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Synthesis of heterocycles via palladium-catalyzed heteroannulation of dienes

Norman Graciano Berríos-Peña
Iowa State University

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Iowa State University, 1989

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Synthesis of heterocycles via palladium-catalyzed heteroannulation of dienes

by

Norman Graciano Berríos-Peña

A Dissertation Submitted to the

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1989

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ABBREVIATIONS

Ac	acetyl
acac	acetylacetone
dba	dibenzylidene acetone
^{13}C NMR	carbon thirteen nuclear magnetic resonance
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane (diphos)
GC-MS	gas chromatography-mass spectrometry
Hfacac	1,1,1,5,5,5-hexafluoroacetylacetone
^{1}H NMR	hydrogen nuclear magnetic resonance
HRMS	high resolution mass spectrometry
LDA	lithium diisopropylamide
mp	melting point
Ms	methanesulfonyl
NOE	Nuclear Overhauser Effect
rt	room temperature
TBDMS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMM-Pd	trimethylenemethane-palladium
Ts	*p*-toluenesulfonyl
UV	ultraviolet

DEDICATION

I would like to dedicate this dissertation to my wife Sandra for all the years she has put up with me, for her patience, love, and understanding, and for helping me turn a dream into a reality.

GENERAL INTRODUCTION

Organopalladium chemistry has found considerable synthetic utility in organic chemistry because of its ability to accommodate a large number of functional groups. Since the discovery of π-allylpalladium compounds, these intermediates have found wide applicability in the synthesis of natural products.

Arylpalladium species are known to add across a carbon-carbon double bond and when these species add to 1,2-, 1,3-, and 1,4-dienes π-allylpalladium intermediates are generated. These intermediates usually undergo nucleophilic displacement by a variety of nucleophiles to generate the corresponding allylic substrates. The work that is presented in this dissertation involves this key reaction and is divided into three parts. The first part deals with the preparation of heterocycles via π-allylpalladium formation and subsequent intramolecular nucleophilic attack on the π-allylpalladium intermediate. These π-allyl–palladium intermediates are prepared from the palladium-catalyzed addition of functionalized aryl iodides to 1,3-dienes. The second and third parts deals with similar heterocyclizations, but where the intermediate π-allylpalladium species are prepared from the palladium-catalyzed addition of functionalized aryl iodides to 1,4- and 1,2-dienes, respectively.

PART I: PALLADIUM-CATALYZED HETEROANNULATION OF 1,3-DIENES

INTRODUCTION

Heterocyclic compounds comprise the largest family of compounds in organic chemistry. Many of these are natural products, but the majority are synthetic. In general, heterocycles have found applications as antibiotics, anticancer agents, analeptics, analgesics, hypnotic and vasopressor modifiers, anthelmintics, antiprotozoals, ectoparasiticides, as plant growth regulators, insecticides, fungicides, herbicides, and as photographic sensitizers and developers, solvents, copolymers, additives, and dyes and pigments. Recently, their use has been extended to the synthesis of non-heterocyclic species. As the field of heterocycles is vast and well covered by numerous reviews, books, and monographs,[1] it is my intention in this introduction to survey only that area of heterocyclic chemistry which deals with the synthesis of this fascinating family of compounds from π-allylpalladium intermediates.

Organopalladium chemistry has found considerable synthetic utility in organic chemistry because of its ability to accommodate a large number of functional groups. Since the discovery of π-allylpalladium compounds in 1957,[2] these intermediates have found wide applicability in the synthesis of natural products.[3-5] A variety of methods[6-9] have been reported for their synthesis. However, only two of them have found widespread applicability. The first method involves the reaction of a palladium(II) reagent with alkenes,[10-15] while the second method consists of the insertion of a palladium(0) reagent into the carbon-halogen or carbon-oxygen bond of allylic halides or esters, respectively.[16-19]

More recently, π-allylpalladium species have been prepared from the reaction of organopalladium intermediates with conjugated dienes (eq 1),[20, 21] nonconjugated dienes (eq 2),[22] and vinylcyclopropanes (eq 3), vinylcyclobutanes, methylene-cyclopropanes and cyclobutanes (eq 4),[23] and allenic compounds (eq 5).[24, 25] The reaction of vinylpalladium intermediates with simple acyclic or cyclic alkenes has also afforded π-allylpalladium species


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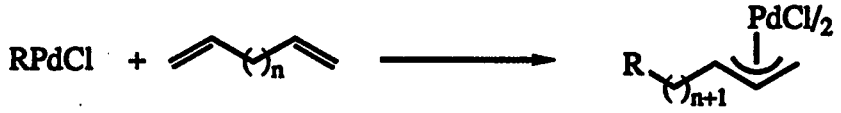
(1)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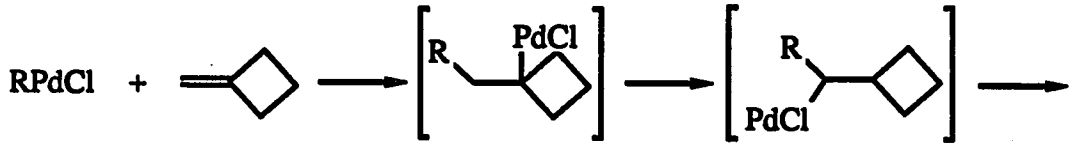
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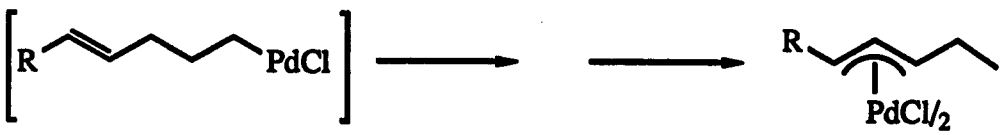
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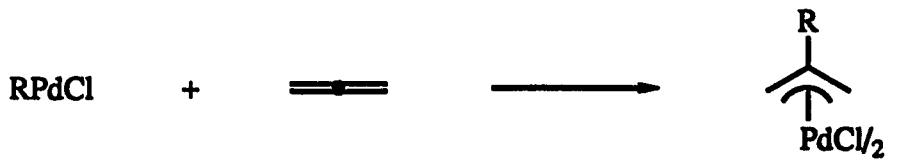
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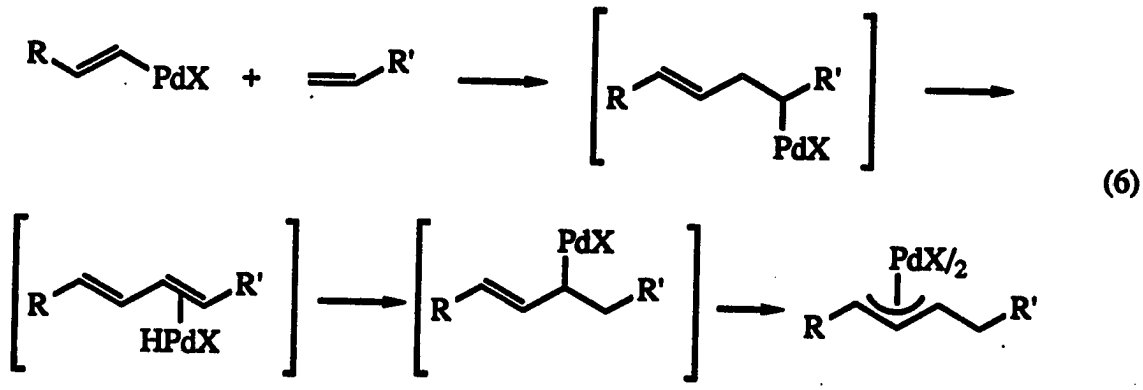
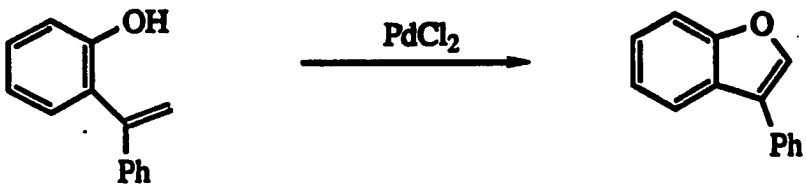


(6)

via palladium hydride rearrangement (eq 6).[26-33]

To date, the most important application of π-allylpalladium compounds has been their displacement by amines,[34, 35] stabilized carbon nucleophiles,[36-40] and oxygen nucleophiles.[22, 41-45]

There are many examples of the palladium-assisted synthesis of heterocycles. The majority of them involve the intramolecular oxy- (eq 7)[46-48] and aminopalladation[49-52] (eq 8) of alkenes or involve the synthesis of a carbon-heteroatom bond via π-allylpalladium formation followed by intramolecular nucleophilic displacement of the palladium moiety.



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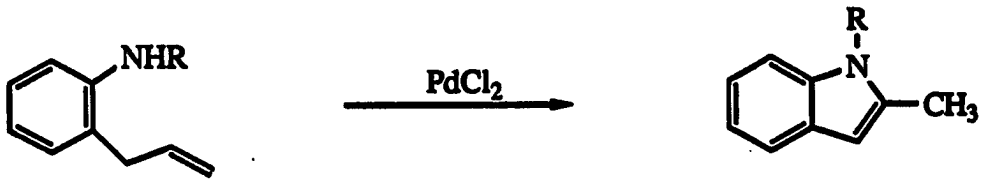
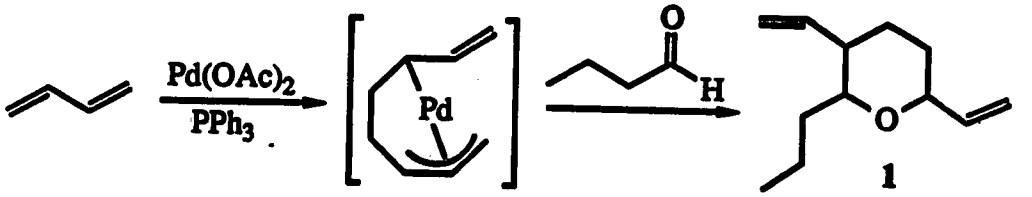


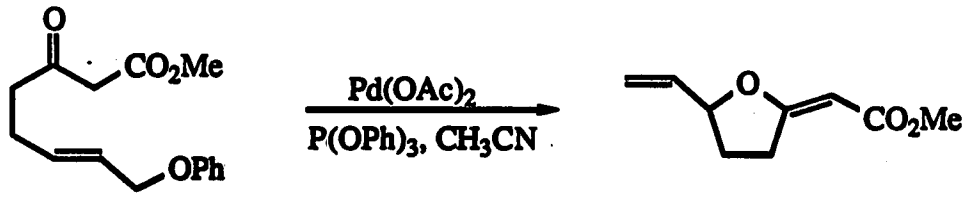
(8)

In 1972, Ohno et al.[53] reported the palladium-catalyzed reaction of butadiene with aldehydes to yield 1-substituted-2-vinyl-4,6-heptadien-1-ols or 2-substituted-3,6-divinyl-tetrahydropyrans in good yields. For example, the reaction of butanal with butadiene afforded good yields (67%) of compound **1** (eq 9). A similar reaction[54] using carbon dioxide, instead of aldehydes, was also reported. However, this reaction produced not one product, but a mixture of products.



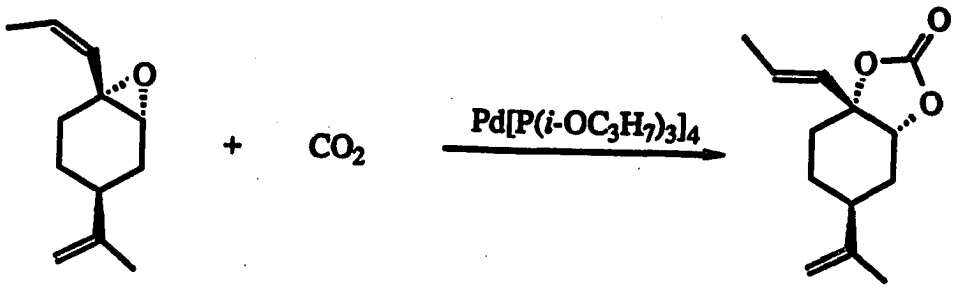
(9)

Tsuji et al.[55] and Trost and Runge[56] have reported the first example of the palladium-catalyzed *O*-alkylation of enolates via π-allylpalladium intermediates. These reactions are usually complicated by the formation of the thermodynamically more stable *C*-alkylated products. However, by using triphenylphosphite [$P(OPh)_3$], only the *O*-alkylated product is obtained (eq 10). Other phosphine ligands gave only mixtures of the five- and seven-membered ring carbocycles.



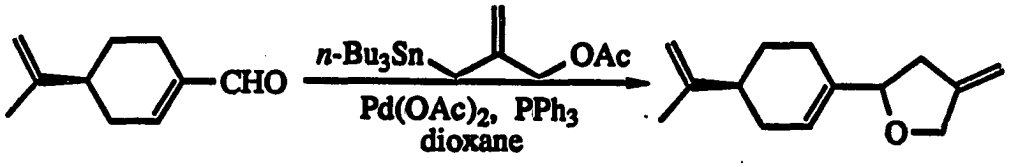
(10)

Trost and Angle[57] have reported the synthesis of cyclic carbonates from the palladium-mediated vicinal cleavage of vinylic epoxides (eq 11). The initially formed π-allylpalladium alkoxide reacts with carbon dioxide to generate a carbonate anion. Intramolecular displacement of palladium by this carbonate anion, yields a cyclic vinylic carbonate.



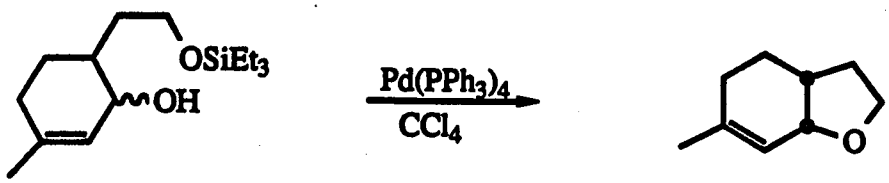
(11)

Recently, trimethylenemethane intermediates have also been used in the synthesis of heterocycles. Trost and Bonk[58] have reported the use of a trimethylenemethane-palladium (TMM-Pd) intermediate to prepare a variety of methylenetetrahydrofuran derivatives in good to excellent yields (eq 12). This TMM-Pd intermediate was prepared in situ from an allylic-tri-*n*-butyltin acetate and readily added to aldehydes. Unfortunately, its reaction with ketones provided poor yields of products.



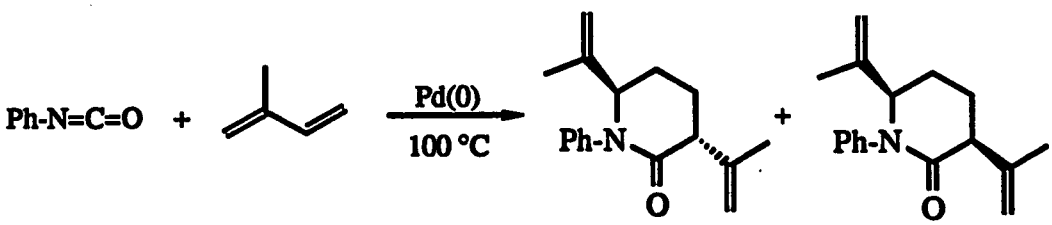
(12)

Oxygen heterocycles have also been prepared by the use of alkoxides as nucleophiles in π-allylpalladium chemistry. Alkoxides have found limited utility as nucleophiles in π-allylpalladium chemistry and only salts of methanol, benzyl alcohol, and phenol have been successfully employed.[59] Stanton et al.[43] have reported a new methodology for the use of alkoxides as nucleophiles towards π-allylpalladium intermediates, and have prepared oxygen-containing heterocycles based on this methodology (eq 13). The authors have stated that the alkoxides may exhibit a small difference between backside attack on the π-allyl ligand and attack at the metal center followed by reductive elimination.



(13)

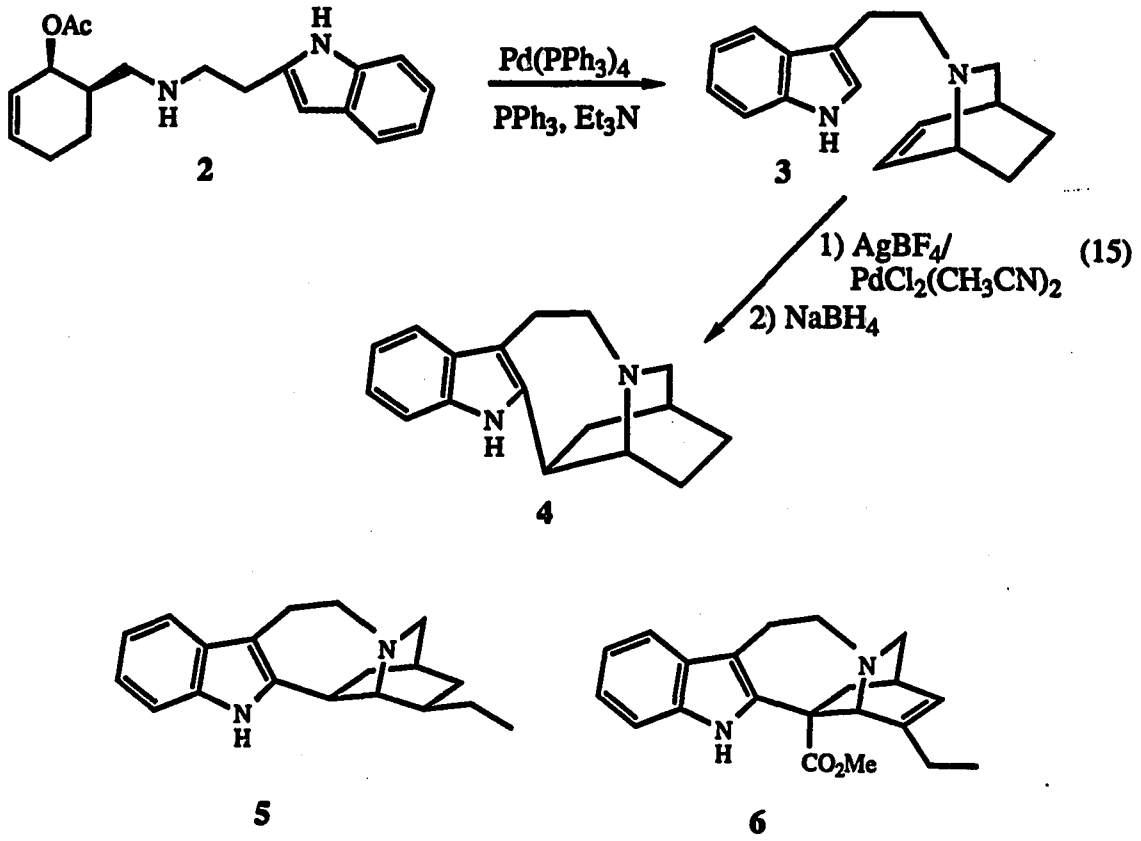
Carbon-nitrogen bonds leading to heterocycles have also been prepared via π-allyl-palladium formation, followed by intramolecular nucleophilic displacement of the palladium species. Ohno and Tsuji[60] have reported the reaction of conjugated dienes with isocyanate in the presence of a palladium(0) catalyst to form divinylpiperidones (eq 14).



(14)

Organopalladium intermediates can also be used in the synthesis of alkaloids. Since the difficulty in alkaloid chemistry comes in part from the high reactivity of the nitrogen, the mildness of organopalladium chemistry should prove very useful in these systems. In fact, Trost and Genet[61] have reported the synthesis of the basic ring system of three different classes of alkaloids. For example, they have demonstrated the utility of the palladium-catalyzed allylation of amines by means of a regiocontrolled total synthesis of desethylibogamine. After preparing the requisite allylic acetate **2**, addition of catalytic amounts of tetrakis(triphenylphosphine)palladium(0) afforded isoquinuclidine **3** which was taken on to desethylibogamine (**4**) via a palladium-catalyzed olefin cyclization (eq 15).

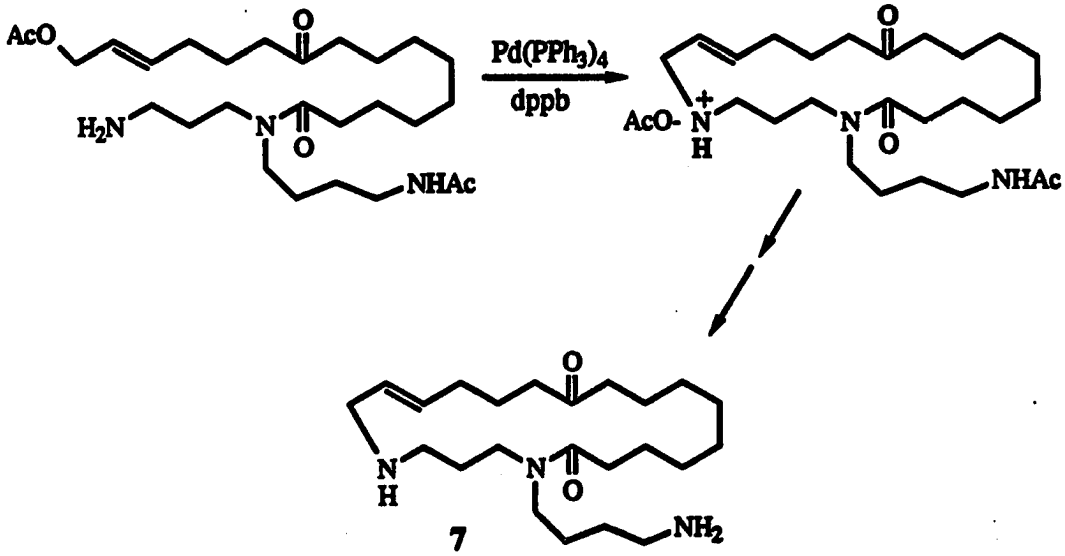
By following a similar approach, Trost et al.[62] have reported a short, stereo-controlled synthesis of racemic ibogamine (**5**). They have also synthesized the chiral form of compound **5**, producing an 80:20 mixture of (+) - (**5**) : (-) - (**5**). Andriamialisoa et al.[63] using a similar nucleophilic displacement of a π-allylpalladium species in the last step of the



synthetic sequence has synthesized catharanthine (**6**).

Trost and Cossy[64] have extended this palladium-catalyzed allylation of amines to the synthesis of large heterocyclic rings. The interest in macroheterocyclic rings lies in their ionophoric properties. With their new approach, Trost and Cossy were able to synthesize inandenin-12-one (**7**), a 21-membered ring macrolide (eq 16).

Godleski et al.[65] and Carruthers and Cumming[66] have utilized π-allylpalladium species in the key cyclization step to form 1-azaspirocycles. This methodology provides entry into the histrionicotoxin family, which has shown promise in the study of the phenomena involved in neuromuscular transmission. Carruthers and Cumming have applied this methodology to the synthesis of (±)-depentylperhydrohistrionicotoxin (**8**) (eq 17).



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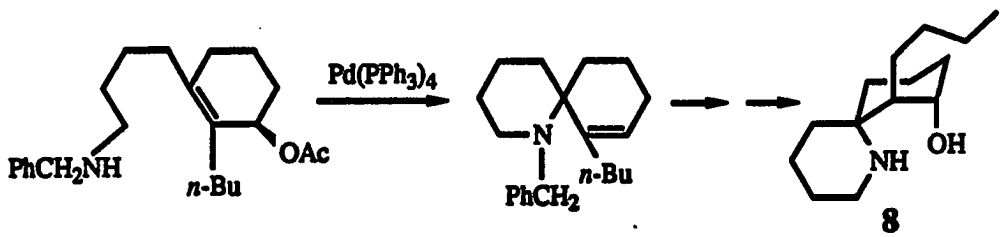
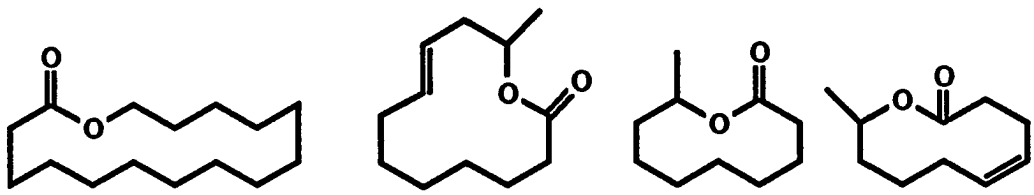
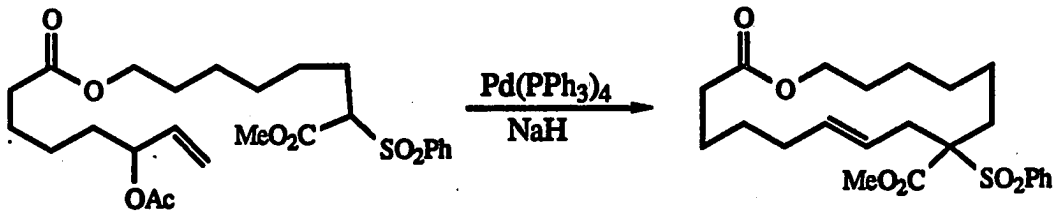


(17)

Palladium-promoted carbon-carbon bond formation to give heterocycles has also been reported in the literature. Trost and Verhoeven have reported the synthesis of macrolides like exaltolide (**9**)[67], recifeiolide (**10**)[68], and phoracantholide I (**11**) and J (**12**)[69, 70] by forming a carbon-carbon bond in the key step of the synthetic scheme via a π-allylpalladium intermediate. These macrolide skeletons are constructed by the intramolecular reaction of alkyl phenylsulfonyl acetates with allylic acetates in the presence of catalytic amounts of $Pd(PPh_3)_4$ (eq 18).

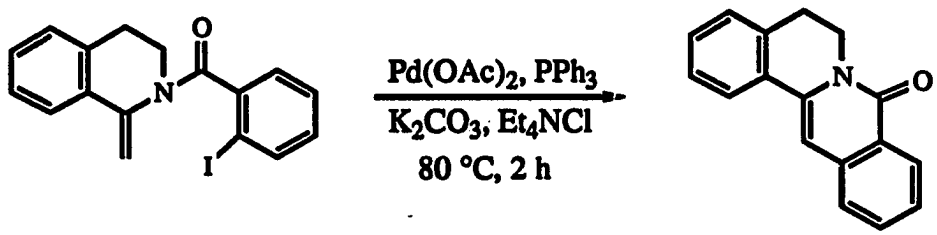


9 10 11 12



(18)

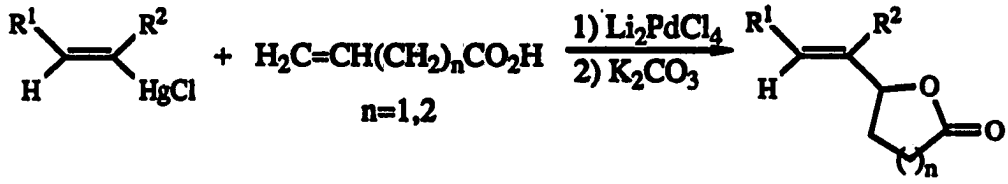
The palladium-promoted carbon-carbon coupling to generate heterocycles has also been accomplished by the insertion of a Pd(0) species into the carbon-halogen bond of aryl[71-77] and alkenyl halides[78, 79] followed by the intramolecular arylation or alkenylation of an olefin (eq 19).



(19)

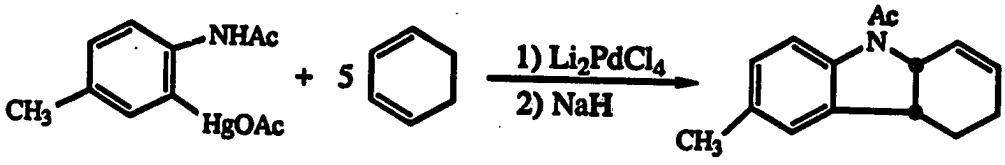
In most of the cyclizations described above, the requisite allylic substrate is usually synthesized via a multi-step sequence before cyclization is effected. Recent reports from the Larock group have shown a novel approach to heterocycles where readily available organo-mercurials, vinyl halides or triflates, dienes and alkenes are utilized. An advantage of these novel procedures is the ability to form a carbon-carbon bond and a carbon-heteroatom bond in one-pot from readily available starting materials.

Larock et al.[80a] reported the reaction of alkenoic acids with vinylmercurials in the presence of Pd(II) salts to afford π-allylpalladium intermediates, which after addition of a base are intramolecularly displaced by the generated nucleophile to produce the desired lactones in high yields (eq 20). More recently, they have found that the same type of lactonization can be effected from vinylic halides or triflates and catalytic amounts of palladium.[80b]



(20)

Larock and Varaprath[23] have also reported the reaction of conjugated or non-conjugated dienes, or vinylcyclopropanes with functionalized organomercurials. These substrates in the presence of a palladium(II) salt form an initial π-allylpalladium species that is intramolecularly displaced by an oxygen or nitrogen nucleophile (e.g., eq 21). More recently, they have extended this approach to the use of heterosubstituted dienes (eq 22).[81] Unfortunately, most of these processess use stoichiometric amounts of expensive palladium salts besides the need to prepare the requisite organomercurials which are well known for their toxic properties.



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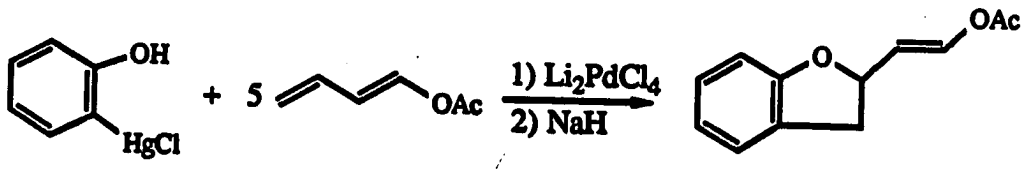


(22)

It is my intention in this dissertation to discuss research directed towards the development of a similar, but more efficient process, where catalytic amounts of palladium and readily available aryl iodides and dienes are utilized.

RESULTS AND DISCUSSION

O-Heterocycles

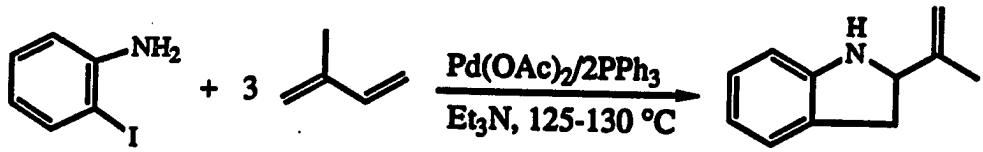
The palladium(0)-catalyzed addition reaction of organic halides to olefins under solid-liquid phase transfer conditions has been recentiy reported by Jeffery.[82] The reaction consists of treating a vinylic, alkynyl or aryl iodide with an olefin in the presence of catalytic amounts of palladium acetate (1 or 2 mole %), a base (K_2CO_3 or $NaHCO_3$) and tetra-*n*-butylammonium chloride (phase transfer reagent) in *N*,*N*-dimethylformamide (DMF) at or near room temperature (eq 23).

$$PhI + H_2C{=}CHCO_2CH_3 \xrightarrow[(n\text{-}Bu)_4NCl,\ DMF]{\text{cat. } Pd(OAc)_2,\ NaHCO_3} PhCH{=}CHCO_2CH_3 \qquad (23)$$
$$25\ ^\circ C$$

Virtually, all olefins used were monosubstituted and electron-deficient, enhancing their reactivity. The high yields of products obtained, in addition to the mild conditions and small amounts of catalyst necessary, make this an attractive synthetic procedure. The disadvantage of previously reported Heck-type reactions involving organic halides has been the relatively high temperatures required, compared to those employing organometallic reagents as starting materials. Even though modified conditions have been reported[83] which allow the use of lower temperatures, large amounts of the palladium catalyst were required. Furthermore, these modified conditions were applicable only to vinylic halides and aromatic halides possessing a nitro substituent.

Employing the above solid-liquid phase transfer conditions with functionalized aryl halides and dienes, in theory, should provide a variety of heterocyclic compounds in one-pot under mild conditions, since the base required for cyclization is already present in the

reaction mixture. Two examples of a similar type of cyclization were recently reported by O'Connor et al.[84] They reported that the reaction of 2-iodoaniline with isoprene and 1,3-cyclohexadiene in the presence of catalytic amounts of $Pd(OAc)_2/PPh_3$ yields the corresponding heterocyclic products (eqs 24 and 25).



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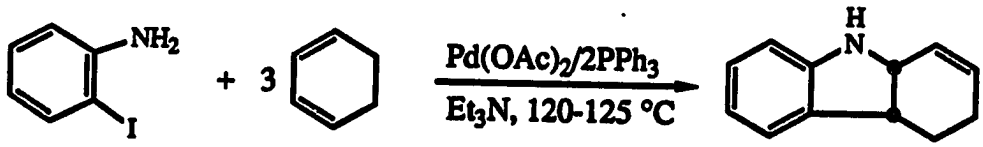


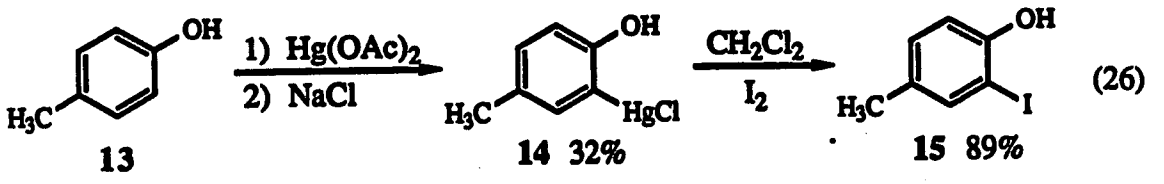
(25)

In an attempt to make this type of cyclization general, it was decided to utilize the above solid-liquid phase transfer procedure as the standard reaction conditions. Further studies in our laboratories[85] have indicated that other bases (Na_2CO_3, NaOAc, KOAc, Et_3N) work as well or better than the two reported by Jeffery; thus, we set about to try these bases on our systems.

Initial studies in this area proved quite disappointing. We attempted to use 2-iodoaniline and 1,3-cyclohexadiene as our first reagents so as to compare our results with those of O'Connor et al.[84] Unfortunately, we were unable to obtain but traces of the expected tetrahydrocarbazole (see eq 25).

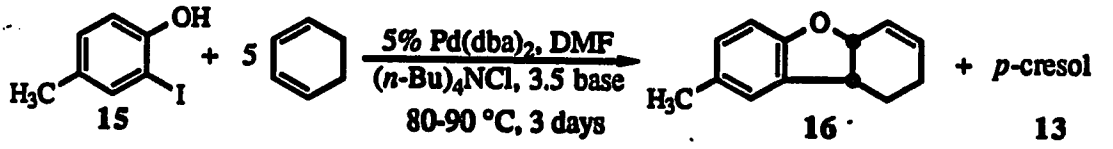
From these reactions, however, we were able to assess that temperatures above room temperature (80 °C or above) were required to see the disappearance of the starting material. In the mean time, we had extended this process to 2-iodo-4-methylphenol and 1,3-cyclo-hexadiene, and somewhat better results were obtained with this system. The required

starting material (**15**) was prepared[86] from the corresponding arylmercurial **14**, which in turn was prepared[87] from *p*-cresol (**13**) and $Hg(OAc)_2$, followed by the addition of NaCl (eq 26).



13 **14** 32% **15** 89% (26)

Reaction of **15** with 1,3-cyclohexadiene (eq 27), under the conditions shown in Table 1, gave low yields of the desired product. In entries 1, 2, and 4, the major product of the reaction was *p*-cresol, and in entry 3 the sole product was **16**.[22] When the reaction was run at a higher temperature (130 °C), a slightly higher yield of **16** was obtained; the reaction also proceeded at a faster rate (1 day) and produced only a trace amount of *p*-cresol (entry 5).



15 **16** **13** (27)

At this point, we decided to utilize *o*-iodophenol for further studies instead of **15**. For one reason, *o*-iodophenol is commercially available, and secondly, the arene ring would be less electron rich which we thought would help to improve the yield. This was indeed the case since better yields were obtained with this system. Thus, we utilized *o*-iodophenol/1,3-cyclohexadiene as our model system.

In our search for a set of reaction conditions that would maximize the yield of this reaction, we made the changes in reaction conditions shown in Table 2. First, we wanted to examine the effect of different bases on the product yield while utilizing $Pd(OAc)_2$ as the catalyst and DMF as the solvent. Initial studies using the carbonate bases (Na_2CO_3, K_2CO_3) indicated that Na_2CO_3 provided better results than K_2CO_3 (entries 1-6) without the need of

Table 1. Palladium-catalyzed reaction of 2-iodo-4-methylphenol with 1,3-cyclohexadiene

Entry	Base	% Yield of **16**	% Yield of **13**
1	Na_2CO_3	13	38
2	Et_3N	trace	47
3[a]	K_2CO_3	12	0
4	NaOAc	9	20
5[b]	NaOAc	18	---

[a]No *p*-cresol detected. However, 45% of compound **15** was recovered.

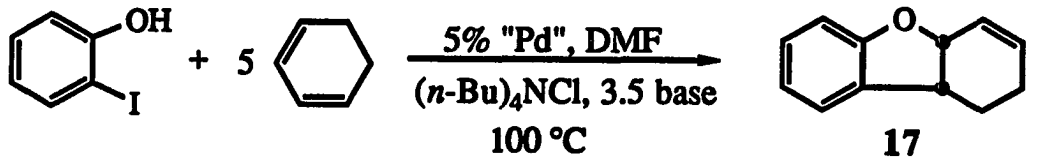
[b]Reaction run for 1 day at 130 °C.

adding triphenylphosphine. Other bases (entries 7-17) were also explored, but only Et_3N (entries 10 and 11) showed any promise. Solvent variations were also explored. Reactions using CH_3CN as solvent gave lower yields of products (entries 2 and 12), while the yield was slightly improved when DMA, instead of DMF, was use as the solvent (entry 3).

