 3068, 2968, 2934, 1454, 1371, 1229, 1188, 1155, 1092, 910, 812, 735, 704, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture) δ 1.13 (t, 3H, J = 7.5 Hz, CH_3), 1.27 (t, 3H, J = 7.2 Hz, CH_3), 2.14 (s, 3H, CH_3), 2.31 (s, 3H, $ArCH_3$), 2.33 (s, 3H, $ArCH_3$), 2.53 (s, 3H, CH_3), 2.60 (q, 2H, J = 7.5 Hz, CH_2), 3.01 (q, 2H, J = 7.2 Hz, CH_2), 7.23 (m, 8H, ArH), 7.38 (m, 2H, ArH), 7.60 (q, 4H, J = 8.4 Hz, ArH), 8.18 (d, 2H, J = 7.8 Hz, ArH) ; ^{13}C NMR ($CDCl_3$, 1:1 mixture) δ 8.71, 12.53, 14.40, 15.00, 17.35, 19.77, 21.46, 114.57, 114.99, 116.03, 118.20, 118.24, 122.23, 123.08, 123.25, 123.70, 123.91, 129.58, 129.67, 131.45, 131.83, 136.11, 136.31, 136.43, 138.78, 144.26, 144.35.

Preparation of 3-isopropenyl-2-(1-hydroxy-1-methylethyl)-1-tosylindole (**41**)

Compound **41** was obtained as a slightly yellow oil in 45% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 2,5-dimethyl-5-hexen-3-yn-2-ol using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 100 °C (Table 3, entry 91): IR (neat) 3479, 2976, 2928, 1452, 1366, 1188, 1070, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.28 (s, 3H, =C-CH_3), 2.32 (s, 3H, ArCH_3), 2.66 (br s, 1H, OH), 4.79 (s, 1H, C=CH), 5.24 (s, 1H, C=CH), 6.8-7.4 (m, 8H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 21.66, 25.95, 31.01, 32.04, 71.91, 115.11, 120.63, 122.42, 123.20, 124.54, 126.80, 127.11, 128.72, 129.59, 135.44, 136.38, 136.65, 140.92, 144.69 ; HRMS calculated for $C_{21}H_{23}NO_2$: 369.13987. Found: 369.13960.

Preparation of 1-acetyl-3-methylindole (**42**)[41]

1-Acetyl-3-methyl-2-(trimethylsilyl)indole (51 mg, 0.25 mmol) and $AlCl_3$ (33 mg, 0.25 mmol) were added to 5 ml of CH_2Cl_2 and the reaction mixture stirred 30 min at 0 °C. Water was added and the reaction mixture was extracted with ether, dried over $MgSO_4$ and concentrated. Flash column chromatography using 4:1 hexane/ ethyl acetate afforded 38 mg of crystalline product : mp 66-67 °C (lit.[43] mp 66 °C); IR ($CDCl_3$) 2920, 1695, 1448, 1391, 1346, 1246, 1048, 993, 743, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 2.56 (s, 3H, Ac), 7.18 (s, 1H, ArH), 7.30 (m, 2H, ArH), 7.50 (d, 1H, J = 4.5 Hz, ArH), 8.41 (d, 1H, J = 4.5 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 9.58, 23.83, 116.42, 118.16, 118.66, 122.09, 123.22, 125.00, 131.27, 135.67, 168.11; HRMS calculated for $C_{11}H_{11}NO$: 173.08406. Found: 173.08423.

Preparation of 1-acetyl-2-bromo-3-methylindole (**43**)

1-Acetyl-3-methyl-2-(trimethylsilyl)indole (51 mg, 0.25 mmol) and NBS (89 mg, 0.50 mmol) were dissolved in 5 ml of CH_2Cl_2 and refluxed 30 min. The reaction mixture was concentrated and purified by flash chromatography using 4:1 hexane/ethyl acetate to give 44 mg (70 %) of crystalline product: mp 61-62 °C (lit.[42] mp 49-50.5 °C); IR ($CDCl_3$) 2922, 1699, 1609, 1447, 1391, 1346, 1248, 933, 731, 648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.83 (s, 3H, $COCH_3$), 7.27 (m, 2H, ArH), 7.43 (d, 1H, J = 7.8 Hz, ArH), 8.20 (d, 1H, J = 7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 10.46, 28.14, 107.45, 118.07, 118.10, 120.84, 123.47, 125.18, 129.38, 136.96, 169.76; rapidly decomposed, so no mass spectrum or elemental analysis could be obtained.

Preparation of ethyl *E*-3-(1-acetyl-3-methyl-2-indolyl)acrylate (**44**)

1-Acetyl-3-methyl-2-(trimethylsilyl)indole (102 mg, 0.50 mmol), ethyl acrylate (100 mg, 1.0 mmol), palladium acetate (112 mg, 0.5 mmol) and 10 ml of DMF were added to a 4 dram vial equipped with a stirring bar and teflon-lined screwcap. After being heated for 2 days at 100 °C, the reaction mixture was diluted with ether, washed with saturated aqueous NH_4Cl and water , dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography using 4:1 hexane/ethyl acetate to afford 102 mg (75%) of a crystalline solid: mp 70-71 °C; IR ($CDCl_3$) 3022, 2986, 1705, 1630, 1537, 1454, 1375, 1281, 1217, 1034, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3H, J = 7.2 Hz, CH_3), 2.37 (s, 3H, CH_3), 2.67 (s, 3H, $COCH_3$), 4.31 (q, 2H, J = 7.2 Hz, CH_2), 6.10 (d, 1H, J = 15.9 Hz, =CH), 7.25-7.42 (m, 2H, ArH), 7.54 (d, 1H, J = 7.8 Hz, ArH), 7.89 (d, 1H, J = 15.9 Hz, =CH), 8.07 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 10.36, 14.40, 27.44, 60.73, 115.21, 119.67, 121.28, 121.92, 123.44, 126.40, 130.55, 131.30, 135.53, 136.50, 166.40, 169.85; HRMS calculated for $C_{14}H_{17}NO_3$: 271.12084. Found: 271.12061.

Preparation of *E*-4-(1-acetyl-3-methyl-2-indolyl)-3-buten-2-one (**45**)

Compound **45** was obtained as a yellow oil in 50% isolated yield from the reaction of 1-acetyl-3-methyl-2-(trimethylsilyl)indole and methyl vinyl ketone using the same method reported above for the synthesis of ethyl *E*-3-(1-acetyl-3-methyl-2-indolyl)acrylate: IR (neat) 2920, 1695, 1653, 1603, 1452, 1375, 1346, 1254, 1207, 909, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, $COCH_3$), 2.42 (s, 3H, CH_3), 2.72 (s, 3H, $COCH_3$), 6.36 (d, 1H, J = 16.2 Hz, =CH), 7.34 (m, 2H, ArH), 7.57 (d, 1H, J = 9.0 Hz, ArH), 7.83 (d, 1H, J = 16.2 Hz, =CH), 7.94 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 10.46, 27.38, 27.45, 114.81, 119.94, 122.20, 123.50, 126.41, 129.74, 130.90, 131.75, 134.87, 136.35, 169.95, 197.96 ; HRMS calculated for $C_{15}H_{15}NO_2$: 241.11028. Found: 241.11054.

REFERENCES

1. (a) Sundberg, R. J. *Prog. Heterocyclic Chem.* **1989**, *1*, 111. (b) Saxon, J. E. *Nat. Prod. Rep.* **1986**, *3*, 357; **1987**, *4*, 591; **1989**, *6*, 1. (c) Manske, R. H. F. *"The Alkaloids"* , Vol. 1-17, Wiley, New York, **1959-1979**. (d) Hesse, M. *" Indolalkaloide in Tabellin"*, Springer, Berlin, **1964**. (e) Glasby, J. S. *Encyclopedia of Alkaloids*, Plenum Press, NewYork, **1975**.

2. Horwell, D. C. *Tetrahedron* **1980**, *36*, 3123.

3. Oikawa, Y.; Yonemitsu. *J. Chem. Soc., Perkin Trans. I* **1976**, 1479; *J. Org. Chem.* **1976**, *41*, 3123.

4. Mangeney, P.; Andriamialisoa, R.; Langlois, Y. *J. Am. Chem. Soc.* **1979**, *101*, 2243.

5. (a) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*, Vol. 4, Pergaman, Oxford, **1984**. (b) Sundberg, R. J. *Pyrroles and their Benzo Derivatives: Synthesis and Applications* in reference 5a, p 313-376.

6. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, J. R. *Principles and Applications of Organotransition Metal Chemistry,* 2nd edition, University Science Books, Mill Valley, CA (USA), **1987**.

7. Kametani, T.; Takahashi, K.; Ihara, M.; Fukumato, K. *Heterocycles* **1975**, *3*, 691.

8. Osuka, A.; Mori, Y.; Suzuki, H. *Chem. Lett.* **1982**, 2031.

9. Kametani, T. Ohsawa, J.; Ihara, M. *Heterocycles* **1980**, *14*, 277.

10. Maruyama, K.; Nagai, N.; Naruta, Y. *Chem. Lett.* **1987**, 97.

11. Crotti, C.; Ceninic, S.; Rindone, B.; Tollari, S. *J. Chem. Soc., Chem Commun.* **1986**, 1575.

12. (a) Tsuji, J.; Huh, K.T.; Yokoyama, Y.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1575. (b) Tsuji, J.; Huh, K. T.; Watanabe, Y. *Tetrahedron Lett.* **1986**, *27*, 377. (c) Tsuji, J.; Huh, K. T.; Watanabe, Y. *J. Org. Chem.* **1982**, *52*, 1673.

13. Grotjahn, D. B.; Vollhart, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2091.

14. Sheppard, G. S.; Vollhart, K. P. C. *J. Org. Chem.* **1986**, *51*, 5496.

15. Nechvatal, G.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1982**, 467.

16. Nechvatal, G.; Widdowson, D. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1260.

17. Mori, M.; Kudo, S.; Ban, Y. *J. Chem. Soc., Perkin Trans. I* **1979**, 771.

18. Mori, M.; Kudo, S.; Ban, Y. *Tetrahedron Lett.* **1976**, 1803.

19. Miller, R. B.; Moock, T. *Tetrahedron Lett.* **1980**, *21*, 3319.

20. (a) Somei, M.; Saida, Y. Komura, N. *Chem. Pharm. Bull.* **1986**, *34*, 4116. (b) Somei, M., Yamada, F.; Naka, K. *Chem. Pharm. Bull.* **1987**, *35*, 1322. (c) Somei, M.; Amari, H.; Makita, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3971.

21. Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5088.

22. Weider, P. R.; Hegedus, L. S.; Asada, H.; D'Andrew, S. V. *J. Org. Chem.* **1985**, 50, 4276.

23. Larock, R. C.; Liu, C. L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1985**, *26*, 4459.

24. Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H. *Tetrahedron Lett.* **1985**, *26*, 5963.

25. Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.

26. Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581.

27. Kondo, Y.; Sakamoto, T.; Yamanaka, H. *Heterocycles* **1987**, *29*, 1013.

28. Iritani, K.; Matsubra, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799.

39. Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4282.

30. Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1671. (b) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515.

31. Larock, R. C.; Berrios-Peña, N. G.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447.

32. Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930.

33. Naruse, Y.; Ito, Y.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 2256.

34. Cacchi, S. *Pure Appl. Chem.* **1990**, *62*, 713.

35. Pouchert, C. J. *Aldrich Library of NMR Spectra*, Edition II, Vol. 2, Compound 519-D.

36. Russell, G. A.; Yao, C. F.; Toshtoush, H. I.; Russell, J. E.; Dedolph, D. F. *J. Org. Chem.* **1991**, *56*, 663.

37. Ito, Y.; Kabayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73.

38. Itahara, T. *J. Org. Chem.* **1985**, *50*, 5272.

39. Gassman, P. G.; Campbell, G. A.; Mehta, G. *Tetrahedron* **1972**, *28*, 1749.

40. Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567.

41. Pindur, U.; Flo, C.; Akgun, E.; Tunali, M. *J. Liebigs Ann. Chem.* **1986**, 1621.

42. Hino, T.; Nakamura, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1975**, *23*, 2990.

43. Berrios-Peña, N. G. Ph. D. Dissertation, Iowa State University, **1989**.

44. Harrison, L. W. Ph. D. Dissertation, Iowa State University, **1984**.

PART IV. PALLADIUM-CATALYZED CARBO- AND HETERO-ANNULATION OF INTERNAL ALKYNES

INTRODUCTION

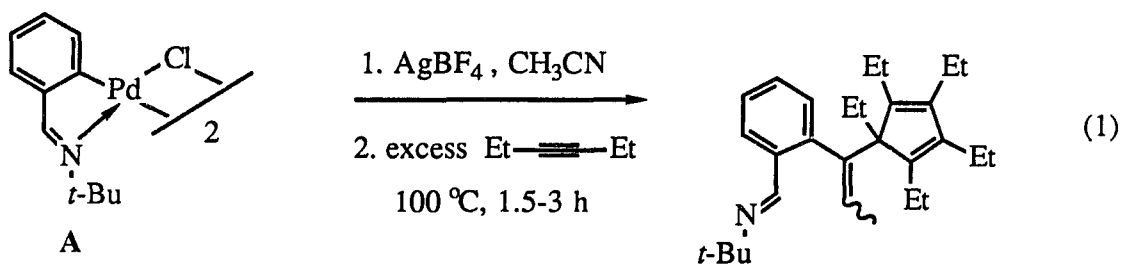
The discovery of the cyclometallation of organic compounds,[1] leading to the formation of both metal-carbon and metal-donor atom bonds, has initiated a thorough study of intramolecular organometallic compounds. Much work has been reported on the preparation and characterization of cyclopalladation compounds and this has been summarized in recent reviews.[2-10] Although this is now becoming a subject of rapidly growing interest, only limited applications to organic synthesis have been developed.[11]

The reactions of cyclometallated compounds with alkynes can produce a great variety of products. The reaction products are dependent upon several parameters, including the nature of the cyclometallated ligand, the substituents on the alkynes, the stoichiometry, and other ligands on the metal atom. So far, palladium(II) is the most efficient metal for achieving intramolecular C-H activation of a great variety of functionalized arenes.[12] Alkynes are also known to be very useful building blocks for organic synthesis, since they display a wide range of reactivity and can be considered as either electrophiles or nucleophiles, depending upon the nature of the substituents.[13] This introduction examines the synthetic approaches of cyclometallated compounds with alkynes.

Most cyclopalladated compounds are quite stable, especially toward thermal decomposition. However, it has been shown that the reactivity of organopalladium compounds can be dramatically increased by using their cation derivatives instead of the chloride-substituted compounds. This simple change in the coordination sphere of the metal enhances the reactivity of the carbon-palladium bond towards any kind of insertion, and also significantly lowers the thermal stability of the new compound. Another efficient way of activating palladium compounds is to use their iodide complexes; however, the substitution of

iodide often has a side effect, since depalladation of the organopalladium compound occurs with some decomposition of the resulting organic moiety.

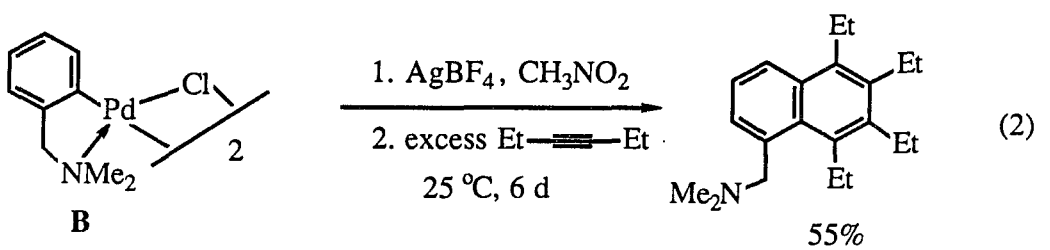
The cyclopalladated complex **A** reacts readily with 3-hexyne to afford the three alkyne unit insertion product (eq. 1).[14] This type of reaction takes place when β-elimination is possible after alkyne insertion. One possible way to prevent multiple insertion is to adjust



(1)

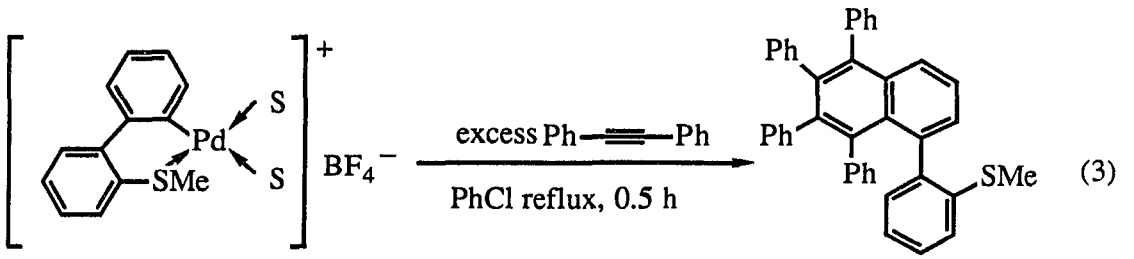
the palladium-alkyne stoichiometry so that no multiple insertion can take place, but this method is not always effective.[14]

Aryl ring annulation has been observed during the reaction of cyclopalladated *N,N*-dimethylbenzylamine (**B**) and 3-hexyne (eq. 2).[15]



(2)

The reaction of *o*-palladated biphenyl compounds stabilized by the intramolecular coordination of an SCH_3 unit with diphenylacetylene leads to aryl rings when carried out at relatively high temperatures (eq. 3).[16]

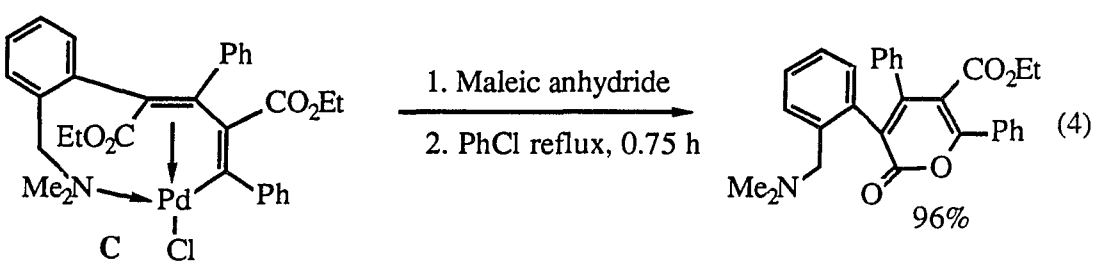


S = THF, MeCN

65-80%

(3)

Reaction of the alkoxycarbonyl-containing compound **C** with maleic anhydride led to the cleavage of an O-Et bond and formation of the corresponding pyrone in high yield (eq. 4).[17] The failure to form a new C-N bond during this reaction may be a consequence of

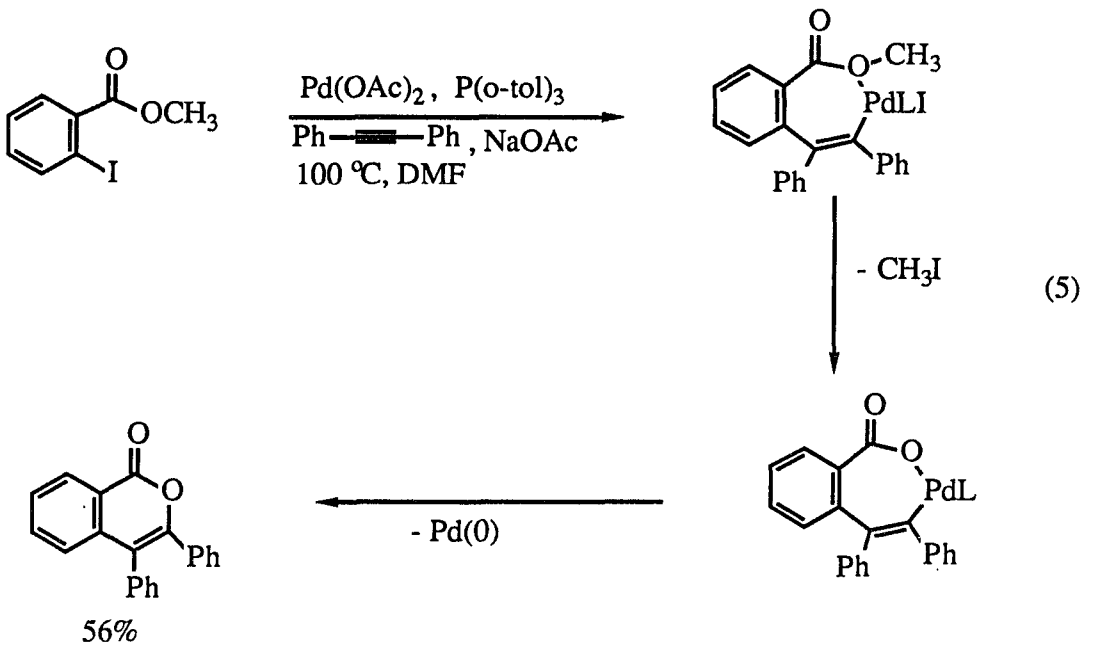


C

(4)

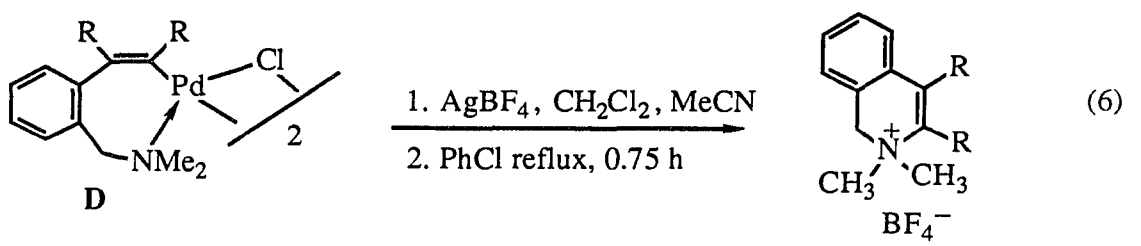
the greater flexibility of the $ArCH_2NMe_2$ unit. This prevents the N atom from remaining in the coordination sphere of the palladium; hence, nucleophilic attack by the NMe_2 group on the activated alkene cannot occur.[18]

The mechanism by which the O-alkyl bond is broken above is not yet clear. A related result was found by Heck[19] when investigating the reaction between methyl 2-iodobenzoate and diphenylacetylene in the presence of a catalytic amount of palladium. This reaction gave a good yield of 3,4-diphenylbenzopyrone, which is probably formed via a seven-membered cyclopalladated ring (eq. 5).



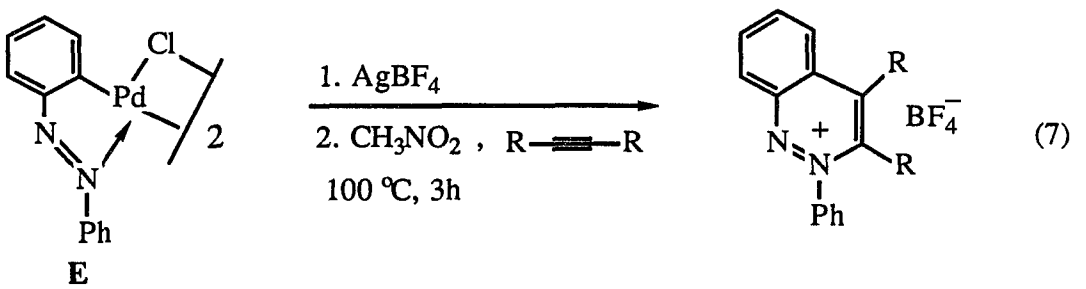
(5)

The mono-inserted complex **D** was activated by abstraction of the chloride ion by a silver salt, producing the heterocyclic compound in a moderate yield (eq. 6).[20]



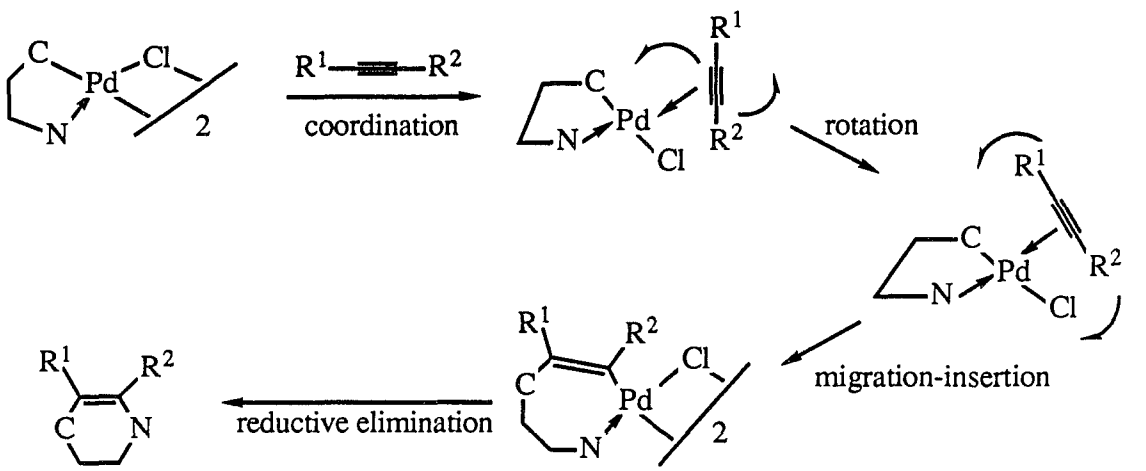
(6)

The reactivity of the cyclopalladated azobenzene dimer **E** is greatly enhanced when the chloride ligands are replaced by tetrafluoroborate ions. Disubstituted alkynes react with this complex under mild conditions to form 2-phenyl cinnolinium tetrafluoroborates in moderate to good yields (eq. 7).[21]



E (7)

Reactions of cyclopalladated compounds with asymmetric alkynes are highly regioselective. The regioselectivity is explained in Scheme 1. The first step is thought to

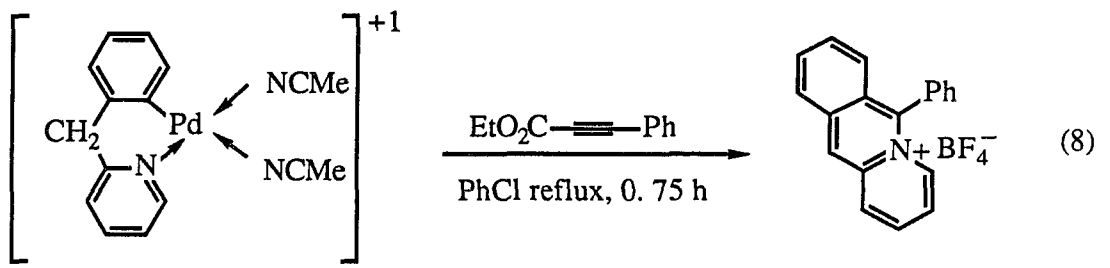


Scheme 1

involve π-system coordination of the alkyne to the metal; definite evidence for this step has not yet been obtained. However, it is rationalized by analogy with the coordination of alkenes to palladium. The alkyne is thus perpendicular to the coordination plane of the metal and it should be able to "rotate" to locate one of the carbon atoms close to the carbon-palladium σ-bond. The regioselectivity of the reaction is in accord with this suggestion, since the carbon bearing the smaller R group is found on the metal and this reduces the steric hindrance at the palladium center.[12] Formation of the C-N bond can be rationalized by a simple reductive elimination