At this point, we investigated the effect of using $Pd(dba)_2$ as the catalyst, while varying the base in the reaction. The use of Na_2CO_3 (entries 18-20) provided yields similar to those obtained when $Pd(OAc)_2$ was used as the catalyst. Furthermore, when DMA was used as the solvent together with Na_2CO_3 as the base (entry 21), a 44% isolated yield of compound **17** was isolated. Other bases (entries 22-24) were also investigated, but no real improvement in yield could be obtained. In one instance, $Pd(PPh_3)_4$ was used as a catalyst to afford compound **17** in only 30% yield (entry 25).

Table 2 also indicates that there is not a significant difference in product yield when $Pd(dba)_2$ or $Pd(OAc)_2$ is used as the catalyst; we have thus decided to use $Pd(OAc)_2$ as our

Table 2. Palladium-catalyzed reaction of *o*-iodophenol with 1,3-cyclohexadiene



17

Entry	"Pd"	Base	Day(s)	% Isolated Yield
1	$Pd(OAc)_2$	Na_2CO_3	1	35
2[a]	$Pd(OAc)_2$	Na_2CO_3	1	29
3[b]	$Pd(OAc)_2$	Na_2CO_3	1	40
4	$Pd(OAc)_2$	K_2CO_3	1	5
5[c]	$Pd(OAc)_2$	K_2CO_3	1	30
6[d]	$Pd(OAc)_2$	K_2CO_3	2	19
7	$Pd(OAc)_2$	NaOAc	1	27
8[c]	$Pd(OAc)_2$	NaOAc	2	20
9	$Pd(OAc)_2$	KOAc	1	31
10	$Pd(OAc)_2$	Et_3N	1	35
11	$Pd(OAc)_2$	Et_3N	1	32
12[a]	$Pd(OAc)_2$	Et_3N	1	24
13[c]	$Pd(OAc)_2$	Et_3N	2	14

[a]Run in CH_3CN at reflux (80 °C).

[b]Run in *N*,*N*-dimethylacetamide.

[c]10% PPh_3 added.

[d]5% PPh_3 added.

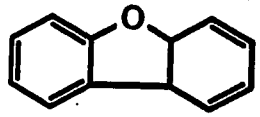
Table 2. (continued)

Entry	"Pd"	Base	Day(s)	% Isolated Yield
14	$Pd(OAc)_2$	$(i\text{-}Pr)_2NEt$	1	25
15	$Pd(OAc)_2$	*t*-BuOK	1	5
16	$Pd(OAc)_2$	NaO_2CPh	1	16
17	$Pd(OAc)_2$	$PhNMe_2$	1	4
18	$Pd(dba)_2$	Na_2CO_3	2	30
19	$Pd(dba)_2$	Na_2CO_3	2	30
20	$Pd(dba)_2$	Na_2CO_3	3	37
21[b]	$Pd(dba)_2$	Na_2CO_3	1	44
22	$Pd(dba)_2$	Et_3N	1	10
23	$Pd(dba)_2$	NaOAc	1	26
24	$Pd(dba)_2$	KOAc	1	30
25	$Pd(PPh_3)_4$	KOAc	2	30

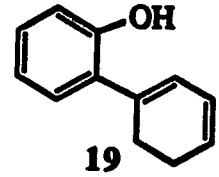
primary catalyst, since this prevents the dibenzylidene acetone from the $Pd(dba)_2$ catalyst from interfering with the isolation of the desired products from the reaction mixture. Table 2, in general, also indicates that Et_3N, NaOAc, KOAc, and Na_2CO_3 are the best bases for this type of heteroannulation.

It should be pointed out, that in many of these reactions the starting aryl iodide could be detected by TLC and in a few cases (entries 4, 7, 9, 10, 12, and 14) the starting aryl iodide was isolated in yields ranging from 10-60%. Besides starting aryl iodide, in almost all of the above reactions (Table 2) another minor spot on TLC could be detected. In one instance (entry 9) this spot was isolated via flash column chromatography and shown to be a

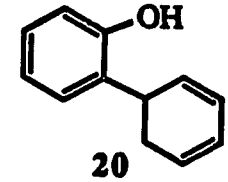
mixture of three compounds from its GC trace. GC-MS analyses of the mixture suggested these to be compounds **18, 19,** and **20.**



18

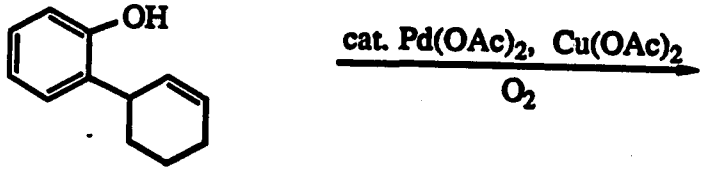


19



20

3,4,4a,9a-Tetrahydrodibenzofuran (**17**) has been previously prepared[46] by the intramolecular oxypalladation of 2-(2-cyclohexenyl)phenol in the presence of palladium acetate, cuprous acetate monohydrate, and a slow stream of oxygen (eq 28).



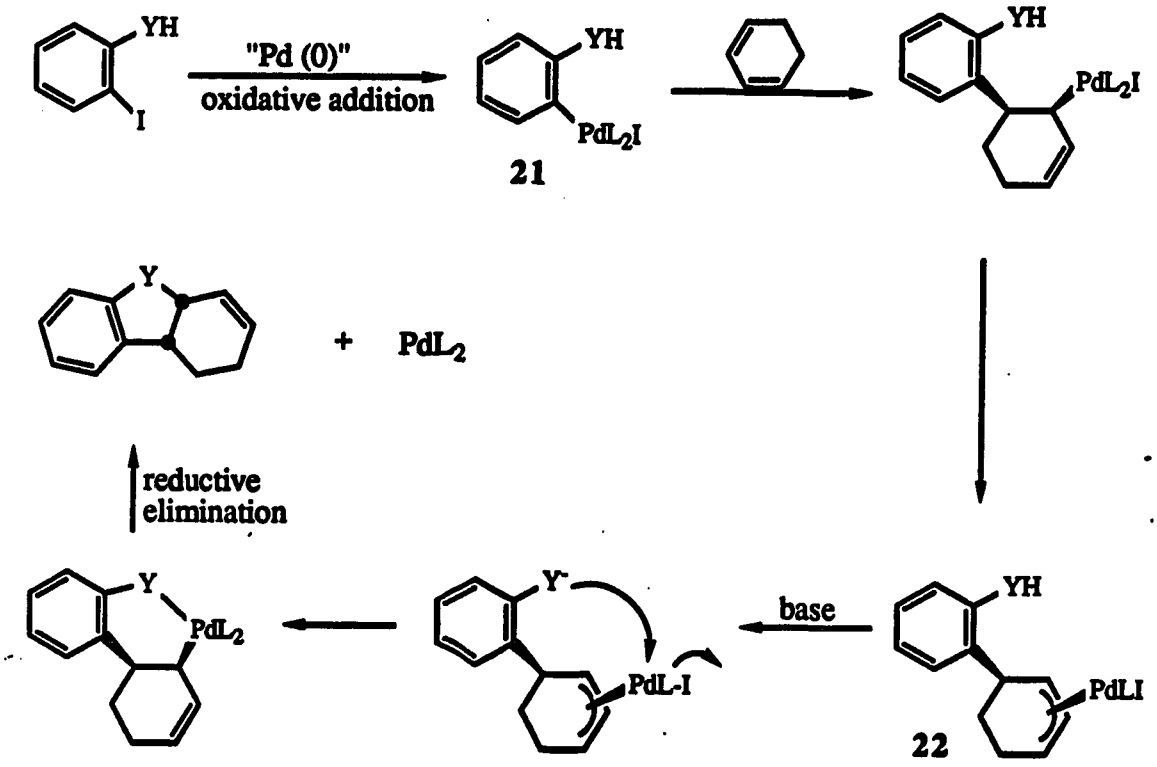
(28)

17

The stereochemistry of the ring junction in compounds **16** and **17** (obtained through a π-allylpalladium intermediate, Table 2) was determined by comparison of their spectral data with that reported by Hosokawa et al.[46] for the same compound (eq 28). Since organopalladium addition to alkenes is known to be cis,[88] the cis stereochemistry observed could arise from attack of the alkoxide on palladium followed by reductive elimination. The mechanism of the reactions summarized in Tables 1 and 2 is shown in Scheme 1.

The first step of the mechanism is the insertion of a Pd(0) species (which one can start with or prepare in situ) into the carbon-iodide bond to generate an ortho-functionalized arylpalladium iodide intermediate (**21**) which adds in a cis fashion to a diene (1,3-cyclohexadiene in this case) to give a σ-palladium intermediate which is allylic to a double bond and thus collapses to the more stable π-allylpalladium intermediate **22.** At this point, the in situ generated nucleophilic anion attacks the palladium metal center displacing one of the ligands

Scheme I



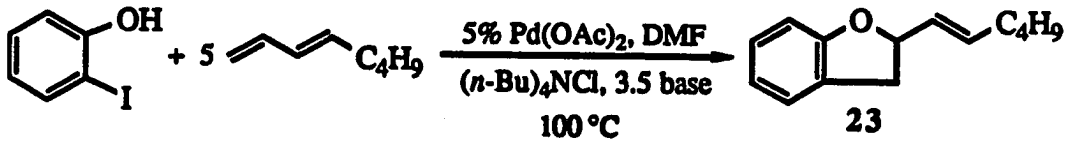
on the metal (possibly the iodide). This generates a cyclic palladium intermediate which undergoes reductive elimination to give the desired product while regenerating the Pd(0) species, which can now re-enter the cycle. Note that this mechanism explains the cis ring-fusion obtained in all of our fused ring systems. This mechanism is also a general mechanism for the reactions that will follow where this new palladium-catalyzed heteroannulation methodology is utilized.

A similar type of intramolecular heteroannulation has been recently reported.[22, 81] There, the initial organopalladium intermediate (e.g., **21**) is prepared via transmetalation of the corresponding organomercurial with stoichiometric amounts of a palladium(II) salt. Using this approach the authors were able to prepare compound **16** as shown in equation 29.

14 16 (29)

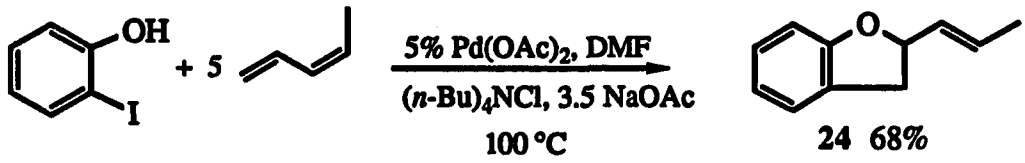
2,3-Dihydrobenzofurans occur widely in nature and the high toxicity of many of its derivatives render them of considerable interest.[89] In wanting to extend our synthetic approach to the synthesis of dihydrobenzofurans, we have reacted *o*-iodophenol with (*E*)-1,3-octadiene and isoprene to obtain moderate to good yields of the expected products.

The reaction of *o*-iodophenol with (*E*)-1,3-octadiene (eq 30) using $Pd(OAc)_2$ as catalyst and Et_3N as base afforded a 59% isolated yield of compound **23**. The same reaction, but using NaOAc as the base, afforded compound **23** in 75% yield. Since good yields were obtained with NaOAc, no other bases were explored with this system. The (*E*)-stereochemistry of **23** was established from the coupling constant between the two olefinic hydrogens (J = 15.3 Hz). No (*Z*)-isomer could be detected in the ^1H NMR spectrum. However, the ^1H NMR and ^{13}C NMR spectra did indicate that this compound was contaminated with an unidentified impurity.



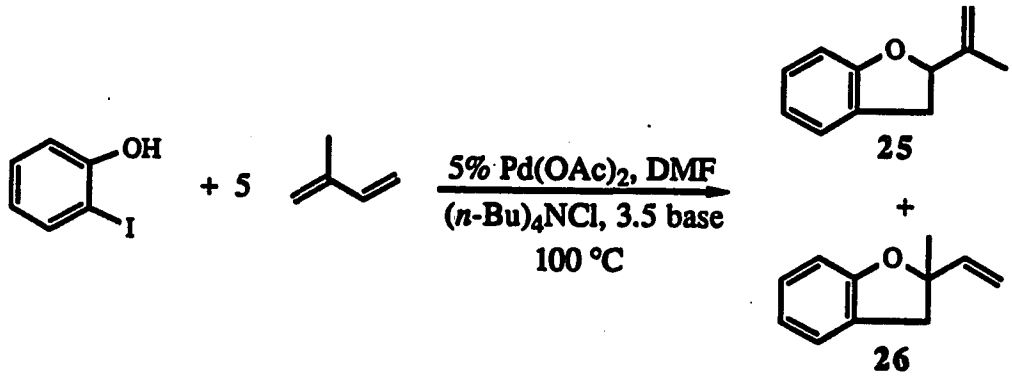
23 (30)

The (*E*)-isomer of 2-(1-propenyl)-2,3-dihydrobenzofuran (**24**) was obtained when *cis*-1,3-pentadiene was reacted with *o*-iodophenol (eq 31). However, the ^1H NMR spectrum of this compound (**24**) also showed the presence of a small impurity which could not be identified. The same reaction in the presence of Et_3N gave a 64% yield of **24** showing the same impurity.



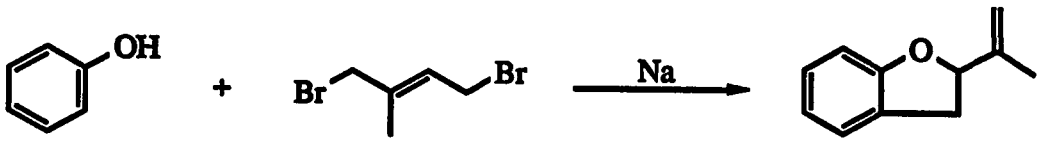
(31)

Isoprene was also allowed to react with *o*-iodophenol to give an inseparable mixture of the two dihydrobenzofurans **25** and **26** (eq 32). The reactions of isoprene with *o*-iodophenol were performed in the presence of $Pd(OAc)_2$ using NaOAc, Et_3N, Na_2CO_3, and $NaHCO_3$ as the bases, to give a mixture of **25** and **26** in 41, 37, 51, and 50% isolated yield, respectively. The ratios of **25** : **26** were 10:1, 19:1, 7:1, and 7:1 for the same bases, respectively.



(32)

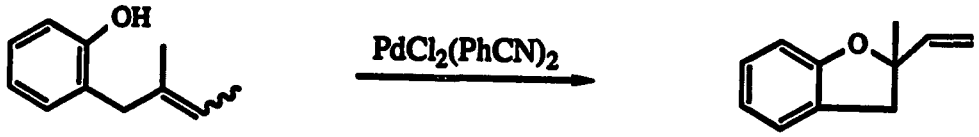
DeGraw et al.[90] in 1963 reported the preparation of **25** in low yields by two different methods. Later, Kawase et al.[91] reported the synthesis of 2-isopropenyl-2,3-dihydrobenzofuran (**25**) by the Nickl procedure. Here, the reaction of phenol with 1,4-dibromo-2-methyl-2-butene in the presence of sodium metal afforded a 43% yield of **25** (eq 33). Bigi et al.[92] have also reported the synthesis of **25** (46% isolated yield) by a modification of the Nickl reaction. Our spectral data for compound **25** "proved identical"



(33)

25 43%

with that reported by Bigi et al. Our procedure to prepare compound **25** has the advantage that both starting materials are readily available. Also, the reaction takes place in one-pot. Unfortunately, the desired product is always contaminated with its regioisomer. The synthesis of compound **26** has been reported by Hosokawa et al.[46] from the oxypalladation of 2-(2-methyl-2-butenyl)phenol in the presence of dichlorobis(benzonitrile)palladium(II) (eq 34).

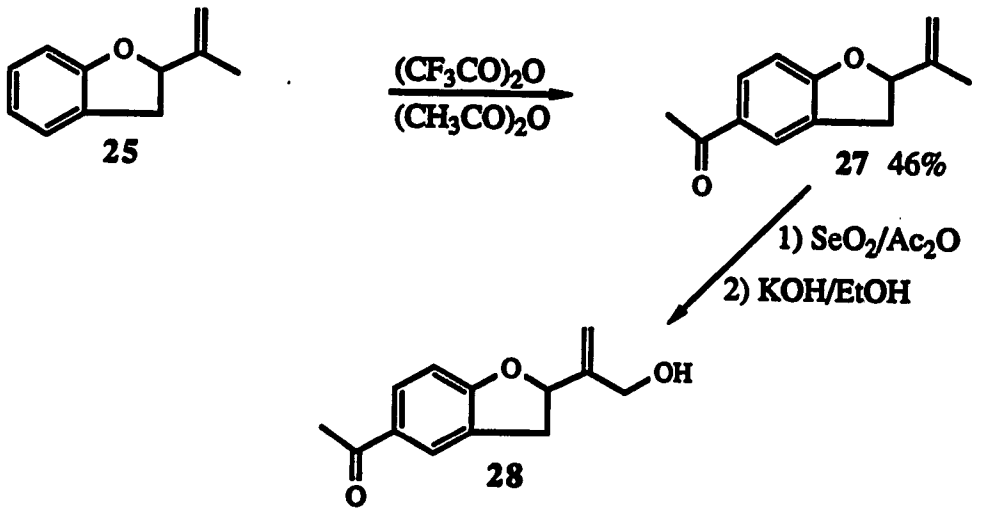


(34)

26 41%

Compound **26**, as prepared in equation 32, was identified from the peaks seen in the ^{1}H NMR spectrum of the mixture and by comparing them with the ^{1}H NMR spectral data reported by Hosokawa et al.[46] for the same compound. The interest in compound **25** stems from its usefulness as a precursor to a variety of natural products. For example, Yamaguchi et al.[91b] made use of this precursor in the synthesis of racemic tremetone (**27**) (a toxic ketone isolated from "white snakeroot"), which he then took on to 5-acetyl-2-[1-(hydroxy-methyl)vinyl]-2,3-dihydrobenzofuran (**28**) (eq 35), another natural product isolated from plant sources.

Our first step in shortening the synthetic approach to tremetone was to make use of 4-hydroxy-3-iodoacetophenone (**29**).[93] Reaction of **29** with isoprene provided a one-pot synthesis of tremetone under our catalytic conditions as shown in Table 3.



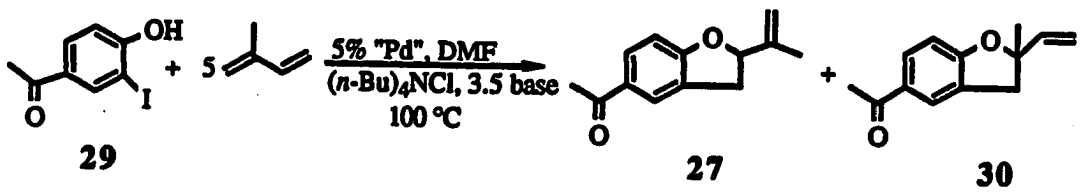
(35)

The reaction of isoprene with compound **29** at 80 °C (entry 1) proceeded very sluggishly to give a 40% yield of a mixture of **27** and **30** and required 5 days to consume all of the starting aryl iodide. However, when the reaction was run at 100 °C, it proceeded quite cleanly, and in 24 h gave a 75% combined yield of compounds **27** and **30** (entry 2). The presence of $(n\text{-Bu})_4NCl$ in the reaction is indeed required to provide good yields and faster reaction times (cf. entries 2 and 3).

The addition of PPh_3, which should provide higher regioselectivity because it increases the steric bulk around the palladium,[13, 94] gave lower yields of products and no improvement in regioselectivity. Other bases were also employed (entries 5-8), but only Et_3N (entry 6) gave comparable results relative to the best previous condition (entry 2). When we utilized $Pd(dba)_2$ as the catalyst and NaOAc as the base, an 83% yield of compounds **27** and **30** was isolated. The addition of PPh_3 (entry 10) provided a lower yield of products and no significant change in regioselectivity. Reactions in the presence of $Pd(dba)_2$ using a variety of bases (entries 11-13) provided lower yields of products.

It is somewhat puzzling that the same general type of reactions require different

Table 3. Palladium-catalyzed reaction of 3-iodo-4-hydroxyacetophenone with isoprene



29 27 30

Entry	"Pd"	Base	Day(s)	% Isolated Yield (27 : 30)[a]
1[b]	$Pd(OAc)_2$	NaOAc	5	40 (11:1)
2	$Pd(OAc)_2$	NaOAc	1	75 (9:1)
3[c]	$Pd(OAc)_2$	NaOAc	8	33 (8:1)
4[d]	$Pd(OAc)_2$	NaOAc	4	34 (10:1)
5	$Pd(OAc)_2$	KOAc	1	63 (7:1)
6	$Pd(OAc)_2$	Et_3N	1	72 (8:1)
7	$Pd(OAc)_2$	$(i\text{-}Pr)_2NEt$	1	56 (8:1)
8	$Pd(OAc)_2$	*t*-BuOK	1	49 (10:1)
9	$Pd(dba)_2$	NaOAc	1	83 (7:1)
10[d]	$Pd(dba)_2$	NaOAc	4	34 (9:1)
11	$Pd(dba)_2$	KOAc	1	58 (8:1)
12	$Pd(dba)_2$	Et_3N	1	50 (8:1)
13	$Pd(dba)_2$	Na_2CO_3	1	30 (10:1)

[a]GC ratios.

[b]Reaction run at 80 °C.

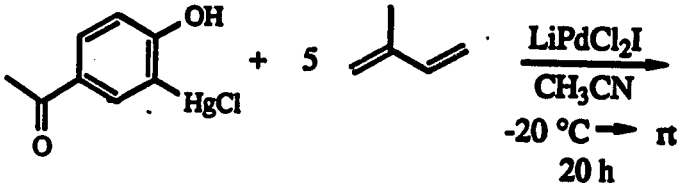
[c]No $(n\text{-}Bu)_4NCl$ used.

[d]5% PPh_3 added.

conditions to provide good yields of products. At this point, a mechanistic explanation for this is not obvious. Also, the role of $(n\text{-Bu})_4NCl$ to afford high yields of products and shorter reaction times is not well understood. Recently, Amatore et al.[95] reported the electrochemical reduction of $Cl_2Pd(PPh_3)_2$ to give low coordinated zerovalent palladium complexes that are stabilized by chloride anions. These complexes appear to be of the type $[x(n\text{-}Bu_4N), Cl_xPd^{\circ}(PPh_3)_2]_n$ which are analogous to the $LiClPd^{\circ}(PPh_3)_n$ intermediates reported by Negishi et al.[96] and which Scott and Stille[97] have recently postulated to be the effective agents in the catalysis of cross-coupling reactions. Amatore et al. have found that the rate of oxidative addition of PhI to these complexes is faster than the addition of PhI to $Pd(PPh_3)_3$ or $Pd(PPh_3)_4$. Similar types of complexes are probably involved as intermediates in our reactions, and they may account for the shorter reaction times and high yields of products obtained under our reaction conditions.

The structure of tremetone (**27**) in Table 3, was confirmed by comparing its ^1H NMR and IR spectra with those reported in the literature.[91b] The structure assigned to compound **30** was based solely on the peaks seen in the ^1H NMR spectrum of the mixture.

Recently we have prepared[98] a mixture of compounds **27** and **30** in a 4:1 ratio from the palladium-induced reaction of 3-chloromercurio-4-hydroxyacetophenone with isoprene in 95% isolated yield (eq 36).

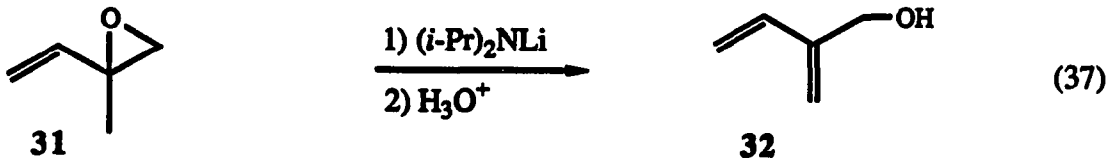


(36)

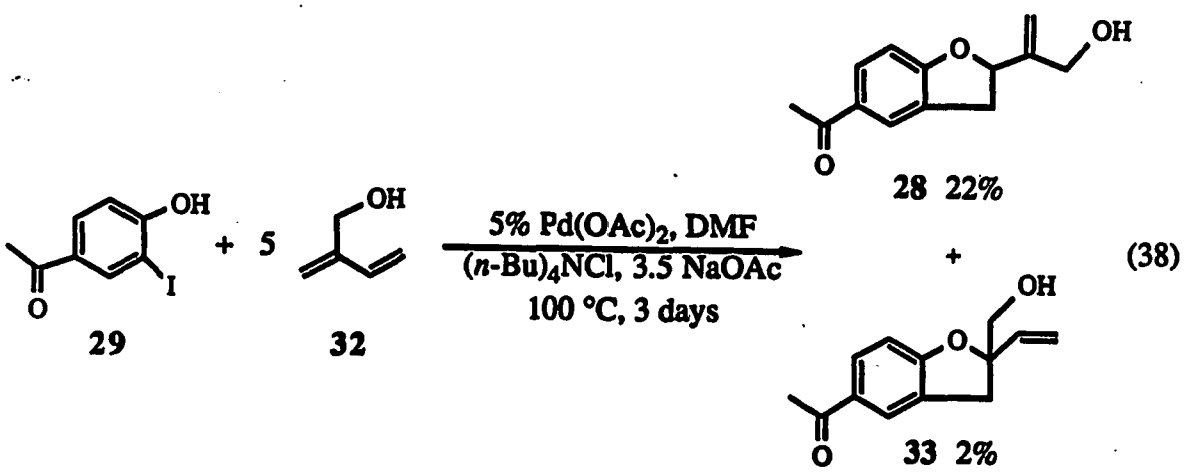
Because of the exciting results obtained with the above system (Table 3), we have examine the reaction of 4-hydroxy-3-iodoacetophenone (**29**) with 2-hydroxymethyl-1,3-butadiene (**32**). Compound **32** was prepared by a modification of the procedure reported by

Riley and Silverstein[99] from the base-induced rearrangement of 3,4-epoxy-3-methyl-1-butene (**31**) in 20% distilled yield (eq 37). Using $Pd(OAc)_2$ as the catalyst, and NaOAc as the base (eq 38) 22 and 2% isolated yields of compounds **28** and **33** were isolated, respectively.

This approach (eq 38) constitutes the shortest synthetic approach yet to compound **28**. Of significance is the fact that other natural products can be prepared using compound



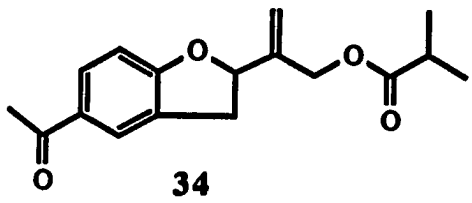
31 **32** (37)



29 **32** (38)

28 as a starting material. For example, Kawase et al.[91a] has reported the synthesis of compounds **34** and **35** by esterification of compound **28** with the corresponding acid chlorides in the presence of pyridine.

Fomes annosus is a fungi known to cause the death of host cells in living trees. It also causes extensive decay in the heartwood of diseased trees. Fomannoxin, a dihydro-



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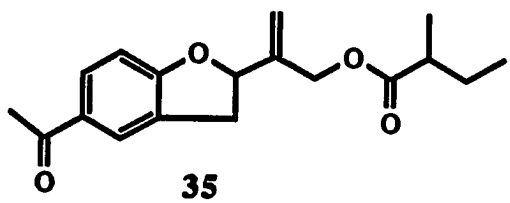
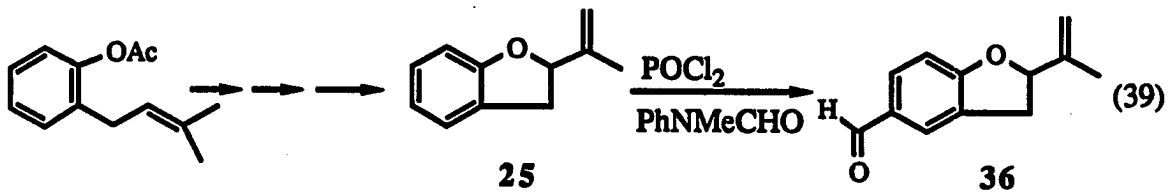
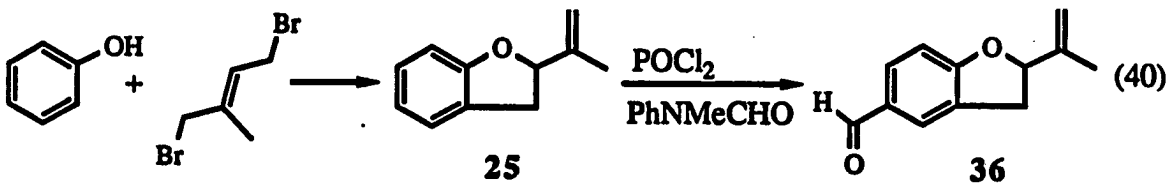


35

benzofuran, was recently isolated from *Fomes annosus* [100] and was found to be toxic to Chorella pyrenoidosa, and thus it was classified as a phytopathogen. Duffley and Stevenson[101] in 1978 reported the first synthetic approach to racemic fomannoxin via an eight-step synthetic scheme starting from methyl anodendroate. Donnelly and O'Reilly[102] have also reported a synthetic approach to fomannoxin (**36**) from compound **25**, which they have prepared in three steps from 2-methyl-4-(2-acetoxyphenyl)but-2-ene (eq 39). More recently, Yamaguchi et al.[91b] reported a two-step synthesis of compound **36** as shown in equation 40. Enantioselective syntheses to fomannoxin have also been reported.[102, 103]

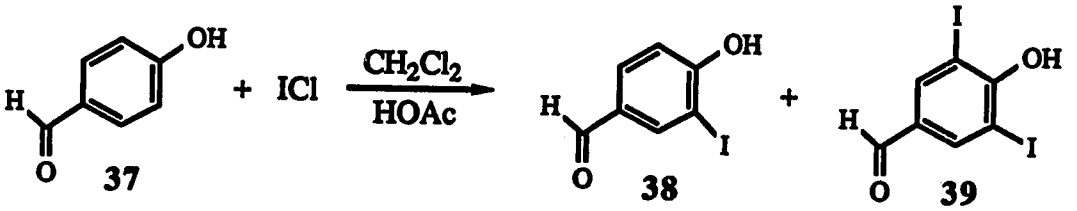


25 36 (39)



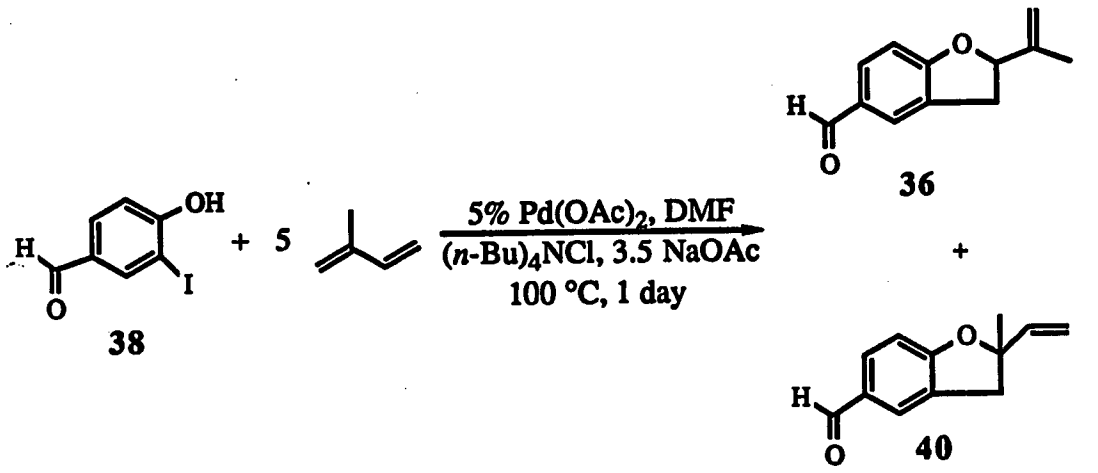
25 36 (40)

By using our methodology, we have developed a one-pot synthetic approach to fomannoxin. The requisite 4-hydroxy-3-iodobenzaldehyde (**38**) was prepared by the procedure reported by Schawartz et al.[104] Reaction of compound **37** with iodine mono-chloride (ICl) afforded a 7.4:1 ratio (from the ^{1}H NMR spectrum) of a mixture of **38** and



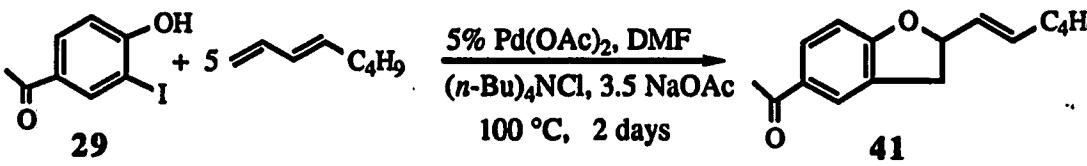
(41)

3,5-diiodo-4-hydroxybenzaldehyde (**39**) in 67% isolated yield (eq 41). Reaction of this mixture with isoprene (eq 42) afforded a 43% isolated yield of an inseparable mixture of fomannoxin (**36**) and compound **40** in a 10:1 ratio (from the ^{1}H NMR spectrum), respectively.



(42)

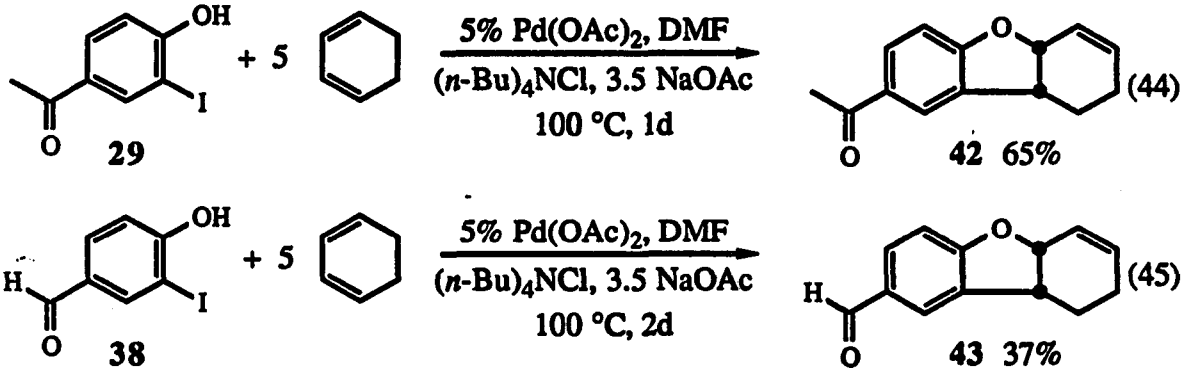
Using one of the best reaction conditions from Table 3 (entry 2), we have reacted (*E*)-1,3-octadiene with compound **29** to give 5-acetyl-2-[(*E*)-1-hexenyl]-2,3-dihydrobenzofuran (**41**) in 53% isolated yield (eq 43). A 1:1 mixture (from the ^{1}H NMR spectrum) of **29** and of dehalogenated **29** was also isolated from this reaction in 14%



(43)

combined yield after extracting them from the "purified" product with 10% NaOH. When the reaction was run for seven days to consume all of the starting aryl iodide, a 55% yield of compound **41** was obtained. The only other products obtained were a mixture of compounds in ca. 2% yield; these were not identified. Even though a comparable yield of compound **41** was obtained after two days, the reaction mixture was easier to work-up when all of the starting aryl iodide had been consumed.

Compounds **29** and **38** were also reacted with 1,3-cyclohexadiene to give the corresponding dibenzofuran derivatives (eqs 44 and 45). It should be pointed out, that

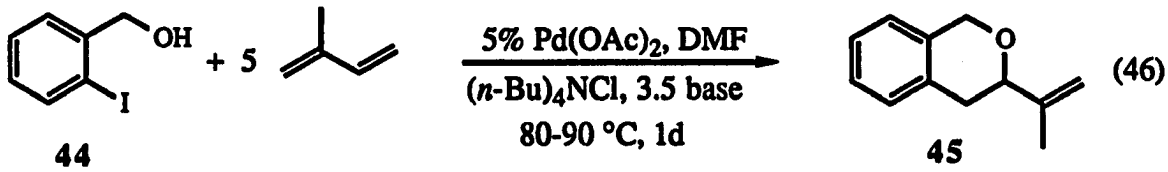


the reaction shown in equation 44 gives more than twice the yield of that reported using *o*-iodophenol as the starting material under identical reaction conditions. This suggests that an electron-withdrawing group on the aryl halide indeed facilitates the reaction. For one, the electron-withdrawing group should facilitate the oxidative-addition of the carbon-halide bond to palladium. Also, it should decrease the intermolecular interaction between the palladium metal center and the hydroxyl group of another molecule of starting aryl iodide. This should facilitate coordination of the olefin on the metal center, thus facilitating the addition of the arylpalladium intermediate to the carbon-carbon double bond of the diene to form the π-allyl-palladium intermediate.