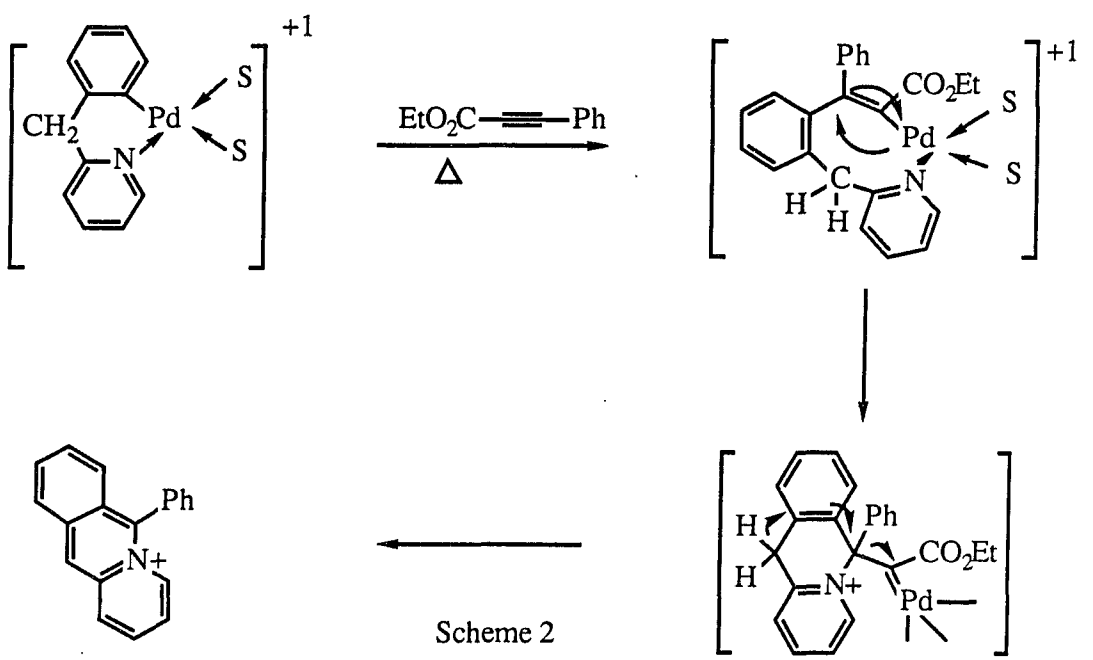
process[22] through which the organic ligand is oxidized, while the carbon-nitrogen bond is produced.

The reaction between the cationic palladated 2-benzylpyridine complex and ethyl 3-phenylpropynoate gave a benzoquinolizinium derivative in moderate yield (eq. 8).[23] A



(8)

possible reaction pathway for its formation is described in Scheme 2. The first step

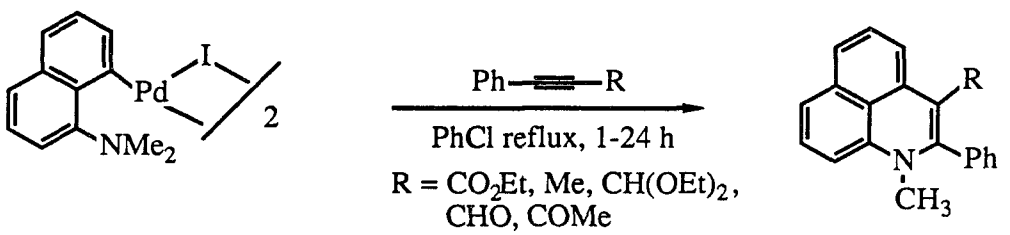


Scheme 2

involves nucleophilic attack of the nitrogen atom on the palladated vinyl group at the carbon not bonded to the palladium, similar to a classical Michael-type addition of a tertiary amine to

an alkene activated by an ester group. This can occur via dissociation of the nitrogen from the palladium to form a transient palladium(II) complex that is coordinatively unsaturated. Such a 14-electron species has never been structurally characterized. Nevertheless, it has been postulated to be an intermediate in the reductive-elimination process for palladium(II) compounds, based on theoretical calculations.[24]

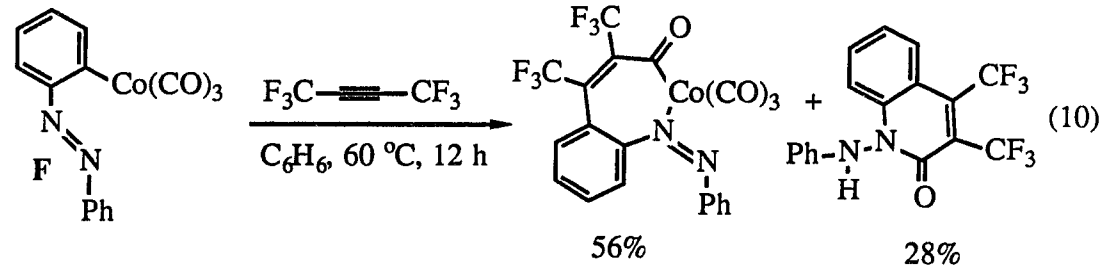
Another efficient method for synthesizing heterocyclic compounds is to use iodide derivatives, which have been shown to display thermal behavior similar to that observed for related cationic complexes (eq. 9).[25] The loss of a methyl group has often been observed



(9)

for ligands containing an NMe unit. The iodide ligand in the reaction promoted formation of the C-N bond during the depalladation of the complex. This might be due largely to its poor σ-donor properties compared to those of the chloride ligand. Pfeffer[25] concluded that the regioselectivity of the reaction was being controlled by steric effects due to the alkynyl substituents, rather than by electronic factors.[26]

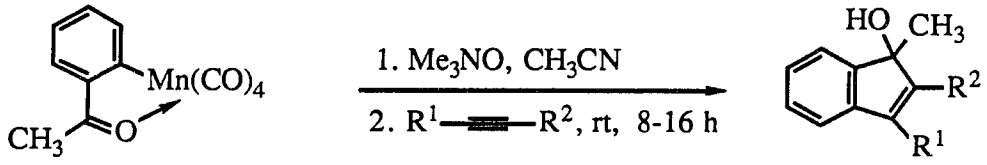
Related syntheses of heterocycles have also been performed with other transition metals. The cobalt azobenzene complex **F** reacted with hexafluoro-2-butyne to give 2-quinolone derivatives (eq. 10).[27] Unfortunately, the cobalt compound must be synthesized by a



(10)

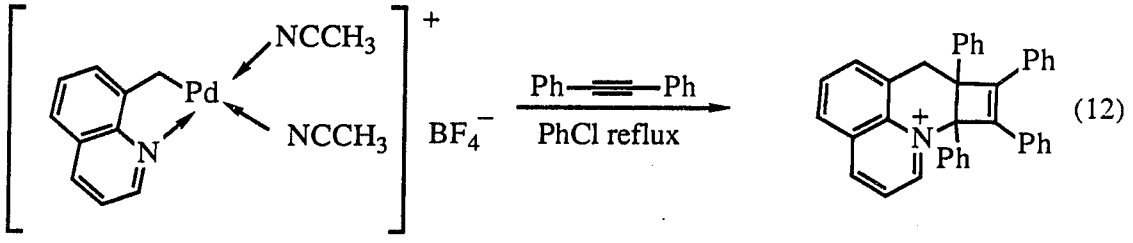
transmetallation reaction between cyclopalladated azobenzene and $Co(CO)_4^-$. This reaction is rather limited in scope, since it cannot be extended to other alkynes.[28]

(η^2-2-Acetylphenyl)tetracarbonylmanganese can be converted into indenols in high yield and with excellent regioselectivity upon reaction with alkynes (eq. 11).[29]



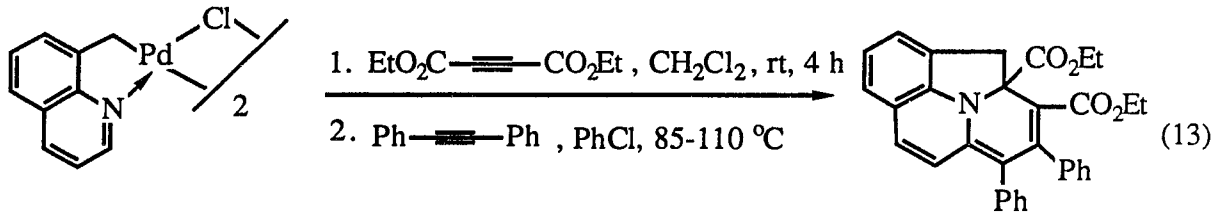
(11)

The formation of heterocycles for those compounds where two alkynes have been inserted into the palladium-carbon bond is frequently observed (eq. 12).[30] Markedly



(12)

different products were produced when a sequence of alkynes activated with electron-withdrawing groups and other internal alkynes were used (eq. 13).[30]



(13)

From the above results, the possibility of synthesizing carbo- and heterocycles via palladium-catalyzed annulation of functionalized aryl halides with internal alkynes, without any multiple-insertion product, was investigated. Such methodology might prove useful for the synthesis of a variety of biologically active substrates.

RESULTS AND DISCUSSION

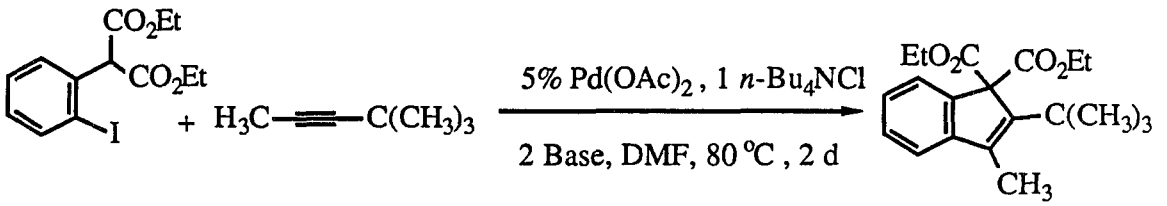
Carboannulation

Initial studies were aimed at finding general reaction conditions for the palladium-catalyzed carboannulation of internal alkynes. The reaction between diethyl 2-iodophenyl - malonate and 4,4-dimethyl-2-pentyne was chosen for the initial model study, and the results are summarized in Table 1.

The reactions were first attempted at 80 ^{o}C using KOAc or Na_2CO_3 as the base. These bases were chosen because they had generally provided good results in the *n*-Bu_4NCl-mediated, palladium-catalyzed carboannulation of vinylic cyclopropanes and vinylic cyclobutanes discussed in the second part of this dissertaion. The reactions using KOAc as the base provided a moderate yield of the desired product with small amounts of multiple-insertion products. To decrease the multiple-insertion products, the concentration of reactant was lowered. These reactions provided an 85% yield of the carboannulation product without any side products, but the reactions required longer reaction times (entries 3 and 4). Using PPh_3 with the same base in this reaction did not change the ratio of the desired product to multiple-insertion products. The reactions using Na_2CO_3 as the base afforded 20-45% yields of the desired product with a small amount of unreacted starting material (entries 5-8). When less than five equivalents of 4,4-dimethyl-2-pentyne were used, the reactions were slow, and the yields were slightly lower compared to the reactions with five equivalents of the alkyne (entries 9-12).

Having gained an understanding of the factors that were influencing the carboannulation process, we explored the scope and limitation of our annulation methodology. In some cases, the *n*-Bu_4NCl-mediated reactions were very sensitive to the purity of the salt and thus LiCl was used instead of *n*-Bu_4NCl to overcome the difficulty of reproducibility.

Table 1. Reaction of diethyl 2-iodophenylmalonate with 4,4-dimethyl-2-pentyne.



Entry[a]	Equiv. of acetylene	Base	% Isolated yield	Comments
1[b,c]	5	KOAc	49	formation of multi-insertion products
2[b,c,d]	5	KOAc	55	formation of multi-insertion products
3	5	KOAc	86	-
4[d]	5	KOAc	85	-
5[b]	5	Na_2CO_3	42	formation of multi-insertion products
6[b,d]	5	Na_2CO_3	20	30% aryl halide recovered
7	5	Na_2CO_3	45	30% aryl halide recovered
8[d]	5	Na_2CO_3	25	50% aryl halide recovered
9	4	KOAc	86	-
10	3	KOAc	73	-
11	2	KOAc	73	-
12	1	KOAc	60	-

[a]All reactions were run on a 0.25 mmol scale in 5 ml DMF.

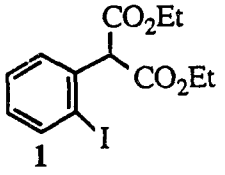
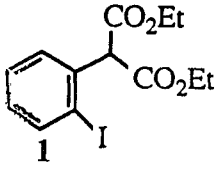
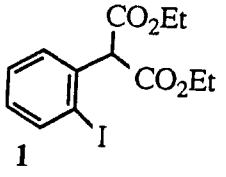
[b]1 ml DMF used.

[c]1 day reaction.

[d]5% PPh_3 added.

The carboannulation was attempted using standard conditions (5% $Pd(OAc)_2$, 1 *n*-Bu_4NCl or LiCl, 2 equivalents of base, 2-5 equivalents of internal alkyne, DMF, 80 °C). Occasionally, 5% PPh_3 was added to the reactions. The carboannulation results are summarized in Table 2.

Table 2. Palladium-catalyzed carboannulation of internal alkynes.