The low yields obtained in the reactions illustrated in equations 42 and 45 are thought

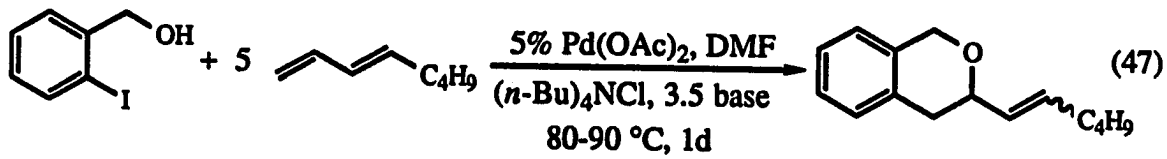
to be due to the instability of compound **38**, and not to problems in any of the organopalladium steps. Compound **38** slowly turns from colorless to a slight violet while sitting in the refrigerator. Thus, the fast decomposition of compound **38** under our reaction conditions (100 °C) could account for the low yields obtained.

As an extension of this project, we have reacted 2-iodobenzyl alcohol (**44**) with isoprene using Na_2CO_3, NaOAc, and Et_3N as the bases (eq 46). These reactions showed the presence of some product in the crude mixture. However, when using the above bases, the starting aryl iodide was recovered in 35, 67, and 18% yields, respectively, and no product could be isolated. The desired product **45** seemed to be too volatile to be isolated.



44 **45** (46)

To make the isolation of the desired product easier, we thought to use (*E*)-1,3-octadiene instead of isoprene as the diene since (*E*)-1,3-octadiene is a high boiling diene, and thus it should afford a relatively high boiling product. Reaction of compound **44** with (*E*)-1,3-octadiene (Table 4) (eq 47) using $Pd(OAc)_2$ as the catalyst and NaOAc, Et_3N, and Na_2CO_3 as the bases afforded only small amounts of products that contained the desired product **46** (entries 1-4). When KOAc was used as the base (entry 5), a 24% yield of the



44 **46** (*E*) ; **47** (*Z*) (47)

Table 4. Palladium-catalyzed reaction of 2-iodobenzyl alcohol (44) with (*E*)-1,3-octadiene

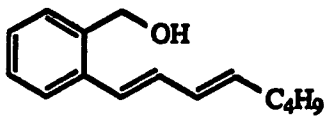
Entry	"Pd"	Base	Temp. (°C)	Day(s)	% Isolated Yield of 46 plus 47
1	$Pd(OAc)_2$	NaOAc	80	3	ca. 10
2	$Pd(OAc)_2$	NaOAc	100	2	ca. 4
3	$Pd(OAc)_2$	Et_3N	80	3	----
4	$Pd(OAc)_2$	Na_2CO_3	80	3	ca. 10
5	$Pd(OAc)_2$	KOAc	80	1	24
6[a]	$Pd(OAc)_2$	KOAc	80	1	56
7[a]	$Pd(dba)_2$	KOAc	80	1	38

[a]5% PPh_3 added.

desired product **46** was obtained. From this reaction (entry 5), a 45% yield of the expected Heck product **48** was also isolated.

Contrary to earlier results, when this reaction was run in the presence of PPh_3 (entry 6), a 56% yield of a mixture of compounds was isolated. GC-MS analysis of this mixture showed two peaks in a 16:1 ratio, both with a mass of 216. The structure of the major isomer **46** was assigned based on its spectroscopic data. However, since the mass spectrum of both compounds looked identical, the structure of the other isomer can only be attributed to the *cis* double bond isomer **47**. Also, ca. a 7% yield of impure **48** was isolated. Running the reaction in the presence of PPh_3 and using $Pd(dba)_2$ as the catalyst (entry 7) afforded a low yield of a mixture of products. GC-MS analysis, showed 4 peaks in an 86:7:4:3 ratio. The major isomer was compound **46**, while the second major isomer was compound **47**.

The structure of the other two minor isomers were assigned as **49** and **50**, respectively, based solely on their mass spectra. For entries 5 and 6, a second fraction containing a mixture of products was isolated, but these were not identified.



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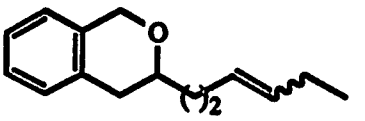

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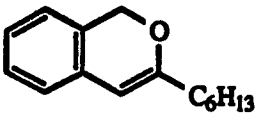
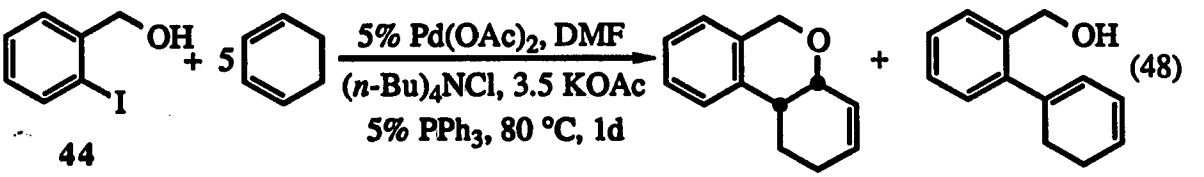


50

The reaction of alcohol **44** with acyclic dienes provided entry into the 1*H*-2-benzopyran system. On the other hand, reaction of **44** with 1,3-cyclohexadiene provided entry into the 6*H*-dibenzo[*b*,*d*] pyran system as shown in equation 48. Reaction of **44** with

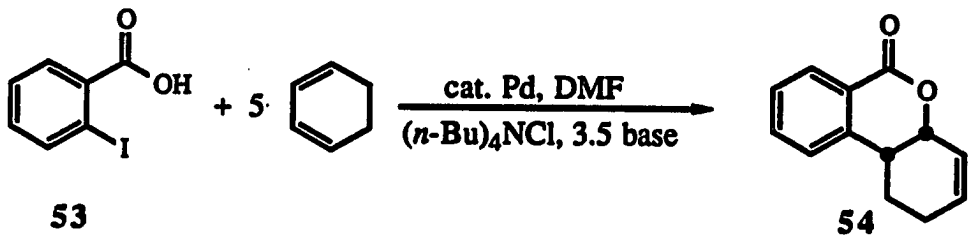


44 **51** **52**

1,3-cyclohexadiene using $Pd(OAc)_2$ as the catalyst in the presence of KOAc as the base (eq 48) afforded a 25% yield of **51** and a 29% yield of **52**. Using $Pd(dba)_2$ as the catalyst instead, afforded similar results. A 26% yield of **51** and a 31% yield of **52** were isolated in this case.

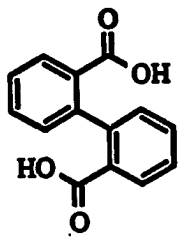
We have also attempted to develop a method to synthesize six-membered ring lactones. Unfortunately, our attempts were void of positive results. The study of this lactone approach was attempted using 2-iodobenzoic acid (**53**) and 1,3-cyclohexadiene (eq 49) as starting materials, which should have given compound **54** as the desired product.

Variations on reaction conditions afforded only diphenic acid (**55**) and benzoic acid (as a mixture) as the only products. None of the desired product **54** was detected in any of



53 54 (49)

the reactions. The yields of the diphenic acid/benzoic acid mixture ranged from 26-82%. In many cases, only the starting acid could be isolated from the reaction mixture. Similar results were obtained, under a variety of conditions, when 1,3-octadiene was used as the diene.



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It is the author's opinion, that the lack of desired product with this acid is due to strong chelation of the palladium metal center to the carboxylic oxygen atom of the acid, or more likely, to the carboxylate anion itself. Patel et al.[105] have reported that the reaction of *o*-bromobenzoic acid with activated olefins provided none of the desired products. However, when the corresponding methyl ester was reacted with the same olefins, under conditions identical to those used with the acid, high yields of products were obtained. Heck and co-workers, then proposed the above type of chelation as an explanation for the lack of reactivity when the acid itself was utilized.

As part of this research project, we have extended this methodology to the synthesis of nitrogen heterocycles and this is covered in the section that follows.

N-Heterocycles

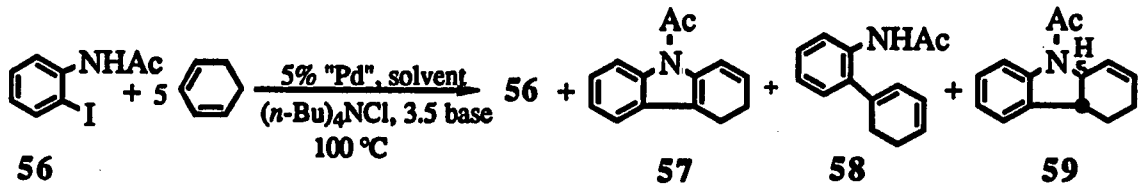
As mentioned previously, we started this project using 2-iodoaniline and 1,3-cyclohexadiene as our initial reagents. Unfortunately, even after changing the reaction conditions by varying the palladium salt, base, solvent, temperature, and the amount of $(n\text{-Bu})_4NCl$, we were not able to obtain via isolation anything but traces (from ^1H NMR spectral data) of the desired product.

However, Horino[106] has reported that acetanilide can be orthopalladated to produce a stable arylpalladium compound, which can be reacted with olefins to give the expected coupling products. With this in mind, we prepared 2-iodoacetanilide (**56**) as reported by Korner and Wender[107] and reacted it with 1,3-cyclohexadiene under a variety of conditions to give the results shown in Table 5.

Table 5 shows that DMA as the solvent provides better yields of products than DMF when either $Pd(OAc)_2$ or $Pd(dba)_2$ is used as the catalyst (see entries 1-4 and 6-7). It is also obvious from these entries (cf. entries 1 and 3, and 2 and 4) that Na_2CO_3 provides a better ratio of desired product **59** to diene product **58** than NaOAc. From entries 4 and 5, it can be seen that the addition of PPh_3 provided lower yields of products and a higher ratio of **58**:**59**. When the reaction is run using a combination of $Pd(dba)_2$ and Na_2CO_3, a higher yield of product is obtained (entries 6 and 7). $Pd(dba)_2$ also gives a better ratio of desired product **59** to diene product **58** than $Pd(OAc)_2$.

It should be noted that in almost all of the reactions the starting anilide was still present even after two days at 100 °C; since no apparent change was detected by either TLC or GC as to the consumption of the starting anilide, the reaction mixture was worked up at this time. In order to completely consume all of the starting anilide, we had to resort to adding the catalyst in two portions. The first portion being added at the start of the reaction

Table 5. Palladium-catalyzed reaction of 2-iodoacetanilide (56) with 1,3-cyclohexadiene



56 57 58 59

Entry	"Pd"	Base	Solvent	Day(s)	% Isolated Yield (56 : 57 : 58 : 59)[a]
1	$Pd(OAc)_2$	NaOAc	DMF	1	23 (38 : 0 : 50 : 12)
2	$Pd(OAc)_2$	NaOAc	DMA	2	60 (0 : 0 : 96 : 4)
3	$Pd(OAc)_2$	Na_2CO_3	DMF	1	15 (23 : 8 : 31 : 38)
4	$Pd(OAc)_2$	Na_2CO_3	DMA	1	54 (20 : 4 : 44 : 32)
5	$Pd(OAc)_2/2PPh_3$	Na_2CO_3	DMA	2	35 (0 : 5 : 75 : 20)
6	$Pd(dba)_2$	Na_2CO_3	DMA	2	70 (12 : 0 : 25 : 63)
7	$Pd(dba)_2$	Na_2CO_3	DMF	1	51 (7 : 0 : 21 : 72)
8[b]	$Pd(dba)_2$	Na_2CO_3	DMA	2	66 (0 : 0 : 20 : 80)
9[c]	$Pd(dba)_2$	Na_2CO_3	DMA	2	63 (10 : 0 : 20 : 70)
10	$Pd(dba)_2/2PPh_3$	Na_2CO_3	DMA	2	45 (0 : 0 : 67 : 33)
11	$Pd(dba)_2/2PPh_3$	Na_2CO_3	DMA	3	45 (0 : 0 : 25 : 75)

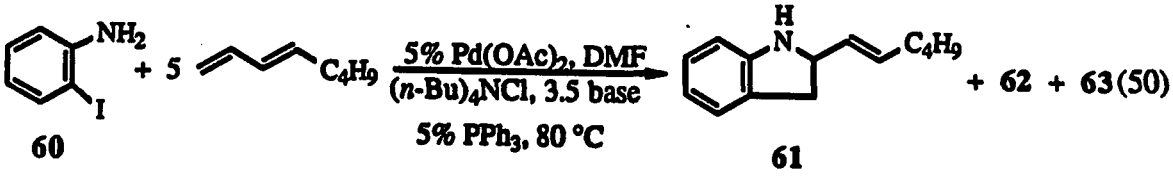
[a]GC ratios.

[b]Palladium catalyst added in 2 portions of 5% each.

[c]Palladium catalyst added in 2 portions of 2.5% each.

and the second portion after 24 h. Apparently, portions of 5 mole percent of catalyst are needed as a minimum (see entries 8 and 9). Addition of PPh_3 (entries 5, 10, and 11) also helped to consume all of the starting material, but lower yields were obtained. It should be noted that when two equivalents of PPh_3 per equivalent of palladium salt (entry 10) were utilized, the major isomer was compound **58** and not **59**. However, when one equivalent of PPh_3 was used, the ratio was inverted, the desired product **59** being the major isomer now. Furthermore, from the ^1H NMR spectrum, one has to assume that compound **59** was contaminated with some of the trans-fused isomer, even though this isomer was not detected during GC analyses. The ^1H NMR spectral ratio of **59** to its trans-isomer is ca. 2:1.

In conjunction with our initial work, 2-iodoaniline (**60**) was allowed to react with (*E*)-1,3-octadiene (eq 50) under the conditions shown in Table 6. Since this diene contains a terminal olefin, the reaction was expected to proceed to give compound **61** with more ease than the reaction of **60** with 1,3-cyclohexadiene.



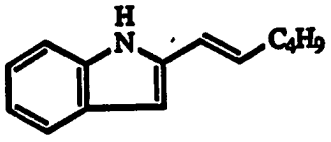
60 **61**

As expected, we were able to isolate compound **61** from the reaction mixture. However, compound **61** was contaminated with small amounts of compounds **62** and **63** in the ratios shown in Table 6. The structures of compounds **62** and **63** were assigned based on their GC-MS data alone. The different bases used in this system had no effect on product yield, but when KOAc was used as the base, none of compound **63** could be detected by GC. Even though we were able to obtain the desired product with this system, we were not quite satisfied with the yields obtained.

Table 6. Palladium-catalyzed reactions of 2-iodoaniline (60) with 1,3-octadiene

Entry	Base	Day(s)	% Isolated Yield (61 : 62 : 63)[a]
1	Na_2CO_3	2	45 (69 : 28 : 3)
2	NaOAc	3.6	46 (75 : 21 : 4)
3	KOAc	3.6	45 (93 : 7 : 0)

[a]GC ratios.



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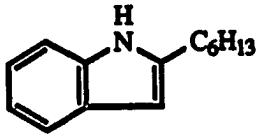
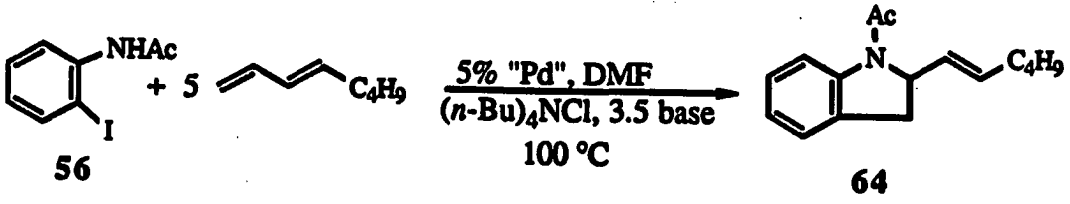


63

Since compound 56 gave higher yields than compound 60 in the reaction with 1,3-cyclohexadiene (see Table 5), we decided to extend its use to the synthesis of compound 64 (eq 51). These results are shown in Table 7. Table 7 shows that after many variations in reaction conditions, a maximum yield for compound 64 of 63% could be obtained (entry 4).



56 64 (51)

Of the bases used, Na_2CO_3 and $NaHCO_3$ provided the best results (entries 3-5, and 8-12). Changes in solvent or palladium salt while using Na_2CO_3 or $NaHCO_3$ as the bases provided no significant improvement in product yield.

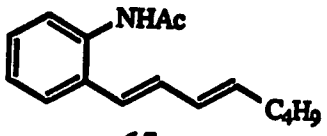
Table 7. Palladium-catalyzed reaction of 2-iodoacetanilide (56) with (*E*)-1,3-octadiene

Entry	"Pd"	Base	Day (s)	% Isolated Yield of compound 64
1	$Pd(OAc)_2$	NaOAc	2	25
2	$Pd(OAc)_2$	KOAc	2	20
3	$Pd(OAc)_2$	Na_2CO_3	1	46
4[a]	$Pd(OAc)_2$	Na_2CO_3	2	63
5	$Pd(OAc)_2$	$NaHCO_3$	1	40
6	$Pd(OAc)_2$	K_2CO_3	2	2
7	$Pd(OAc)_2$	Et_3N	1	4
8	$Pd(OAc)_2$	Et_3N	2	10
9	$Pd(dba)_2$	Na_2CO_3	1	40
10	$Pd(dba)_2$	$NaHCO_3$	1	44
11[b]	$Pd(dba)_2$	$NaHCO_3$	2	44
12[b]	$Pd(dba)_2$	Na_2CO_3	2	44
13	$Pd(dba)_2/PPh_3$	Na_2CO_3	3	40

[a] 5% PPh_3 added.

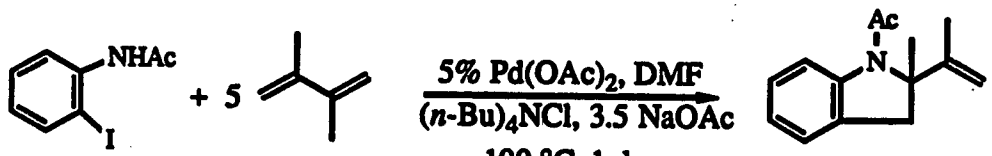
[b] *N,N*-Dimethylacetamide use as solvent.

product yield. An advantage of using compound **56** as the starting aryl iodide for this reaction is the fact that no other products, besides the desired product, were obtained. The only exception is entry 12 where a mixture of **64** and **65** (10%), and an unidentified isomer was obtained. 2-Iodoacetanilide (**56**) was also allowed to react with 2,3-dimethyl-1,3-



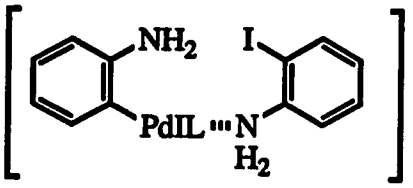
65

butadiene (66) in the presence of NaOAc to give a 29% isolated yield of *N*-acetyl-2-methyl-2-isopropenyl-2,3-dihydroindole (67) (eq 52). The same reaction using $Pd(dba)_2$ as the catalyst and Na_2CO_3 as the base gave only an 11% isolated yield of compound 67.



56 66 67 29% (52)

Based on the mechanism for these reactions, it is believed that the poor results with the nitrogen systems is due to the fact that the functionalized arylpalladium iodide intermediate (21) could exist as a coordinated complex. The palladium atom being strongly coordinated to the heteroatom of another molecule of aryl iodide, and thus preventing this intermediate from coordinating to the olefin (the coordinated species is shown below).



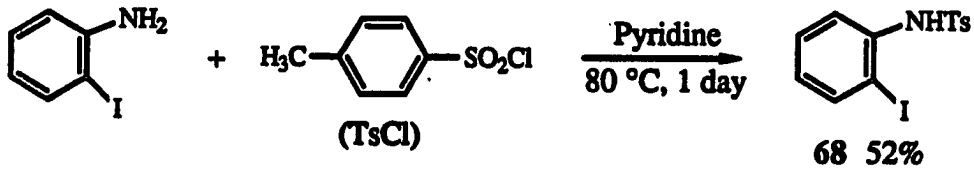
L may be equal to 2-iodoaniline

The use of an electron-withdrawing group (the acetyl group for example) attached to the nitrogen atom of 2-iodoaniline supports this argument, since an electron-withdrawing group on the nitrogen should diminish coordination of the nitrogen to the palladium atom thus favoring coordination of the olefin to intermediate 21.

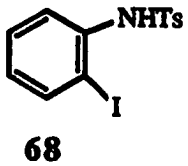
Heck[5] has recently reviewed the chemistry of palladium and dedicated a chapter to the

orthopalladation of *N*, *N*-disubstituted arylamines. In this chapter many examples of stable, very unreactive chelated palladium intermediates were presented. Only when running reactions at a high temperature (115 °C) and or when using activated olefins did some of these intermediates undergo carbon-carbon coupling.

Based on the above results and those reviewed by Heck, it was thought that the attachment of a strong electron-withdrawing group on to the nitrogen atom of 2-iodoaniline would provide us with higher yields of the corresponding cyclization products. With this in mind, the corresponding *N*-tosyl derivative (**68**, eq 53) was prepared. Compound **68** was prepared in 52% recrystallized yield by a modification of the procedure reported by Ratcliffe[108] for the synthesis of *N*-tosyl-4-iodoaniline. Knowing that sodium carbonate and bicarbonate provided the best yields when using 2-iodoacetanilide, we proceeded to react **68** with 1,3-cyclohexadiene and (*E*)-1,3-octadiene (eq 54) in the presence of Na_2CO_3. This afforded excellent yields of products **69** and **70**, respectively (Table 8).



(53)

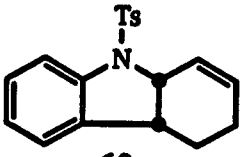
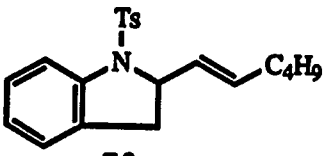


+ 5 diene $\xrightarrow[(n\text{-Bu})_4\text{NCl, 3.5 } Na_2CO_3]{\text{5\% "Pd", DMA}}$ **69** or **70** (54)

100 °C

Using $Pd(OAc)_2$ or $Pd(dba)_2$ in this system had no significant effect, within experimental error, on the yields of compounds **69** and **70**. Use of the tosyl group has two advantages. For one, it provides excellent yields of the above products. Secondly, the

Table 8. Palladium-catalyzed reactions of *N*-tosyl-2-iodoaniline (**68**) with dienes

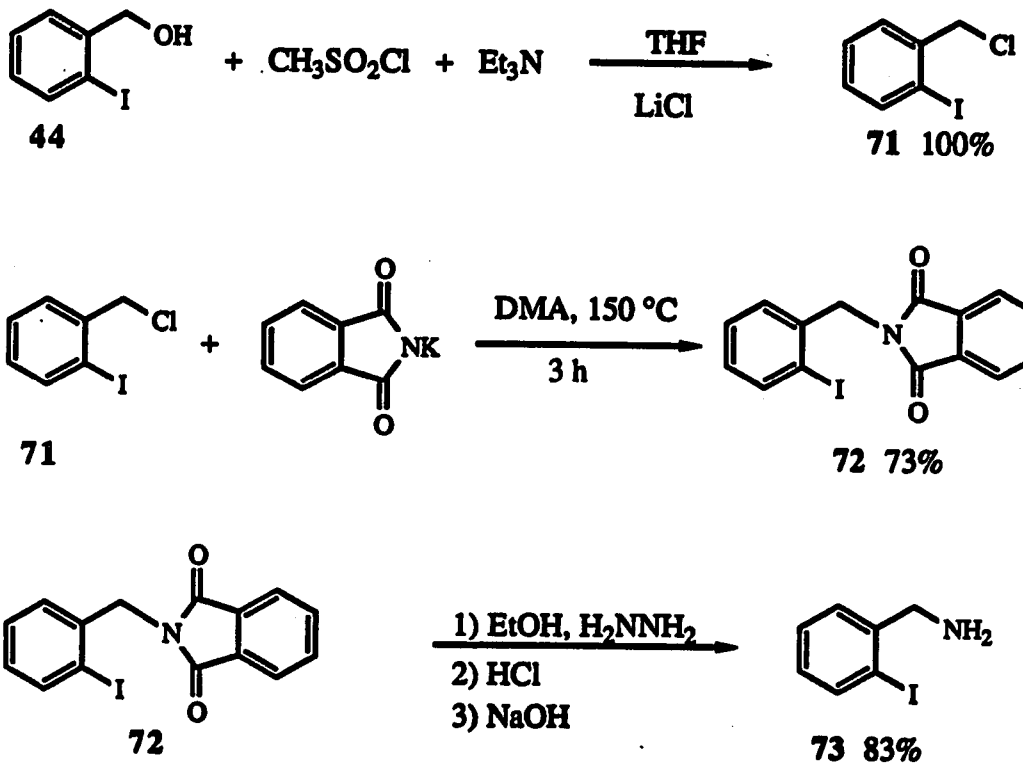
Entry	"Pd"	Diene	Day(s)	Product	% Isolated Yield
1	$Pd(OAc)_2$		2	 **69**	86
2	$Pd(OAc)_2$		1	 **70**	84
3	$Pd(dba)_2$		1	**70**	82
4	$Pd(dba)_2$		2	**69**	87

products obtained were easy to isolate and purify. After column chromatography, a thick paste was obtained for both compound **69** and compound **70**. These were dissolved in hot 100% EtOH to give, after cooling, colorless crystals for both compounds.

At this point, we diverted our attention to the synthesis of isoquinoline derivatives. The required starting material (2-iodobenzylamine) for the reactions to follow was finally prepared by the sequence of steps starting from 2-iodobenzyl alcohol shown in Scheme II.

Formation of the mesylate derivative of **44**, followed by its in situ displacement with LiCl,[109] afforded a quantitative yield of 2-(chloromethyl)-1-iodobenzene (**71**). Reaction of

Scheme II

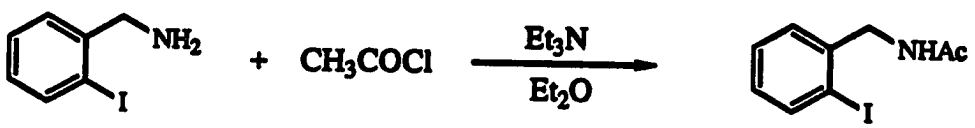


71 with potassium phthalimide[110] while heating at 150 °C for 3 h yielded a 93% isolated yield of 2-iodobenzyl phthalimide (**72**). Recrystallization of **72** from glacial acetic acid afforded a 73% yield of colorless crystals. Treatment of **72** with an 85% solution of hydrazine hydrate,[111] followed by warming with excess HCl, and basification with NaOH afforded, after work up, an 83% isolated yield of 2-iodobenzylamine (**73**). The overall yield from **44** was 60%.

The reaction of 2-iodobenzylamine (**73**) with 1,3-cyclohexadiene was first investigated. However, no starting material or product could be isolated from the reaction mixture after work-up. Since the reaction of 2-iodoaniline with (*E*)-1,3-octadiene provided the desired product , albeit in low yield, it was thought that this diene on reaction with 2-

iodobenzylamine would provide the expected isoquinoline derivative. Unfortunately, only a mixture of compounds in an 8% isolated yield could be obtained. These results are in agreement with the results reported by O'Connor et al.[84] They have reported that the reactions of 2-iodobenzylamine with 1,3-cyclohexadiene and isoprene in the presence of catalytic amounts of $Pd(OAc)_2/PPh_3$ failed to yield heterocyclic products. Since they were able to obtain good yields of heterocycles by reacting 2-iodoaniline with 1,3-cyclohexadiene and isoprene, they concluded that these reactions may be limited to the synthesis of five-membered ring heterocycles.

We thought that we could obtain heterocyclic species if we were to follow the same systematic approach done for the reactions with the 2-iodoaniline derivatives. Thus, our next step was to prepare the requisite *N*-acetyl-2-iodobenzylamine (**74**). This compound was prepared in 75% isolated yield by the method reported for the synthesis of 2-iodoacetanilide (**56**) (eq 55). Compound **74** has also been previously obtained from the acetylation of **73** with acetic anhydride at room temperature.[112]

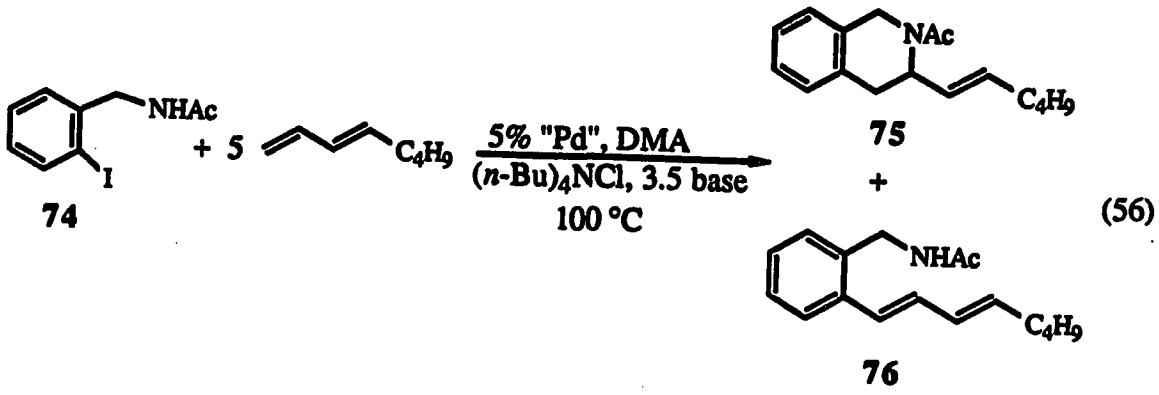


(55)

73 **74**

Reaction of **74** with (*E*)-1,3-octadiene (eq 56) under the conditions shown in Table 9 afforded none of the desired cyclized product **75**. When any product was present, only the diene product **76** was obtained.

In entries 1, 3, and 7, where no product was obtained, the starting aryl iodide was isolated in 84, 63, and 100% yield, respectively. The results in entries 2, 3, and 7 have shown that high temperatures (100 °C) are required to consume all of the starting aryl iodide (cf. entries 2 and 3). Also, the presence of PPh_3 seems to be required in cases were Et_3N is



(56)

Table 9. Palladium-catalyzed reaction of *N*-acetyl-2-iodobenzylamine with (*E*)-1,3-octadiene

Entry	"Pd"	Base	Day(s)	% Isolated Yield of **76**
1	$Pd(OAc)_2$	Et_3N	2	----
2	$Pd(OAc)_2$	Et_3N	4	51 (mixture)
3	$Pd(OAc)_2$	Et_3N	4	----
4	$Pd(OAc)_2$	$NaHCO_3$	2	33
5	$Pd(OAc)_2$	$NaHCO_3$	4	26
6	$Pd(dba)_2$	Et_3N	2	40
7	$Pd(dba)_2$	Et_3N	4	----

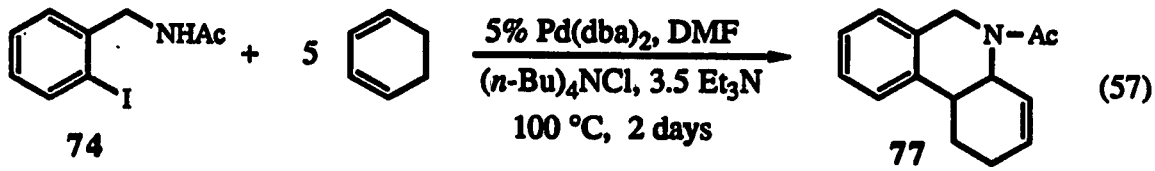
[a]5% PPh_3 added.

[b]Reaction run at 80 °C.

used as the base as only starting aryl iodide is obtained when no PPh_3 is used (cf. entries 1 and 2). When the reaction was run using $NaHCO_3$ as the base, a lower yield of product was obtained (entries 4 and 5). Using $Pd(dba)_2$ as the catalyst did not improve the results (entries 6 and 7). However, $Pd(dba)_2$ facilitated the reaction with Et_3N, since a 40% yield of **76**

was obtained without the need for PPh_3.

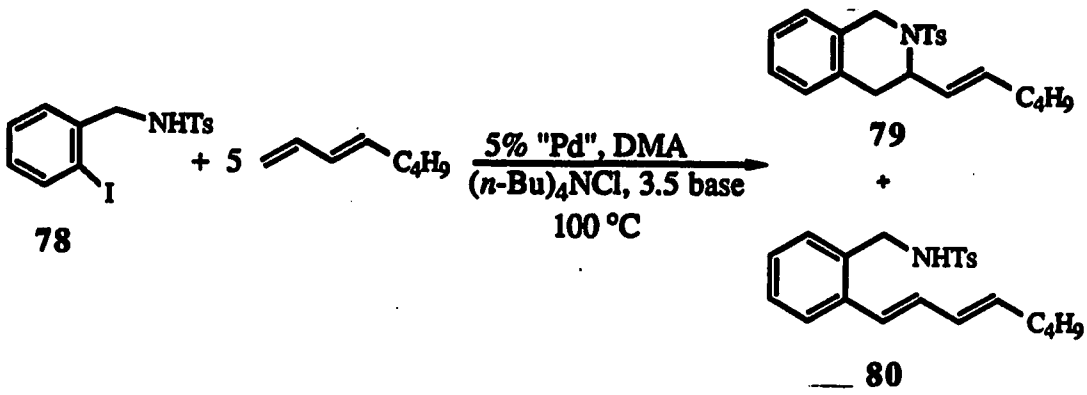
The reaction of *N*-acetyl-2-iodobenzylamine (**74**) with 1,3-cyclohexadiene (eq 57) in the presence of $Pd(dba)_2$ and Et_3N gave only a 95% recovery of the starting amine; none of the desired product could be detected in the ^1H NMR spectrum of the crude reaction product. Because of the poor results, no more efforts were expended on this system.



74 **77** (57)

It seems that a better electron-withdrawing group attached to the nitrogen is required to make these reactions proceed more satisfactorily. As with the aniline derivatives, the tosylamide of 2-iodobenzylamine was then prepared in 74% isolated yield as reported for compound **68** (see eq 53). *N*-Tosyl-2-iodobenzylamine (**78**) was then reacted with (*E*)-1,3-octadiene under the conditions shown in Table 10 to give, in all but one case, only compound **79**. As shown in Table 10, the use of one equivalent of PPh_3 per equivalent of $Pd(OAc)_2$ in the presence of Na_2CO_3 as base, increased the yield to 43% (entry 4) as compared to the 20% yield isolated when no PPh_3 was added (entry 3). When $Pd(dba)_2$ was used under similar reaction conditions, only a 9% yield of the desired product **79** was obtained (entry 10). When the base was changed to Et_3N and no PPh_3 was added, a 30% yield of **79** was isolated. Using $Pd(dba)_2$ in this reaction gave a 50% yield of **79**, together with a 15% yield of **80**. Even better results were obtained when the reaction was performed at a lower temperature (80 °C) in the presence of $Pd(OAc)_2/PPh_3$ and Et_3N. An 81% yield of **79** was isolated under these conditions. The use of $Pd(dba)_2$ under these same conditions

Table 10. Palladium-catalyzed reaction of *N*-tosyl-2-iodobenzylamine with (*E*)-1,3-octadiene

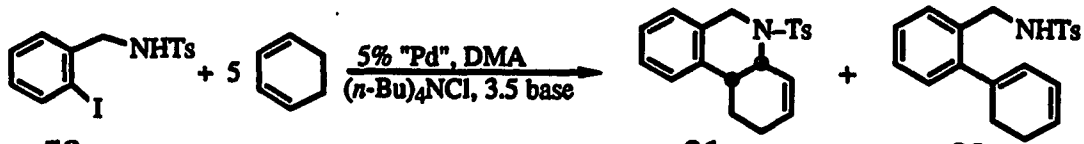


Entry	"Pd"	Base	% Yield of compound 79
1	$Pd(OAc)_2$	NaOAc	14
2	$Pd(OAc)_2$	$NaHCO_3$	15
3	$Pd(OAc)_2$	Na_2CO_3	20
4[a]	$Pd(OAc)_2$	Na_2CO_3	43
5	$Pd(OAc)_2$	Et_3N	30
6[a]	$Pd(OAc)_2$	Et_3N	60
7[a,b]	$Pd(OAc)_2$	Et_3N	81
8[a,b]	$Pd(dba)_2$	Et_3N	77
9	$Pd(dba)_2$	Et_3N	50
10	$Pd(dba)_2$	Na_2CO_3	9

[a]5% PPh_3 added.

[b]Reaction run at 80 °C.

Table 11. Palladium-catalyzed reaction of *N*-tosyl-2-iodobenzylamine with 1,3-cyclohexadiene



78 81 82

Entry	"Pd"	Base	Temp. (°C)	Day(s)	% Yield of 81	% Yield of 82
1	$Pd(OAc)_2$	NaOAc	100	1	----	23
2	$Pd(OAc)_2$	$NaHCO_3$	100	1	----	34
3	$Pd(OAc)_2$	$NaHCO_3$	100	2	----	29
4	$Pd(OAc)_2$	Na_2CO_3	100	2	----	25
5[a]	$Pd(OAc)_2$	Na_2CO_3	60	6	----	27
6[a]	$Pd(OAc)_2$	Na_2CO_3	100	2	ca.10	26
7	$Pd(OAc)_2$	Et_3N	100	1	----	55
8[a]	$Pd(OAc)_2$	Et_3N	100	2	ca.15	37
9[a]	$Pd(OAc)_2$	Et_3N	60	6	----	51
10	$Pd(dba)_2$	Et_3N	100	2	----	67
11	$Pd(dba)_2$	Na_2CO_3	100	2	----	----
12	$Pd(dba)_2$	$NaHCO_3$	100	2	----	----
13	$Pd(dba)_2$	Et_3N	80	1	----	91
14[a]	$Pd(dba)_2$	Et_3N	100	1	----	67

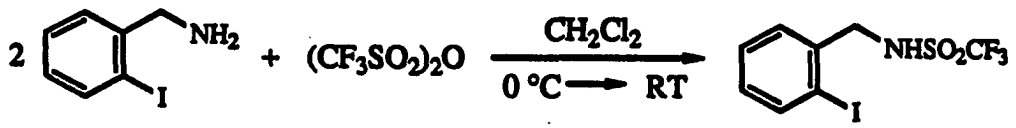
[a] 5% PPh_3 added.