Entry[a]	Aryl halide	Alkyne	Halide source	Base
1	 1	5 CH_3—≡—$C(CH_3)_3$	*n*-Bu_4NCl	KOAc
2			*n*-Bu_4NCl	KOAc
3			LiCl	K_2CO_3
4			LiCl	KOAc
5	 1	5 CH_3—≡—$Si(CH_3)_3$	*n*-Bu_4NCl	KOAc
6			*n*-Bu_4NCl	NaOAc
7			LiCl	KOAc
8			LiCl	NaOAc
9			LiCl	K_2CO_3
10			LiCl	Na_2CO_3
11	 1	3 *n*-Pr—≡—*n*-Pr	*n*-Bu_4NCl	KOAc

[a]All reactions were run on a 0.25 mmol scale at 80 °C in 5 ml DMF.

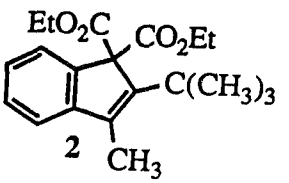
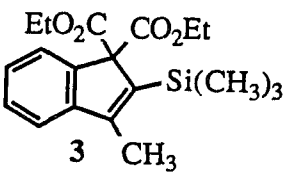
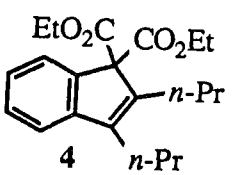
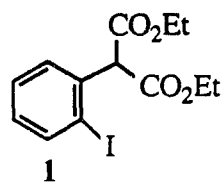
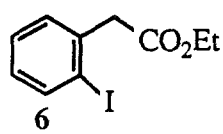
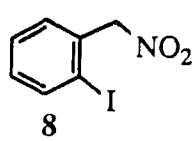
5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	48	 **2**	86
+	48		85
–	24		49
–	48		85
–	24	 **3**	40
–	24		40
–	16		69
–	16		0
–	16		81
–	16		0
–	12	 **4**	58

Table 2. (continued)

Entry[a]	Aryl halide	Alkyne	Halide source	Base
12			*n*-Bu_4NCl	KOAc
13			*n*-Bu_4NCl	NaOAc
14			*n*-Bu_4NCl	Na_2CO_3
15			LiCl	KOAc
16			LiCl	K_2CO_3
17	 **1**	2 Ph—≡—Ph	*n*-Bu_4NCl	Na_2CO_3
18			*n*-Bu_4NCl	KOAc
19			*n*-Bu_4NCl	KOAc
20			LiCl	K_2CO_3
21			LiCl	KOAc
22	 **6**	2 Ph—≡—Ph	*n*-Bu_4NCl	KOAc
23[b]			LiCl	KOAc
24[b]			LiCl	K_2CO_3
25	 **8**	5 CH_3—≡—$C(CH_3)_3$	*n*-Bu_4NCl	KOAc

[b]Reaction was run at 100 °C.

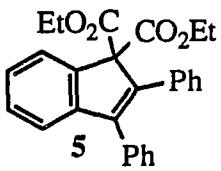
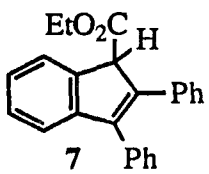
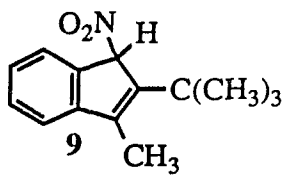
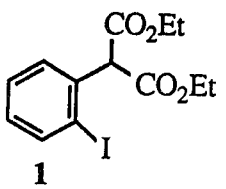
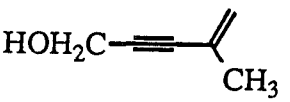
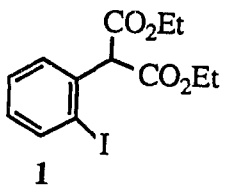
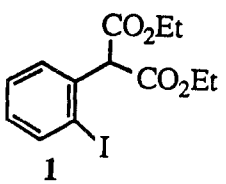
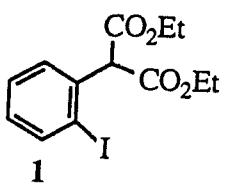
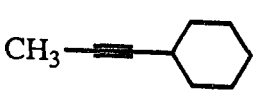
5% PPh_3	Reaction time (h)	Product	% Isolated yield
+	12		69
–	12		35
+	12		20
–	48		72
–	48		57
–	24	 **5**	61
–	24		66
+	24		66
–	48		20
–	48		61
–	36	 **7**	40
–	48		76
–	48		29
–	24	 **9**	50

Table 2. (continued)

Entry[a]	Aryl halide	Alkyne	Halide source	Base
26			LiCl	KOAc
27			LiCl	K_2CO_3
28	 **1**	2 	*n*-Bu_4NCl	KOAc
29			LiCl	KOAc
30			LiCl	K_2CO_3
31	 **1**	2 	LiCl	KOAc
32			LiCl	K_2CO_3
33	 **1**	5 	LiCl	KOAc
34			LiCl	K_2CO_3
35	 **1**	2 	LiCl	KOAc

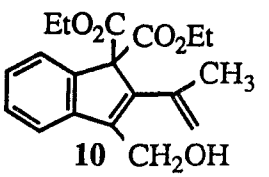
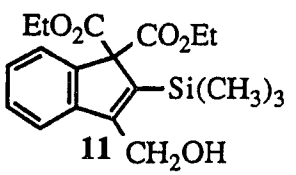
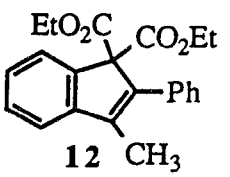
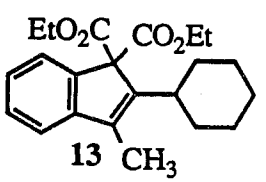
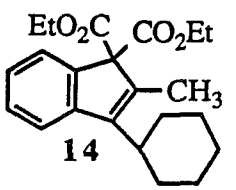
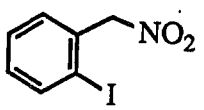
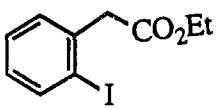
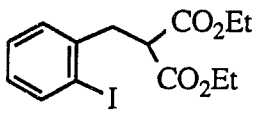
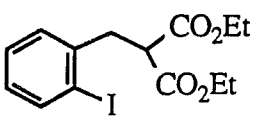
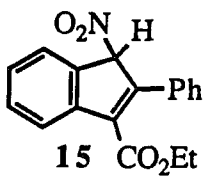
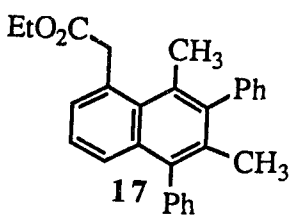
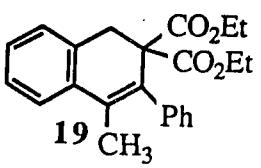
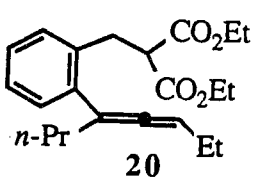
5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	24		50
–	24		50
–	24	 **10**	40
–	48		40
–	48		40
–	24	 **11**	36
–	24		38
–	48	 **12**	63
–	48		60
–	48	 **13**  **14**	63 (6:1)

Table 2. (continued)

Entry[a]	Aryl halide	Alkyne	Halide source	Base
36	 **8**	2 EtO_2C—≡—Ph	LiCl	KOAc
37			LiCl	K_2CO_3
38	 **16**	2 CH_3—≡—Ph	LiCl	KOAc
39			LiCl	K_2CO_3
40[c]	 **18**	2 CH_3—≡—Ph	LiCl	KOAc
41[c]			LiCl	NaOAc
42[c]			LiCl	KOAc
43[c]			LiCl	NaOAc
44[c]	 **18**	3 *n*-Bu—≡—*n*-Bu	LiCl	KOAc
45[c]			LiCl	NaOAc

[c]The reaction provided many side products.

5% PPh_3	Reaction time (h)	Product	% Isolated yield
–	24	 **15**	50
–	24		50
–	48	 **17**	75
–	48		43
+	48	 **19**	27
+	48		20
–	48		-
–	48		-
–	48	 **20**	30
–	48		20

The reactions of diethyl 2-iodophenylmalonate and 4,4-dimethyl-2-pentyne with and without PPh_3 were examined with KOAc as the base in the presence of *n*-Bu_4NCl (entries 1 and 2). The use of PPh_3 in this reaction afforded virtually the same yield of the desired product as the reaction run in the absence of PPh_3. Another reaction using KOAc as the base in the presence of LiCl provided an 85% yield of the desired product (entry 4). These results show that the reaction using LiCl afforded the same yield of the desired product as the reaction using *n*-Bu_4NCl.

The reactions of diethyl-2-iodophenylmalonate with 1-trimethylsilyl-1-propyne were examined with KOAc or NaOAc as the base in the presence of *n*-Bu_4NCl (entries 5 and 6). Both reactions provided a 40% yield of the desired product with several side products. The reactions using KOAc or K_2CO_3 as the base in the presence of LiCl provided a high yield of the desired product without multiple-insertion products, but the reactions using Na_2CO_3 and NaOAc were very slow and only low yields of the desired product were observed. Based on the above results, subsequent reactions using LiCl were examined using KOAc and K_2CO_3 as the base.

The reactions of diethyl-2-iodophenylmalonate with 4-octyne were examined using several bases in the presence of *n*-Bu_4NCl (entries 11-14). These reactions afforded a moderate yield of the desired product and various amounts of multiple-insertion products depending on the base used. The reaction of diethyl 2-iodophenylmalonate with 4-octyne using KOAc as the base in the presence of LiCl provided a higher yield of the desired product than the reaction using K_2CO_3 as the base (entries 15 and 16).

The reaction of diethyl 2-iodophenylmalonate with diphenylacetylene was also examined (entries 17-21). The reaction using KOAc in the presence of *n*-Bu_4NCl provided a slightly higher yield of the desired product and a shorter reaction time than the reaction using the same base in the presence of LiCl (entries 18 and 21).

The reaction of ethyl 2-iodophenylacetate with diphenylacetylene using KOAc as the base in the presence of LiCl provided a much higher yield of the desired product compared to the same reaction using *n*-Bu_4NCl (entries 22 and 23).

The reaction of 2-iodophenylnitromethane with 4,4-dimethyl-2-pentyne and several different bases and chloride sources provided a 50% yield of the desired product with only a small amount of multiple-insertion products (entries 25-27).

The next set of experiments explored the annulation using aryl halides and alkynes containing an hydroxy group (entries 28-32). The reaction of diethyl 2-iodophenylmalonate with 4-methyl-4-penten-2-yn-1-ol provided a 40% yield of the desired product without any side product (entries 28-30). The regiochemistry of the product is uncertain, but both the ^1H NMR and ^{13}C NMR spectra showed only a single regioisomer. The reactions of diethyl 2-iodophenylmalonate with 3-trimethylsilyl-2-propyn-1-ol provided 36-38% yields of the desired product alongside a small amount of side products (entries 31 and 32).

The reactions of diethyl-2-iodophenylmalonate with 1-phenyl-1-propyne provided 60-63% yields of the desired product without any side products (entries 33 and 34). The reaction of diethyl-2-iodophenylmalonate with 1-cyclohexyl-1-propyne provided two regioisomers in a ratio of 6:1 (entry 35). The isomeric ratio was determined by GC and GC-MS, but only the major product was recognizable by ^1H NMR spectroscopy. The assignment of regiochemistry is based on analogy with our earlier indole work.

The reaction of 2-iodophenylnitromethane with ethyl 3-phenyl-2-propynoate was examined employing KOAc and K_2CO_3 as the bases. The reactions provided a 50% yield of a single regioisomeric product, plus small amounts of decomposed aryl halide (entries 36 and 37).

The reaction of ethyl 2-iodophenylacetate with 1-phenyl-1-propyne was examined using KOAc and K_2CO_3 in the presence of LiCl. The reaction provided only double insertion

product in a moderate to high yield. The product was identified by ^{1}H and ^{13}C NMR spectroscopy.

In an attempt to form six-membered carbocyclic compounds, the reaction of 2-iodobenzylmalonate with 1-phenyl-1-propyne was examined (entries 40-43). The reaction provided about 20-27% of the desired product, but the product contained decarboalkoxylation side product. Another reaction using 4-octyne provided the eliminated product and multiple-insertion products (entries 44 and 45).

The following reactions did not provide any of the desired product: dimethyl 2-iodophenylmalonate with ethyl 3-phenylpropynoate or 3-phenylpropynal; 2-iodoacetophenone with diphenylacetylene, 1-phenyl-1-propyne, 4-octyne or 4,4-dimethyl-2-pentyne.

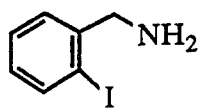
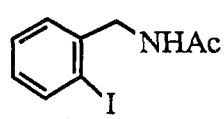
From the above results, the palladium-catalyzed carboannulation of internal alkynes provides 2,3-disubstituted indenes with good regioselectivity. The formation of six-membered ring products is much more difficult than formation of the five-membered ring compounds.

Heteroannulation

With the success of our heteroannulation approach to indoles, we were encouraged to look at the heteroannulation of alkynes using other aryl halides. The heteroannulation of internal alkynes was therefore examined using LiCl or *n*-Bu_4NCl as the chloride source. The results are summarized in Table 3.

The reactions of 2-iodobenzylamine with 4-octyne were examined using several different bases (entries 1-8). The results show that the reactions using KOAc or NaOAc as the base provided a low yield of the desired product alongside a small amount of multiple-insertion

Table 3. Palladium-catalyzed reactions of hetero-substituted aryl halides with internal alkynes.