(entry 8) gave an almost identical yield (77%). Apparently, for this system, the lower temperature reduces the amount of decomposition of the π-allylpalladium intermediate (see Scheme 1) to the undesired Heck product, and affords good yields of compound **79**.

We then employed this same starting aryl halide in an attempted synthesis of phenanthridine derivative **81**. The conditions used for the attempted synthesis of **81** are shown in Table 11.

The synthesis of **81** has proven quite difficult, since we have not been able to obtain this product in more than ca. 10% yield (entries 6 and 8). The isolated material in those two cases was also found not to be pure **81**, but a mixture of compounds. The major product in these reactions is the undesired diene product **82** (Table 11). All attempts to get only compound **81** in the above reactions have brought about only improvements in the yield of diene product **82**. Compound **82** can actually be obtained in a 91% isolated yield (entry 13).

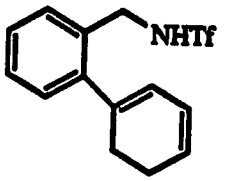
The above results seem to indicate that the better the electron-withdrawing ability of the group attached to the nitrogen is, the higher the yield of cyclization product that is obtained. We thus prepared triflamide **83** (eq 58) in 78% yield using the procedure reported by Bergeron et al.[113] for the synthesis of *N*-benzyltriflamide.



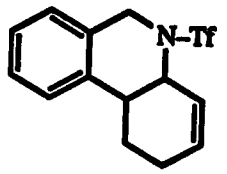
(58)

83 78%

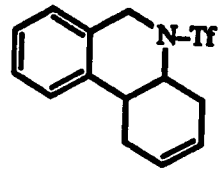
Reaction of **83** with 1,3-cyclohexadiene (5% $Pd(OAc)_2$, DMF, $(n\text{-}Bu)_4NCl$, 3.5 Et_3N, 5% PPh_3, 80 °C, 4 d) afforded an 8% yield of a mixture of three compounds whose structures were tentatively assigned as **84**, **85**, and **86** on the basis of their GC-MS. Another fraction was also isolated in ca. 12% yield, but this time the fraction contained about nine different compounds (GC) and no effort was expended to determine their structures.



84

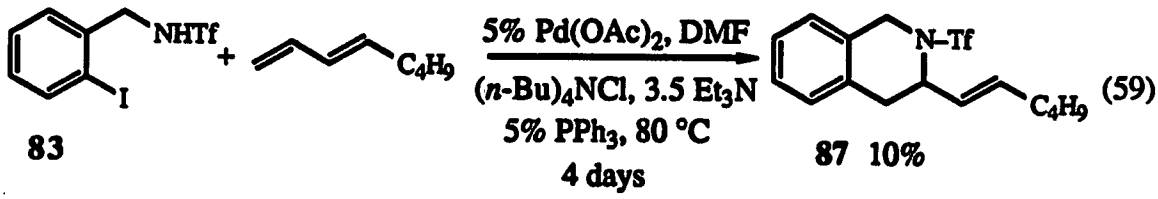


85



86

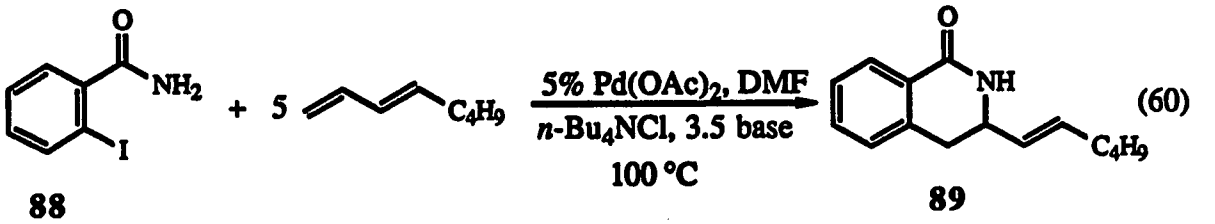
Since the results from the reaction using 1,3-cyclohexadiene (eq 58) proved unfruitful, we decided to examine the reaction of compound **83** with (*E*)-1,3-octadiene (eq 59). Again a low yield (10%) of desired product was obtained and two other compounds



83 **87** 10% (59)

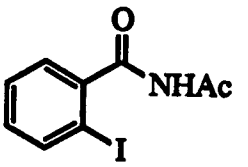
were contaminating it. However, the major component **87** could be fully characterized from its ^{1}H NMR and IR spectra, and high resolution mass spectra (HRMS). Since better yields were obtained using the corresponding tosylamide derivatives, this approach was terminated at this point.

We also attempted to develop a method to synthesize a six-membered ring lactam. Unfortunately, no positive results could be obtained when this cyclization was studied under a variety of conditions. This approach, using **88** and 1,3-octadiene as starting materials, was anticipated to yield product **89** (eq 60). However, none of product **89** could be detected in any of the reactions. Only a complicated mixture of compounds could be seen in the ^{1}H NMR spectrum and GC trace of the crude mixture. Similar results were also



88 89 (60)

obtained when *N*-acetyl-2-iodobenzamide (**90**) was used as the starting aryl iodide.



90

We have since then extended this chemistry to the use of non-conjugated dienes and allenes and this will be shown in parts II and III, respectively, of this dissertation.

CONCLUSION

In this first part of this dissertation, the syntheses of a variety of nitrogen- and oxygen-containing heterocycles were accomplished from the reactions of functionalized aryl iodides with 1,3-dienes in the presence of catalytic amounts of palladium. It was shown that benzofuran, dibenzofuran, dibenzopyran, indole, tetrahydrocarbazole, isoquinoline, and phenanthridine derivatives can be prepared with this methodology. The reactions with the oxygen-containing aryl iodides gave higher yields when an electron-withdrawing group was attached to the aromatic ring. With the nitrogen-containing aryl iodides better yields were obtained when an electron-withdrawing group was attached to the nitrogen atom, best yields being obtained when a tosyl group was attached to this nitrogen atom.

In general, the majority of these reactions provided their best yields when $Pd(OAc)_2$ was used as the catalyst and Na_2CO_3 as the base. However, in some instance, the use of $Pd(dba)_2$ as the catalyst, DMA as the solvent, or the addition of PPh_3 provided even better yields of products. In addition, the reactions were found to be regioselective providing the products coming from attack of the intermediate arylpalladium species on the less substituted carbon of the diene.

EXPERIMENTAL SECTION

Equipment

^1H NMR spectra were recorded on a Nicolet NT-300 (operating at 300 MHz for proton nuclei) spectrometer or on an EM-360 (operating at 60 MHz for proton nuclei) spectrometer using $CDCl_3$ as the solvent (unless otherwise noted) and tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded on a Nicolet NT-300 (operating at 75 MHz for carbon nuclei) spectrometer using $CDCl_3$ both as the solvent and internal standard. Infrared spectra were recorded on either an IBM IR/98 FT-IR spectrophotometer or on a Beckman-42050 spectrophotometer. High resolution mass spectral data were obtained on a Kratos high resolution mass spectrometer or on an MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with a 3% OV-101 on Chromosorb W packed column and a DB5 glass capillary column or on an HP 5890 gas chromatograph equipped with an HP-1 Megabore column. GC-MS data were obtained on a Finnigan MS-50 mass spectrometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Thin layer analytical chromatography (TLC) was performed on commercially prepared 60 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm), $KMnO_4$ solution (3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH + 300 mL H_2O), or in an iodine chamber. Flash chromatography[114] was carried out on 230-400 mesh silica gel or aluminum oxide (activated neutral, Brockmann I). Purifications using a Harrison Research Chromatotron Model 7924 were carried out on 1 mm silica gel plates made with silica gel (60 PF-254, EM-Science) as described by Harrison Research, Palo Alto, CA.

Reagents

All chemicals were used directly as obtained from commercial sources unless otherwise noted. When appropriate, commercial sources are shown in parenthesis. *N,N*-Dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) were distilled from CaH_2 at reduced pressure; acetyl chloride was distilled from CaH_2; Et_3N (Eastman Kodak), pyridine (Fisher), and diisopropylamine (Aldrich) were distilled from KOH pellets; THF was distilled from benzophenone-sodium ketyl. The anhydrous form of $NaHCO_3$ (Fisher), Na_2CO_3 (Fisher), and K_2CO_3 (J.T. Baker) and the fused form of KOAc (Fisher) and NaOAc (Fisher) were utilized for the catalytic reactions. $Pd(OAc)_2$ and $PdCl_2$ were generously provided by Johnson Matthey, Inc. $Pd(dba)_2$ was prepared as reported by Takahashi et al.[115]

2-Chloromercurio-4-methylphenol (**14**) was prepared by a modification of the procedure reported by Kido and Tamura.[87] 2-Iodo-4-methylphenol (**15**) was prepared by the method of Whitmore and Hanson.[86] 4-Hydroxy-3-iodoacetophenone (**29**) was prepared as reported by Schreiber and Stevenson.[93] 4-Hydroxy-3-iodobenzaldehyde (**38**) was prepared as reported by Schawartz et al.[104] *N*-Tosyl-2-iodoaniline (**64**) and *N*-tosyl-2-iodobenzylamine (**73**) were prepared using the method of Ratcliffe [108] for the synthesis of *N*-tosyl-4-iodoaniline. 2-(Chloromethyl)-1-iodobenzene (**67**) was prepared as reported by Ciufolini and Browne.[109] 2-Iodobenzyl phthalimide (**68**) was prepared by a modification of the method reported by Maske for the synthesis of benzyl phthalimide.[110] 2-Iodobenzylamine (**73**) was prepared as reported by Raymond and Manske for the synthesis of benzylamine.[111] 2-Iodoacetanilide and *N*-acetyl-2-iodobenzylamine (**74**) were prepared by the method of Korner and Wender.[107] 2-Iodobenzyltriflamide (**83**) was prepared as reported by Bergeron et al.[113] for the synthesis of benzyltriflamide. 2-Iodobenzamide was

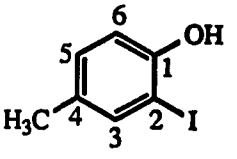
prepared as reported by Harrison.[22b] *N*-Acetyl-2-iodobenzamide was prepared as reported by Polya and Spotswood.[116] 2-Hydroxymethyl-1,3-butadiene (**29**) was prepared as reported by Riley and Silverstein,[99] but using freshly prepared lithium diisopropylamide (LDA).

Preparation of the starting aryl iodides

Synthesis of 2-iodo-4-methylphenol (15) Compound **15** was prepared by iodinating organomercurial **14**, which was prepared from *p*-cresol.

2-Chloromercurio-4-methylphenol (14) *p*-Cresol (5.4 g, 50 mmol) dissolved in 50 mL of 95% EtOH is added to a solution containing 16.0 g (50 mmol) of $Hg(OAc)_2$, 5 mL of glacial acetic acid and 125 mL of H_2O. After refluxing for 2 h, the reaction mixture is added to 300 mL of boiling water and allowed to boil for 5 min. The resulting hot solution is filtered into 30 mL of saturated NaCl. The crystals formed in the filtrate are filtered off and then recrystallized from 40% EtOH to give 32% of white powdered crystals: mp 159-161 °C (lit.[87] mp 160 °C).

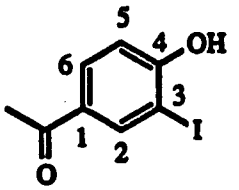
2-Iodo-4-methylphenol (15)



Compound **14** (1.54 g, 5 mmol) was dissolved in 30 mL of CH_2Cl_2. Iodine (1.27 g, 5 mmol) dissolved in 30 mL of CH_2Cl_2 was added to this solution. The mixture was stirred at room temperature for 3 h and a red precipitate formed (HgI_2) which was filtered off (Celite). The filtrate was washed with 50 mL of a KI solution (6 g/50 mL H_2O), and 20 mL of a

saturated $Na_2S_2O_3$ solution, dried ($MgSO_4$), and concentrated to give 0.98 g (90%) of a yellow oil. This was distilled (Kugelrohr, 60 °C/2mm Hg) to afford 0.81 g (75%) of a colorless oil which crystallized on standing: mp 34-36 °C; ^{1}H NMR δ 2.24 (s, 3H, CH_3), 5.11 (s, 1H, OH), 6.87 (d, 1H, J = 8.1 Hz, 6-H), 7.03 (dd, 1H, J = 8.1, 1.5 Hz, 5-H), 7.46 (d, 1H, J = 1.5 Hz, 3-H).

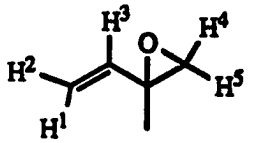
4-Hydroxy-3-iodoacetophenone (29)



Prepared by a procedure similar to that reported by Schreiber and Stevenson.[93] To a solution of p-hydroxyacetophenone in concentrated ammonium hydroxide (250 mL) was added rapidly and with stirring a solution of potassium iodide (185 mL, 30.7 g) and iodine (37.90 mmoL, 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 (Celite). 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 (Et_2O) and treated with activated charcoal. Filtration, concentration, and purification via flash column chromatography (silica gel, 4:1 hexane/EtOAc) gave 5.52 g (56%) of the desired product. Recrystallization from 1:2 MeOH/H_2O afforded 4.86 g (49%) of 4-hydroxy-3-iodoacetophenone: mp 153-155 °C (lit.[93] mp 154-156 °C); IR ($CHCl_3$) 3483 (OH), 1680 (C=O) cm^{-1}; ^{1}H NMR δ 2.55 (s, 3H, CH_3CO), 5.91 (s, 1H, OH), 7.02 (d, 1H, J = 8.4 Hz, 5-H), 7.87 (dd, 1H, J = 8.3, 2.0 Hz, 6-H), 8.30 (d, 1H, J = 2.1 Hz, 2-H).

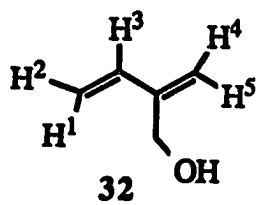
Synthesis of 2-hydroxymethyl-1,3-butadiene (32) Alcohol **32** was prepared via the base induced rearrangement of 3,4-epoxy-3-methyl-1-butene (**31**) with LDA. Compound **31** was prepared from the epoxidation of isoprene.

3,4-Epoxy-3-methyl-1-butene (31)



This epoxide was prepared as reported by Riley and Silverstein.[99] Isoprene (34 g, 0.5 mol) was emulsified by rapidly stirring it in 112 mL of H_2O cooled to 0 °C. *N*-Bromosuccinimide (89 g, 0.5 mol) was added over a period of 0.5 h and stirred for an additional 3 h at 0 °C. The organic layer was separated, combined with an ether extract of the aqueous phase, and dried ($MgSO_4$). Removal of the solvent under vacuum gave a yellow oil; yield 100%. This crude oil was added over a 20 min period to 140 mL of 30% NaOH at 0 °C, and was stirred for an additional 2 h at 0 °C. The organic phase was removed, combined with an ether extract of the aqueous phase, dried ($MgSO_4$), and fractionally distilled to give 10.61 g (25%) of **31**: IR ($CHCl_3$) 3095 (C=CH), 1641 (C=C) cm^{-1}; ^1H NMR δ 1.46 (s, 3H, CH_3), 2.73 (d, 1H, J = 5.4 Hz, 5-H), 2.82 (d, 1H, J = 5.4 Hz, 4-H), 5.23 (dd, 1H, J = 10.8, 0.9 Hz, 2-H), 5.36 (dd, 1H, J = 17.4, 0.9 Hz, 1-H), 5.64 (dd, 1H, J = 17.4, 10.5 Hz, 3-H).

2-Hydroxymethyl-1,3-butadiene (32)

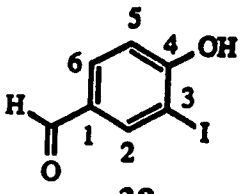


32

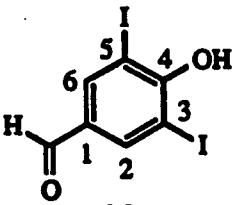
This alcohol was prepared according to a modification of the procedure reported by Riley and

Silverstein.[99] To a round bottom flask (50 mL) was added 26 mmol of a 2.24 M solution of *n*-BuLi in hexanes, 2.0 mL (14.3 mmol) of diisopropylamine, and 3 mL of THF (the reaction was exothermic and the solvent refluxed gently). At this point 1.92 mL of diisopropylamine was added, followed by an additional 3 mL of THF. Dropwise addition (in ca. 15 min) of 2.06 mL (20 mmol) of compound **31** caused a gentle refluxing. After cooling, the reaction mixture was quenched with 5% HCl, washed several times with 5% HCl, followed by saturated $NaHCO_3$, and H_2O, dried ($MgSO_4$) and concentrated to give 1.91 g of a brownish oil. Distillation of the crude product from 120 mg of hydroquinone afforded 340 mg (20%) of ca. 90% pure **32**: bp 72 °C/35 mm of Hg (lit.[99] bp 69 °C/35 mm of Hg); IR (neat) 3356 (OH), 1597 (C=C-C=C) cm^{-1}; ^1H NMR δ 4.35 (s, 2H, CH_2), 5.13 (d, 1H, J = 11.5 Hz, 2-H), 5.15 (bs, 1H, 4-H), 5.27 (d, 1H, J = 17.9 Hz, 1-H), 5.28 (bs, 1H, 5-H), 6.40 (dd, 1H, J = 17.9, 11 Hz , 3-H).

4-Hydroxy-3-iodobenzaldehyde (38) and 3,5-diiodo-4-hydroxy-benzaldehyde (39)



38



39

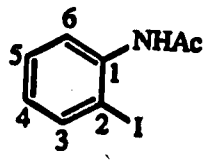
These were prepared by a procedure similar to that reported by Schawartz et al.[104] To a solution of 4-hydroxybenzaldehyde (10 mmoL, 1.22 g) in CH_2Cl_2 (40 mL) was added 0.5 mL (10 mmol) of ICl in glacial HOAc (13 mL). After flushing with nitrogen, the reaction mixture was gently refluxed for 68 h. At this time 0.25 mL of ICl was added and the reaction mixture refluxed for an additional 64 h. The times given were required to completely consume the starting material as indicated by ^1H NMR spectral analyses at

intervals. The reaction mixture was then concentrated and the solid obtained was dissolved in ether, washed with saturated NH_4Cl, saturated $NaHCO_3$, and saturated $Na_2S_2O_3$, dried ($MgSO_4$) and concentrated to give 2.38 g of a yellowish solid. Flash column chromatography (silica gel, 2:1 hexane/EtOAc) gave 1.67 g (67%) of a mixture of **38** and **39** in a ratio of 7.4 : 1(from ^1H NMR spectra), respectively. Attempted separation of **38** and **39** by flash column chromatography was not very successful, and attempted recrystallization of the mixture caused only decomposition. However, a small amount of **39** could be obtained for characterization.

Compound 38: mp 104-107 °C; IR ($CHCl_3$) 3692-3500 (OH), 3026 (C=CH), 2731-2826 (-CHO Fermi resonance), 1699 (-CHO), 1591, 1578, 1483 (C=C), 1177 (C-O) cm^{-1}; ^1H NMR δ 7.03 (d, 1H, J = 8.4 Hz, 5-H), 7.72 (dd, 1H, J = 8.4, 1.8 Hz, 6-H), 8.15 (d, 1H, J = 2.1 Hz, 2-H), 9.73 (s, 1H, -CHO).

Compound 39: mp 201-203 °C; ^1H NMR δ 8.2 (s, 2H, Ar), 9.97 (s, 1H, CHO).

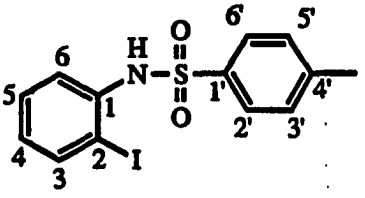
2-Iodoacetanilide (56)



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 h, the reaction mixture was allowed to reach room temperature and then it was stirred overnight. Filtration (to remove Et_3NHCl) 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 (lit.[107] mp 109.5-110 °C); IR ($CHCl_3$) 3407, 3026, 1697, 1585, 1431, 1518 cm^{-1}; ^1H NMR δ 2.24 (s, 3H, CH_3CO), 6.84 (dd, 1H, J = 7.5, 7.5 Hz, 4-H), 7.34 (ddd, 1H, J = 7.8, 7.8, 1.2 Hz, 5-H), 7.41 (m, 1H, NH), 7.78 (d, 1H, J = 7.5 Hz, 6-H), 8.21 (d, 1H, J = 8.4 Hz, 3-H).

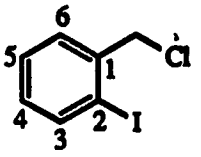
***N*-Tosyl-2-iodoaniline (68)**



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 tosyl chloride was completed the reaction mixture was heated for 1 h 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 ($MgSO_4$) and activated charcoal added. Filtration and concentration of the filtrate afforded a yellowish solid. Recrystallization of the solid obtained from EtOH(100%)/H_2O afforded 4.9 g (52%) of the desired product as white flakes: mp 90-92 °C; IR ($CHCl_3$) 3327 (NH), 2980, 1339, 1167 (SO_2) cm^{-1}; ^1H NMR (d^6-acetone) δ 2.4 (s, 3H, CH_3), 6.95 (ddd, 1H, J = 7.5, 7.5, 1.5 Hz, 5-H), 7.34 (d, 2H, J = 7.8 Hz, 2'-H and 6'-H), 7.37 (ddd, 1H, J = 8.1, 7.5, 1.5 Hz, 4-H), 7.47 (dd, 1H, J = 8.1, 1.5 Hz, 3-H), 7.65 (d, 2H, J = 8.1 Hz, 3'-H and 5'-H), 7.79 (dd, 1H, J = 8.1, 1.5 Hz, 6-H), 8.0 (bs, 1H, NH). Anal. Calcd for $C_{13}H_{12}INO_2S$: C, 41.82; H, 3.22. Found: C, 41.77; H, 3.47.

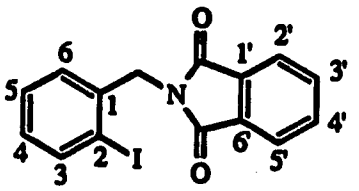
Synthesis 2-iodobenzylamine (73) Compound **73** was prepared via the Gabriel synthesis starting from 2-iodobenzyl alcohol, which was taken on to compound **71.**

1-(Chloromethyl)-2-iodobenzene (71)



To a solution of 2-iodobenzyl alcohol (11.7 g, 50 mmol) in THF (100 mL) cooled to 0 °C was added LiCl (5.84 g, 137.5 mmol), Et_3N (11.2 mL, 80 mmol), and MsCl (5.5 mL, 70 mmol), sequentially. Immediately after injection of MsCl a thick precipitate formed (Et_3NHCl). After 20 min, the reaction mixture was allowed to warm to room temperature (1 h) with stirring and then refluxed for 4 h. After cooling to room temperature (at this point the reaction mixture becomes very thick and gelatinous), 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, and H_2O, dried ($MgSO_4$), and concentrated to give a quantitative yield of 2-(chloromethyl)-1-iodobenzene (12.83 g); ^1H NMR δ 4.68 (s, 2H, 2-CH_2), 7.01 (ddd, 1H, J = 8.0, 7.5, 1.5 Hz, 5-H), 7.35 (ddd, 1H, J = 7.8, 7.5, 0.9 Hz, 4-H), 7.48 (dd, 1H, J = 7.8, 1.5 Hz, 3-H), 7.86 (dd, 1H, J = 8.0, 0.9 Hz, 6-H).

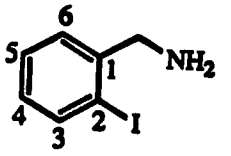
***N*-(2-Iodobenzyl)phthalimide (72)**



A 250 mL round bottom flask charged with compound **71** (50 mmol), potassium phthalimide (9.26 g, 50 mmol), and *N*,*N*-dimethylacetamide (50 mL) was heated at 150 °C

for 3 h. The reaction mixture was allowed to cool to room temperature and then 50 mL of H_2O was added. The mixture was then cooled in an ice bath before vacuum filtration. The solid material obtained was washed with cold H_2O and 20 mL of cold 60% EtOH. The solid material was 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 (72): mp 145-147 °C; IR ($CHCl_3$) 3055 (C=CH), 1774 (C=O, medium), 1720 (C=O, strong), 1470, 1439, 1421 (Ar) cm^{-1}; ^1H NMR δ 4.90 (s, 2H, 1-CH_2), 6.96 (ddd, 1H, J = 7.8, 7.5, 1.2 Hz, 4-H), 7.05 (bd, 1H, J = 7.8 Hz, 6-H), 7.26 (ddd, 1H, J = 7.8, 7.5, 1.2 Hz, 5-H), 7.76 (dd, 2H, J = 5.4, 3.0 Hz, 3'-H and 4'-H), 7.86 (dd, 1H, J = 7.8, 1.2 Hz, 3-H), 7.9 (dd, 2H, J = 5.4, 3.0 Hz, 2'-H and 5'-H); ^{13}C NMR δ 51.25, 98.93, 128.41, 128.56, 128.59, 139.38, 144.91.

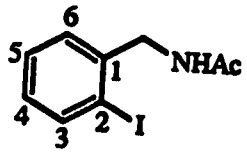
2-Iodobenzylamine (73)



A 250-mL round-bottom flask was charged with compound 72 (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 close to reflux, and swirled while heating for ca. 30 min. 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 compound 72 could still be seen on the funnel. This was retreated with EtOH (25 mL), hydrazine hydrate (0.75 g), and heated for another 30 min. It was then treated with HCl (1 mL), filtered, and the filtrate 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,

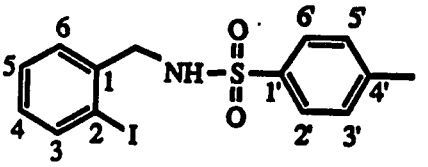
cooled and filtered. The filtrate was made alkaline (with 30% NaOH) and extracted with Et_2O. The organic layer was dried ($MgSO_4$), and concentrated to give 7.08 g (83%) of 2-iodobenzylamine (**73**): IR (neat) 3371, 3288 (NH_2), 2920, 2864 (CH_2), 1657 (NH bend), 1583, 1562, 1464, 1435 (Ar), 874, 852 (NH-wag), 748 (CH bend, ortho) cm^{-1}; ^1H NMR δ 1.51 (s, 2H, NH_2), 3.86 (s, 2H, 1-CH_2), 6.95 (ddd, 1H, J = 8.0, 7.0, 2.0 Hz, 4-H), 7.33 (ddd, 1H, J = 7.5, 7.0, 1.0 Hz, 5-H), 7.36 (dd, 1H, J = 7.5, 2.0 Hz, 6-H), 7.82 (dd, 1H, J = 8.0, 1.0 Hz, 3-H).

N-Acetyl-2-iodobenzylamine (74)



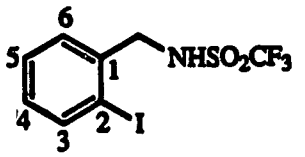
Prepared by the method reported for the synthesis of 2-iodoacetanilide (**56**). 2-Iodobenzylamine (**73**)was dissolved in 60 mL of Et_2O; Et_3N was added, and the solution cooled to 0 °C. Acetyl chloride, dissolved in 6 mL of Et_2O, was added dropwise. The reaction mixture was then stirred at 0 °C for 1 h, and allowed to reach room temperature overnight. The reaction mixture was filtered, and the solid washed with 5% HCl and water, leaving the desired product in the Büchner funnel. After air-drying, 2.06 g (75%) of the desired product was obtained: mp 129-134 °C (lit.[112] mp 134-135 °C); IR ($CHCl_3$) 3447 (NH), 3045 (C=CH), 3005 (CH_3), 1672 (C=O), 1516, 1468, 1439 (C=C) cm^{-1}; ^1H NMR δ 2.02 (s, 3H, CH_3CO), 4.46 (d, 2H, J = 6.0 Hz, 1-CH_2), 5.96 (m, 1H, NH), 6.97 (ddd, 1H, J = 7.5, 7.5, 2.1 Hz, 4-H), 7.31 (ddd, 1H, J = 7.5, 7.2, 2.1 Hz, 5-H), 7.37 (dd, 1H, J = 7.5, 2.1 Hz, 6-H), 7.82 (d, 1H, J = 7.8 Hz, 3-H); mass spectrum mH^+/z 275.98895 (calcd for $C_9H_{11}INO$, 275.98855).

N-Tosyl-2-iodobenzylamine (78)



Prepared as reported for compound **68** in 74% isolated yield: mp 102-104 °C; IR ($CHCl_3$) 3383 (NH), 3049 (C=CH), 1599, 1566, 1470, 1439 (C=C), 1335, 1161 (SO_2) cm^{-1}; ^1H NMR δ 2.41 (s, 3H, 4'-CH_3), 4.19 (d, 2H, J = 6.6 Hz, 1-CH_2), 4.86 (t, 1H, J = 6.3 Hz, NH), 6.94 (ddd, 1H, J = 7.5, 7.5, 2.1 Hz, 5-H), 7.2-7.34 (m, 2H, 3-H and 4-H), 7.26 (d, 2H, J = 8.0 Hz, 5'-H and 3'-H), 7.72 (d, 2H, J = 8.0 Hz, 2'-H and 6'-H), 7.73 (dd, 1H, J =7.8, 1.0 Hz, 6-H); mass spectrum m/z 386.97963 (calcd for $C_{14}H_{14}INO_2S$, 386.97901).

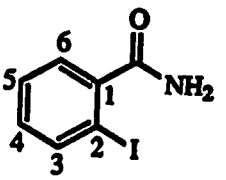
2-Iodobenzyltriflamide (83)



Prepared as reported for the synthesis of *N*-benzyl triflamide.[113] Triflic anhydride (2.12 g, 7.5 mmol) in 7.5 mL of CH_2Cl_2 was added dropwise to a stirred solution of 2-iodobenzylamine (3.5 g, 15 mmol) in 22.5 mL of CH_2Cl_2 cooled to 0 °C. The reaction mixture was allowed to warm to room temperature while stirring. After stirring for 1 h at room temperature, the reaction mixture was washed with 2 x 10 mL of 10% HCl, 3 x 10 mL of water, dried ($MgSO_4$), and evaporated in vacuo leaving 2.15 g (78%) of a white solid: mp 56-58 °C; IR ($CHCl_3$) 3373 (NH), 3071, 3074 (C=CH), 1587, 1568, 1472, 1425 (C=C),

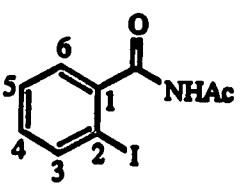
1377, 1190 (SO_2), 1146 cm^{-1}; ^1H NMR δ 4.49 (s, 2H, 1-CH_2), 5.45 (bs, 1H, NH), 7.06 (ddd, 1H, J = 7.8, 6.0, 3.0 Hz, 4-H), 7.35-7.45 (m, 2H, 5-H and 6-H), 7.85 (d, 1H, J = 7.8 Hz, 3-H); ^{13}C NMR δ 52.5, 98.7, 121.59, 129.0, 130.0, 130.4, 137.7, 139.7; mass spectrum m/z 364.91998 (calcd for $C_8H_7F_3INO_2S$, 364.91944).

2-Iodobenzamide (88)



A solution of 2-iodobenzoic acid (12.4 g, 50 mmol) and thionyl chloride (12.25 g, 7.5 mL, 103 mmol) was refluxed for 4 h. The excess thionyl chloride was then evaporated and the residue added to 40 mL of ice cold NH_4OH. After stirring for 30 min, the solid was filtered off and washed with water. After air-drying, 11.23 g (91%) of a white powdery solid was obtained; mp 179-182 °C; IR ($CHCl_3$) 3528, 3402 (NH_2), 3020 (C=CH), 1684 (C=O), 1589, 1489, 1466 (C=C) cm^{-1}; ^1H NMR δ 5.9 (m, 2H, NH_2), 7.12 (ddd, 1H, J = 8.0, 7.0, 2.0 Hz, 5-H), 7.397 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, 4-H), 7.48 (dd, 1H, J = 8.0, 2.0 Hz, 3-H), 7.90 (dd, 1H, J = 8.0, 1.0 Hz, 6-H).

***N*-Acetyl-2-iodobenzamide (90)**



A 25 mL round bottom flask charged with 4.94 g (20 mmol) of 2-iodobenzamide (88), 4.6 g

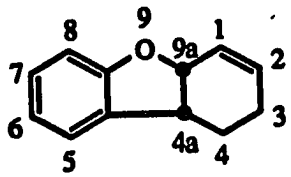
(45.1 mmol, 4.25 mL) of acetic anhydride, and three drops of acetyl chloride was brought to reflux for 30 min. The clear solution was allowed to cool to room temperature and the solvent evaporated to give 5.17 g (89%) of a thick oil. Trituration with hexane/Et_2O gave a solid melting at 88-93 °C. Further recrystallizations from hexane/EtOAc brought the melting point to 99-102 °C. IR ($CHCl_3$) 3387 (NH), 3009, 1713 (C=O), 1585, 1562, 1472, 1458 (C=C, aromatic) cm^{-1}; ^1H NMR δ 2.58 (s, 3H, CH_3CO), 7.14-7.24 (m, 1H, 5-H), 7.4-7.5 (m, 2H, 3-H and 4-H), 7.925 (d, 1H, J = 7.8 Hz, 6-H), 8.20 (bs, 1H, NH); mass spectrum m/z 288.95988 (calcd for $C_9H_8INO_2$, 288.95998).

General procedure for the palladium-catalyzed reactions

To a 1 dram vial are added the palladium reagent (0.025 mmol, 5%), the corresponding iodo compound (0.5 mmol), a base (1.75 mmol), tetra-*n*-butylammonium chloride (0.5 mmol), DMF or DMA (1 mL), and the corresponding diene (2.5 mmol). If the base is a liquid, it is added via syringe after adding DMF or DMA. The vial is then flushed with nitrogen and capped with a screw-cap containing a teflon liner. After heating at the desired temperature for x number of days, the reaction mixture is diluted with ether (Et_2O) and washed with saturated ammonium chloride, followed by H_2O. The organic layer was dried ($MgSO_4$), a pinch of activated charcoal added, and the reaction mixture filtered, concentrated, and purified via "flash column chromatography"[108] (silica gel, hexanes/EtOAc as eluents). When using an amine as the base, the organic phase is washed with 5% HCl instead of saturated ammonium chloride.

The following compounds were prepared using the above general procedure.

3,4,4a,9a-Tetrahydrodibenzofuran (17)



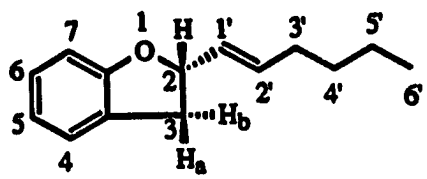
Obtained in 44% isolated yield from the reaction of 2-iodophenol and 1,3-cyclohexadiene as a colorless oil using $Pd(dba)_2$, sodium carbonate, DMA, and stirring for one day at 100 °C.[46] TLC (4:1 hexane/EtOAc), R_f = 0.67; IR (neat) 3045, 1660, 1625 cm^{-1}; ^1H NMR δ 1.5-1.7 (m, 1H, 4-H), 1.9-2.2 (m, 3H, 3-H and 4-H), 3.4 (m, 1H, 4a-H), 5.0 (dd, 1H, J = 8.0, 2.0 Hz, 9a-H), 5.9-6.2 (m, 2H, 1-H and 2-H), 6.75-7.2 (m, 4H, Ar); ^{13}C NMR δ 22.52, 25.04, 39.76, 78.32, 109.59, 120.11, 123.70, 124.27, 127.80, 131.16, 132.91, 158.79; mass spectrum m/z 172.08873 (calcd for $C_{12}H_{12}O$, 172.08882).

Compound 18: GC-MS m/z (intensity) 170 (M,100), 169 (66), 141 (27), 115 (21), 63 (9), 39 (10).

Compound 19: GC-MS m/z (intensity) 172 (M,100), 157 (38), 152 (23), 144 (17), 131 (22), 107 (55), 76 (31).

Compound 20: GC-MS m/z (intensity) 172 (M,100), 157 (33), 152 (24), 144 (18), 131 (22), 107 (61), 94 (9), 77 (29).