Entry[a]	Aryl halide	Alkyne	Halide source	Base
1	 **21**	3 *n*-Pr—≡—*n*-Pr	LiCl	KOAc
2[b]			LiCl	KOAc
3[b]			*n*-Bu_4NCl	KOAc
4[b]			*n*-Bu_4NCl	K_2CO_3
5[c]			LiCl	KOAc
6[c]			LiCl	KOAc
7[c]			LiCl	NaOAc
8[c]			LiCl	NaOAc
9	 **23**	2 EtO_2C—≡—Et	LiCl	K_2CO_3
10			LiCl	K_2CO_3
11			LiCl	KOAc
12			LiCl	KOAc
13			*n*-Bu_4NCl	K_2CO_3
14[b]			*n*-Bu_4NCl	KOAc

[a]The reactions were run on a 0.25 mmol scale.

[b]The reaction provided multiple-insertion products as the major products.

[c]The reaction provided a small amount of multiple insertion product.

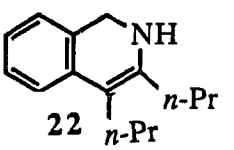
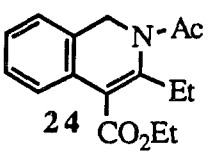
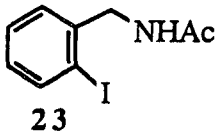
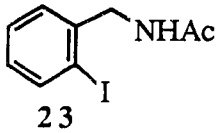
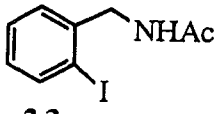
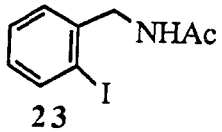
5% PPh_3	Reaction conditions	Product	% Isolated yield
+	120 °C, 2 d	 **22**	34
–	120 °C, 2 d		0
+	120 °C, 2 d		0
+	120 °C, 2 d		0
–	140 °C, 1 d		20
+	140 °C, 1 d		27
–	140 °C, 1 d		20
+	140 °C, 1 d		39
+	100 °C, 1 d	 **24**	30
–	100 °C, 1 d		15
–	100 °C, 1 d		10
+	100 °C, 1 d		45
+	100 °C, 1 d		30
–	100 °C, 1 d		0

Table 3. (continued)

Entry[a]	Aryl halide	Alkyne	Halide source	Base
15	 **23**	2 $EtO_2C{-}{\equiv}{-}Ph$	LiCl	NaOAc
16			LiCl	KOAc
17	 **23**	2 $Ph{-}{\equiv}{-}Ph$	*n*-Bu_4NCl	KOAc
18			*n*-Bu_4NCl	NaOAc
19	 **23**	2 $CH_3{-}{\equiv}{-}Ph$	*n*-Bu_4NCl	KOAc
20			*n*-Bu_4NCl	NaOAc
21			*n*-Bu_4NCl	Na_2CO_3
22	 **23**	2 $HOH_2C{-}{\equiv}{-}Ph$	LiCl	KOAc

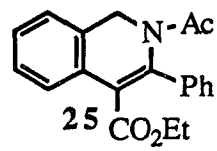
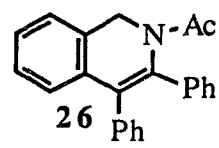
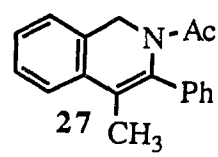
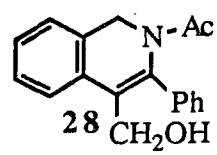
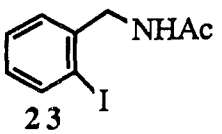
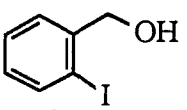
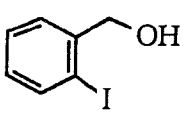
5% PPh_3	Reaction conditions	Product	% Isolated yield
–	100°C, 1 d	 **25**	80
–	100°C, 1 d		80
–	120 °C, 1 d	 **26**	83
–	120 °C, 1 d		69
–	100 °C, 2 d	 **27**	58
–	100 °C, 2 d		58
+	100 °C, 2 d		62
–	100 °C, 1 d	 **28**	43

Table 3. (continued)

Entry[a]	Aryl halide		Alkyne	Halide source	Base
23				LiCl	NaOAc
24	 **23**	2	OHC—≡—Ph	LiCl	KOAc
25				LiCl	NaOAc
26[c]	 **30**	2	CH_3—≡—$C(CH_3)_2$	*n*-Bu_4NCl	KOAc
27[c]				*n*-Bu_4NCl	NaOAc
28[c]				*n*-Bu_4NCl	Na_2CO_3
29[c]				LiCl	KOAc
30[c]				LiCl	K_2CO_3
31	 **30**	2	Et—≡— 	LiCl	KOAc
32				LiCl	K_2CO_3

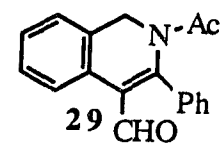
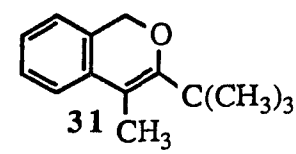
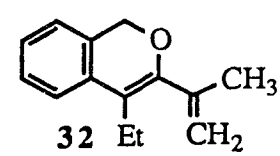
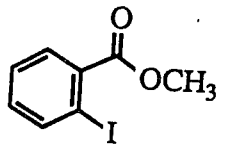
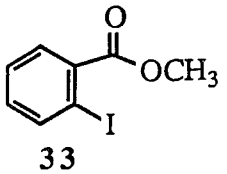
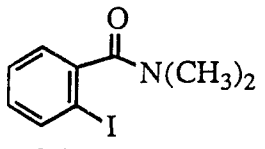
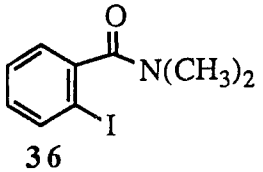
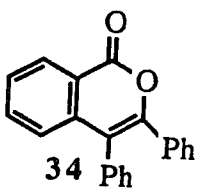
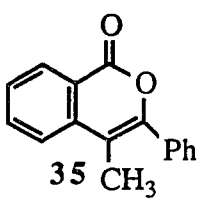
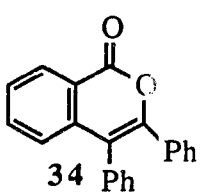
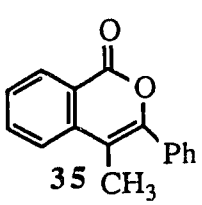
5% PPh_3	Reaction conditions	Product	% Isolated yield
–	100 °C, 1 d		42
–	100 °C, 1 d	 **29**	50
–	100 °C, 1 d		56
–	100 °C, 2 d	 **31**	53
–	100 °C, 2 d		53
–	100 °C, 2 d		45
–	100 °C, 2 d		60
–	100 °C, 2 d		65
–	100 °C, 2 d	 **32**	50
–	100 °C, 2 d		46

Table 3. (continued)

Entry[a]	Aryl halide		Alkyne	Halide source	Base
33	 **33**	2	Ph—≡—Ph	LiCl	KOAc
34				LiCl	NaOAc
35				LiCl	K_2CO_3
36				LiCl	Na_2CO_3
37	 **33**	2	CH_3—≡—Ph	LiCl	KOAc
38				LiCl	NaOAc
39				LiCl	K_2CO_3
40				LiCl	Na_2CO_3
41	 **36**	2	Ph—≡—Ph	LiI	KOAc
42				LiI	NaOAc
43				LiCl	KOAc
44	 **36**	2	CH_3—≡—Ph	LiI	KOAc
45				LiI	NaOAc

5% PPh_3	Reaction conditions	Product	% Isolated yield
–	100 °C, 1 d	 **34**	65
–	100 °C, 1 d		69
–	100 °C, 1 d		69
–	100 °C, 1 d		70
–	100 °C, 1 d	 **35**	20
–	100 °C, 1 d		27
–	100 °C, 1 d		25
–	100 °C, 1 d		30
–	100 °C, 1 d	 **34**	80
–	100 °C, 1 d		65
–	100 °C, 1 d		30
–	100 °C, 1 d	 **35**	10
–	100 °C, 1d		10

products, but the reactions using the same bases in the presence of PPh_3 afforded a slightly improved yield of the desired product alongside multiple-insertion products. The reactions conducted at 100 °C provided more multiple-insertion products than the same reactions run at 140 °C. The reactions using KOAc in the presence of *n*-Bu_4NCl, instead of LiCl, provided only multiple-insertion products (entries 1 and 3). The reactions of 2-iodobenzylamine with 4,4-dimethyl-2-pentyne and 1-trimethylsilyl-1-propyne using several different bases provided only side products which included multiple-insertion products. Also, the reactions of 2-iodobenzylamine with diphenylacetylene and 1-phenyl-1-propyne were examined using several bases in the presence of LiCl or *n*-Bu_4NCl; however, none of the desired product was formed and all of the 2-iodobenzylamine disappeared without any side products being formed.

The reactions of *N*-acetyl-2-iodobenzylamine with ethyl 2-pentynoate were examined using K_2CO_3 and KOAc as the bases (entries 9-14). The reaction using KOAc with PPh_3 in the presence of LiCl provided a 45% yield of the desired product with only a small amount of multiple-insertion products (entry 12). Using K_2CO_3 as the base and 5% PPh_3 in the presence of *n*-Bu_4NCl or LiCl, the reaction afforded only a 30% yield of the desired product with a small amount of multiple-insertion products (entries 9 and 13).

The reactions of N-acetyl-2-iodobenzylamine with a variety of different alkynes were next examined. The reaction of *N*-acetyl-2-iodobenzylamine with ethyl 3-phenylpropynoate was examined using KOAc or NaOAc as the base. The results show an 80% yield of the desired product without any side product (entries 15 and 16). The reactions of *N*-acetyl-2-iodobenzylamine with diphenylacetylene and 1-phenyl-1-propyne using KOAc or NaOAc as the base in the presence of *n*-Bu_4NCl provided good yields of the desired products without any side products or regioisomers (entries 17-21). The reaction of *N*-acetyl-2-iodobenzylamine with 3-phenyl-2-propyn-1-ol in the presence of LiCl provided a 42-43% yield of the desired product without any side products (entries 22 and 23). The reaction of *N*-acetyl-2-

iodobenzylamine with 3-phenyl-2-propynal also provided a 50-56% yield of the desired product (entries 24 and 25).

Aryl halides containing oxygen nucleophiles were next examined with several different internal alkynes in the presence of LiCl or *n*-Bu_4NCl. The reaction of 2-iodophenol with 4,4-dimethyl-2-pentyne was first examined. The reaction provided an 83% yield of what at the time appeared to be a single benzofuran (5% $Pd(OAc)_2$, 1 *n*-Bu_4NCl, Na_2CO_3, 100 °C, 2d), but in subsequent work this reaction appears to give a mixture of regioisomers. The reaction of 2-iodophenol with internal alkynes was deemed worthy of further study and is presently being studied by another member of the Larock group.

The reaction of 2-iodobenzyl alcohol with 4,4-dimethyl-2-pentyne in the presence of acetate bases and *n*-Bu_4NCl afforded 53% of the desired product which contained a small amount of multiple-insertion product (entries 26 and 27). The reaction using Na_2CO_3 as the base provided a 45% yield of the desired product alongside multiple-insertion products, but the isolated products did not contain any multiple-insertion products. The same reactions were examined in the presence of LiCl. This resulted in a 60-65% yield of the desired product with only a small amount of side product being formed (entries 29 and 30).

The reaction of 2-iodobenzyl alcohol with 2-methyl-1-hexen-3-yne was also examined with K_2CO_3 and KOAc in the presence of LiCl (entries 31 and 32). The reaction provided a 46-50% yield of the desired product which contained a small amount of an unknown compound. The reaction of 2-iodobenzyl alcohol with 4-octyne afforded many products whose structures could not be identified, because there was no main product.

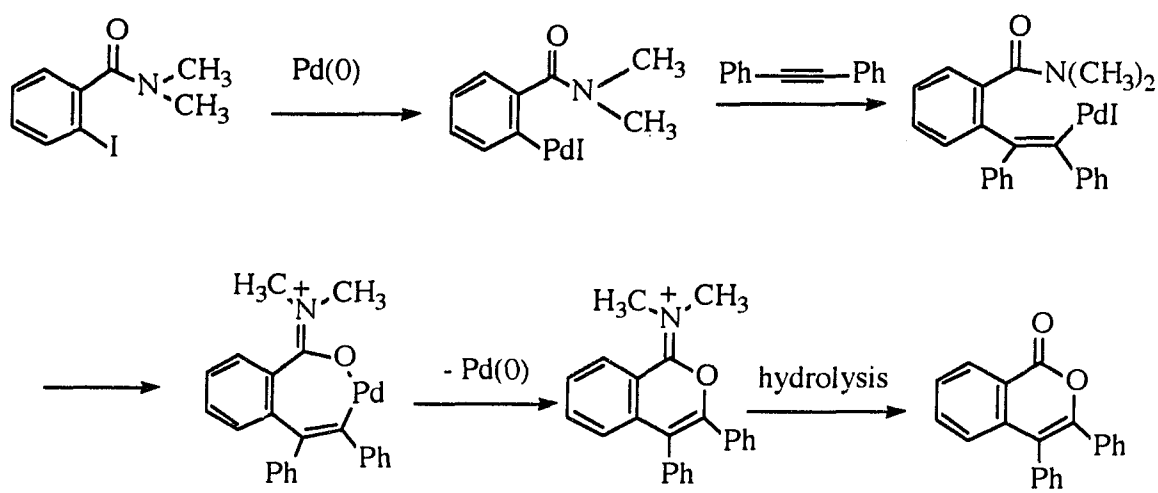
Heck observed that the palladium-catalyzed cyclization of methyl 2-iodobenzoate with diphenylacetylene provided a 56% yield of 3,4-diphenylisocoumarin, but the reaction of methyl 2-iodobenzoate with other internal alkynes provided only low yields of cyclization products.[19] In an attempt to extend the reaction, we examined the reaction using our general annulation

procedure. The reaction of methyl 2-iodobenzoate with diphenylacetylene using LiCl provided a 65-70% yield of the desired product without any major side products (entries 33-36). The reactions using carbonate bases provided cleaner products compared with those using acetate bases.