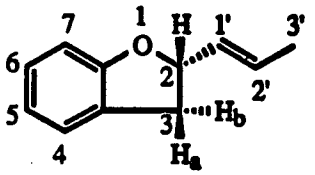
2-[(*E*)-1-Hexenyl]-2,3-dihydrobenzofuran (23)



Obtained as a slightly yellowish oil in 75% isolated yield from the reaction of 2-iodophenol

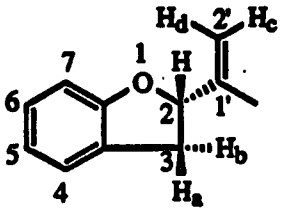
and 1,3-octadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for one day at 100 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.65; bp 80 °C/1 mm; IR (neat) 3040 (C=CH), 2940, 2860 (CH_2, CH_3), 1670 (C=C), 1600, 1470 (Ar), 1230 (C-O-C) cm^{-1}; ^1H NMR δ 0.9 (t, 3H, J = 6.9 Hz, 6'-H), 1.2-1.5 (m, 4H, 4'- H and 5'-H), 2.07 (m, 2H, 3'-H), 2.97 (dd, 1H, J = 15.6, 8.0 Hz, H_a), 3.32 (dd, 1H, J = 15.6, 9.0 Hz, H_b), 5.0-5.2 (m, 1H, 2-H), 5.6-5.7 (m, 1H, 1'-H), 5.75-5.9 (dt, 1H, J = 15.3, 6.6 Hz, 2'-H), 6.77 (d, 1H, J = 8.0 Hz, 7-H), 6.80-6.86 (m, 1H, 5-H), 7.0-7.2 (m, 2H, 4- H and 6-H); ^{13}C NMR δ 13.87, 22.16, 31.00, 31.78, 36.12, 83.80, 109.21, 120.14, 124.65, 126.79, 127.84, 129.01, 134.70, 159.28; mass spectrum m/z 202.13544 (calcd for $C_{14}H_{18}O$, 202.13577). This compound slowly decomposes, and thus it was not sent for elemental analysis.

2-[(*E*)-1-Propenyl]-2,3-dihydrobenzofuran (24)



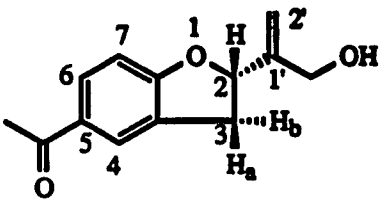
Obtained as a colorless oil in 68% isolated yield from the reaction of 2-iodophenol and *cis*-1,3-pentadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for one day at 100 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.60; IR (neat) 3015 (C=CH), 1675 (C=C), 1615, 1510, 1490, 1260 (C-O-C) cm^{-1}; ^1H NMR δ 1.75 (dd, 3H, J = 6.5, 1.3 Hz, 3'-H), 2.97 (dd, 1H, J = 15.6, 8.0 Hz, H_a), 3.32 (dd, 1H, J = 15.6, 9.2 Hz, H_b), 5.0-5.2 (m, 1H, 2-H), 5.60-5.75 (m, 1H, 1'-H), 5.75-5.95 (dq, 1H, J = 15.3, 6.3 Hz, 2'-H), 6.7-6.9 (m, 2H, 5-H and 7-H), 7.0-7.2 (m, 2H, 4-H and 6-H); mass spectrum m/z 160.08853 (calcd for $C_{11}H_{12}O$, 160.08882). Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 81.34; H, 7.63.

2-Isopropenyl-2,3-dihydrobenzofuran (25)



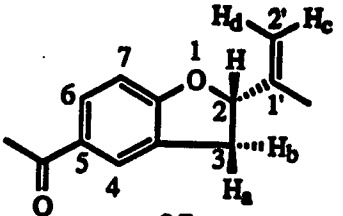
Obtained as a colorless oil in a 7:1 ratio (GC) of a mixture of isomers in 51% isolated yield from the reaction of 2-iodophenol and isoprene using $Pd(OAc)_2$, Na_2CO_3, DMF, and stirring for one day at 100 °C.[92] Mixture, TLC (7.5:1 hexane/EtOAc), $R_f = 0.68$; IR (neat) 3072, 3051, 3031 (C=CH), 2960, 2920, 2856 (CH_2, CH_3), 1655 (C=C), 1595, 1481, 1462 (Ar), 1231, 1018 (C-O-C) cm^{-1}; ^1H NMR δ 1.80 (s, 3H, 1'-CH_3), 3.04 (dd, 1H, J = 15.6, 8.1 Hz, H_a), 3.34 (dd, 1H, J = 15.6, 9.6 Hz, H_b), 4.9 (s, 1H, H_c), 5.1 (s, 1H, H_d), 5.16 (t, 1H, J = 9, 8.7 Hz, 2-H), 6.7-6.9 (m, 2H, 5-H and 7-H), 7.0-7.2 (m, 2H, 4-H and 6-H).

5-Acetyl-2-[1-(hydroxymethyl)vinyl]-2,3-dihydrobenzofuran (28)

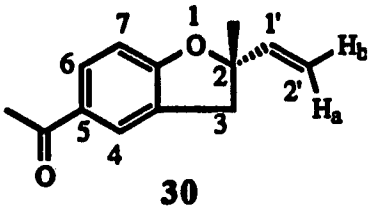


Obtained in 22% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and 2-hydroxymethyl-1,3-butadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for three days at 100 °C.[91b] IR (neat) 3408 (OH), 1672 (C=O), 1606 (C=C), 1589, 1489, 1439 (Ar), 1288, 1269 (C-O-C) cm^{-1}; ^1H NMR δ 2.54 (s, 3H, CH_3CO), 3.19 (dd, 1H, J = 15.6, 8.3 Hz, H_a), 3.47 (dd, 1H, J = 15.6, 9.8 Hz, H_b), 4.27 (bs, 2H, 1'-CH_2), 5.27 (bs, 2H, 2'-H), 5.43 (t, 1H, J = 9.0 Hz, 2-H), 6.83 (d, 1H, J = 8.0 Hz, 7-H), 7.75-7.85 (m, 2H, 4-H and 6-H).

5-Acetyl-2-isopropenyl-2,3-dihydrobenzofuran (27) and 5-acetyl-2-methyl-2-vinyl-2,3-dihydrobenzofuran (30)



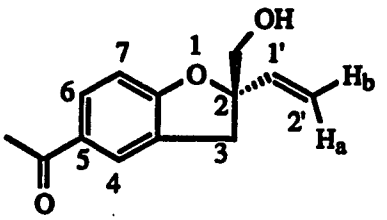
27



30

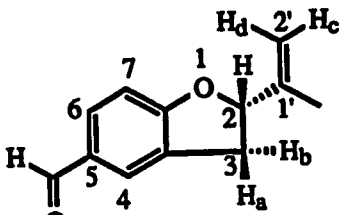
Obtained as a colorless oil in a 7:1 ratio (GC) of a mixture of **27** and **30** in 83% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone (**29**) and isoprene using $Pd(dba)_2$, NaOAc, DMF, and stirring for one day at 100 °C. The ^1H NMR spectrum of the desired product **27** was in agreement with the literature.[91b] Data from the mixture: TLC (4:1 hexane/EtOAc), $R_f = 0.35$; IR (neat) 1678 (C=O), 1607, 1589 (C=C), 1489, 1439 (C=C), 1288, 1269, 1240 (C-O-C) cm^{-1}; ^1H NMR δ 1.51 (s, 3H, 2-CH_3 of **30**), 1.69 (bs, 3H, 1'-CH_3 of **27**), 2.47 (s, 3H, CH_3CO of **30**), 2.47 (s, 3H, CH_3CO of **27**), 3.0 (dd, 1H, J = 15.9, 8.1 Hz, H_a of **27**), 3.14 (d, 2H, J = 15.9 Hz, 3-H of **30**), 3.32 (dd, 1H, J = 16, 9.7 Hz, H_b of **27**), 4.87 (bs, 1H, H_c of **27**), 5.02 (bs, 1H, H_d of **27**), 5.06 (dd, 1H, J = 10.8, 0.6 Hz, H_b of **30**), 5.20 (t, 1H, J = 9.3 Hz, 2-H of **27**), 5.27 (dd, 1H, J = 17.7, 0.9 Hz, H_a of **30**), 5.97 (dd, 1H, J = 17.4, 10.8 Hz, 1'-H of **30**), 6.74 (d, 1H, J = 6 Hz, 7-H of **30**), 6.75 (d, 1H, J = 8.3 Hz, 7-H of **27**), 7.74 (m, 4H, 4-H and 6-H of **27** and **30**); ^{13}C NMR δ 16.86, 25.92, 26.15, 33.70, 41.04, 86.64, 89.20, 108.50, 108.83, 112.27, 113.01, 125.20, 125.50, 127.00, 127.12, 130.21, 130.41, 140.71, 143.07, 162.80, 163.71, 196.19.

5-Acetyl-2-hydroxymethyl-2-vinyl-2,3-dihydrobenzofuran (33)

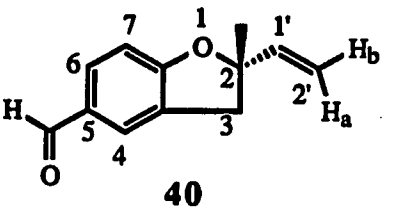


Obtained in 2% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and 2-hydroxymethyl-1,3-butadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for three days at 100 °C. TLC (1:1 hexane/EtOAc); ^{1}H NMR δ 2.54 (s, 3H, CH_3CO), 3.1 (d, 1H, J = 15.6 Hz, 3-H), 3.4 (d, 1H, J = 15.9 Hz, 3-H), 3.65-3.85 (m, 2H, 2-CH_2), 5.27 (dd, 1H, J = 10.8, 0.6 Hz, H_a), 5.42 (dd, 1H, J = 16.8, 0.6 Hz, H_b), 5.95 (dd, 1H, J = 16.8, 10.8 Hz, 1'-H), 6.85 (d, 1H, J = 9.0 Hz, 7-H), 7.78-7.85 (m, 2H, Ar).

2-Isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (36) and 2-methyl-2-vinyl-2,3-dihydrobenzofuran-5-carbaldehyde (40)



36

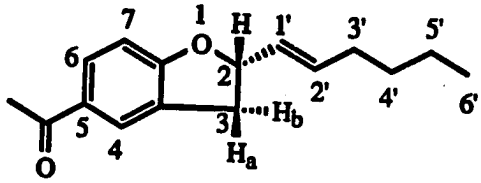


40

Obtained in 43% isolated yield as a mixture of two isomers in a 10:1 ratio (^{1}H NMR) from the reaction of 4-hydroxy-3-iodobenzaldehyde and isoprene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for one day at 100 °C.[100] Data from the mixture: bp 95 °C/1 mm of Hg; TLC (7.5:1 hexane/EtOAc), R_f = 0.68; IR of mixture: (neat) 3070 (C=CH), 2930, 2740, 2826 (aldehydic H), 1688 (C=O), 1607 (C=C), 1485 (Ar), 1248 (C-O-C) cm^{-1}; ^{1}H NMR δ 1.8 (s, 3H, 1'-CH_3 of **36**), 1.59 (s, 3H, 2-CH_3 of **40**), 3.1 (dd, 1H, J = 16.4, 8.3 Hz, H_a of **36**), 3.23 (d, 2H, J = 15.3 Hz, 3-H of **40**), 3.4 (dd, 1H, J = 16.1, 9.8 Hz, H_b of **36**),

4.95 (bs, 1H, H_c of **36**), 5.1 (bs, 1H, H_d of **36**), 5.14 (d, 1H, J = 10.5 Hz, H_b of **40**), 5.3 (t, 1H, J = 8.7 Hz, 2-H of **36**), 5.32 (d, 1H, J = 16 Hz, H_a of **40**), 6.04 (dd, 1H, J = 17.1, 10.8 Hz, 1'-H of **40**), 6.9 (d, 1H, J = 8.1 Hz, 7-H of **36** and **40**), 7.68 (d, 1H, J = 8.4 Hz, 6-H of **36** and **40**), 7.70 (m, 2H, 4-H and 6-H of **40**), 7.72 (s, 1H, H-9 of **36** and **40**), 9.83 (s, 1H, -CHO of **36** and **40**); ^{13}C NMR of mixture: δ 16.86, 25.94, 33.46, 40.79, 66.91, 69.62, 109.20, 109.52, 112.44, 113.16, 125.61, 125.95, 126.93, 127.93, 130.12, 130.21, 131.58, 132.79, 140.54, 142.84, 164.06, 164.94, 190.25 (one sp^2 signal overlaps).

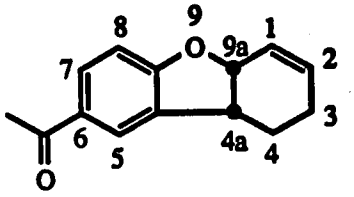
5-Acetyl-2-[(*E*)-1-hexenyl]-2,3-dihydrobenzofuran (41)



Obtained as a colorless oil in 55% isolated yield from the reaction of 4-hydroxy-3-iodo-acetophenone and 1,3-octadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for seven days at 100 °C. TLC (10:1 hexane/EtOAc), R_f = 0.24; IR (neat) 2957, 2928, 2871, 2856 (CH_2, CH_3), 1676 (C=O, C=C (trans)), 1605, 1587, 1487, 1465 (Ar), 1267 (C-O-C) cm^{-1}; ^{1}H NMR δ 0.90 (t, 3H, J = 7.2 Hz, 6'-H), 1.20-1.46 (m, 4H, 4'-H and 5'-H), 2.09 (td, 2H, J = 6.6, 6.6 Hz, 3'-H), 2.54 (s, 3H, CH_3CO), 3.0 (dd, 1H, J = 16.0, 8.0 Hz, H_a), 3.4 (dd, 1H, J = 16.0, 9.0 Hz, H_b), 5.19-5.30 (m [looks like a quartet], 1H, 2-H), 5.64 (ddt, 1H, J = 15.0, 7.7, 1.2 Hz, 1'-H), 5.86 (dt, 1H, J = 15.6, 6.6 Hz, 2'-H), 6.79 (d, 1H, J = 7.8 Hz, 7-H), 7.76-7.84 (m, 2H, 4-H and 6-H); ^{13}C NMR δ 13.81, 22.10, 26.27, 30.86, 31.70, 35.29, 85.22, 108.75, 108.83, 125.30, 128.25, 130.29, 130.45, 135.46, 163.55, 196.39; mass spectrum m/z 244.14668 (calcd for $C_{16}H_{20}O_2$,

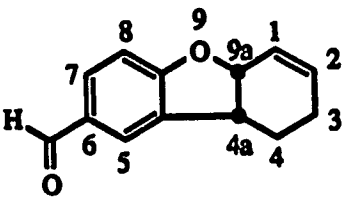
244.14632).

6-Acetyl-3,4,4a,9a-tetrahydrodibenzofuran (42).



Obtained as a colorless oil in 65% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and 1,3-cyclohexadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for one day at 100 °C. This product was purified using a chromatotron. TLC (4:1 hexane/EtOAc), $R_f = 0.39$; IR (neat) 3030 (C=CH), 2928, 2880 (CH_2), 1672 (C=O), 1609 (C=C), 1587, 1485, 1435 (Ar), 1256, 1242 (C-O-C) cm^{-1}; ^1H NMR δ 1.6-2.2 (m, 4H, 3-H and 4-H), 2.54 (s, 3H, CH_3CO), 3.45 (m, 1H, 4a-H), 5.11 (m, 1H, 9a-H), 5.9-6.0 (m, 1H, 1-H), 6.08-6.19 (m, 1H, 2-H), 6.79 (d, 1H, J = 8.4 Hz, 8-H), 7.8 (d, 1H, J = 8.1 Hz, 7-H), 7.84 (s, 1H, 5-H); ^{13}C NMR δ 22.38, 24.92, 26.34, 39.71, 80.04, 109.33, 123.73, 124.43, 130.56, 132.1, 133.78, 163.35, 196.57. Anal. Calcd for $C_{14}H_{14}O$: C, 78.48; H, 6.59. Found: C, 78.31; H, 6.60.

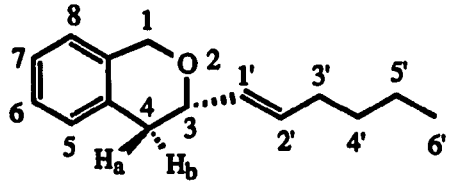
6-Formyl-3,4,4a,9a-tetrahydrodibenzofuran (43)



Obtained in 37% isolated yield from the reaction of 4-hydroxy-3-iodobenzaldehyde and 1,3-cyclohexadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for two days at 100 °C. TLC

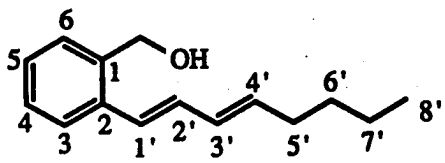
(4:1 hexane/EtOAc), R_f= 0.56; IR (neat) 3055 (C=CH), 2940 (CH_2), 2742 (C-H, aldehyde), 1688 (C=O), 1654 (C=C), 1607, 1587, 1485, 1445 (Ar), 1244 (C-O-C) cm^{-1}; ^1H NMR δ 1.6-1.7 (m, 2H, 4-H), 2.0-2.18 (m, 2H, 3-H), 3.4-3.5 (m, 1H, 4a-H), 5.1-5.2 (m, 1H, 9a-H), 5.9-6.0 (m, 1H, 1-H), 6.1-6.2 (m, 1H, 2-H), 6.87 (d, 1H, J = 8.2 Hz, 8-H), 7.66 (dd, 1H, J = 8.2, 1.8 Hz, 7-H), 7.74 (bs, 1H, 5-H), 9.83 (s, 1H, CHO); ^{13}C NMR δ 22.33, 24.89, 39.05, 80.37, 110.01, 123.66, 124.73, 130.38, 132.87, 133.38, 133.91, 164.71, 190.59; mass spectrum m/z 200.08340 (calcd for $C_{13}H_{12}O_2$, 200.08373).

3-[(*E*)-1-Hexenyl]-1*H*-2-benzopyran (46)



Obtained in 56% yield as a mixture of stereoisomers in a 16:1 trans/cis GC ratio. These were obtained from the reaction of 2-iodobenzyl alcohol and 1,3-octadiene using $Pd(OAc)_2$, KOAc, DMF, PPh_3 and stirring for one day at 80 °C. TLC (7.5:1 hexane/EtOAc), R_f= 0.65; IR (neat) 3022 (C=CH), 2957, 2872 (CH_2,CH_3), 1674 (C=C, trans), 1585, 1495, 1466 (Ar), 1088 (C-O-C) cm^{-1}; ^1H NMR δ 0.90 (t, 3H, J = 6.9 Hz, 6'-H), 1.36 (m, 4H, 4'-H and 5'-H), 2.08 (q, 2H, J = 6.6 Hz, 3'-H), 2.73 (dd, 1H, J = 16, 3.6 Hz, H_a), 2.85 (dd, 1H, J = 10.5, 16 Hz, H_b), 4.14 (m, 1H, 3-H), 4.86 (s, 2H, 1-H), 5.61 (ddt, 1H, J = 15.6, 6.3, 1.2 Hz, 1'-H), 5.8 (dt, 1H, J = 15.6, 6.7 Hz, 2'-H), 6.95-7.17 (m, 4H, Ar); ^{13}C NMR δ 14.0, 22.2, 31.2, 32.0, 34.2, 67.9, 75.2, 124.0, 125.9, 126.3, 128.7, 129.9, 133.2, 134.5 (overlapping sp^2 signals); mass spectrum m/z 216.15149 (calcd for $C_{15}H_{20}O$, 216.15142).

1-(Hydroxymethyl)-2-[(1*E*,3*E*)-octadienyl]benzene (48)



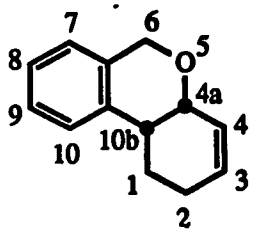
Obtained in 45% yield from the reaction of 2-iodobenzyl alcohol and 1,3-octadiene using $Pd(OAc)_2$, KOAc, and DMF, and stirring for five days at 80 °C. TLC (4:1 hexane/EtOAc), R_f = 0.36; IR (neat) 3362 (OH), 2957, 2928, 2872, 2860 (CH_2, CH_3), 1011 (C-O), 750 (C-H) cm^{-1}; ^1H NMR δ 0.91 (t, 3H, J = 7.0 Hz, 8'-H), 1.2-1.5 (m, 4H, 6'-H and 7'-H), 1.79 (bs, 1H, OH), 2.15 (m, 2H, 5'-H), 4.71 (s, 2H, 1-CH_2), 5.84 (dt, 1H, J = 15.0, 7.2 Hz, 4'-H), 6.24 (ddd, 1H, J = 15.0, 7.8, 1.2 Hz, 3'-H), 6.6-6.8 (m, 2H, 1'H and 2'-H), 7.1-7.4 (m, 3H, Ar), 7.52 (d, 1H, J = 7.5 Hz, 3-H); ^{13}C NMR δ 13.95, 22.28, 31.41, 32.52, 63.41, 125.42, 127.14, 128.04, 128.14, 128.42, 130.62, 131.74, 136.34, 136.50, 137.31; mass spectrum m/z 216.15174 (calcd for $C_{15}H_{20}O$, 216.15142).

Compound 49: GC-MS m/z (intensity) 216 (M, 1), 202 (15), 201 (100), 173 (1), 159 (7), 145 (32), 133 (39).

Compound 50: GC-MS m/z (intensity) 216 (M, 10), 201 (0.5), 187 (2), 173 (8), 159 (13), 145 (100), 91 (16).

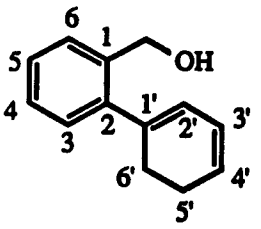
Compounds **51** and **52** were both isolated and separated via flash column chromatography from the reaction of 2-iodobenzyl alcohol and 1,3-cyclohexadiene using $Pd(dba)_2$, KOAc, DMF, PPh_3 and stirring for one day at 80 °C.

1,2,4a,10b-Tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (51)



Isolated in 26% yield from the reaction of compound **44** and 1,3-cyclohexadiene using $Pd(dba)_2$, KOAc, DMA, PPh_3, and stirring for one day at 80 °C. TLC (20:1 hexane/EtOAc), R_f = 0.26; IR (neat,NaCl) 3063 , 3028 (C=CH), 2928, 2831 (CH_2), 1657 (C=C), 1577, 1489, 1447 (Ar), 1096, 1084 (C-O-C) cm^{-1}; ^1H NMR δ 1.83 (m, 2H, 1-H), 2.2 (m, 2H, 2-H), 2.66 (ddd, 1H, J = 11.4, 4.5, 4.5 Hz, 10b-H), 4.07 (dd, 1H, J = 4.5, 4.5 Hz, 4a-H), 4.83 (s, 2H, 6-H), 5.93 (ddt, 1H, J = 10.8, 4.8, 2.4 Hz, 4-H), 6.08 (dt, 1H, J = 10, 3.9 Hz, 3-H), 6.90-7.25 (m, 4H, Ar); ^{13}C NMR δ 26.07, 27.16, 37.15, 68.26, 69.75, 123.97, 125.65, 125.96, 126.52, 128.78, 133.0, 134.46, 138.12; mass spectrum m/z 186.10453 (calcd for $C_{13}H_{14}O$, 186.10447).

2-[1,3-Cyclohexadienyl]-1-(hydroxymethyl)benzene (52)

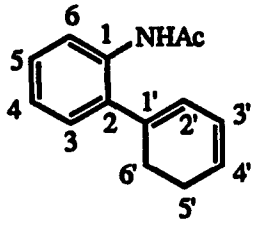


Isolated in 31% yield from the reaction of compound **44** and 1,3-cyclohexadiene using $Pd(dba)_2$, KOAc, DMA, PPh_3, and stirring for one day at 80 °C. TLC (20:1 hexane/EtOAc), R_f = 0.12; IR (neat) 3339 (OH), 3034 (C=CH), 2930, 2870, 2821 (CH_2), 1635 (C=C), 1481, 1447 (Ar), 1034, 1011 (C-O-C) cm^{-1}; ^1H NMR δ 1.84 (bs, 1H, OH), 2.23–2.36 (m, 2H, 5'-H), 2.39-2.49 (m, 2H, 6'-H), 4.72 (s, 2H, 1-CH_2), 5.87 (dd, 1H,

J = 9.6, 4.8 Hz, 4'-H), 5.91 (d, 1H, J = 5.4 Hz, 2'-H), 6.05 (ddt, 1H, J = 9.6, 5.1, 1.8 Hz, 3'-H), 7.14-7.20 (m, 1H, Ar), 7.22-7.29 (m, 2H, Ar), 7.42-7.49 (m, 1H, Ar); ^{13}C NMR δ 23.1, 28.2, 63.2, 123.6, 124.7, 125.7, 127.1, 127.5, 128.1, 129.0, 137.0, 137.5, 142.3; mass spectrum m/z 186.10434 (calcd for $C_{13}H_{14}O$, 186.10447).

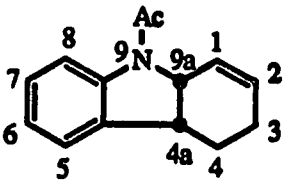
***N*-Acetyl-3,4-dihydrocarbazole (57):** GC-MS m/z (intensity) 211 (41), 169 (100), 168 (64), 43 (34).

2-[1,3-Cyclohexadienyl]acetanilide (58)



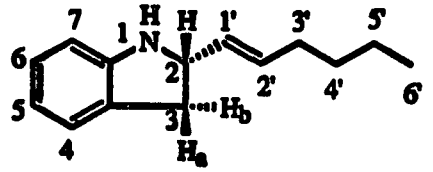
Obtained as a white solid in 60% isolated yield as a 24:1 (GC) ratio of **58** and **59** from 2-iodoacetanilide and 1,3-cyclohexadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and stirring for one day at 100 °C: mp 100-101 °C, recrystallized from 20:1 hexane/EtOAc to give a 33% yield; TLC (1:1 hexane/EtOAc), R_f = 0.36; IR ($CHCl_3$) 3414 (NH), 3026 (C=CH), 2943, 2875, 2827 (CH_2), 1686 (C=O), 1583, 1516, 1445 (Ar) cm^{-1}; ^{1}H NMR δ 2.15 (s, 3H, CH_3CO), 2.26-2.48 (m, 4H, 5'-H and 6'-H), 5.93 (ddd, 1H, J = 9.3, 3.9, 3.9 Hz, 4'-H), 6.02 (d, 1H, J = 4.8 Hz, 2'-H), 6.05-6.12 (ddt, 1H, J = 9.3, 5.3, 1.5 Hz, 3'-H), 7.05-7.2 (m, 2H, Ar), 7.26 (ddd, 1H, J = 7.5, 7.5, 1.8 Hz, 5-H), 7.40 (m, 1H, NH), 8.17 (d, 1H, J = 8.1 Hz, 6-H); ^{13}C NMR δ 23.09, 27.54, 121.66, 124.17, 124.43, 124.60, 126.51, 127.73, 127.85, 127.99, 133.48, 134.16, 134.99, 167.99; GC-MS m/z (intensity) 213 (20), 212 (21), 170 (100), 43 (49); mass spectrum m/z 213.11546 (calcd for $C_{14}H_{15}NO$, 213.11537).

N-Acetyl-3,4,4a,9a-tetrahydrocarbazole (59)



Obtained as a mixture of **58** and **59**. In addition, compound **59** was found to be a mixture of *cis*- and *trans*-fused products. IR of the mixture: (neat) 3286, 3028, 2928, 1649, 1597, 1481, 1461, 1404 cm^{-1}; ^1H NMR δ 1.8-2.6 (m and s, 7H, ring methylenes and CH_3CO), 3.6-3.7 (bs, 1H, 4a-H of *trans*-fused product), 3.7-3.8 (bs, 1H, 4a-H of *cis*-fused product), 4.8 (d, 1H, J = 7.5 Hz, 9a-H of *cis*-fused product), 5.4 (bs, 9a-H of *trans*-fused product), 5.6-6.1 (m, 2H, 1-H and 2-H), 7.0-7.25 (m, 3H, Ar), 8.2 (d, 1H, *J* = 8 Hz, Ar). GC-MS of *cis*-fused product m/z (intensity) 213 (M, 80), 171 (70), 170 (90), 156 (13), 143 (58), 130 (100), 117 (20), 93 (32), 77 (17), 43 (64). GC-MS of *trans*-fused product m/z (intensity) 213 (M, 21), 212 (22), 152 (9), 128 (6), 115 (5), 93 (6), 77 (6), 43 (36).

2-[(*E*)-1-Hexenyl]-2,3-dihydroindole (61)



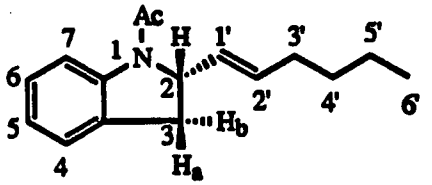
Obtained in 45% isolated yield as a mixture of **61** and **62** in a 13:1 GC ratio from 2-iodoaniline and 1,3-octadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for two days at 80 °C. TLC (20:1 hexane/EtOAc), R_f = 0.25 ; IR (neat) 3375 (NH), 3053, 3030 (C=CH), 2958, 2931, 2871, 2856, 1668 (C=C), 1609, 1485, 1466 (C=C), 1246 (C-N), 970 cm^{-1}; ^1H NMR δ 0.89 (t, 3H, *J* = 6.6 Hz, 6'-H), 1.33 (m, 4H, 4'-H and

5'-H), 2.01 (m [looks like a quartet], 2H, J = 5.4 Hz, 3'-H), 2.77 (dd, 1H, J = 15.6, 8.0, Hz, H_a), 3.15 (dd, 1H, J = 15.6, 8.4, Hz, H_b), 4.28 (m [looks like a quartet], 1H, 2-H), 5.61 (m, 2H, 1'-H and 2'-H), 6.59 (d, 1H, J = 7.5 Hz, 7-H), 6.68 (t, 1H, J = 7.5 Hz, 5-H), 7.0 (t, 1H, J = 7.5 Hz, 6-H), 7.06 (d, 1H, J = 7.5 Hz, 4-H); mass spectrum m/z 201.15171 (calcd for $C_{14}H_{19}N$, 201.15175).

Compound 62: GC-MS m/z (intensity) 199 (M, 100), 198 (7), 184 (6), 170 (50), 156 (95), 143 (10), 129 (37), 117 (12), 77 (8).

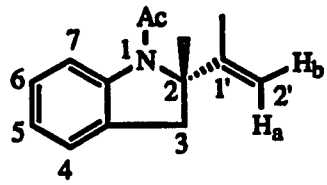
Compound 63: GC-MS m/z (intensity) 201 (M, 37), 186 (1), 172 (4), 144 (31), 131 (64), 130 (100), 117 (5), 103 (7), 77 (9).

N-Acetyl-2-[(*E*)-1-hexenyl]-2,3-dihydroindole (64)



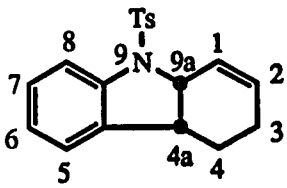
Obtained as a colorless oil in 46% isolated yield from the reaction of 2-iodoacetanilide and 1,3-octadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and stirring for one day at 100 °C. TLC (4:1 hexane/EtOAc), R_f = 0.24; IR (neat) 3040 (C=CH), 2940, 2860 (CH_2, CH_3), 1710 (C=O), 1650 (C=C), 1540, 1450 (Ar) cm^{-1}; ^1H NMR δ 0.87 (t, 3H, J = 6.9 Hz, 6'-H), 1.2-1.4 (m, 4H, 4'-H and 5'-H), 1.9-2.05 (m, 2H, 3'-H), 2.23 (s, 3H, CH_3CON), 2.8 (d, 1H, J = 16 Hz, H_a), 3.49 (dd, 1H, J = 15, 10.2 Hz, H_b), 4.65-4.85 (m, 1H, 2-H), 5.4-5.7 (m, 2H, 1'-H and 2'-H), 6.95-7.25 (m, 3H, Ar), 8.2 (m, 1H, Ar); mass spectrum m/z 243.16214 (calcd for $C_{16}H_{21}NO$, 243.16232). This compound decomposed slowly, and thus it was not sent for elemental analysis.

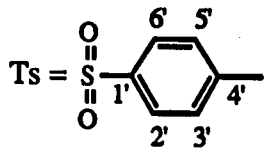
***N*-Acetyl-2-isopropenyl-2-methyl-2,3-dihydroindole (67).**



Obtained in 29% isolated yield from the reaction of 2-iodoacetanilide and 2,3-dimethyl-1,3-butadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for one day at 100 °C. IR (neat) 3030, 2974, 2941, 1704, 1654, 1600, 1481, 1379 cm^{-1}; ^1H NMR δ 1.69 (s, 3H, 2-CH_3), 1.75 (s, 3H, 1'-CH_3), 2.23 (bs, 3H, CH_3CO), 2.9-3.36 (m, 2H, 3-CH_2), 4.96 (bs, 1H, 2'-H), 5.05 (bs, 1H, 2'-H), 6.95-7.23 (m, 4H, Ar); mass spectrum m/z 215.13126 (calcd for $C_{14}H_{17}NO$, 215.13102). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. Found: C, 77.87; H, 8.15.

***N*-Tosyl-3,4,4a,9a-tetrahydrocarbazole (69).**

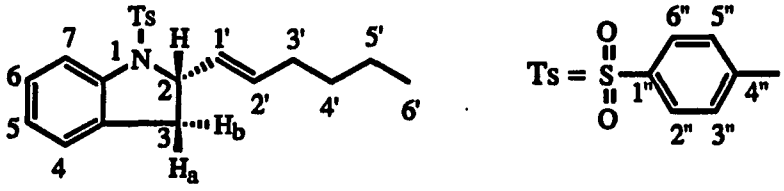




Obtained as a white solid in 87% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 1,3-cyclohexadiene using $Pd(dba)_2$, Na_2CO_3, DMA, and stirring for two days at 100 °C: mp 135-136 °C (100% EtOH); TLC (7.5:1 hexane/EtOAc), R_f = 0.55; IR ($CHCl_3$) 3049 (C=CH), 2932 (CH_2), 1601 (C=C), 1475, 1460 (Ar), 1352, 1165 (SO_2) cm^{-1}; ^1H NMR δ 1.8-2.0 (m, 4H, 3-H and 4-H), 2.35 (s, 3H, 4'-CH_3), 3.05 (m, 1H, 4a-H), 4.71 (dd, 1H, J = 8.1, 1.8 Hz, 9a-H), 5.87 (s, 2H, 1-H and 2-H), 7.0 (d, 1H, J = 6.9 Hz, 5-H), 7.06 (ddd, 1H, J = 7.2, 7.2, 1.0 Hz, 7-H), 7.16 (d, 2H, J = 8.1 Hz, 3'-H and 5'-H), 7.21 (dd,

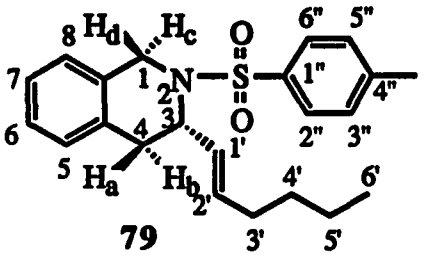
1H, J = 7.5, 7.5 Hz, 6-H), 7.57 (d, 2H, J = 8.4 Hz, 2'-H and 6'-H), 7.64 (d, 1H, J = 8.1 Hz, 8-H); ^{13}C NMR δ 20.09, 21.49, 22.66, 38.60, 61.43, 117.97, 123.34, 124.63, 126.06, 126.86, 127.77, 129.50, 131.20, 135.00, 135.65, 141.60, 143.64 (overlapping sp^2 signals). Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.15; H, 5.85. Found: C, 69.94; H, 6.31.

***N*-Tosyl-2-[(*E*)-1-hexenyl]-2,3-dihydroindole (70).**



Obtained as a colorless solid in 84% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 1,3-octadiene using $Pd(OAc)_2$, Na_2CO_3, DMA, and stirring for 1 day at 100 °C. Mp 58-59 °C (100% EtOH); TLC (7.5:1 hexane/EtOAc), R_f = 0.40; IR (neat) 3066, 3032 (C=CH), 2957, 2928, 2871, 1670 (C=C), 1598, 1494, 1479, 1462 (Ar), 1356, 1184 (SO_2) cm^{-1}; ^{1}H NMR δ 0.87 (t, 3H, J = 7.2 Hz, 6'-H), 1.29 (m, 4H, 4'-H and 5'-H), 2.0 (m, 2H, 3'-H), 2.35 (s, 3H, 4"-CH_3), 2.6 (dd, 1H, J = 16.2, 3 Hz, H_a), 2.96 (dd, 1H, J = 16, 9.6 Hz, H_b), 4.73 (ddd, 1H, J = 9.6, 6.9, 3 Hz, 2-H), 5.5 (ddt, 1H, J = 15.3, 6.9, 1.5 Hz, 1'-H), 5.73 (dt, 1H, J = 15.3, 7.0 Hz, 2'-H), 6.99 (ddd, 1H, J = 7.2, 7.2, 0.6 Hz, 6-H), 7.04 (d, 1H, J = 6.3 Hz, 4-H), 7.17 (d, 2H, J = 8.1 Hz, 3"-H and 5"-H), 7.2 (dd, 1H, J = 7.5, 7.5 Hz, 5-H), 7.59 (d, 2H, J = 8.4 Hz, 2"-H and 6"-H), 7.62 (d 1H, J = 8.1 Hz, 7-H); ^{13}C NMR δ 13.95, 21.50, 22.21, 31.01, 31.68, 35.50, 63.84, 116.58, 124.18, 124.99, 127.05, 127.61, 129.25, 129.41, 131.41, 132.61, 135.75, 141.38, 143.60. Anal. Calcd for $C_{21}H_{25}NO_2S$: C, 70.96; H, 7.04. Found: C, 71.12; H, 7.06.