The reaction of methyl 2-iodobenzoate with 1-phenyl-1-propyne provided a 20-30% yield of a single regioisomeric six-membered ring lactone with some side products. A possible mechanism for this conversion has been suggested by Heck[19] and has been described earlier in this thesis (see eq. 5).

Another functionally-substituted aryl halide can be used for the formation of six-membered ring lactones. The reaction of *N,N*-dimethyl 2-iodobenzamide with diphenyl-acetylene using LiI also provided a 65-80% yield of the six-membered ring lactone, on the other hand, the same reaction using LiCl provided 30% of the lactone. The reaction using LiI and 1-phenyl-1-propyne provided only a 10% yield of the six-membered ring lactone (entries 41-45).

A possible mechanism for this transformation is shown in Scheme 4. The starting



Scheme 4

halide reacts with palladium(0) to form an arylpalladium intermediate. Insertion of the alkyne into the arylpalladium intermediate provides a vinylic palladium intermediate. After intramolecular nucleophilic attack of oxygen on palladium, a seven-membered cyclopalladated intermediate is formed. Reductive elimination of this intermediate provides the six-membered ring compound which is hydrolyzed to the lactone.

The reactions of *o*-iodobenzoic acid with 1-trimethylsilyl-1-propyne or 4-octyne were examined under our standard reaction conditions. The reaction using 1-trimethylsilyl-1-propyne provided about 20-30% yields of products, but the ^{13}C NMR spectrum and HRMS didn't match that of the desired product. The reaction using 4-octyne appear to provide about 5-10% yields of product, but the product 's NMR spectrum and GC trace showed none of the desired product. Under our reaction conditions, the reactions of *o*-iodobenzoic acid with internal alkynes didn't give very encouraging results.

In conclusion, the heteroannulation of alkynes can provide a variety of heterocyclic compounds with good regioselectivity. The reactions of *o*-iodobenzoic acid with internal alkynes didn't provide very encouraging results. The results show that the substituent on the aryl halide strongly influences the formation of the heterocycle and multiple-insertion products. The regiochemistry of the products was assigned based on literature reports[25] of analogous alkyne insertion processes and the results obtained in the third part of this dissertation. Usually, the more sterically bulky group present on the alkyne ends up nearer the nucleophilic atom.

CONCLUSION

In the fourth part of this dissertation, the synthesis of a variety of carbocycles and heterocycles has been accomplished by the reaction of functionalized aryl halides with internal alkynes in the presence of a catalytic amount of palladium.

The carboannulation reactions provide five-membered ring carbocycles with good regioselectivity, but success is highly dependent on the nature of the substituents stabilizing the carbanion nucleophile. Nitrogen- and oxygen- containing six-membered ring heterocycles are obtained from the reactions of 2-iodobenzylamine derivatives , 2-iodophenol, 2-iodobenzyl alcohol, methyl 2-iodobenzoate, and *N,N*-dimethyl 2-iodobenzamide with internal alkynes. The heteroannulation process also provides excellent regioselectivity and good yields, but the reaction of *o*-iodobenzoic acid with internal alkynes didn't give encouraging results.

The products show that the nucleophile attacks the more sterically hindered end of the internal alkyne. Generally, the reactions using KOAc as the base in the presence of LiCl provided higher yields compared to the reactions using other bases.

EXPERIMENTAL SECTION

A. Equipment

The infrared spectra were obtained on an IBM IR/98 FT spectrophotometer, and the ^{1}H NMR and ^{13}C NMR spectra on a Nicolet NT-300 NMR spectrometer. The GC-MS spectral data were obtained on a Finnegan 4023 GC/MS and on a Kratos MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with an OV-101 packed column.

B. Reagents

All chemicals were used directly as obtained from commercial sources unless otherwise noted. The anhydrous form of $NaHCO_3$, Na_2CO_3, K_2CO_3, NaOAc and KOAc utilized for the catalytic reactions and DMF were all purchased from Fisher Scientific. $Pd(OAc)_2$ was provided by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. 4,4-Dimethyl-2-pentyne, 1-trimethylsilyl-1-propyne, 4-octyne, diphenylacetylene, 4-methyl-4-penten-2-yn-1-ol, 3-trimethylsilyl-2-propyn-1-ol, 1-phenyl-1-propyne and ethyl 3-phenylpropynoate were purchased from Farchan Scientific Co. Diethyl 2-iodophenylmalonate and ethyl (2-iodophenyl)acetate were obtained by the methods indicated in part two of this dissertation.

Preparation of the starting materials

Preparation of 1-(chloromethyl)-2-iodobenzene

This compound was prepared by the procedure reported by Berrios-Peña.[31] To a solution of 2-iodobenzyl alcohol (11.7 g, 50 mmol, Aldrich) in THF (100 ml) cooled to 0 ^{o}C was added Et_3N (11.2 ml, 80 mmol) and MsCl (5.5 ml, 70 mmol, Aldrich), sequentially. Immediately after injection of the MsCl, a thick precipitate formed ($Et_3N{\cdot}HCl$). After 20

minutes, the reaction mixture was allowed to warm to room temperature for 1 hour with stirring. Lithium chloride (5.84 g, 137.5 mmol) was added to the reaction mixture which was then refluxed overnight. After cooling to room temperature, the reaction mixture was quenched with 100 ml of H_2O and extracted with 3 x 50 ml of Et_2O. The ether layers were combined and washed with 5% HCl solution, and water, dried with $MgSO_4$, filtered, and concentrated to give a quantitative yield of 1-(chloromethyl)-2-iodobenzene (12.38 g): ^1H NMR ($CDCl_3$) δ 4.68 (s, 2H, $ArCH_2Cl$), 7.01 (dd, 1H, J = 8.1 Hz, J = 7.5 Hz, ArH), 7.35 (dd, 1H, J = 7.8 Hz, J = 7.5 Hz, ArH), 7.48 (d, 1H, J = 7.8 Hz, ArH), 7.86 (d, 1H, J = 8.1 Hz, ArH).

Preparation of diethyl 2-iodobenzylmalonate (**18**)

Compound **18** was prepared from 2-iodobenzyl alcohol by the procedure reported by Fried:[32] ^1H NMR ($CDCl_3$) δ 1.21 (t, 6H, J = 6.9 Hz, CH_3's), 3.82 (d, 2H, J = 7.8 Hz, $ArCH_2$), 3.82 (t, 1H, J = 7.8 Hz, CH), 4.16 (q, 4H, J = 6.9 Hz, OCH_2's), 6.91 (m, 1H, ArH), 7.24 (m, 2H, ArH), 7.82 (d, 1H, J = 7.8 Hz, ArH).

Preparation of *N*-(2-iodobenzyl)phthalimide

This compound was prepared by the procedure reported by Berrios-Peña.[31] The IR and ^1H NMR spectra was identical with Berrios-Peña's reports. A 250 ml round-bottom flask charged with 1-(chloromethyl)-2-iodobenzene (12.38 g, 50 mmol), potassium phthalimide (9.26 g, 50 mmol, Aldrich), and *N,N*-dimethylacetamide (50 ml, Fisher Scientific) was heated at 150 °C for 3 hours. The reaction mixture was allowed to cool to room temperature and then 50 ml of H_2O was added. The mixture was cooled in an ice bath before vacuum filtration. The solid material obtained was washed with cold water and 20 ml of cold 60 % EtOH and then air-dried to give 16.80 g (93%) of the desired product. Recrystallization from glacial acetic acid (45 ml) gave 13.28 g (73%) of *N*-(2-iodobenzyl)phthalimide: mp 145-147 °C; IR ($CDCl_3$)

3055, 1774, 1720, 1470, 1439, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.90 (s, 2H, $ArCH_2$), 6.96 (ddd, 1H, J = 7.8 Hz, J = 7.5 Hz, J = 1.2 Hz, ArH), 7.05 (d, 1H, J = 7.8 Hz, ArH), 7.26 (ddd, 1H, J = 7.8 Hz, J = 7.5 Hz, J = 1.2 Hz, ArH), 7.76 (dd, 2H, J = 5.4 Hz, J = 3.0 Hz, ArH), 7.86 (dd, 1H, J = 7.8 Hz, J = 1.2 Hz, ArH), 7.90 (dd, 2H, J = 5.4 Hz, J = 3.0 Hz, ArH).

Preparation of 2-iodobenzylamine (**21**)

This compound was prepared by the procedure reported by Berrios-Peña.[31] A 250 ml round-bottom flask was charged with *N*-(2-iodobenzyl)phthalimide (13.28 g, 36.6 mmol), EtOH (100 ml), and 2.74 g (46.6 mmol) of an 85% solution of hydrazine hydrate. The solution was then heated to reflux and stirred while heating for 30 minutes. The precipitate formed (phthalylhydrazide) was decomposed by warming with excess HCl (5 ml) and the solution obtained was filtered. At this point some of the *N*-(2-iodobenzyl)phthalimide could still be seen on the funnel. This was retreated with EtOH (25 ml) and hydrazine hydrate (0.75 g), and heated for another 30 minutes. The solution was then treated with HCl (1 ml) and filtered, and the filtrate was combined with the previous filtrate. After cooling in an ice bath, any insoluble phthalylhydrazide was filtered off and washed with water. The filtrate was concentrated to remove the EtOH, cooled and filtered. The filtrate was made alkaline with 30% NaOH and extracted with Et_2O. The organic layer was dried with $MgSO_4$, and concentrated to give 7.08 g (83%) of 2-iodobenzylamine: IR (neat) 3371, 3288, 2920, 2864, 1657, 1583, 1562, 1464, 1432, 876, 852, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51(br s, 2H, NH_2), 3.86 (s, 2H, $ArCH_2N$), 6.95 (dd, 1H, J = 8.0 Hz, J = 7.2 Hz, ArH), 7.33 (dd, 1H, J = 7.5 Hz, J = 7.2 Hz, ArH), 7.36 (dd, 1H, J = 7.5 Hz, J = 2.1 Hz, ArH), 7.82 (dd, 1H, J = 8.1 Hz, J = 1.2 Hz, ArH).

Preparation of *N*-acetyl-2-iodobenzylamine (**23**)

Compound **23** was prepared by the method reported for the synthesis of 2-iodoacetanilide in the second part of this dissertation. *N*-Acetyl-2-iodobenzylamine was obtained in a 75% isolated yield: mp 129-134 °C; IR ($CDCl_3$) 3447, 3045, 3005, 1672, 1516, 1468, 1439 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H, CH_3CO), 4.46 (d, 2H, J = 6.0 Hz, $ArCH_2$), 5.96 (m, 1H, NH), 6.97 (ddd, 1H, J = 7.5 Hz, J = 7.5 Hz, J = 2.1 Hz, ArH), 7.31 (ddd, 1H, J = 7.5 Hz, J = 7.2 Hz, J = 2.1 Hz, ArH), 7.37 (dd, 1H, J = 7.5 Hz, J = 2.1 Hz, ArH), 7.82 (d, 1H, J = 7.8 Hz, ArH); HRMS calculated for $C_9H_{11}INO$: 275.98855. Found: 295.98895.

General procedure for the palladium-catalyzed carbo- and heteroannulation of alkynes

Palladium acetate (0.0125 mmol), LiCl (Mallinckrodt, 0.25 mmol) or *n*-Bu_4NCl (Lancaster, 0.25 mmol), the appropriate base (0.5 mmol), the aryl halide (0.25 mmol), the alkyne (0.50-2.50 mmol), DMF (5 ml) and, where indicated, PPh_3 (0.0125 mmol) were added to a 2 dram vial equipped with a stirring bar and teflon-lined screwcap. After being heated for the appropriate time at 80-100 °C, the reaction mixture was diluted with diethyl ether and washed with saturated aqueous ammonium chloride and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and the product was purified by flash column chromatography using hexane-ethyl acetate as the eluent. The following compounds were prepared using the above general procedure.

Preparation of compound **2**

Compound **2** was obtained as a pale yellow oil in 86% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 4,4-dimethyl-2-pentyne using *n*-Bu_4NCl and KOAc, and stirring for 48 hours at 80 °C (Table 2, entry 1): IR (neat) 2982, 2908, 1757, 1736, 1223,

1055, 910, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, 6H, J = 6.9 Hz, CH_3's), 1.52 (s, 9H, $C(CH_3)_3$), 2.45 (s, 3H, CH_3), 4.29 (m, 4H, OCH_2's), 7.32 (m, 2H, ArH), 7.69 (m, 1H, ArH), 7.64 (d, 1H, J = 7.5 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 13.32, 13.38, 30.07, 34.28, 61.34, 118.24, 122.07, 125.34, 128.27, 137.36, 140.38, 147.21, 148.84, 168.02, one peak missing; HRMS calculated for $C_{20}H_{26}O_4$: 330.18311. Found: 330.18347.

Preparation of compound **3**

Compound **3** was obtained as a pale yellow oil in 81% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 1-trimethylsilyl-1-propyne using LiCl and K_2CO_3, and stirring for 16 hours at 80 °C (Table 2, entry 9): IR (neat) 2957, 1732, 1466, 1246, 1051, 943, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.45 (s, 9H, $Si(CH_3)_3$), 1.39 (t, 6H, J = 7.2 Hz, CH_3's), 2.44 (s, 3H, CH_3), 4.33 (m, 4H, OCH_2's), 7.35-7.54 (m, 3H, ArH), 7.63 (d, 1H, J = 7.2 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 0.24, 13.32, 13.38, 14.70, 61.60, 118.81, 124.02, 126.09, 128.21, 140.52, 143.10, 146.01, 152.06, 168.81; HRMS calculated for $C_{19}H_{26}O_4Si$: 346.16004. Found: 346.16044.