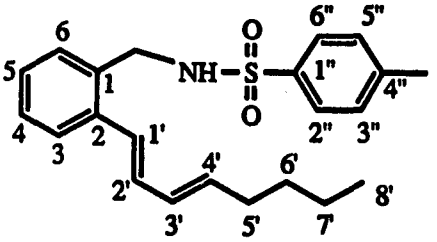
***N*-Tosyl-3-[(*E*)-1-hexenyl]-1,2,3,4-tetrahydroisoquinoline (79).**



79

Obtained in 81% isolated yield from the reaction of *N*-tosyl-2-iodobenzylamine and 1,3-octadiene using $Pd(OAc)_2$, Et_3N, DMA, PPh_3 and stirring for two days at 80 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.28; IR (neat) 3064, 3026, 2957, 2928, 2871, 2856, 1654, 1598, 1496, 1454, 1350, 1337, 1165 (SO_2) cm^{-1}; ^1H NMR δ 0.79 (t, 3H, *J* = 6.6 Hz, 6'-H), 1.05-1.15 (m, 4H, 4'-H and 5'-H), 1.78 (m, 2H, 3'-H), 2.39 (s, 3H, 4"-CH_3), 2.69 (dd, 1H, *J* = 16.2, 1.5 Hz, H_a), 3.1 (dd, 1H, *J* = 16.2, 6 Hz, H_b), 4.19 (d, 1H, *J* = 16 Hz, H_c), 4.68 (d, 1H, *J* = 16 Hz, H_d), 4.81 (t, 1H, *J* = 6.3 Hz, 3-H), 5.14 (ddt, 1H, *J* = 15, 6.6, 1.5 Hz, 1'-H), 5.52 (dtd, 1H, *J* = 15, 6.6, 0.9 Hz, 2'-H), 7.04 (m, 2H, 6-H and 7-H), 7.14 (m, 2H, 5-H and 8-H), 7.24 (d, 2H, *J* = 8.0 Hz, 3'-H and 5'-H), 7.70 (d, 2H, *J* = 8.0 Hz, 2'-H and 6'-H); ^{13}C NMR δ 143.0, 136.7, 134.7, 132.2, 131.5, 129.4, 129.0, 127.4, 126.7, 126.1, 125.8, 125.6, 53.1, 43.4, 33.9, 31.7, 30.9, 22.0, 21.4, 13.8; mass spectrum m/z 369.17594 (calcd for $C_{22}H_{27}NO_2S$, 369.17624).

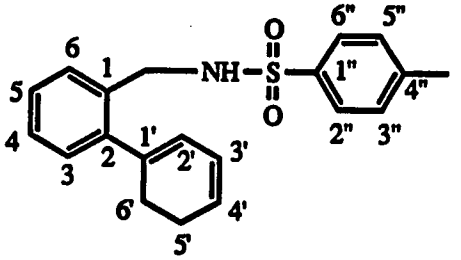
***N*-Tosyl-2-[(1*E*,3*E*)-1,3-octadienyl]benzylamine (80).**



Obtained in 15% isolated yield from the reaction of *N*-tosyl-2-iodobenzylamine and (*E*)-1,3-octadiene using TLC (7.5:1 hexane/EtOAc), R_f = 0.30; IR (neat) 3281 (NH), 2957, 2928,

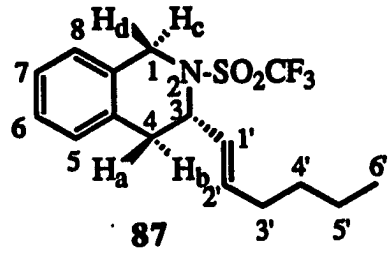
1674 (C=C), 1598 (Ar), 1329, 1161 (SO_2) cm^{-1}; ^1H NMR δ 0.94 (t, 3H, J = 7.2, 8'-H), 1.3-1.5 (m, 4H, 6'-H and 7'-H), 2.16 (q, 2H, J = 6.9 Hz, 5'-H), 2.46 (s, 3H, 4"-CH_3), 4.15 (d, 2H, J = 5.7 Hz,1-CH_2), 4.37 (t, 1H, J = 5.4 Hz, NH), 5.83 (dt, 1H, J = 15, 7.5 Hz, 4'-H), 6.05 (dd, 1H, J = 15.0, 10.2 Hz, 3'-H), 6.37 (d, 1H, J = 15.3 Hz, 2'-H), 6.62 (dd, 1H, J = 15.3, 10.3 Hz, 1'-H), 7.08-7.16 (m, 2H, 4-H and 5-H), 7.19-7.24 (m, 1H, Ar), 7.33 (d, 2H, J = 8.1 Hz, 3'-H and 5'-H), 7.45 (d, 1H, J = 6.9 Hz, 3-H), 7.77 (d, 2H, J = 8.1 Hz, 2'-H and 6'-H).

_N_-Tosyl-2-[1,3-cyclohexadienyl]-1-(aminomethyl)benzene (82).



Obtained in 91% isolated yield from the reaction of *N*-tosyl-2-iodobenzylamine and 1,3-cyclohexadiene using $Pd(dba)_2$, Et_3N, DMA, and stirring for one day at 80 °C. TLC (4:1 hexane/EtOAc), R_f = 0.31; IR ($CHCl_3$) 3368 (NH), 3051, 3003 (C=CH), 2930 (CH_2), 1599 (C=C-C=C), 1333, 1161 (SO_2) cm^{-1}; ^1H NMR δ 2.1-2.21 (m, 2H, 5'-H), 2.21-2.31 (m, 2H, 6'-H), 2.43 (s, 3H, 4"-CH_3), 4.17 (d, 2H, J = 6.0 Hz, 1-CH_2), 4.74 (t, 1H, J = 6.0 Hz, NH), 5.75 (d, 1H, J = 5.1 Hz, 2'-H), 5.83 (dt, 1H, J = 9.3, 4.3 Hz, 4'-H), 5.95 (ddt, 1H, J = 9.5, 5.1, 1.8 Hz, 3'-H), 7.07-7.4 (m, 4H, Ar), 7.28 (d, 2H, J = 8.4 Hz, 2"-H and 6"-H), 7.72 (d, 2H, J = 8.4 Hz, 3"-H and 5"-H); ^{13}C NMR δ 26.17, 27.55, 32.81, 49.88, 128.53, 129.21, 130.40, 131.78, 131.89, 132.46, 133.16, 133.94, 134.28, 137.49, 141.25, 141.37, 147.58, 147.98; mass spectrum m/z 339.12918 (calcd for $C_{20}H_{21}NO_2S$, 339.12931).

***N*-Trifluoromethanesulfonyl-3-[(*E*)-1-hexenyl]-1,2,3,4-tetrahydroisoquinoline (87).**



87

Obtained in 10% isolated yield from the reaction of 2-iodobenzyltriflamide and 1,3-octadiene using $Pd(OAc)_2$, Et_3N, DMF, PPh_3, and stirring for four days at 80 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.65; IR (neat) 2959, 2932, 2873, 2860, 1668 (C=C), 1600, 1587, 1498, 1456 (Ar), 1391, 1192 (SO_2) cm^{-1}; ^1H NMR δ 0.82 (t, 3H, J = 6.9 Hz, 6'-H), 1.1-1.3 (m, 4H, 4'-H and 5'-H), 1.96 (td, 2H, J = 6.9, 6.9 Hz, 3'-H), 2.87 (d, 1H, J = 16.2 Hz, H_a), 3.28 (dd, 1H, J = 5.4, 16.5 Hz, H_b), 4.46 (d, 1H, J = 16.2 Hz, H_c), 4.77 (d, 1H, J = 16.2 Hz, H_d), 4.85 (m, 1H, 3-H), 5.39 (dd, 1H, J = 15.6, 6.3 Hz, 1'-H), 5.71 (dt, 1H, J = 15.6, 6.9 Hz, 2'-H), 7.2-7.6 (m, 4H, Ar); ^{13}C NMR δ 13.75, 21.97, 30.96, 31.87, 33.50, 44.15, 54.76, 68.14, 125.19, 125.66, 126.30, 127.35, 129.38, 130.32, 131.42, 136.45; mass spectrum m/z 347.11626 (calcd for $C_{16}H_{20}F_3NO_2S$, 347.11670).

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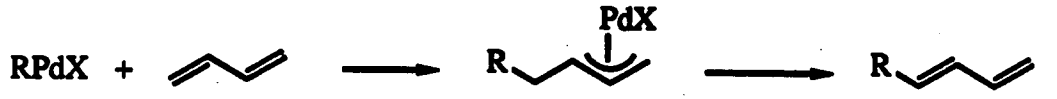
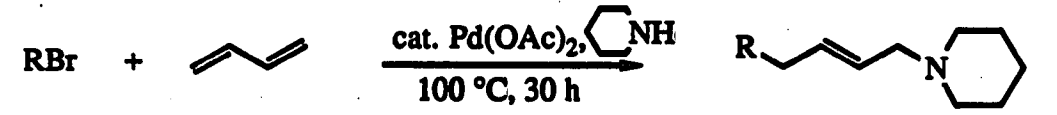
PART II: PALLADIUM-CATALYZED HETEROANNULATION OF 1,4-DIENES

INTRODUCTION

The palladium-promoted addition of arylmercurials to 1,3-dienes[1] and vinylmercurials to alkenes[2,3] has provided new routes to π-allylpalladium compounds. Recently, the palladium-catalyzed arylation and vinylation of conjugated dienes with aryl and vinyl halides, respectively, to provide π-allylpalladium intermediates have been reported.[4,5] Patel et al. and Heck and Stakem have utilized these organopalladium additions to dienes to synthesize substituted 1,3-dienes[4,5] (eq 1) and allylic amines[5,6] (eq 2).



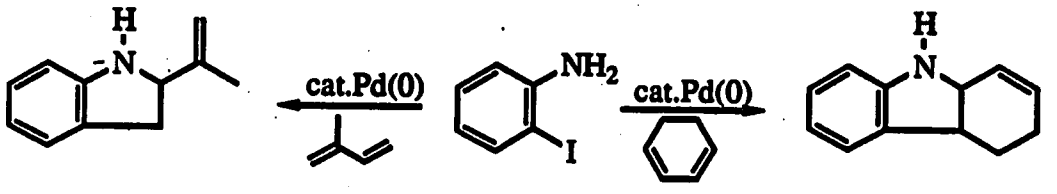
(1)



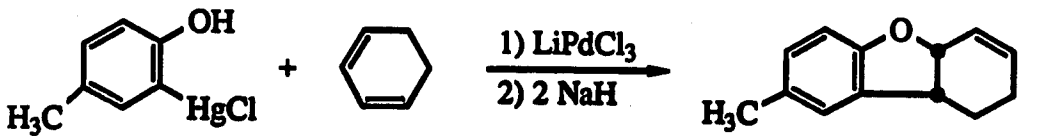
(2)

R= aryl or vinylic

Additionally, O'Connor et al.[7] (eq 3) and Larock et al.,[8a,d] Harrison,[8b] and Song[8c] (eq 4) have made use of these addition reactions to dienes to prepare heterocycles. Furthermore, the vinylation of simple acyclic[2] and cyclic[3,9] alkenes (eq 5) has afforded excellent yields of π-allylpalladium compounds apparently through palladium hydride rearrangement of a homoallylic palladium intermediate.



(3)



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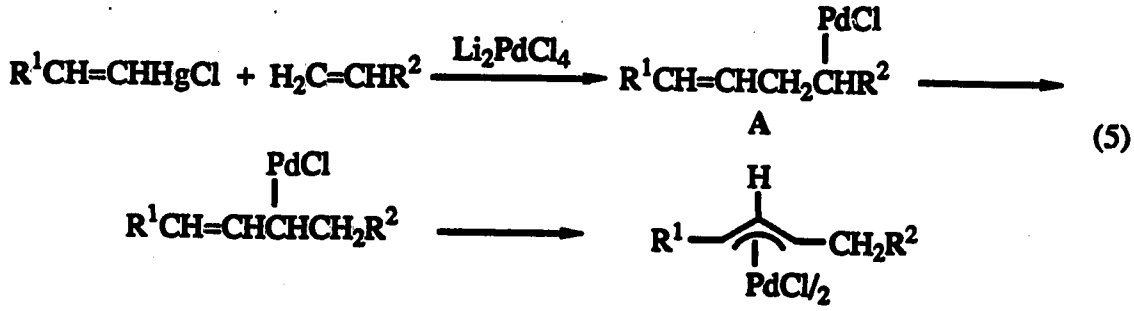
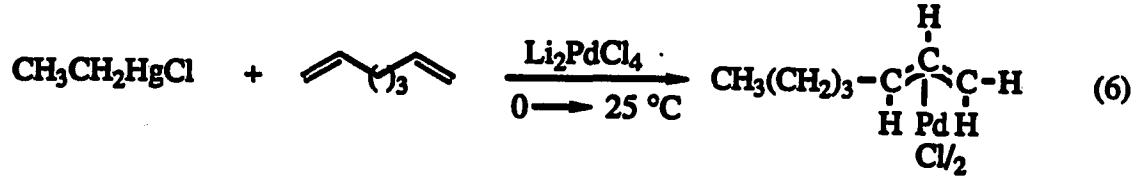


(5)

This type of homoallylic palladium intermediate (A) has recently been prepared from organopalladium additions to non-conjugated dienes to afford π-allylpalladium compounds. Bender et al. has reported[10] that the palladium-catalyzed arylation and vinylation of 1,4-dienes apparently proceeds by palladium migration to afford π-allylpalladium intermediates. Under appropriate conditions, these useful intermediates can be transformed into allylic amines and substituted 1,3-dienes. Larock and Takagi have synthesized π-allylpalladium compounds from the addition of organomercurials to 1,4-, 1,5-, 1,6-, and 1,7-dienes in the presence of a palladium salt (e.g., eq 6).[11, 12]

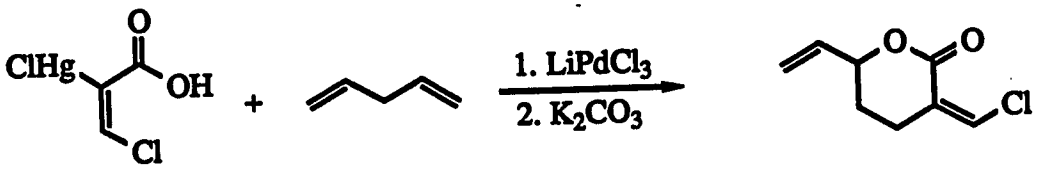


(6)

By taking advantage of this facile palladium hydride rearrangement of organo-palladium compounds derived from non-conjugated dienes, Larock et al.[8d] were able to synthesize a 7-membered ring lactone from the thallation-olefination of benzoic acid in the presence of a palladium salt (eq 7).

(7)

A six-membered ring α-methylene lactone and a 2-vinylbenzopyran derivative[11a, b] have also been prepared[8a, b] from the corresponding organomercurials and 1,4-dienes (eqs 8 and 9). These simple heteroannulation procedures provide access to a large number of heterocyclic systems of varying ring sizes.



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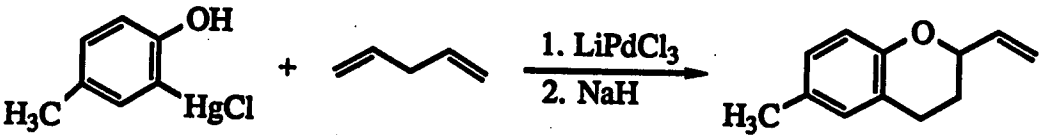


(9)

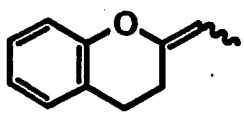
In recent years the use of π-allylpalladium compounds has become widespread in organic synthesis.[13-15] Thus, we wanted to investigate the possibility of utilizing these intermediates in the synthesis of heterocycles by the palladium-catalyzed heteroannulation of 1,4-dienes using functionalized aryl iodides. With this methodology we hoped to prepare a variety of heterocycles by forming two new bonds in a single step. Our results in this fascinating area of organometallic chemistry follow.

RESULTS AND DISCUSSION

O-Heterocycles

Our work described in part I of this dissertation has indicated the need to run these cyclizations under a variety of conditions so as to find a set of conditions which will provide reasonable yields of the desired products. Higher temperatures, usually around 100 °C, were also shown to be necessary to completely convert the starting aryl iodide to products. Realizing this, the reaction of 2-iodophenol (**1**) with a series of 1,4-dienes was investigated. These reactions afforded moderate to good yields of the corresponding benzopyran derivatives as shown by the results in Table 1.

In the reaction of **1** with **2** (entries 1-4), a mixture of four compounds was isolated. These compounds were found to be isomers after a GC-MS analysis of the sample was performed. It was also found that, in all of the reactions in entries 1-4 the same isomer ratio (83:8:6:3) was obtained after GC analysis. Unambiguous assignments for the structure of the three minor isomers could not be made from analysis of the ^{1}H NMR spectrum and GC-MS spectral data of the mixture. However, structures **4**, **5**, and **6** might correspond to the structures of these three isomers. The major isomer of the mixture was assigned structure **3**[16] based on the analysis of the ^{1}H NMR spectrum of the mixture. For these entries, good yields of products were obtained only when Na_2CO_3 and $NaHCO_3$ were used as bases (entries 3 and 4).



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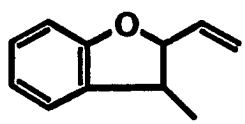

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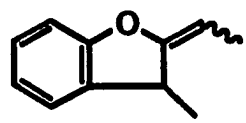
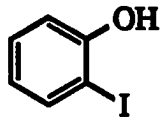
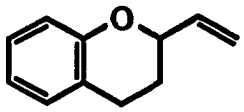
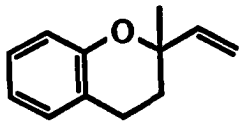
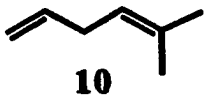
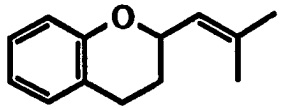


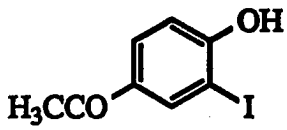
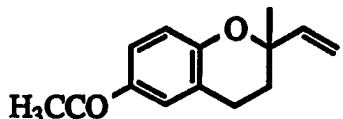
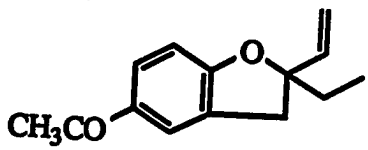
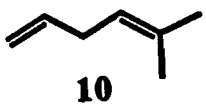
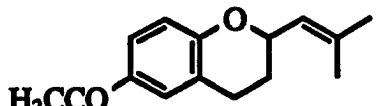
6

Table 1. Palladium-catalyzed reactions of phenolic aryl iodides with 1,4-dienes

Entry [a]	Aryl Iodide	Diene	Base	Product	% Yield
1	 1	 2	NaOAc	 3	42
2			Et_3N		44
3			Na_2CO_3		61
4			$NaHCO_3$		63
5		 7	NaOAc	 8	67
6			Et_3N		72
7			Na_2CO_3		66
8			$NaHCO_3$		68
9		 10	NaOAc	 11 (82:10:8:0)	43
10			Et_3N	11 (82:10:8:0)	28
11			Na_2CO_3	11 (91:6:2:1)	61
12			$NaHCO_3$	11 (95:8:3:2)	50

[a]Reactions were run at 100 °C for one day using 5% $Pd(OAc)_2$, DMF, $(n\text{-}Bu)_4NCl$, 3.5 equivalents of base, and 5 equivalents of diene.

Table 1. (continued)

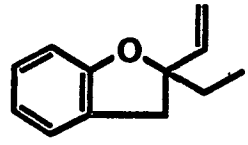
Entry [a]	Aryl Iodide	Diene	Base	Product	% Yield
13	 **12**	 **7**	NaOAc	 **13** +  **14**	67
14			Et_3N		71
15			$NaHCO_3$		63
16			Na_2CO_3		71
17[b]			Na_2CO_3		47
18[c]	 **10**		NaOAc	 **15**	46
19[d]			Na_2CO_3		44
20[b,d]			Na_2CO_3		53
21[b,d]			K_2CO_3		35

[b] 5% PPh_3 added.

[c] Run for six days.

[d] Run for two days.

Good yields of a mixture of four isomers were also obtained when **1** was reacted with diene **7** irrespective of the base utilized. These isomers were found to be present in an 82:13:3:2 GC ratio for all entries (5-8). The structure of the major isomer **8** was clearly assigned from analysis of the ^{1}H NMR spectrum of the mixture. The second major isomer is believed to be compound **9** as indicated from the residual signals in the ^{1}H NMR spectrum and its GC-MS spectrum. Unfortunately, not all of the signals expected for compound **9** were clearly visible in the ^{1}H NMR spectrum, and only the signals seen are reported.



9

Results similar to those in entries 1-8 were also obtained when **1** was reacted with diene **10** (Table 1, entries 9-12). In these cases also, four isomers were found to be present in the ratios shown in Table 1; compound **11** being the major isomer in all entries (entries 9-12). No structural assignments could be made for the other isomers, however. This system again afforded good yields of **11** in the presence of the carbonate bases (Na_2CO_3, $NaHCO_3$), but when Et_3N and NaOAc were used as the bases, lower yields of **11** were obtained.

It is evident from the above sets of reactions that, the 3-methyl group on the 1,4-pentadiene skeleton is promoting cyclization. Since at present, the nucleophilic displacement of π-allylpalladium species is best considered as a nucleophilic attack on η^3-allylpalladium cationic complexes,[17] the presence of this 3-methyl substituent should favor formation of a positive charge preferentially at the more substituted end of the unsymmetrical η^3-allyl system. This should lead to preference for reaction at this terminus and at a higher reaction

rate, thus making the difference in basicity among the bases insignificant when this substituent is present.

Åkermark et al.[18] recently reported that the use of acceptor ligands (e.g., phosphines and olefins) on the palladium metal leads to preference for reaction by a nucleophile at the more substituted end of an unsymmetrical η^3-allyl system. The use of donor ligands (e.g., amines) directs attack towards the less substituted end of the η^3-allyl system. This explains why Et_3N (a donor ligand) provides low yields of the desired product when the 3-methyl substituent is not present. When the 3-methyl substituent is present, the effect of the donor ligand Et_3N is insignificant.

With the hope of obtaining higher product yields than those obtained using 2-iodophenol (**1**), the reaction of 4-hydroxy-3-iodoacetophenone (**12**) (Table 1) with dienes **7** and **10** was also investigated. Reaction of compound **12** with diene **7** (entries 13-17) afforded good yields of a mixture of two products. Once again, the product yield obtained using this diene was independent of the different bases employed in the reactions. GC-MS analysis of samples taken from the reactions described in entries 13-17 revealed two peaks which proved to be a mixture of isomers. These were present in a 7:1 ratio of product **13** to its isomer **14** for all of the bases used. The structure assigned to these isomers was based on the ^1H NMR spectrum of the mixture. However, since not all signals for compound **14** were seen in the ^1H NMR spectrum, the structural assignment for this isomer may not be correct.

In an attempt to improve the yield by adding an acceptor ligand, the reaction of **12** with diene **7** in the presence of PPh_3 (entry 17) was investigated. Surprisingly, a lower yield of **13** (47%) was isolated. Besides electronic effects, steric factors should also be considered when postulating reaction mechanisms. Addition of PPh_3 increases the bulk around palladium, making it more difficult for the nucleophile to attack the η^3-allyl intermediate, and thus possibly favoring other reaction pathways bringing about lower yields

of cyclized product.

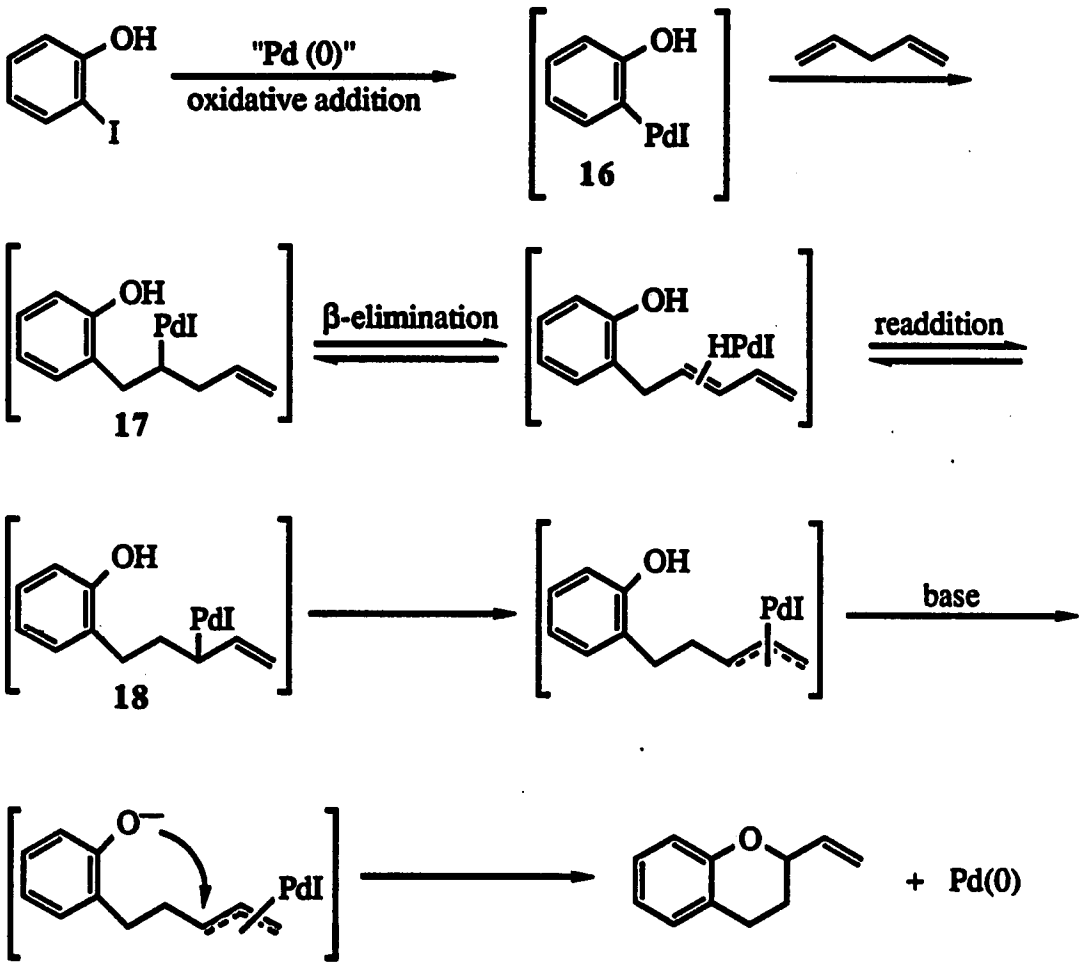
The reaction of 4-hydroxy-3-iodoacetophenone (**12**) with 5-methyl-1,4-hexadiene (**10**) afforded moderate yields of product **15**. The reaction run in the presence of NaOAc as the base (entry 18) was much slower than the same reaction in the presence of Na_2CO_3 (entry 19). Using NaOAc as the base required six days at 100 °C for complete disappearance of the starting material, while in the presence of Na_2CO_3 only two days were required. Contrary to the results obtained in entry 17, the use of PPh_3 in this reaction (entry 20) afforded a slightly higher yield than the reaction run in the absence of PPh_3. Attempts to improve the yield by using K_2CO_3 as the base (entry 21) failed to increase the yield as only a 35% yield of compound **15** could be isolated.

The proposed mechanism for the above reactions and reactions to follow is slightly different from that shown in part I of this dissertation, and it is represented in Scheme I. The first step of the mechanism is the oxidative addition of the aryl iodide onto the palladium metal to generate an intermediate arylpalladium species (**16**). This intermediate then adds in a *cis* manner to the 1,4-diene to form a σ-alkylpalladium intermediate (**17**) which undergoes β-hydride elimination and re-addition to generate a second σ-alkylpalladium intermediate (**18**). Subsequent π-allylpalladium formation, followed by intramolecular nucleophilic attack on the unsymmetrical π-allylpalladium species generates the observed benzopyran derivatives.

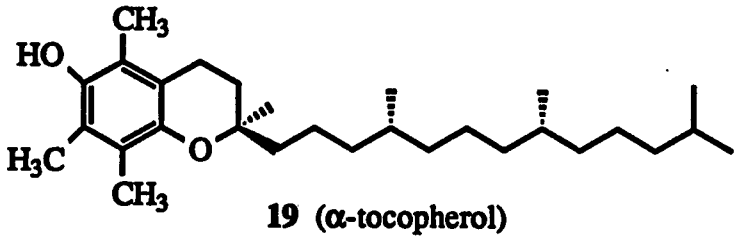
The substituents on the π-allylpalladium intermediate are expected[15] to be *syn* relative to the substituent at the central carbon of the π-allyl unit, thus diminishing the steric interaction between the substituents and the palladium atom. This would explain the high *E*-stereoselectivity obtained in these reactions.

Formation of the final product is thought to occur via nucleophilic attack on the unsymmetrical π-allylpalladium intermediate. However, another possibility exists for

Scheme I

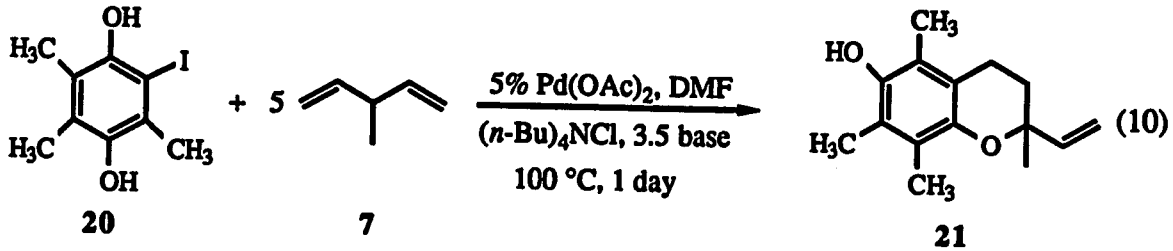


product formation, nucleophilic attack on the palladium atom followed by reductive elimination. For this process to occur, a seven-membered ring cyclic intermediate is required, but this is not expected to happen readily. Furthermore, the presence of a 3-methyl substituent, which has been shown to result in higher yields, should disfavor the formation of this cyclic intermediate (based on steric arguments), thus making this a less unlikely alternative.



19 (α-tocopherol)

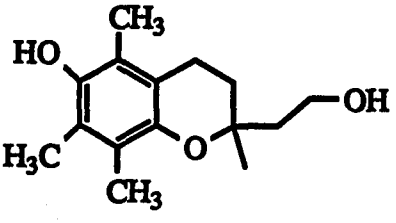
The attempted synthesis of a precursor to α-tocopherol (**19**) was also investigated by reacting 2-iodo-3,5,6-trimethylhydroquinone (**20**)[19] with 3-methyl-1,4-pentadiene (eq 10, Table 2).



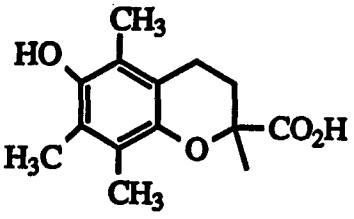
20 **7** **21** (10)

Compound **21** was isolated in yields ranging from traces to 19% as shown in Table 2. The reactions using NaOAc as the base in the presence or absence of PPh_3 (entries 1 and 2) gave yields ranging from 8-10%, but the desired product isolated was always contaminated with some major impurities and could not be obtained pure. When PPh_3 was added to the reaction mixture, mostly starting aryl iodide was recovered after two days (entry 2). When using $Pd(dba)_2$ as the catalyst, complete disappearance of the starting aryl iodide resulted, but only a trace of **21** was produced. Results similar to those obtained with NaOAc were also obtained when Et_3N was used as the base to afford ca. 7% of impure **21**. Further experimentation indicated that Na_2CO_3 as the base provided slightly higher yields. In the absence of PPh_3 (entry 5) a 14% yield of **21** was isolated, in the presence of PPh_3 a 19% yield of **21** was obtained (entry 6), but in the presence of dppe only traces of product (ca. 5% from GC) could be detected. If further work on this system is desired, it might be desirable to selectively protect the hydroxy group at position four.

It is believed that once suitable conditions have been found to prepare compound **21**, they can be used for synthesizing ethoxychroman **22**[20] or acid **23**,[21] which have been already used as precursors to α-tocopherol.



22



23

Table 2. Palladium-catalyzed reaction of 2-iodo-3,5,6-trimethylhydroquinone with 3-methyl-1,4-pentadiene

Entry	Base	Days	% Isolated Yield of **21**
1	NaOAc	2	ca. 8
2[a,b]	NaOAc	2	8-10
3[c]	NaOAc	2	trace
4	Et_3N	2	ca. 7
5	Na_2CO_3	1	14
6[a]	Na_2CO_3	1	19
7[d]	Na_2CO_3	2	trace

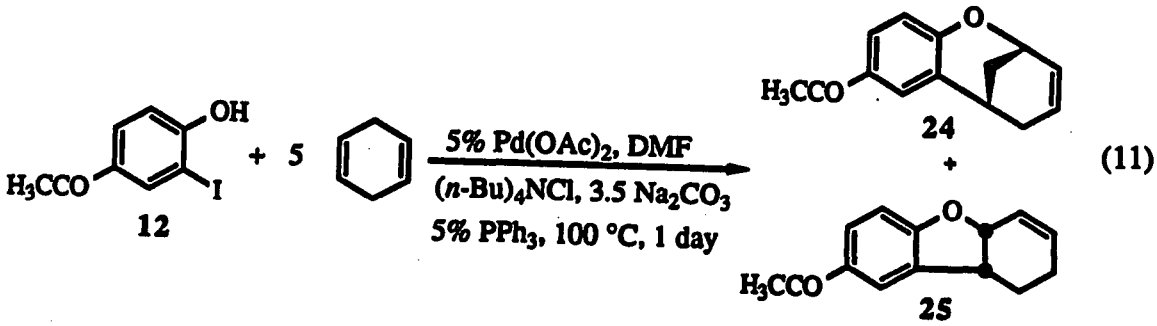
[a] 5% PPh_3 added.

[b] Mostly starting material was recovered.

[c] $Pd(dba)_2$ used as catalyst.

[d] 5% dppe added.

Besides benzopyran derivatives, synthesis of a bicyclic ether was also accomplished by reacting 4-hydroxy-3-iodoacetophenone (**12**) with 1,4-cyclohexadiene (eq 11). Utilizing the most consistent reaction conditions found for previous systems (eq 11), a 31% isolated yield of a mixture of compounds was obtained. GC analysis of the mixture revealed a single peak, but analysis of the ^{1}H NMR spectrum clearly indicated the presence of two major



(11)

components. These were found to be compounds **24** and **25** and were present in a 2.3:1 ^{1}H NMR ratio, respectively. The minor component **25** was identified by comparing the residual ^{1}H NMR spectral signals in the mixture with those of an authentic sample of **25** which had already been synthesized (see part I of this dissertation). Other very minor impurities were also detected, but could not be identified. The same reaction run in the absence of PPh_3 provided only a 16% isolated yield of a mixture of compounds **24** and **25** in the same ratio.

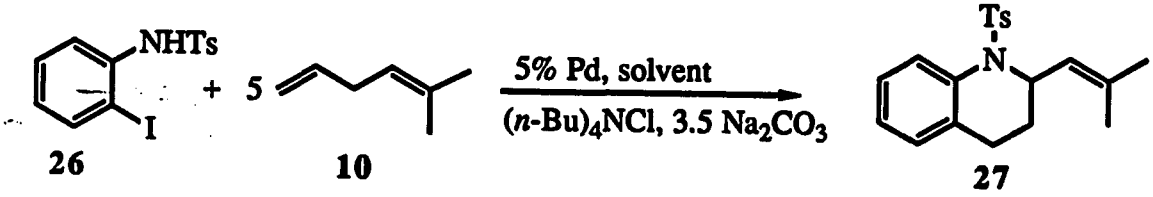
N-Heterocycles

In addition to the above oxygen heterocycles, the heteroannulation of 1,4-dienes with nitrogen-containing aryl iodides to give nitrogen-containing heterocycles was also investigated. Because of the poor results reported in part I of this dissertation, the reaction of 2-iodoaniline with 1,4-dienes was not attempted. However, the reaction of 2-iodo-acetanilide with 1,4-pentadiene (**2**) and 5-methyl-1,4-hexadiene (**10**) was attempted. Unfortunately, none of the desired products could be detected in the crude product mixtures.

On the other hand, since excellent results were obtained when *N*-tosyl-2-iodoaniline was reacted with 1,3-dienes, it was thought that this tosylamide would provide similar positive results upon reaction with 1,4-dienes. This was indeed the case as demonstrated by the results shown in Tables 3 and 4.

The reaction of *N*-tosyl-2-iodoaniline (**26**) with 5-methyl-1,4-hexadiene (**10**) afforded the results shown in Table 3. It is clear from the results of 1,4-dienes which give oxygen heterocycles and those in part I of this dissertation that the reactions in the presence of catalytic amounts of $Pd(dba)_2$ or $Pd(OAc)_2$ using Na_2CO_3 as the base provided, in

Table 3. Palladium-catalyzed reaction of *N*-tosyl-2-iodoaniline with 5-methyl-1,4-hexadiene



26 **10** **27**

Entry	Pd	Solvent	Temp. (°C)	Days	% Isolated Yield of **27**
1	$Pd(dba)_2$	DMA	100	2	62
2	$Pd(OAc)_2$	DMA	100	2	68
3[a]	$Pd(OAc)_2$	DMA	100	2	76
4[a]	$Pd(OAc)_2$	DMF	100	2	75
5[b]	$Pd(OAc)_2$	DMF	80	5	49
6[a,c]	$Pd(OAc)_2$	DMF	80	2	57

[a]5% PPh_3 added.

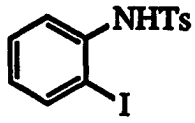
[b]Twenty-four percent of compound **26** was recovered.

[c]Twenty-one percent of compound **26** was recovered.

general, the most consistent results. Thus, the reaction of **26** with **10** in the presence of the two different palladium catalysts and in the presence of Na_2CO_3 was performed to provided 62 and 68% isolated yields of **27** (entries 1 and 2), respectively. Again, $Pd(OAc)_2$ afforded slightly better yields than $Pd(dba)_2$, and thus it was chosen as the catalyst of choice for further reactions. Addition of PPh_3 was found to slightly increase the yield, however. In this case (entry 3), a 76% yield of **27** was isolated. A comparison of the results of entries 3 and 4 indicated that there was no difference in product yield between the use of DMA or DMF as solvent, so DMF was chosen as the primary solvent for the reactions that follow. Additionally, attempts to reduce the reaction temperature (to 80 °C) afforded incomplete reaction, longer reaction times, and lower yields of product (entries 5 and 6).

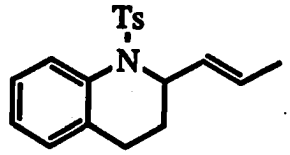
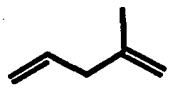
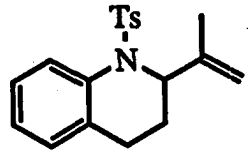
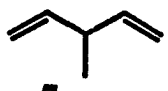
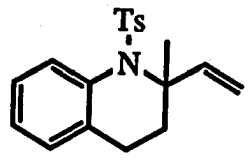
At this point, an investigation was undertaken to determine the effect on the yield of heterocycle of different substituents on the 1,4-diene skeleton. Our results in this particular area are presented in Table 4. As one might have expected, the reaction of *N*-tosyl-2-iodo-aniline (**26**) with (*E*)-1,4-hexadiene (**28**) (one methyl group less than diene **10**) provided results similar to those obtained in Table 3 under the best reaction conditions. A 73% isolated yield of **29** was obtained when no PPh_3 was added (Table 4, entry 1). Addition of PPh_3 had little effect on the overall yield and provided a 71% yield of **26** (entry 2). This reaction was also found to afford complete consumption of starting aryl iodide after two days at 100 °C in agreement with the reactions in Table 3. It should be stressed that a GC trace of the purified material revealed the presence of some minor impurities estimated to be less than 5% of the product. It also revealed two poorly resolved peaks for the desired product. GC-MS analyses of these two peaks showed that they had the same mass and fragmentation pattern which suggested that they could be double bond isomers. However, no evidence for this was visible from analysis of the ^1H NMR and ^{13}C NMR spectroscopy data which were entirely consistent with the structure of compound **29**. On the other hand, when the methyl

Table 4. Palladium-catalyzed reaction of *N*-tosyl-2-iodoaniline with 1,4-dienes



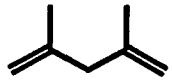
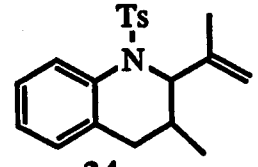
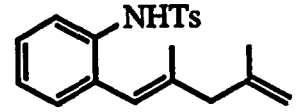
26 + 5 diene $\xrightarrow[(n\text{-Bu})_4NCl,\ 3.5\ Na_2CO_3]{5\%\ Pd(OAc)_2,\ DMF}$ **29, 31, 32, 34, 35**

100 °C

Entry	Diene	Day(s)	Product	% Isolated Yield
1	 **28**	2	 **29**	73
2[a]		2		71
3	 **30**	3	 **31**	55
4[a]				43
5	 **7**	1	 **32**	41
6		3		43

[a]5% PPh_3 added.

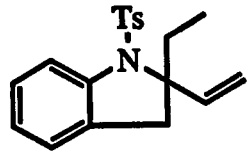
Table 4. Continued.

Entry	Diene	Day(s)	Product	% Isolated Yield
7[a]		2		mixture
8[b]		1		mixture
9	 33	5	 34 +  35	14 16
10[a]		6	34	18
			35	18

[b]Reaction run in DMSO.

substituent was present at the 2-position of the 1,4-pentadiene skeleton (compound **30**, entries 3 and 4), and thus closer to the reaction site, lower yields of product **31** were obtained. The reaction in the absence of PPh_3 afforded a 55% yield of **31** (entry 3), while the reaction in the presence of PPh_3 (entry 4) provided only a 43% yield of the desired product. It was also evident that longer reaction times (three days instead of two days) were required to completely consume the starting material (**26**) when diene **30** was used.

Similarly, when **26** was reacted with 3-methyl-1,4-pentadiene (**7**), moderate yields of tetrahydroquinoline **32** were isolated. The reaction of compound **26** with compound **7** afforded 41 and 43% yields of compound **32** (entries 5 and 6) when the reaction was run for 1 and 3 days, respectively. Besides product **32** (R_f= 0.46) another fraction (R_f= 0.52) was isolated in an 8% yield after column chromatography. GC-MS analysis of this fraction revealed the presence of one major peak with mass 327 suggesting only a single product. However, the ^{1}H NMR spectrum of this fraction indicated the presence of at least three components. The major component was assigned to be structure **36** based on some of the ^{1}H NMR signals from the mixture. In an attempt to improve the yield of the desired compound by the addition of an acceptor ligand, PPh_3 was added to the reaction mixture (entry 7). Unfortunately, a 36% yield of a mixture of five products was isolated. When this



36

sample was submitted for GC-MS analysis, all five components in the GC trace possessed a mass of 327. Identification of each of these compounds was not attempted since previous conditions did not produce any of these isomers. It seems that the addition of PPh_3 inhibited cyclization and promoted isomerization, possibly due to steric factors.

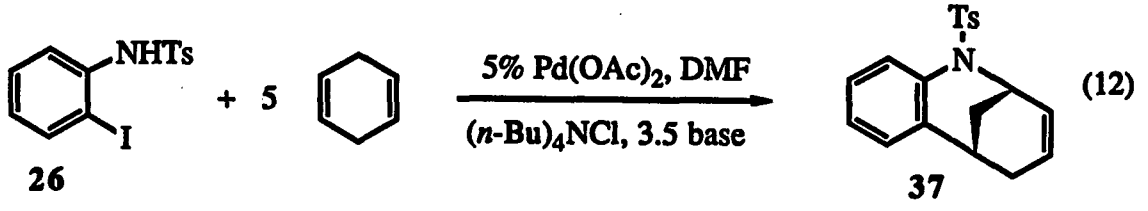
Recently, Friess et al.[22] reported that using DMSO as solvent instead of THF in their π-allylpalladium reactions provided a higher yield of products. Apparently, DMSO stabilizes the intermediate π-allylpalladium species long enough to be trapped by the nucleophile to provide the desired product. With this in mind, an attempt was made to improve the yield of compound **32** by using DMSO as the solvent, but when the reaction was performed (entry 8), a mixture of products was obtained. These products had the same retention time as those

reported for entry 7, and were not identified. It appears obvious from these results that PPh_3 and DMSO were of no help in these reactions.

This heteroannulation process was also extended to 2,4-dimethyl-1,4-pentadiene (**33**) which on reaction with *N*-tosyl-2-iodoaniline (**26**) afforded a mixture of products (entry 9). Flash column chromatography using 10:1 hexane/EtOAc as eluent afforded two fractions. The first fraction (R_f = 0.20) was found to be a mixture of compounds which could not be separated by column. However, after trituration with hexanes, colorless crystals precipitated out. These crystals, when analyzed spectroscopically, were found to correspond to structure **34** and were obtained in a 14% yield. The mother liquor contained a mixture (in a 9% yield) of **34** and other compounds whose structures could not be determine from the ^1H NMR spectrum. The second fraction (R_f = 0.32) was found to contain only compound **35** (entry 9) in a 16% isolated yield. Attempts to increase the yield by using PPh_3 as a co-catalyst gave similar results. An 18% isolated yield for each compound (**34** and **35**) was obtained under these conditions.

These nitrogen annulations presumably follow the mechanism shown in Scheme I. The results in Table 4 have shown that the closer the substituents are to the site to be attacked by the nucleophile, the lower the yield of the corresponding products obtained. This might be due to steric congestion around the reacting end of the unsymmetrical π-allyl moiety, thus favoring other possible reaction pathways.

Our attempts to prepare a nitrogen-containing bicyclic alkene, as shown in eq 12, have been without success. Employing the reaction conditions presented in Table 5 provided none of the desired product **37**. Only significant amounts of starting material were isolated each time. In some instances, *N*-tosylaniline was obtained as a mixture with **26**.



26 37 (12)

Table 5. Palladium-catalyzed reaction of *N*-tosyl-2-iodoaniline with 1,4-cyclohexadiene

Entry	Base	Temp (°C)	Day(s)	% Yield of 37
1	Na_2CO_3	80	6	0
2[a]	Na_2CO_3	80	6	0
3	Na_2CO_3	100	6	0
4[a]	Na_2CO_3	100	6	0
5	NaOAc	80	6	0
6	NaOAc	100	3	0
7[a]	NaOAc	80	6	0
8[a]	NaOAc	100	3	0
9	NaOAc	80	6	0
10	Na_2CO_3	100	3	0

[a]5% PPh_3 added.

CONCLUSION

Organopalladium chemistry has evolved as a powerful technique in organic synthesis. The ever coming new developments in this chemistry inspired us to develop a new synthetic approach towards the synthesis of heterocycles. In this second part of this dissertation, it was shown that benzopyran, tetrahydroquinoline, and benzoxocin derivatives can be prepared by making use of a catalytic process wherein the corresponding functionalized aryl iodides are reacted with a variety of 1,4-dienes. Best results were found to be obtained when Na_2CO_3 was used as the base and $Pd(OAc)_2$ as the catalyst.

A mechanism involving nucleophilic attack at the more substituted end of an unsymmetrical η^3-allylpalladium intermediate has been postulated based on stereoelectronic factors. It is hoped that future investigations will show that other non-conjugated dienes (1,5-, 1,6-, 1,7-, etc.) can also be applied to this type of heteroannulation.

EXPERIMENTAL SECTION

Equipment

^{1}H NMR spectra were recorded on a Nicolet NT-300 (operating at 300 MHz for proton nuclei) spectrometer using $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded on a Nicolet NT-300 (operating at 75 MHz for carbon nuclei) spectrometer using $CDCl_3$ both as the solvent and internal standard. Infrared spectra were recorded on either an IBM IR/98 FT-IR spectrophotometer or on a Beckman-42050 spectrophotometer. High resolution mass spectral data were obtained on a Kratos high resolution mass spectrometer or on an MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with a 3% OV-101 on Chromosorb W packed column and a DB5 glass capillary column or on an HP 5890 gas chromatograph equipped with an HP-1 Megabore column. GC-MS data were obtained on a Finnigan MS-50 mass spectrometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Thin layer analytical chromatography was performed on commercially prepared 60 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm), $KMnO_4$ solution, or in an iodine chamber. Flash chromatography [23] was carried out on 230-400 mesh silica gel.

Reagents

All chemicals were used directly as obtained from commercial sources unless otherwise noted. When appropriate, commercial sources are shown in parentheses. *N,N*-

Dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) were distilled from CaH_2 at reduced pressure and Et_3N (Eastman Kodak) was distilled from KOH pellets. The anhydrous form of $NaHCO_3$ (Fisher), Na_2CO_3 (Fisher), and K_2CO_3 (J. T. Baker) and the fused form of NaOAc (Fisher) and KOAc (Fisher) were utilized for the catalytic reactions. $Pd(OAc)_2$ and $PdCl_2$ were generously provided by Johnson Matthey, Inc. $Pd(dba)_2$ was prepared as reported by Takahashi et al.[24] 4-Hydroxy-3-iodoacetophenone (**12**), *N*-tosyl-2-iodoaniline (**26**), and 2-iodoacetanilide were prepared as reported in part I of this dissertation.

Preparation of starting aryl iodides

Synthesis of 2-iodo-3,5,6-trimethylhydroquinone (20) Compound **20** was prepared by the iodination-oxidation of 2,3,5-trimethylphenol, followed by reduction of the resulting benzoquinone.

2-Iodo-3,5,6-trimethyl-*p*-benzoquinone A 500 mL round bottom flask was charged with 13.6 g (0.1 mol) of 2,3,5-trimethylphenol, 25.4 g (0.1 mol) of iodine, and 175 mL of 100% EtOH. The reaction mixture was stirred at 65 °C while 50 mL of 30% H_2O_2 (0.49 mol), diluted with 25 mL of 100% EtOH, was added dropwise over a 1 h period. After the reaction mixture had been stirred at 70-75 °C for an additional hour, the brownish solution was cooled to 0 °C. The precipitate was collected and washed successively with 5% $NaHSO_3$ (75 mL), water (100 mL), and cold (0 °C) 70% aqueous methanol (25 mL). After drying, the orange crystalline powder (2-iodo-3,5,6-trimethyl-*p*-benzoquinone) weighed 19 g (69%); mp 68-70 °C (lit.[19] mp 70-73 °C); IR ($CHCl_3$) 1657 (C=O), 1599 (C=C), 1204, 1196 (C-O-C) cm^{-1}.

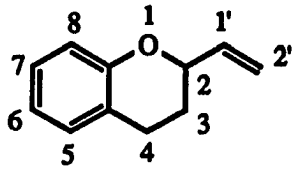
2-Iodo-3,5,6-trimethylhydroquinone 2-Iodo-3,5,6-trimethyl-*p*-benzoquinone (9.5 g, 34 mmol) was dissolved in 400 mL of ether. While the reaction mixture was mechanically stirred, 200 mL of 20% $Na_2S_2O_4$ was added in a continuous stream. After stirring for an additional 15 min, the orange color was completely discharged. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated to give 8.1 g (86%) of a crude colorless solid. This solid was recrystallized from benzene to give 7.22 g (76%) of 2-iodo-3,5,6-trimethylhydroquinone: mp 140-142 °C (dec) (lit.[19] mp 135-136 °C); IR ($CHCl_3$) 3612, 3499 (OH), 1454, 1410 (C=C) cm^{-1}; ^1H NMR δ 2.16 (s, 3H, 6-CH_3), 2.25 (s, 3H, 5-CH_3), 2.39 (s, 3H, 3-CH_3), 4.3 (s, 1H, OH), 5.07 (s, 1H, OH).

General procedure for the palladium-catalyzed reactions

To a 1 dram vial are added the palladium reagent (0.025 mmol, 5%), the corresponding aryl iodide (0.5 mmol), a base (1.75 mmol), tetra-*n*-butylammonium chloride (0.5 mmol), DMF or DMA (1 mL), and the corresponding 1,4-diene (2.5 mmol). If the base is a liquid, it is added via syringe after adding DMF or DMA. The vial is then flushed with nitrogen and capped with a screw-cap containing a teflon liner. After heating at the desired temperature for x number of days, the reaction mixture is diluted with ether (Et_2O) and washed with saturated ammonium chloride, followed by H_2O. The organic layer is then dried ($MgSO_4$), a pinch of activated charcoal added, and the reaction mixture filtered, concentrated, and purified via "flash column chromatography" (silica gel, hexanes/EtOAc as eluents). When using an amine as the base, the organic phase is washed with 5% HCl instead of saturated ammonium chloride.

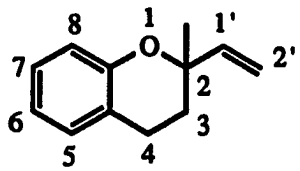
The following compounds were prepared using the above general procedure.

3,4-Dihydro-2-vinyl-2*H*-1-benzopyran (3)

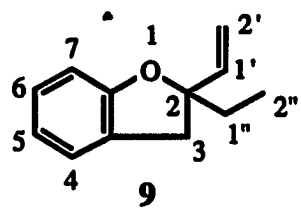


Obtained in 63% isolated yield as a mixture of isomers in an 83:8:6:3 GC ratio from the reaction of 2-iodophenol and 1,4-pentadiene using $Pd(OAc)_2$, $NaHCO_3$, DMF, and stirring for one day at 100 °C. Distillation of the mixture afforded a colorless oil: bp 72 °C/1 mm of Hg. The data of the major isomer follow: TLC (20:1 hexane/EtOAc), R_f = 0.35; IR (neat) 3100, 3040 (C=CH), 2940, 2860 (CH_2), 1640 (C=C), 1600, 1525, 1480 (Ar), 1260 (C-O-C) cm^{-1}; ^1H NMR δ 1.7-2.15 (m, 2H, 3-H), 2.7-2.9 (m, 2H, 4-H), 4.5-4.6 (m, 1H, 2-H), 5.23 (ddd, 1H, *J* = 10.5, 1.35, 1.35 Hz, 2'-H), 5.38 (ddd, 1H, *J* = 17.2, 1.35, 1.35 Hz, 2'-H), 5.98 (ddd, 1H, *J* = 17.2, 10.5, 5.6 Hz, 1'-H), 6.7-6.9 (m, 2H, 6-H and 8-H), 7.0-7.2 (m, 2H, 5-H and 7-H); ^{13}C NMR δ 24.02, 27.35, 75.89, 115.92, 116.64, 119.99, 121.58, 127.12, 129.33, 137.44, 154.32; mass spectrum m/z 160.08835 (calcd for $C_{11}H_{12}O$, 160.08882).

3,4-Dihydro-2-methyl-2-vinyl-2*H*-1-benzopyran (8) and 2-ethyl-2-vinyl-2,3-dihydrobenzofuran (9)



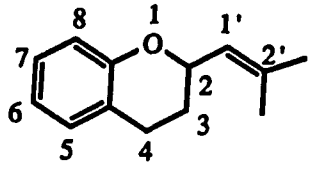
8



9

Obtained as a colorless oil as a mixture of four isomers in an 82:13:3:2 GC ratio in 72% isolated yield from the reaction of 2-iodophenol and 3-methyl-1,4-pentadiene using $Pd(OAc)_2$, Et_3N, DMF, and stirring for one day at 100 °C. Data of the mixture: TLC (20:1 hexane/EtOAc), R_f = 0.41; IR (neat) 3050 (C=CH), 3000, 2940 (CH_2), 1625 (C=C), 1600, 1505, 1475 (Ar) cm^{-1}. ^1H NMR of the two major isomers: δ 1.0 (t, 3H, J = 7.0 Hz, 2"-H of 9), 1.46 (s, 3H, 2-CH_3 of 8), 1.8-2.0 (m, 2H, 3-H of 8), 2.70-2.76 (m, 2H, 4-H of 8), 3.13 (s, 1H, 3-H of 9), 5.10 (dd, 1H, J = 10.8, 1.26 Hz, 2'-H of 8), 5.15 (dd, 1H, J = 10.8, 1.4 Hz, 2'-H of 9), 5.20 (dd, 1H, J = 17.3, 1.26 Hz, 2'-H of 8), 5.33 (dd, 1H, J = 17.3 Hz, 1.4 Hz, 2'-H of 9), 5.90 (dd, 1H, J = 17.3, 10.8 Hz, 1'-H of 8), 5.96 (dd, 1H, J = 17.3, 10.8 Hz, 1'-H of 9), 6.8-7.2 (m, 4H, Ar of 8 and 9); GC-MS of 9: mass (intensity) 174 (M, 39), 159 (18), 145 (100), 127 (13), 117 (24), 107 (13), 91 (14), 77 (12); ^{13}C NMR of 8: δ 22.49, 27.10, 31.71, 76.69, 113.82, 116.75, 119.69, 121.26, 127.22, 129.26, 141.23, 153.94; mass spectrum m/z 174.10439 (calcd for $C_{12}H_{14}O$, 174.10447). Anal. Calcd for $C_{12}H_{14}O$: C, 82.76; H, 8.04. Found: C, 82.60; H, 8.15.

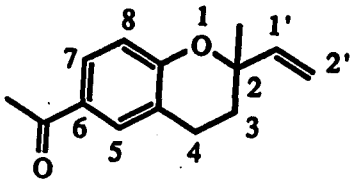
3,4-Dihydro-2-(2-methyl-1-propenyl)-2*H*-1-benzopyran (11)



Obtained as a colorless oil in 61% isolated yield from the reaction of 2-iodophenol and 5-methyl-1,4-hexadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and stirring for one day at 100 °C. TLC (20:1 hexane/EtOAc), R_f = 0.39; IR (neat) 3020 (C=CH), 2930 (CH_2, CH_3), 1680 (C=C), 1582, 1487, 1456 (Ar), 1234 (C-O-C) cm^{-1}; ^1H NMR δ 1.75 (d, 3H, J = 1.2 Hz, 2'-CH_3), 1.79 (d, 3H, J = 1.2 Hz, 2'-CH_3), 1.8-2.0 (m, 2H, 3-H), 2.7-3.0 (m, 2H, 4-H),

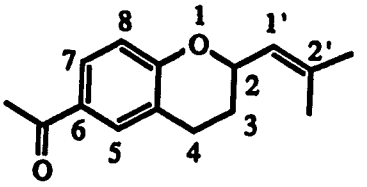
4.65-4.80 (m, 1H, 2-H), 5.3-5.4 (m, 1H, 1'-H), 6.8-6.9 (m, 2H, Ar), 7.0-7.2 (m, 2H, Ar); ^{13}C NMR δ 18.46, 24.75, 25.82, 28.02, 72.89, 116.84, 119.93, 121.68, 124.50, 127.08, 129.42, 136.89, 154.84; mass spectrum m/z 188.12035 (calcd for $C_{13}H_{16}O$, 188.12012). Anal. Calcd for $C_{13}H_{16}O$: C, 82.98; H, 8.51. Found: C, 83.12; H, 8.64.

6-Acetyl-3,4-dihydro-2-methyl-2-vinyl-2*H*-1-benzopyran (13)



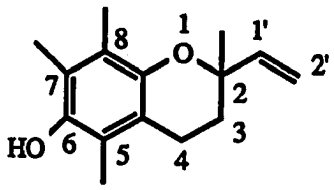
Obtained in 71% isolated yield as a 6:1 (^1H NMR ratio) mixture of two isomers from the reaction of 4-hydroxy-3-iodoacetophenone and 3-methyl-1,4-pentadiene using $Pd(OAc)_2$, Na_2CO_3, and DMF, and stirring for one day at 100 °C. TLC (10:1 hexane/EtOAc), R_f = 0.19; IR (neat) 2978, 2932, 1676, 1607, 1578, 1495, 1266 cm^{-1}; ^1H NMR δ 1.45 (s, 3H, 2-CH_3), 1.75-1.9 (m, 1H, 3-H), 1.96 (dt, 1H, J = 13.8, 5.1 Hz, 3-H), 2.52 (s, 3H, CH_3CO), 2.68-2.77 (m, 2H, 4-H), 5.07 (d, 1H, J = 10.8 Hz, 2'-H), 5.13 (d, 1H, J = 17.1 Hz, 2'-H), 5.83 (dd, 1H, J = 17.1, 10.8 Hz, 1'-H), 6.88 (d, 1H, J = 8.4 Hz, 8-H), 7.65-7.82 (m. 2H, 5-H and 7-H); mass spectrum m/z 216.11527 (calcd for $C_{14}H_{16}O_2$, 216.11503).

6-Acetyl-3,4-dihydro-2-(2-methyl-1-propenyl)-2*H*-1-benzopyran (15)



Obtained in 53% isolated yield as a colorless oil from the reaction of 4-hydroxy-3-iodoacetophenone and 5-methyl-1,4-hexadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for two days at 100 °C. Recrystallization from hexanes afforded white crystals: mp 71-72 °C; TLC (10:1 hexane/EtOAc), R_f = 0.19; IR (neat) 2968, 2922, 2854 (CH_2, CH_3), 1676 (C=O), 1607, 1576, 1497 (Ar), 1285 (C-O-C), 827 cm^{-1}; ^1H NMR δ 1.76 (d, 3H, J = 1.2 Hz, 2'-CH_3), 1.80 (d, 3H, J = 1.2 Hz, 2'-CH_3), 1.82-1.92 (m, 1H, 3-H), 1.95-2.06 (m, 1H, 3-H), 2.53 (s, 3H, CH_3CO), 2.75-3.01 (m, 2H, 4-H), 4.80 (ddd, 1H, J = 9.6, 8.4, 2.7 Hz, 2-H), 5.35 (dq, 1H, J = 8.4, 1.2 Hz, 1'-H), 6.84 (d, 1H, J = 9.0 Hz, 8-H), 7.66-7.75 (m, 2H, 5-H and 7-H); ^{13}C NMR δ 18.52, 24.62, 26.88, 26.34, 27.58, 73.67, 116.74, 121.51, 123.63, 128.18, 129.41, 130.42, 137.89, 159.20, 197.0. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.26; H, 7.89. Found: C, 78.54; H, 8.04.

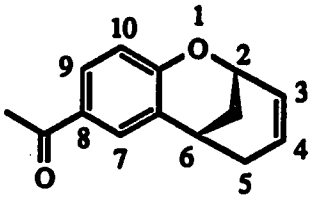
2-Ethenyl-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-6-ol (21)



Obtained in 19% isolated yield from the reaction of 2-iodo-3,5,6-trimethylhydroquinone with 3-methyl-1,4-pentadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for one day at 100 °C. TLC (4:1 hexane/EtOAc), R_f = 0.44; IR (neat) 3500 (OH), 2977, 2899, 2777 (CH_3, CH_2), 1641 (vinylic), 1504, 1489, 1444 (C=C), 1250 (C-O), 1220, 1041 (C-O-C) cm^{-1}; ^1H NMR δ 1.39 (s, 3H, 2-CH_3), 1.98-2.05 (m, 4H, 3-H and 4-H), 2.09 (s, 3H, ArCH_3), 2.17 (s, 6H, ArCH_3), 4.22 (s, 1H, OH), 5.01 (d, 1H, J = 10.5 Hz, 2'-H), 5.11 (d, 1H, J = 17.4 Hz, 2'-H), 5.85 (dd, 1H, J = 17.4, 10.8 Hz, 1'-H); mass spectrum m/z 232. 14617 (calcd for $C_{15}H_{20}O_2$, 232.14633). This compound slowly decomposes,

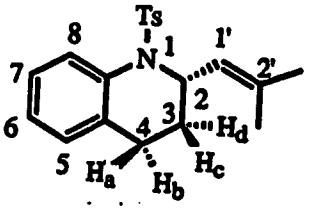
and thus it was not sent for elemental analysis.

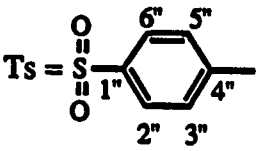
8-Acetyl-5,6-dihydro-2,6-methano-2*H*-1-benzoxocin (24)



Obtained in 31% isolated yield from the reaction of 4-hydroxy-3-iodo-acetophenone and 1,4-cyclohexadiene as a mixture of desired product **24** and dibenzofuran **25** using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for one day at 100 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.18; IR (neat) 3050 (C=CH), 2950 (CH_2), 1680 (C=O), 1660 (C=C), 1615, 1580, 1500 (C=C), 1275 (C-O-C) cm^{-1}; ^1H NMR δ 1.9-2.65 (m, 4H, 2-CH_2 and 5-H), 2.52 (s, 3H, CH_3CO), 3.15 (bs, 1H, 6-H), 4.78-4.87 (m, 1H, 2-H), 5.82-5.98 (m, 2H, 3-H and 4-H), 6.82 (d, 1H, J = 8.4 Hz, 10-H), 7.73 (d, 1H, J = 8.4 Hz, 9-H), 7.75 (s, 1H, 7-H); mass spectrum m/z 214.09941 (calcd for $C_{14}H_{14}O_2$, 214.09938).

***N*-Tosyl-2-(2-methyl-1-propenyl)-1,2,3,4-tetrahydroquinoline (27)**

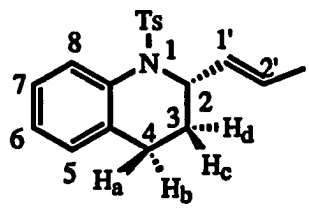


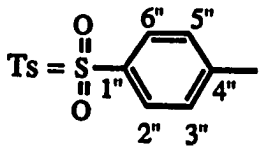


Obtained in 68% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 5-methyl-1,4-hexadiene using $Pd(OAc)_2$, Na_2CO_3, DMA, and stirring for one day at 100 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.37; recrystallized from hexanes to give colorless crystals: mp 74-77 °C; IR (neat) 3064 (C=CH), 3028 (Ar), 2930 (CH, CH_2, CH_3), 1680 (C=C), 1599, 1487,

1452 (Ar), 1344, 1165 (SO_2) cm^{-1}; ^1H NMR δ 1.40-1.52 (m, 1H, H_c), 1.66 (s, 3H, 2'-CH_3), 1.70-1.90 (m, 1H, H_d), 1.78 (s, 3H, 2'-CH_3), 2.06 (dt, 1H, J = 16.0, 6.0 Hz, H_b), 2.37 (s, 3H, 4"-CH_3), 2.54 (ddd, 1H, J = 16.0, 9.0, 6.0 Hz, H_a), 5.08 (m, 2H, 2-H and 1'-H), 6.99 (d, 1H, J = 7.0 Hz, 5-H), 7.08 (td, 1H, J = 7.5, 1.0 Hz, 7-H), 7.17 (d, 2H, J = 8.0 Hz, 3"-H and 5"-H), 7.12-7.22 (t, 1H, J = 7.0 Hz, 6-H), 7.44 (d, 2H, J = 8.0 Hz, 6"-H and 2"-H), 7.7 (d, 1H, J = 8.0 Hz, 8-H); ^{13}C NMR δ 18.08, 21.44, 24.26, 25.63, 28.29, 53.86, 123.54, 124.99, 126.38, 126.56, 126.93, 128.31, 129.31, 132.10, 133.91, 135.50, 136.89, 143.13; mass spectrum m/z 341.14536 (calcd for $C_{20}H_{23}NO_2S$, 341.14496). Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79. Found: C, 70.71; H, 6.85.

N-Tosyl-2-[(*E*)-1-propenyl]-1,2,3,4-tetrahydroquinoline (29)

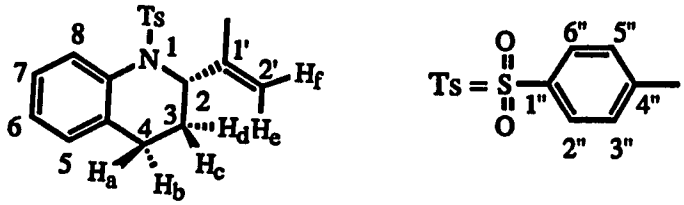




Obtained in 73% isolated yield as a colorless oil from the reaction of *N*-tosyl-2-iodoaniline and (*E*)-1,4-hexadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and stirring for two days at 100 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.36; IR (neat) 3064, 3028 (C=CH), 2937, 2854 (CH_2, CH_3), 1674 (C=C, trans), 1599, 1579, 1487, 1454 (Ar), 1346, 1167 (SO_2) cm^{-1}; ^1H NMR δ 1.45-1.6 (m, 1H, H_c), 1.63 (ddd, 3H, J = 6.6, 1.2, 1.2 Hz, 2'-CH_3), 1.69-1.83 (m, 1H, H_d), 1.97 (ddd, 1H, J = 16.0, 6.0, 6.0 Hz, H_b), 2.38 (s, 3H, 4"-CH_3), 2.47 (ddd, 1H, J = 16.0, 9.0, 6.0 Hz, H_a), 4.77-4.87 (m [looks like a quartet with fine splitting], 1H, 2-H), 5.40 (ddq, 1H, J = 15.4, 5.6, 1.5 Hz, 1'-H), 5.65-5.8 (m, 1H, 2-H), 6.97 (dd, 1H, J = 7.5, 1.2 Hz, 5-H), 7.08 (td, 1H, J = 7.2, 1.2 Hz, 7-H), 7.16 (d, 2H, J = 8.1 Hz, 3"-H and

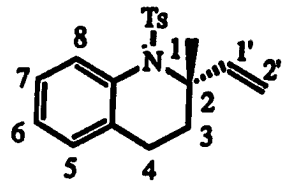
5"-H), 7.14-7.24 (m, 1H, 6-H), 7.42 (d, 2H, J = 8.1 Hz, 2"-H and 6"-H), 7.76 (dd, 1H, J = 8.1, 0.6 Hz, 8-H); ^{13}C NMR δ 17.68, 21.43, 24.21, 27.86, 56.80, 125.02, 126.34, 126.87, 128.20, 129.30, 129.79, 132.16, 135.32, 136.30, 143.24 (two overlapping sp^2 signals); mass spectrum m/z 327.12970 (calcd for $C_{19}H_{21}NO_2S$, 327.12931).

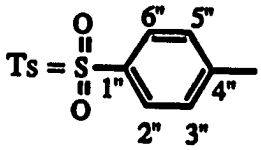
N-Tosyl-2-isopropenyl-1,2,3,4-tetrahydroquinoline (31)



Obtained in 55% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 2-methyl-1,4-pentadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and stirring for two days at 100 °C. Trituration of the oil obtained after column chromatography with hexanes gave a white solid: mp 105-106 °C; TLC (10:1 hexane/EtOAc), R_f = 0.27; IR (neat) 3093, 3058 (C=CH), 2951, 2895 (CH_3, CH_2), 1657 (vinylidine), 1599, 1583, 1487, 1454 (Ar), 1350, 1165 (SO_2) cm^{-1}; ^{1}H NMR δ 1.54-1.7 (m 1H, H_c), 1.72 (s, 3H, 1'-CH_3), 1.75-1.83 (m, 1H, H_d), 1.86-1.98 (m, 1H, H_b), 2.37 (s, 3H, 4"-CH_3), 2.3-2.4 (m [embedded], 1H, H_a), 4.7 (t, 1H, 2-H), 4.82-4.87 (m, 1H, H_e), 4.99 (d, 1H, J = 0.6 Hz, H_f), 6.94 (d, 1H, J = 7.2 Hz, 5-H), 7.16 (d, 2H, J = 8.1 Hz, 3"-H and 5"-H), 7.22 (ddd, 1H, J = 7.2, 7.2, 1.2 Hz, 6-H), 7.40 (d, 2H, J = 8.4 Hz, 2"-H and 6"-H), 7.77 (d, 1H, J = 8.4 Hz, 8-H), 7.82 (ddd, 1H, J = 7.2, 7.2, 1.2 Hz, 7-H); ^{13}C NMR δ 18.99, 21.37, 24.92, 27.96, 60.76, 111.70, 125.30, 126.44, 126.59, 126.84, 127.71, 129.24, 133.66, 135.80, 136.02, 143.26, 144.23; mass spectrum m/z 327.12879 (calcd for $C_{19}H_{21}NO_2S$, 327.12931). Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46. Found: C, 69.79; H, 6.82.

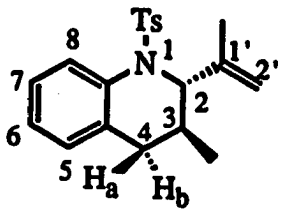
_N_-Tosyl-2-methyl-2-vinyl-1,2,3,4-tetrahydroquinoline (32)



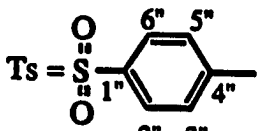


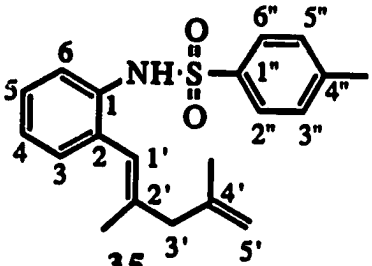
Obtained as a colorless oil in 41% isolated yield from the reaction of _N_-tosyl-2-iodoaniline and 3-methyl-1,4-pentadiene using $Pd(OAc)_2$, NaOAc, DMF, and stirring for one day at 100 °C. TLC (7.5:1 hexane/EtOAc), R_f = 0.15; IR (neat) 3064, 3028 (C=CH), 2979, 2943 (CH_2, CH_3), 1646 (C=C, vinyl), 1598, 1581, 1487, 1454 (Ar), 1352, 1167 (SO_2) cm^{-1}; ^1H NMR δ 1.48 (s, 3H, 2-CH_3), 1.65-1.85 (m, 2H, 3-H), 2.38 (s, 3H, 4"-CH_3), 2.47-2.58 (m, 2H, 4-H), 4.96 (d, 1H, J = 10.8 Hz, 2'-H), 5.02 (d, 1H, J = 17.7 Hz, 2'-H), 6.04 (dd, 1H, J = 17.4, 10.8 Hz, 1'-H), 7.01 (dd, 1H, J = 7.8, 1.5 Hz, 5-H), 7.08-7.20 (m, 4H, Ar), 7.43 (d, 2H, J = 8.4 Hz, 2"-H and 6"-H), 7.63 (dd, 1H, J = 7.5, 1.2 Hz, 8-H); ^{13}C NMR δ 21.4, 23.9, 28.0, 32.1, 62.7, 112.3, 125.6, 127.2, 127.4, 128.0, 128.9, 129.2, 132.9, 137.7, 139.0, 143.0, 143.2; mass spectrum m/z 327.12897 (calcd for $C_{19}H_{21}NO_2S$, 327.12931). Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46. Found: C, 69.13; H, 6.42.