Preparation of compound **4**

Compound **4** was obtained as a pale yellow oil in 72% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 4-octyne using KOAc and LiCl, and stirring for 48 hours at 80 °C (Table 2, entry 15): IR (neat) 3067, 2959, 2932, 1732, 1466, 1367, 1229, 1096, 1047, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (m, 6H, CH_3's), 1.24 (t, 6H, J = 6.9 Hz, CH_3's), 1.47 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.58 (t, 4H, J = 8.1 Hz, allylic CH_2's), 4.20 (m, 4H, OCH_2's), 7.26 (m, 3H, ArH), 7.56 (d, 1H, J = 7.5 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 13.90, 14.07, 14.72, 21.67, 22.86, 23.01, 27.74, 29.41, 61.63, 119.00, 124.46, 125.18,

128.16, 140.25, 142.58, 142.64, 145.62, 168.82; HRMS calculated for $C_{21}H_{28}O_4$: 344.19876. Found: 344.19896.

Preparation of compound **5**

Compound **5** was obtained as pale yellow crystals in 61% isolated yield from the reaction of diethyl 2-iodophenylmalonate and diphenylacetylene using KOAc and LiCl, and stirring for 48 hours at 80 °C (Table 2, entry 21): mp 85-87 °C; IR ($CDCl_3$) 3053, 2980, 2934, 1724, 1443, 1248, 1213, 1190, 1115, 1038, 764, 741, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, 6H, J = 7.2 Hz, CH_3's), 4.13 (q, 4H, J = 7.2 Hz, OCH_2's), 7.1-7.6 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.75, 61.88, 72.69, 121.17, 124.48, 126.57, 127.18, 127.48, 127.66, 128.37, 128.62, 129.48, 130.22, 134.19, 134.94, 140.50, 140.86, 144.70, 144.96, 168.16; HRMS calculated for $C_{27}H_{24}O_4$: 412.16746. Found: 412.1682. Anal. calculated for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C , 78.48; H, 5.92.

Preparation of compound **7**

Compound **7** was obtained as pale yellow crystals in 76% isolated yield from the reaction of ethyl (2-iodophenyl)acetate and diphenylacetylene using KOAc and LiCl, and stirring for 48 hours at 80 °C (Table 2, entry 23): mp 78-80 °C; IR ($CDCl_3$) 3053, 3026, 2928, 1736, 1493, 1443, 1367, 1248, 1155, 1030, 775, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz, CH_3), 4.08 (s, 1H, ArCH), 4.22 (q, 2H, J = 7.2 Hz, OCH_2), 7.0-7.84 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.30, 40.83, 61.05, 118.80, 119.30, 124.58, 126.60, 127.83, 127.95, 128.20, 128.55, 128.93, 130.09, 131.07, 131.60, 136.59, 137.02, 137.55, 138.05, 140.45, 140.70, 168.05; HRMS calculated for $C_{24}H_{20}O_2$: 340.14633. Found: 340.14584.

Preparation of compound **9**

Compound **9** was obtained as a pale yellow oil in 50% isolated yield from the reaction of (2-iodophenyl)nitromethane and 4,4-dimethyl-2-pentyne using KOAc and LiCl, and stirring for 24 hours at 80 °C (Table 2, entry 26): IR ($CDCl_3$) 2961, 2870, 1695, 1597, 1487, 1364, 1128, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 2.16 (s, 3H, CH_3), 4.80 (s, 1H, CH), 7.0-7.30 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.45, 29.62, 36.97, 68.56, 105.63, 120.35, 123.03, 125.34, 126.70, 127.80, 129.06, 136.02; HRMS calculated for $C_{14}H_{17}NO_2$: 231.12618. Found: 231.12606.

Preparation of compound **10**

Compound **10** was obtained as a pale yellow oil in 40% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 4-methyl-4-penten-2-yn-1-ol using KOAc and LiCl, and stirring for 48 hours at 80 °C (Table 2, entry 29): IR (neat) 3519, 2982, 2937, 1730, 1468, 1367, 1242, 1051, 912, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 6H, J = 6.9 Hz, CH_3's), 1.80 (br s, 1H, OH), 2.18 (s, 3H, CH_3), 4.33 (q, 4H, J = 7.2 Hz, OCH_2's), 4.86 (s, 2H, CH_2O), 5.08 (d, 1H, J = 2.4 Hz, =CH), 5.37 (d, 1H, J = 2.4 Hz, =CH), 7.42 (m, 2H, ArH), 7.52 (t, 1H, J = 7.8 Hz, ArH), 7.70 (t, 1H, J = 7.5 Hz, ArH) ; ^{13}C NMR ($CDCl_3$) δ 13.84, 23.48, 30.02, 57.44, 61.92, 118.29, 120.87, 124.29, 126.31, 128.56, 139.54, 140.35, 142.05, 143.69, 144.16, 167.88; HRMS calculated for $C_{19}H_{21}O_5$: 330.14681. Found: 330.14672.

Preparation of compound **11**

Compound **11** was obtained as a pale yellow oil in 38% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 3-trimethylsilyl-2-propyn-1-ol using K_2CO_3 and LiCl,

and stirring for 24 hours at 80 °C (Table 2, entry 32): IR (neat) 3384, 3060, 2982, 2930, 1730, 1468, 1367, 1242, 1051, 912, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.20 (s, 9H, $Si(CH_3)_3$), 1.25 (t, 6H, J = 7.2 Hz, CH_3's), 1.75 (br s, 1H, OH), 4.26 (s, 2H, CH_2O), 4.35 (q, 4H, J = 7.2 Hz, OCH_2's), 7.34 (d, 1H, J = 2.7 Hz, ArH), 7.51 (d, 1H, J = 3.3 Hz, ArH), 7.72 (q, 2H, J = 3.3 Hz, ArH).

Preparation of compound **12**

Compound **12** was obtained as pale yellow crystals in 63% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 1-phenyl-1-propyne using KOAc and LiCl, and stirring for 48 hours at 80 °C (Table 2, entry 33): mp 72-74 °C; IR ($CDCl_3$) 2984, 2930, 1729, 1472, 1367, 1246, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, 6H, J = 7.2 Hz, CH_3's), 2.10 (s, 3H, CH_3), 4.08 (m, 4H, OCH_2's), 7.2-7.6 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$) δ 11.92, 13.71, 30.01, 61.33, 119.69, 124.16, 126.29, 127.22, 127.62, 128.55, 129.30, 135.37, 139.38, 140.51, 140.68, 145.75, 168.29; HRMS calculated for $C_{22}H_{22}O_4$: 350.15181. Found: 350.15225.

Preparation of compounds **13** and **14**

Compounds **13** and **14** were obtained as a pale yellow oil in 63% isolated yield from the reaction of diethyl 2-iodophenylmalonate and 1-cyclohexyl-1-propyne using KOAc and LiCl, and stirring for 2 days at 80 °C (Table 2, entry 35): IR ($CDCl_3$, 6:1 mixture of isomers) 3055, 2980, 2929, 1732, 1470, 1447, 1234, 1042, 744 cm^{-1}; Compound **13**: ^1H NMR ($CDCl_3$) δ 1.25 (m, 6H, CH_3's), 1.33–2.00 (m, 11H, CH and CH_2's), 2.20 (s, 3H, CH_3), 4.20 (m, 4H, OCH_2's), 7.15-7.57 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 6:1 mixture of isomers) δ 12.34, 12.39, 13.92, 26.23, 27.10, 27.17, 30.21, 31.27, 37.77, 38.35, 61.56, 61.64, 118.26, 118.35, 120.42, 124.02, 124.69, 125.32, 127.86, 128.20, 132.10, 134.59, 137.06, 139.44,

140.35, 143.68, 144.01, 145.60, 147.18, 168.46, 168.71; HRMS calculated for $C_{22}H_{22}O_4$: 356.19876. Found: 356.19841.

Preparation of compound **15**

Compound **15** was obtained as a pale yellow oil in 50% isolated yield from the reaction of (2-iodophenyl)nitromethane and ethyl 3-phenylpropynoate using KOAc and LiCl, and stirring for 24 hours at 80 °C (Table 2, entry 36): IR ($CDCl_3$) 3060, 2973, 2870, 1695, 1597, 1487, 1364, 1128, 910, 760, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.2 Hz, CH_3), 4.04 (q, 2H, J = 7.2 Hz, OCH_2), 5.25 (s, 1H, $CHNO_2$), 7.11-7.57 (m, 7H, ArH), 7.97 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 13.50, 69.74, 80.55, 108.95, 122.42, 123.80, 126.51, 126.81, 127.92, 128.47, 129.02, 129.27, 130.02, 134.00, 161.12, 167.94; HRMS calculated for $C_{18}H_{15}NO_4$: 309.10016. Found: 309.10024.

Preparation of compound **17**

Compound **17** was obtained as pale yellow crystals in 75% isolated yield from the reaction of ethyl (2-iodophenyl)acetate and 1-phenyl-1-propyne using KOAc and LiCl, and stirring for 48 hours at 80 °C (Table 2, entry 38): mp 128-129 °C; IR ($CDCl_3$) 2984, 2926, 1732, 1493, 1369, 1177, 1030, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) 1.26 (t, 3H, J = 7.2 Hz, CH_3), 1.77 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.18 (q, 2H, J = 7.2 Hz, OCH_2), 4.30 (s, 2H, CH_2), 7.24-7.48 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.69, 20.09, 22.17, 43.42, 60.02, 124.40, 126.60, 126.74, 127.41, 128.35, 128.49, 129.29, 130.23, 130.68, 130.75, 130.81, 131.59, 131.70, 133.97, 137.60, 141.10, 142.42, 143.22, 172.41 ; HRMS calculated for $C_{28}H_{26}O_2$: 394.19328. Found: 394.19364.

Preparation of compound **19**

Compound **19** was obtained as a pale yellow oil in 27% isolated yield from the reaction of diethyl 2-iodobenzylmalonate and 1-phenyl-1-propyne using KOAc and LiCl, and stirring for 48 hours at 80 °C (Table 2, entry 40): IR ($CDCl_3$) 2984, 2935, 1726, 1265, 1234, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 6H, J = 5.1 Hz, CH_3's), 1.95 (s, 3H, CH_3), 3.53 (m, 2H, $ArCH_2$), 3.88 (m, 4H, OCH_2's), 7.17-7.37 (m, 9H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 13.66, 20.05, 36.02, 60.90, 62.00, 123.89, 126.74, 127.01, 127.22, 127.41, 127.22, 127.41, 127.72, 128.45, 129.76, 130.35, 132.50, 133.51, 139.51, 170.51; HRMS calculated for $C_{23}H_{24}O_4$: 364.16746. Found: 364.16685.

Preparation of compound **20**

Compound **20** was obtained as a yellow oil in a 30% isolated yield from the reaction of diethyl-2-iodobenzylmalonate and 4-octyne using KOAc and LiCl, and stirring for 2 days at 80 °C (Table 2, entry 44): ^1H NMR $(CDCl)_3$ δ 0.96 (m, 6H, CH_3's), 1.25-1.35 (m, 6H, CH_3's), 1.75-2.00 (m, 4H, CH_2), 2.65 (t, 2H, J = 6.9 Hz, CH_2), 2.95 (d, 2H, J = 6.9 Hz, benzylic), 3.50 (s, 1H, allene-H), 3.75 (t, 1H, J = 6.9 Hz, CH), 4.18 (m, 4H, OCH_2's), 6.95-7.20 (m, 4H, ArH).

Preparation of compound **22**

Compound **22** was obtained as a pale yellow oil in 39% isolated yield from the reaction of 2-iodobenzylamine and 4-octyne using NaOAc, PPh_3 and LiCl, and stirring for 1 day at 140 °C (Table 3, entry 8): IR ($CDCl_3$) 3391, 2963, 2932, 1666, 1373, 1184, 908, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, 6H, J = 6.3 Hz, CH_3's), 1.56 (m, 4H, CH_2's), 2.57 (m, 4H, CH_2's), 4.10 (br s, 1H, NH), 4.69 (s, 2H, $ArCH_2$), 7.13-7.23 (m, 4H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 13.85, 14.24, 21.84, 22.84, 29.76, 31.39, 42.83, 122.52, 122.73, 125.40,

126.73, 127.55, 128.71, 132.79, 134.04 ; HRMS calculated for $C_{15}H_{21}N$: 215.16740. Found: 215.16727.

Preparation of compound **24**

Compound **24** was obtained as a pale yellow oil in 45% isolated yield from the reaction of *N*-acetyl 2-iodobenzylamine and ethyl 2-pentynoate using KOAc, PPh_3 and LiCl, and stirring for 24 hours at 100 °C (Table 3, entry 12): IR ($CDCl_3$) 2894, 1717, 1683, 910, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 6.9 Hz, CH_3), 1.30 (t, 3H, J = 7.2 Hz, CH_3), 2.05 (s, 3H, $COCH_3$), 2.80 (q, 2H, J = 6.9 Hz, CH_2), 4.35 (q, 2H, J = 7.2 Hz, OCH_2), 4.65 (s, 2H, $ArCH_2$), 7.0-7.40 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.09, 14.19, 23.26, 28.19, 47.05, 61.21, 119.23, 123.04, 124.04, 127.72, 127.83, 127.88, 130.03, 132.21, 167.43, 168.78; HRMS calculated for $C_{16}H_{19}NO_3$: 273.13649. Found: 273.13629.

Preparation of compound **25**

Compound **25** was obtained as pale yellow crystals in 80% isolated yield from the reaction of *N*-acetyl 2-iodobenzylamine and ethyl 3-phenylpropynoate using KOAc and LiCl, and stirring for 24 hours at 100 °C (Table 3, entry 16): mp 145-147 °C; IR ($CDCl_3$) 3064, 2983, 1717, 1672, 1367, 1232, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, 3H, J = 7.2 Hz, CH_3), 1.54 (s, 3H, $NCOCH_3$), 4.04 (q, 2H, J = 7.2 Hz, OCH_2), 5.05 (s, 2H, $ArCH_2$), 7.26-7.50 (m, 8H, ArH), 7.76 (d, 1H, J = 6.3 Hz, ArH) ; ^{13}C NMR ($CDCl_3$) δ 18.56, 24.53, 40.21, 61.15, 122.29, 123.45, 125.97, 127.78, 128.10, 128.54, 128.71, 129.38, 129.52, 131.98, 138.92, 140.70, 167.39, 171.21 ; HRMS calculated for $C_{20}H_{19}NO_3$: 321.13649. Found: 321.13640.

Preparation of compound **26**

Compound **26** was obtained as pale yellow crystals in 83% isolated yield from the reaction of *N*-acetyl 2-iodobenzylamine and diphenylacetylene using KOAc and *n*-Bu_4NCl, and stirring for 24 hours at 120 °C (Table 3, entry 17): mp 181-182 °C; IR ($CDCl_3$) 3064, 1659, 1377, 908, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 3H, $NCOCH_3$), 5.17 (s, 2H, $ArCH_2$), 7.09-7.37 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.03, 46.03, 118.10, 125.07, 125.18, 126.97, 127.24, 127.50, 127.78, 128.16, 129.68, 129.97, 130.73, 132.82, 133.63, 136.34, 136.57, 137.27, 170.10; HRMS calculated for $C_{23}H_{19}NO$: 325.14666. Found: 325.14579; Anal. calculated for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C, 78.48; H, 5.92.

Preparation of compound **27**

Compound **27** was obtained as a pale yellow oil in 58% isolated yield from the reaction of *N*-acetyl 2-iodobenzylamine and 1-phenyl-1-propyne using KOAc and *n*-Bu_4NCl, and stirring for 48 hours at 100 °C (Table 3, entry 19): IR ($CDCl_3$) 2923, 2893, 1732, 1653, 1387, 1234, 912, 727, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (s, 3H, $NCOCH_3$), 2.41 (s, 3H, CH_3), 5.17 (s, 2H, $ArCH_2$), 7.40-6.59 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$) δ 15.63, 24.13, 45.79, 122.68, 123.63, 123.68, 124.84, 127.38, 127.91, 128.23, 129.91, 133.79, 136.11, 137.60, 137.88, 171.08 ; HRMS calculated for $C_{18}H_{17}NO$: 263.13109. Found: 263.13103.

Preparation of compound **28**

Compound **28** was obtained as a pale yellow oil in 43% isolated yield from the reaction of *N*-acetyl 2-iodobenzylamine and 3-phenyl-2-propyn-1-ol using KOAc and LiCl, and stirring for 24 hours at 100 °C (Table 3, entry 22): IR ($CDCl_3$) 3402, 3062, 2929, 1649, 1607, 1381, 1231, 910, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H, $NCOCH_3$), 2.40 (br s, 1H,

OH), 4.53 (s, 2H, CH_2O), 4.94 (s, 2H, $ArCH_2$), 7.19-7.48 (m, 8H, ArH), 7.83 (d, 1H, J = 7.5 Hz, ArH) ; ^{13}C NMR ($CDCl_3$) δ 24.25, 40.01, 58.82, 119.83, 125.07, 125.40, 127.64, 127.71, 128.50, 128.60, 129.83, 133.28, 133.59, 136.55, 138.30, 171.42; HRMS calculated for $C_{18}H_{17}NO_2$: 279.12593. Found: 279.12664.

Preparation of compound **29**

Compound **29** was obtained as a pale yellow oil in 56% isolated yield from the reaction of *N*-acetyl 2-iodobenzylamine and 3-phenyl-2-propynal using NaOAc and LiCl, and stirring for 24 hours at 100 °C (Table 3, entry 25): IR ($CDCl_3$) 2961, 2930, 1736, 1660, 1545, 1367, 1319, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (s, 3H, $NCOCH_3$), 5.12 (s, 2H, $ArCH_2$), 7.45 (m, 4H, ArH), 7.85 (m, 4H, ArH), 8.51 (d, 1H, J = 7.8 Hz, ArH), 9.75 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) δ 24.99, 48.93, 123.42, 124.98, 125.81, 127.71, 128.00, 128.07, 128.94, 131.32, 131.71, 134.06, 140.10, 155.96, 171.12, 190.87; HRMS calculated for $C_{18}H_{15}NO_2$: 277.11034. Found: 277.11007.

Preparation of compound **31**

Compound **31** was obtained as a pale yellow oil in 65% isolated yield from the reaction of 2-iodobenzyl alcohol and 4,4-dimethyl-2-pentyne using K_2CO_3 and LiCl, and stirring for 48 hours at 100 °C (Table 3, entry 30): IR ($CDCl_3$) 2959, 2930, 1693, 1487, 1464, 1129, 910, 760, 735, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9H, $C(CH_3)_3$), 2.35 (s, 3H, CH_3), 5.00 (s, 2H, $ArCH_2$), 7.21-7.53 (m, 4H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 13.87, 29.60, 37.50, 68.52, 108.90, 120.34, 122.00, 125.29, 127.79, 129.01, 136.79, 168.82 ; HRMS calculated for $C_{14}H_{18}O$: 202.13577. Found: 202.13597.

Preparation of compound **32**

Compound **32** was obtained as a pale yellow oil in 50% isolated yield from the reaction of 2-iodobenzyl alcohol and 2-methyl-1-hexen-3-yne using KOAc and LiCl, and stirring for 2 days at 100 °C (Table 3, entry 31): IR ($CDCl_3$) 2960, 2930, 1606, 1483, 1464, 1129, 910, 760, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J = 7.5 Hz, CH_3), 1.93 (s, 3H, =C-CH_3), 2.17 (q, 2H, J = 7.5 Hz, CH_2), 4.97 (d, 1H, J = 1.5 Hz, =CH), 5.07 (d, 1H, J = 1.5 Hz, =CH), 5.72 (s, 2H, CH_2O), 7.35 (m, 2H, ArH), 7.45 (td, 1H, J = 7.5 Hz, J = 1.5 Hz, ArH), 7.90 (d, 1H, J = 6.6 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 12.99, 23.35, 26.47, 76.78, 115.58, 127.08, 127.51, 128.96, 133.20, 134.40, 134.87, 139.31, 141.05, 148.18 ; HRMS calculated for $C_{14}H_{16}O$: 200.12012. Found: 200.12049.

Preparation of compound **34**[19]

Compound **34** was obtained as a pale yellow oil in 65% isolated yield from the reaction of ethyl 2-iodobenzoate and diphenylacetylene using KOAc and LiI, and stirring for 24 hours at 100 °C (Table 3, entry 33): mp 168-170 °C (literature[19,32] mp 169 °C); IR (neat) 3074, 1742, 1624, 1607, 1491, 1317, 1002, 912, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2-7.70 (m, 13H, ArH), 8.38 (t, 1H, J = 9.6 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 116.03, 120.36, 125.28, 127.79, 128.04, 128.10, 128.87, 128.94, 129.14, 129.46, 131.16, 132.85, 134.13, 134.56, 138.77, 150.87, 162.15 ; HRMS calculated for $C_{21}H_{14}O_2$: 298.09944 . Found: 298.09923.

Preparation of compound **35**

Compound **35** was obtained as a pale yellow oil in 30% isolated yield from the reaction of ethyl 2-iodobenzoate and 1-phenyl-1-propyne using Na_2CO_3 and LiI, and stirring for 1 day at 100 °C (Table 3, entry 40): IR (neat) 3050, 2949, 1722, 1485, 1244, 1032, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 7.2-7.80 (m, 7H, ArH), 7.80 (t, 1H, J = 6.9 Hz, ArH),

8.38 (d, 1H, J = 7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 13.50, 109.03, 120.62, 123.26, 127.79, 128.12, 129.20, 129.34, 129.53, 133.10, 134.64, 138.62, 150.97, 162.35; HRMS calculated for $C_{16}H_{12}O_2$: 236.08313. Found: 236.08435.

REFERENCES

1. Cope, A. C.; Sieckman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272.
2. Dehand, J.; Pfeffer, M. *Coord. Chem. Rev.* **1976**, *18*, 327.
3. Bruce, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 73.
4. Abicht, H. P.; Isslieb, K. *Z. Chem.* **1977**, *17*, 1.
5. Omae, I. *Chem. Rev.* **1979**, *79*, 297.
6. Omae, I. *Organometallic Intramolecular Coordination Compounds* , Elsevier, Amsterdam, **1986**.
7. Shaw, B. L. *J. Organomet. Chem.* **1980**, *200*, 307.
8. Constable, E. C. *Polyhedron* **1984**, *3*, 1037.
9. Rothweel, I. P. *Polyhedron* **1985**, *4*, 177.
10. Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M. *Russ. Chem. Rev.* **1988**, *57*, 250.
11. Rvabov, A. D. *Synthesis* **1985**, 233.
12. Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry* , Pergaman Press, Oxford, **1981**, Vol. 8, p 799-938.
13. Viehe, H. G. *Chemistry of Acetylenes,* Marcel Dekker, New York, **1969**.
14. Dupont, J.; Pfeffer, M. *J. Chem. Soc., Dalton Trans.* **1988**, 2421.
15. Wu, G.; Reingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, 6, 1941.
16. Dupont, J.; Pfeffer, M.; Rotteveel, M. A.; Cian, A.; Fisher, J. *Organometallics* **1989**, *8*, 1116.
17. Pfeffer, M.; Rotteveel, M. A.; Cian, A.; Fisher, J. *J. Organomet. Chem.* **1991**, *413*, C15.
18. Beydown, N.; Pfeffer, M.; Cian, A.; Fisher, J. *Organometallics* **1991**, *10*, 3693.
19. Tao, W.; Silverberg, L. J.; Reingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550.
20. Maassarani, F.; Pfeffer, M.; Borgene, G. *Organometallics* **1987**, *6*, 2097.

21. (a) Wu, G.; Reingold, A. L.; Heck, R. F. *Organometallics* **1987**, *6*, 1386. (b) Wu, G.; Reingold, A. L.; Heck, R. F. *Organometallics* **1986**, *5*, 1922.

22. Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031.

23. March, J. *"Advanced Organic Chemistry"*, Wiley, New York. **1985**, 3th ed., p 689.

24. Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857.

25. Beydoun, N.; Pfeffer, M.; *Synthesis* **1990**, 729.

26. Maassarani, F.; Pfeffer, M.; Borgne, G. *Organometallics* **1987**, *6*, 2029.

27. Bruce, M. I.; Goodall, B. L.; Stone, F. G. *J. Chem. Soc., Dalton Trans.* **1975**, 1651.

28. Janecki, T.; Pauson, P. L.; Pietrzykowski, J. *J. Organomet. Chem.* **1987**, *325*, 247.

29. Thron, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2097.

30. Maassarani, F.; Pfeffer, M.; Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 567.

31. Berrios-Peña, N. G. *Ph. D. Dissertation*, Iowa State University, **1989**.

32. Fried, C. A. *Ph. D. Dissertation*, Iowa State University, **1989**.

33. Legrand, L.; Lozack, N. *Bull. Chem. Soc. Fr.* **1964**, 1787.

GENERAL SUMMARY

In this dissertation, the synthesis of a variety of carbo- and heterocycles has been accomplished via the reactions of ortho-functionalized aryl halides with vinylic cyclopropanes, vinylic cyclobutanes, 1,4- dienes and internal alkynes in the presence of catalytic amounts of palladium.

In the first part of this dissertation, it was shown that the palladium-catalyzed, intermolecular arylation of cyclic alkenes bearing a variety of functional groups provides a valuable route to aryl-substituted cyclic alkenes. The regioselectivity depends not only on the functional group present, but also on the base employed.

In the second part of this dissertation, it was shown that the palladium-catalyzed annulation of vinylic cyclopropanes, vinylic cyclobutanes, and 1,4-dienes with functionally-substituted aryl halides provides a novel route to a wide variety of heterocycles and carbocycles. In general, the best yields of the desired products were obtained using KOAc as the base.

In the third part of this dissertation, it was shown that the palladium-catalyzed, heteroannulation of internal alkynes provides a conceptually new approach to 2,3-disubstituted indoles. The facile annulation of silylalkynes broadens tremendously the scope of this synthetic process allowing further functionalization.

In the fourth part of this dissertation, the synthesis of a variety of carbo- and heterocycles has been accomplished via the reactions of functionalized aryl halides with internal alkynes in the presence of a catalytic amount of palladium. The products obtained indicate that the nucleophile has attacked the more sterically hindered end of the internal alkyne.

In summary, the palladium-catalyzed annulation of alkenes and alkynes provides a convenient new route to the synthesis of a wide variety of carbo- and heterocycles. The

process exhibits high regioselectivity, proceeds under mild reaction conditions in high yield, and tolerates a wide variety of functionality.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude and appreciation to my major professor, Dr. Richard C. Larock. I am indebted to him for his patience, understanding, and financial support during my stay at Iowa State University.

I would also like to thank all members in the Larock research group for the valuable discussions and suggestions that were helpful during the course of this work.

Finally, I would like to thank my uncle, brothers, sister, and most of all my wife, for their love, patience, support and encouragement.