***trans*-_N_-Tosyl-2-isopropenyl-3-methyl-1,2,3,4-tetrahydroquinoline (34) and _N_-tosyl-2-[(_E_)-2,4-dimethyl-1,4-pentadienyl]aniline (35)**



34





35

Obtained each in 18% isolated yield from the reaction of _N_-tosyl-2-iodoaniline and 2,4-dimethyl-1,4-pentadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for six days at 100 °C. Compound **34** was obtained as a mixture after column chromatography and

could only be obtained in its pure form after recrystallization from hexanes to give colorless crystals. The other components (except residual **34**) of the mixture (left in the mother liquor) could not be identified: mp 130-132 °C; TLC (10:1 hexane/EtOAc), R_f = 0.20; IR (neat) 3076, 3032 (C=CH), 2963, 2928, 2871, 2860 (CH_2, CH_3), 1651 (vinylic), 1601, 1487, 1458 (Ar), 1352, 1171 (SO_2) cm^{-1}; ^1H NMR δ 0.98 (d, 3H, J = 6.3 Hz, 3-CH_3), 1.20 (dd, 1H, J = 14.0, 12.0 Hz, H_a), 1.60 (s, 3H, 1'-CH_3), 1.47-1.66 (m, 1H, 3-H), 2.19 (dd, 1H, J = 14.0, 3.3 Hz, H_b), 2.38 (s, 3H, 4"-CH_3), 4.13 (d, 1H, J = 9.3 Hz, 2-H), 4.90 (s, 1H, 2'-H), 4.99 (s, 1H, 2'-H), 6.94 (d, 1H, J = 7.2 Hz, 5-H), 7.10 (t, 1H, J = 7.5 Hz, 7-H), 7.15 (d, 2H, J = 8.1 Hz, 3"-H and 5"-H), 7.24 (t, 1H, J = 7.8 Hz, 6-H), 7.37 (d, 2H, J = 8.1 Hz, 2"-H and 6"-H), 7.67 (d, 1H, J = 8.1 Hz, 8-H); ^{13}C NMR δ 17.54, 20.06, 21.54, 34.41, 36.37, 69.92, 113.52, 125.83, 126.98, 129.25, 135.63, 136.24, 136.30, 143.29, 144.52 (three overlapping sp^2 signals); mass spectrum m/z 341.14541 (calcd for $C_{20}H_{23}NO_2S$, 341.14496). Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79. Found: C, 70.42; H, 6.87. Compound **35** was obtained pure as a colorless oil after column chromatography: TLC (10:1 hexane/EtOAc), R_f = 0.32; IR (neat) 3275 (NH), 3072, 3033 (C=CH), 2968, 2918 (CH_3's), 1645 (C=C), 1598, 1577, 1489, 1452 (Ar), 1337, 1167 (SO_2) cm^{-1}; ^1H NMR δ 1.43 (d, 3H, J = 1.0 Hz, 4'-CH_3), 1.70 (s, 3H, 2'-CH_3), 2.36 (s, 3H, 4"-CH_3), 2.77 (s, 2H, 3'-H), 4.78 (s, 1H, 5'-H), 4.86 (s, 1H, 5'-H), 5.70 (s, 1H, 1'-H), 6.54 (s, 1H, NH), 6.98 (d, 1H, J = 7.0 Hz, 3-H), 7.06 (ddd, 1H, J = 7.0, 7.0, 1.0 Hz, 5-H), 7.14-7.24 (m, 3H, 3"-H, 4-H, and 5"-H), 7.55 (dd, 1H, J = 7.0, 1.0 Hz, 6-H), 7.61 (d, 2H, J = 8.4 Hz, 2"-H and 6"-H); ^{13}C NMR δ 17.09, 21.50, 21.88, 48.30, 112.92, 120.75, 121.0, 121.25, 124.60, 127.03, 127.73, 129.48, 129.97, 134.17, 136.37, 142.09, 142.61, 143.74; mass spectrum m/z 341.14446 (calcd for $C_{20}H_{23}NO_2S$, 341.14496). Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79. Found: C, 63.09; H, 6.86.

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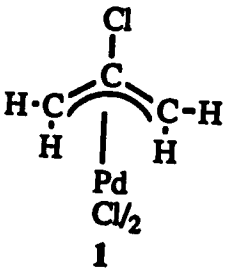
PART III: PALLADIUM-CATALYZED HETEROANNULATION OF 1,2-DIENES

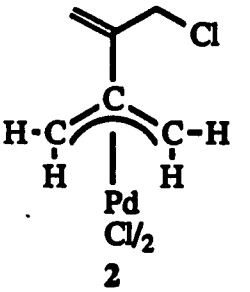
INTRODUCTION

As demonstrated in parts I and II of this dissertation and elsewhere,[1] π-allylpalladium species have become very important synthetic intermediates in organic synthesis. These species can be prepared by a variety of methods as has been shown in part I of this dissertation. One method to generate these intermediates is the addition of organopalladium species to allenes.

The synthesis of π-allylpalladium species from allenes was first reported in 1964 by two independent groups.[2, 3] It was reported that the reaction of 1,2-propadiene with palladium chloride provided selectively and in good yields the two dimeric complexes **1** and **2**. Which complex was obtained depended on the solvent and the mode of addition utilized.

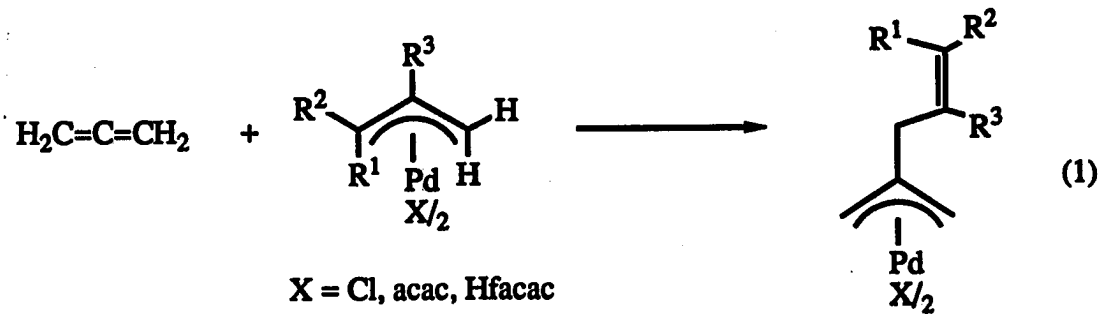


1

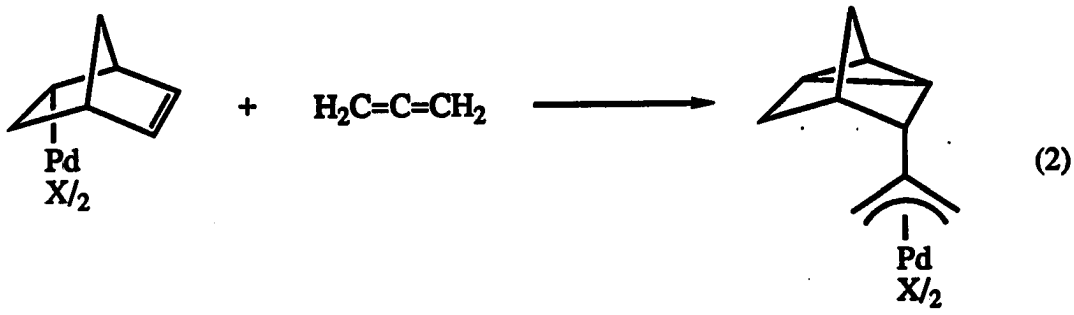


2

Sometime later, the reaction of allenes with π-allylpalladium complexes[4] or a σ-palladionorbornene[5] compound was reported to give new π-allylpalladium complexes (eqs 1 and 2). Hughes and Powell,[4] during their investigation of the insertion of allenes into allylic palladium bonds suggested that a σ-allylpalladium complex is the species that adds to the central carbon of the allene. They also postulated that the migration of this σ-allylpalladium intermediate to the central carbon of the coordinated allene moiety was the rate determining step of the reaction.

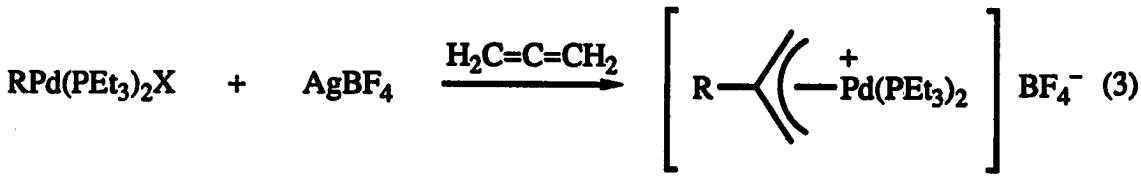


(1)



(2)

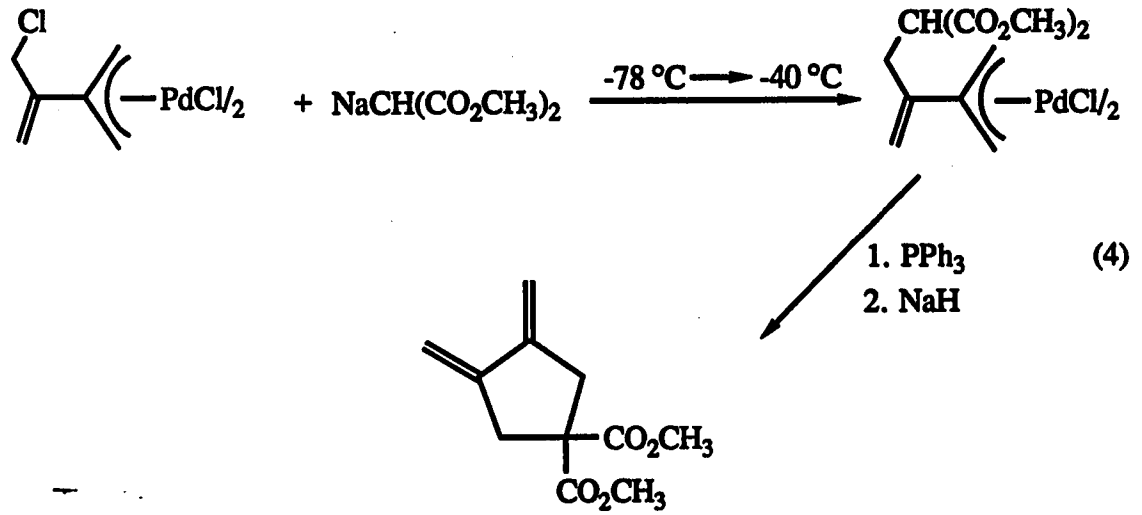
The first example of the addition of a true σ-alkylpalladium species to an allene was reported by Stevens and Shier[6] in 1970. They reported that the reaction of halo(organo)bis-(triethylphosphine)palladium(II) complexes with 1,2-propadiene in the presence of silver tetrafluoroborate generated π-allylpalladium complexes (eq 3). Good yields of these species were obtained when R was methyl or phenyl.



(3)

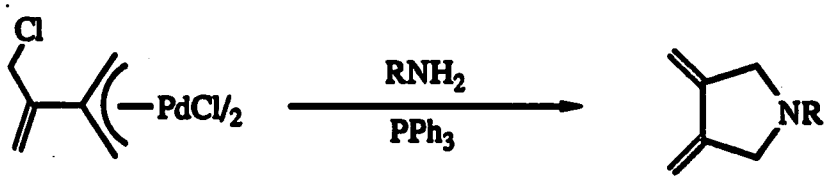
The application of these intermediates in organic synthesis was quite limited until the work of Hegedus et al.[7] They realized that complex **2** possessed two allylic moieties which could be attacked by bifunctional nucleophiles to produce conjugated exocyclic dienes. Since "π-allylpalladium complexes ostensibly do not react with nucleophiles in the absence of ligands" as Hegedus has commented, the bifunctional nucleophile was expected to react first

with the allylic chloride moiety when no ligand was present. Addition of PPh_3 (the ligand), followed by addition of a base (to generate the anion of the nucleophile) would allow the nucleophile to attack the π-allylpalladium moiety generating the corresponding exocyclic dienes (eq 4).



(4)

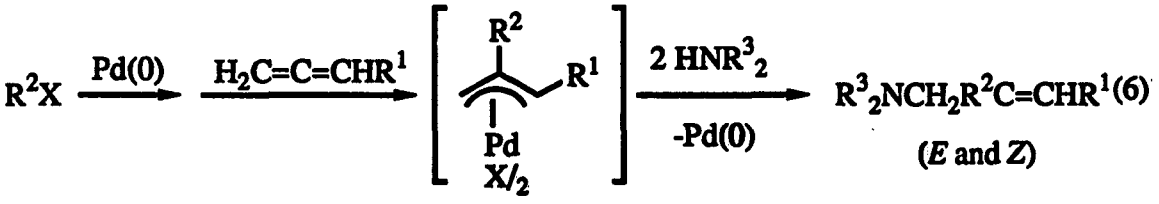
By using primary amines as bifunctional nucleophiles, they were able to prepare the corresponding five-membered ring nitrogen-heterocycles (eq 5). A disadvantage of these reactions was the need for the stoichiometric use of palladium salts and the presence of oligomerization products.



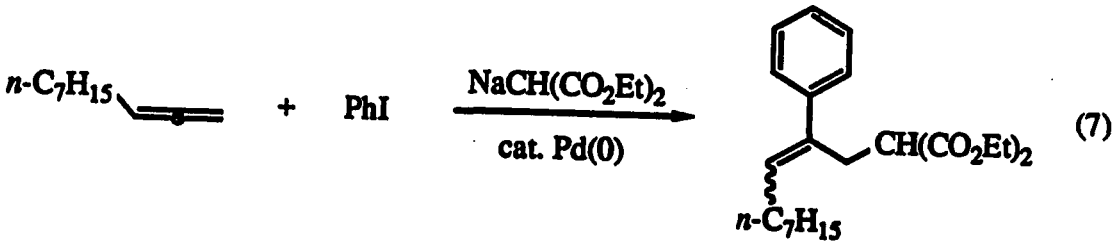
(5)

Recently, Shimizu and Tsuji[8] have reported the catalytic formation of π-allyl-palladium species by insertion of 1,2-dienes into σ-aryl- and σ-alkenylpalladium compounds. These organopalladium compounds have been prepared in situ from Pd(0) reagents and aryl

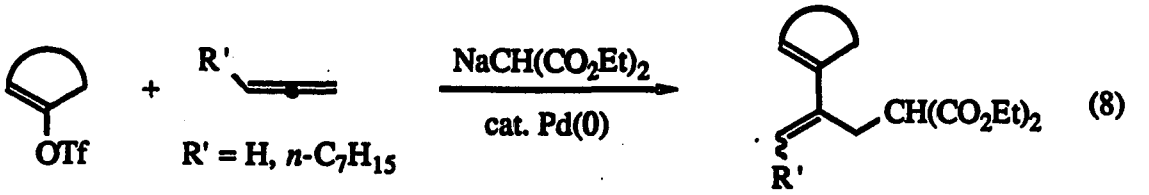
or alkenyl halides. By using secondary amines as nucleophiles to displace the π-allyl-palladium intermediate, they were able to obtain 2,3-disubstituted allyl amines (eq 6).



In addition, Ahmar et al.[9] have synthesized styrenes and 1,3-butadiene derivatives from the palladium-catalyzed reaction of aryl and vinylic halides with allenes in the presence of stabilized carbanions (eq 7). They found that when monoalkyl allenes were used, the reaction was regiospecific with attack of the nucleophile at the unsubstituted end of the π-allylpalladium intermediate. Also, high stereoselectivity was obtained when the incoming aryl or alkenyl iodide was sterically hindered giving predominant formation of the *E* - configuration for the trisubstituted double bond of the resulting olefin.



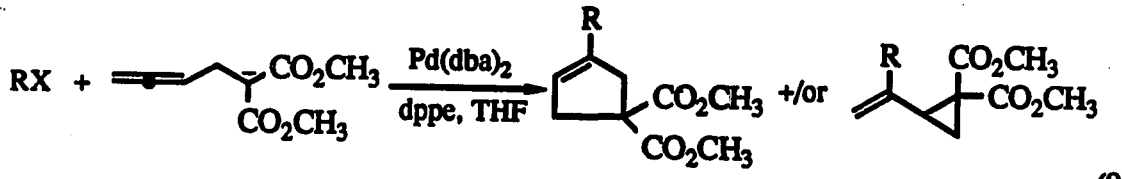
More recently, Friess et al.[10] have reported the same type of reactions, but starting from enol triflates instead of organic halides (eq 8). Kopola et al.[11] have extended these carbopalladation procedures to the synthesis of 1,3-dienic or styryl α-amino acid precursors. Here, they have made use of enol triflates and organic halides as starting reagents for their reactions.



(8)

53-85% (*E* / *Z* ≥ 83/17)

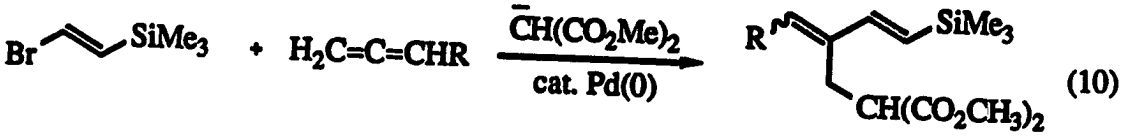
Ahmar et al.[12] have also reported an intramolecular version of the reaction shown in eq 7. They have reported the palladium-catalyzed addition of vinylic or aryl halides to the enolate of β-allenyl malonates to produce the corresponding cyclopentenes or cyclopropanes, or a mixture of these (eq 9). Apparently, the more bulky the organic halide is, the more selective (specific) the reaction becomes. A change in solvent was also found to affect the regioselectivity of the reaction.



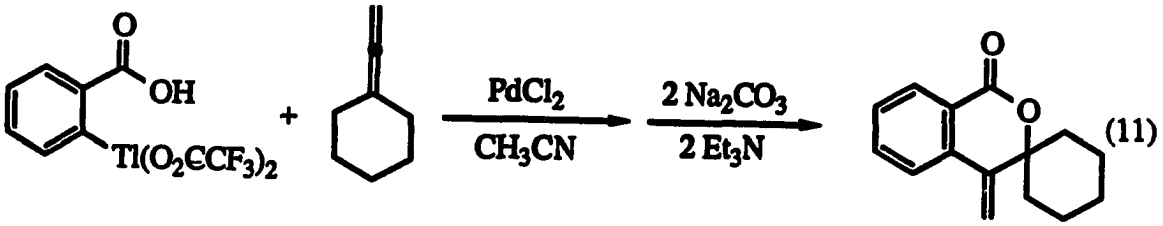
(9)

RX = vinyl bromide	0	:	100
RX = PhI	100	:	0
RX = cyclohexyl bromide	96	:	4

Cazes et al.[13] have applied these carbopalladation procedures to the synthesis of β-difunctionalized silylated dienes, which were obtained in moderate to good yields (eq 10). Furthermore, Larock et al.[14] have reported the thallation-olefination of benzoic acid to give isocoumarins. When using a 1,2-diene (an allene) 4-alkylidene-3,4-dihydroisocoumarins were obtained in moderate to good yields (eq 11).



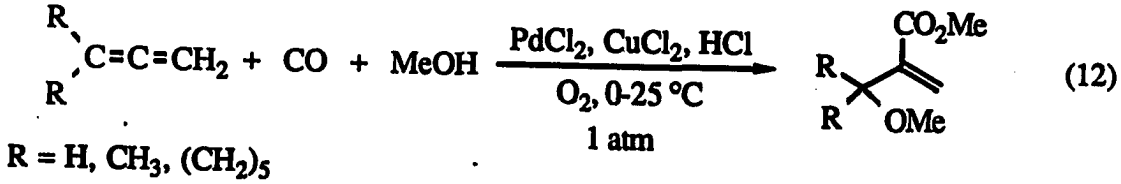
(10)



(11)

70%

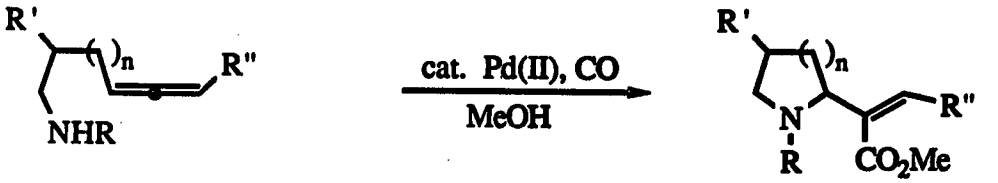
The use of allenes in organopalladium chemistry is not just limited to the synthesis of π-allylpalladium complexes. Allenes have also been used to prepare alkenylpalladium intermediates. This can be seen in the work of Alper et al.[15] They have reported the alkoxy-alkoxycarbonylation of allene and several substituted allenes, under mild reaction conditions, to afford the corresponding acrylates (eq 12).



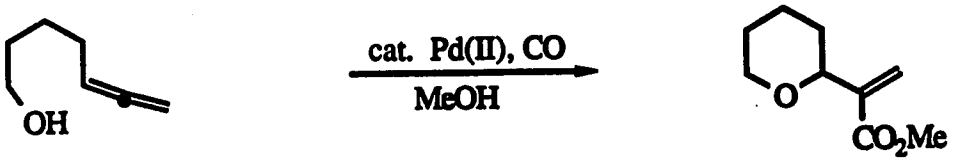
(12)

R = H, CH_3, $(CH_2)_5$

Inter-intramolecular versions of this synthesis of acrylates from allenes have also been reported. In 1986 Lathbury et al.[16] reported the synthesis of α-(heterocyclic)acrylates from the palladium(II)-catalyzed cyclization of allenic amines and amides in the presence of carbon monoxide and methanol (eq 13). They also briefly examined the cyclization of the analogous allenic alcohols (eq 14).

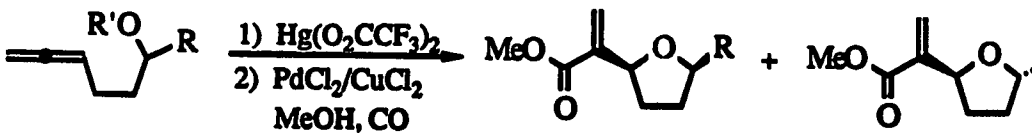


(13)



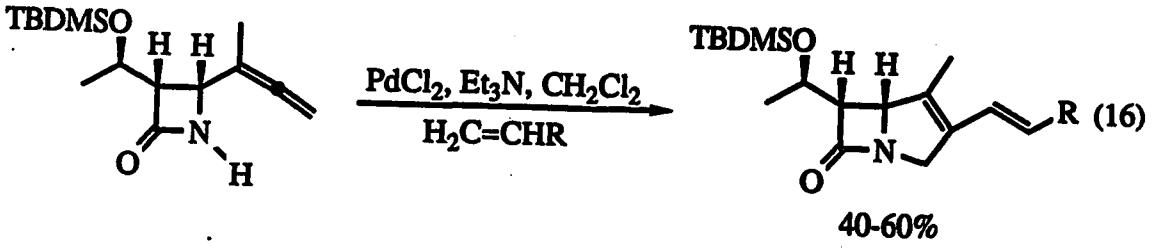
(14)

Similarly, Walkup and Park[17] have synthesized 2-(2-tetrahydrofuranyl)acrylates by the in situ alkoxycarbonylation of vinylpalladium intermediates obtained from the nucleomercuration/transpalladation or direct nucleopalladation of allenic alcohols or their *t*-butyldimethylsilyl derivatives (eq 15).



(15)

Recently, Prasad and Liebeskind[18] extended this type of cyclization to the synthesis of Δ^1-carbapenems. Using a 4-allenylazetidinone and catalytic amounts of a palladium(II) salt and coupling the intermediate alkenylpalladium with allyl halides or activated alkenes, they were able to obtain moderate yields of the corresponding Δ^1-carbapenems (eq 16). They have also reported[19] a similar silver-mediated approach to Δ^1-carbapenems.



(16)

It is my intention in this third part of this dissertation to show you our palladium-catalyzed approach to the synthesis of a variety of heterocycles using functionalized aryl iodides and allenes as starting materials.

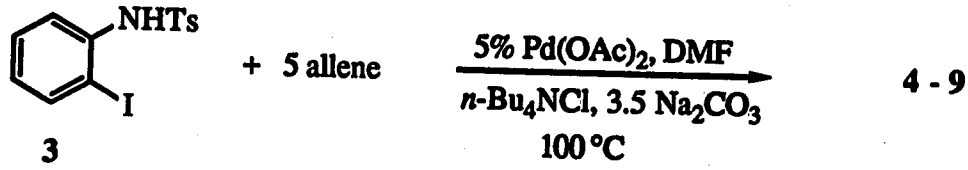
RESULTS AND DISCUSSION

N-Heterocycles

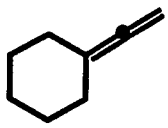
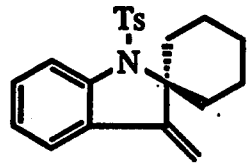
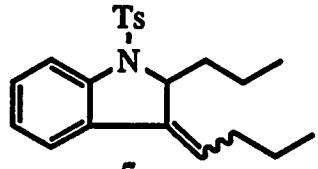
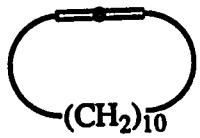
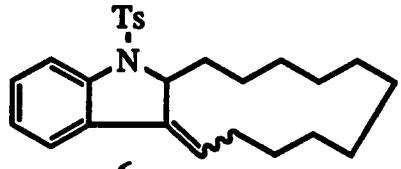
Our initial studies in this particular area of research were initiated by using *N*-tosyl-2-iodoaniline and vinylidene cyclohexane as starting materials. Since the use of $Pd(OAc)_2$ as the catalyst and Na_2CO_3 as the base proved so successful during our initial heteroannulation reactions, and, as a matter of fact, in almost all of the reactions that follow, we initiated our studies in this third part by running our reactions in the presence of the above two reagents. Also, *N*-tosyl-2-iodoaniline was chosen as our model aryl iodide and its reactions with a series of 1,2-dienes were investigated (Table 1). It was hoped that the best reaction conditions found for this model system would be fully applicable to other functionalized aryl iodides.

The reaction of **3** with vinylidene cyclohexane (Table 1), using Na_2CO_3 as the base, in the absence of PPh_3, afforded a 34% isolated yield (entry 1) of spiro compound **4** resulting from nucleophilic attack at the more substituted carbon of the intermediate π-allyl-palladium complex. Analysis of the ^1H NMR spectrum of this sample indicated the presence of trace amounts of what could be the expected regioisomer resulting from attack at the less substituted carbon of the π-allylpalladium intermediate. However, when the reaction was performed in the presence of PPh_3 (entry 2), a higher yield (89%) of compound **4** was isolated. Furthermore, the reaction proceeded at a faster reaction rate as indicated by the complete consumption of starting aryl iodide within two days. Also, no other products could be found by analysis of the ^1H NMR spectrum of this sample. Using K_2CO_3 as the base, in the presence of PPh_3 (entry 3), a 79% isolated yield of compound **4** was obtained as the sole product.

Table 1. Palladium-catalyzed reactions of *N*-tosyl-2-iodoaniline (3) with 1,2-dienes

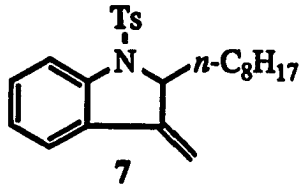
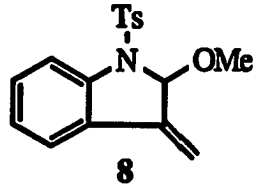
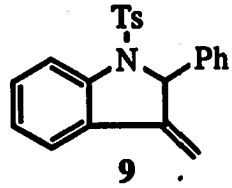


3

Entry	Allene	Day(s)	PPh_3	Product	% Isolated Yield
1		6	–	 4	34
2		2	+	4	89
3[a]		2	+	4	79
4		2	+	 5	78
5		2	+	 6	83

[a] K_2CO_3 used as base.

Table 1. (continued)

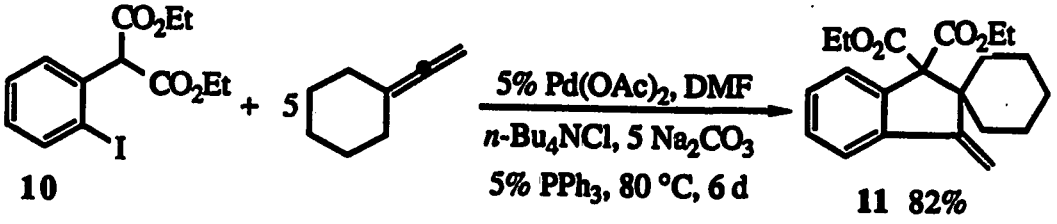
Entry	Allene	Day(s)	PPh_3	Product	% Isolated Yield
6		1	+	 **7**	85
7		3	–	**7**	67
8		2	+	 **8**	0
9		2	–	**8**	0
10		1	–	 **9**	0
11		1	+	**9**	0

Having confirmed that the reaction in the presence of $Pd(OAc)_2$ as the catalyst and Na_2CO_3 as the base, with PPh_3 as a co-catalyst, provided the highest yield (entry 2), it was decided to apply these reaction conditions to other allenes. As shown in entry 4, the reaction of **3** with 4,5-nonadiene afforded a 78% isolated yield of dihydroindole **5** as the major product (making ca. 95% of the mixture). Even though the GC trace of this compound showed a single peak, its ^1H NMR spectrum indicated the presence of a minor product (making ca. 5% of the mixture). The structure of this minor product could not be assigned from the residual signals in the ^1H NMR spectrum, because the signals were not strong enough to see well defined peaks. However, it is possible that this minor isomer is the second stereoisomer of the two possible stereoisomers of dihydroindole **5**. Furthermore, the reaction of **3** with 1,2-cyclotridecadiene (entry 5) has afforded an 83% isolated yield of a decahydrocyclotridec[*b*]indole as the only product.

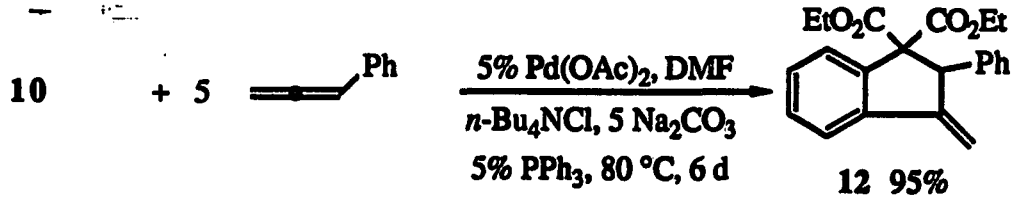
Monosubstituted allenes have also been employed under the above reaction conditions. Utilizing 1,2-undecadiene as the starting allene has afforded an 85% yield of *N*-tosyl-3-methylene-2-*n*-octyl-2,3-dihydroindole (**7**) after reaction with aryl iodide **3** (entry 6). ^1H NMR and ^{13}C NMR spectra indicated the presence of a single product. However, GC-MS analysis showed two peaks in a 6:1 ratio possessing the same molecular mass and similar fragmentation patterns, the only difference being the intensity of the signals in the mass spectra. Since no indication of other products was seen in the ^1H NMR and ^{13}C NMR spectra, it has to be concluded that this compound (**7**) decomposes under our GC conditions.

The synthesis of heterocycles **8** and **9** was also attempted by reacting methoxyallene and phenylallene, respectively, with *N*-tosyl-2-iodoaniline (entries 8-11). Unfortunately, none of the expected products (regio- and stereoisomers) could be extracted from the ^1H NMR spectra of the crude mixtures. These entries (8-11) provided only a very complicated mixture of compounds.

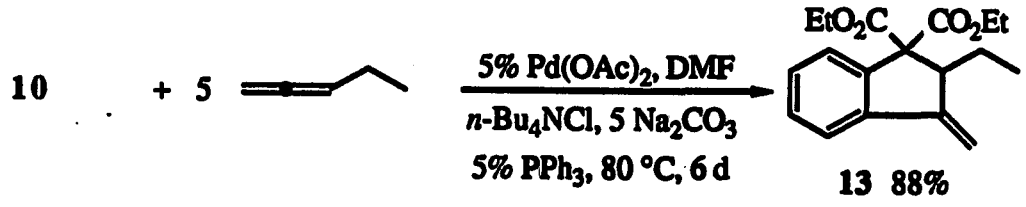
Carbocyclization reactions run under similar reaction conditions as those shown in Table 1 were also found by Fried[20] to be highly regiospecific. Reaction of diethylmalonate **10** with vinylidene cyclohexane (eq 17), phenylallene (eq 18), and 1,2-pentadiene (eq 19) provided 82, 95, and 88% isolated yields of cyclic products **11**, **12**, and **13**, respectively, as the only products. The excellent result obtained on the carbocyclization of phenylallene (eq 18) with malonate **10** contrasts with the poor results obtained in entry 10 of Table 1.



10 **11** 82% (17)



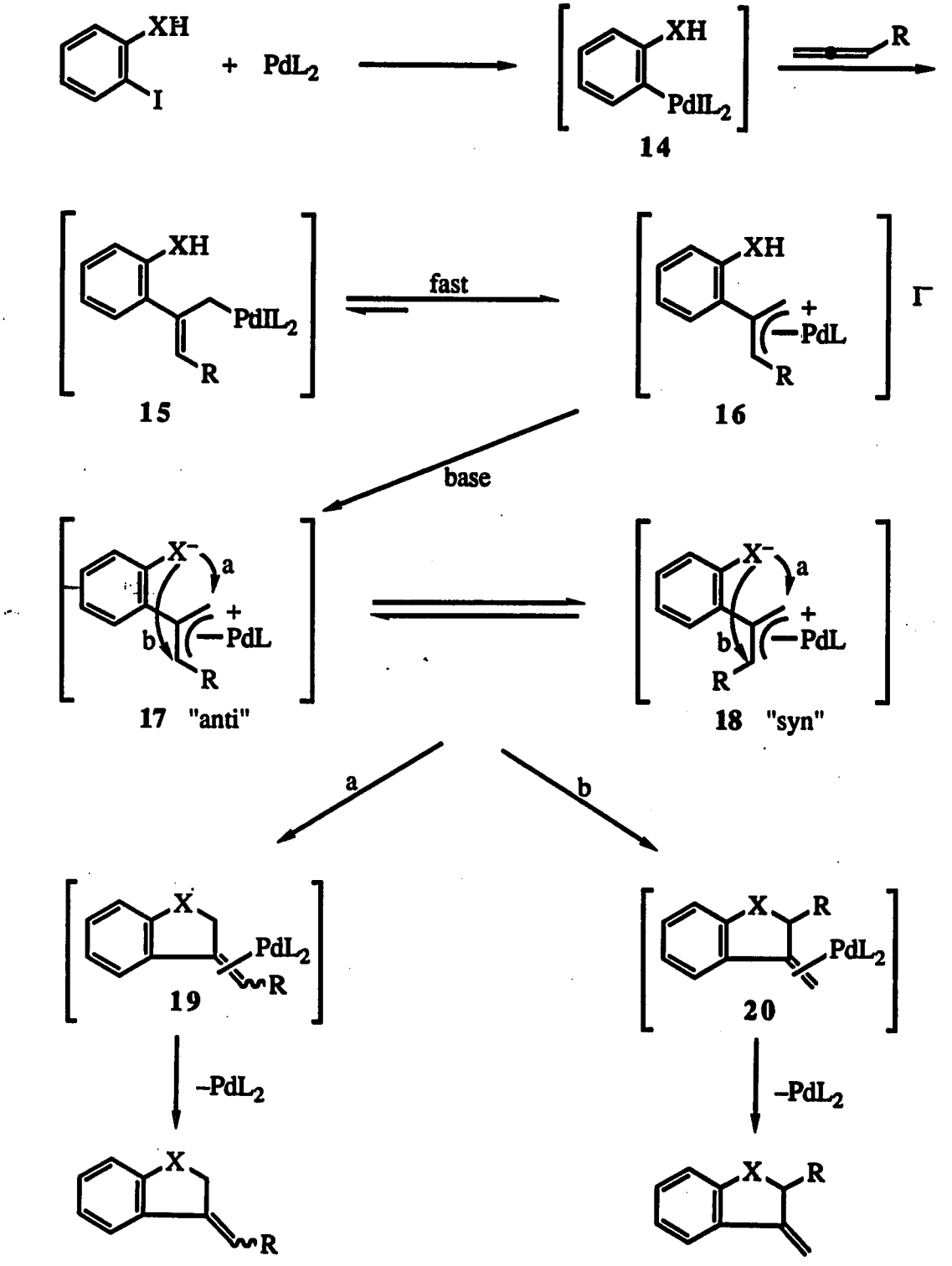
12 95% (18)



13 88% (19)

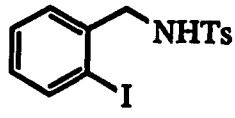
A possible mechanistic explanation for the results of the above heterocyclizations and carbocyclizations is presented in Scheme I. The first step of the mechanism is the oxidative addition of the aryl iodide onto the palladium metal to generate an intermediate arylpalladium species (**14**). This intermediate then adds to the allene (placing the aryl group on the center

Scheme I


XH
I
+ PdL2
XH
PdIIL2
14
R
XH
PdIIL2
R
15
fast
XH
+
PdL
R
16
I⁻
base
X⁻
a
b
+
PdL
R
17 "anti"
X⁻
a
b
+
PdL
R
18 "syn"
a
b
X
PdL2
R
19
X
R
PdL2
20
-PdL2
-PdL2
X
R
X
R

carbon of the allene) generating a σ-allylpalladium intermediate (**15**) which collapses to a π-allylpalladium complex (**16**). Intramolecular nucleophilic attack on the unsymmetrical π-allylpalladium species at the more substituted carbon (path b) provides the observed products. This is in agreement with the need to add PPh_3 to obtain good yields of products, as well as faster reaction times. Being an acceptor ligand,[21] PPh_3 could favor formation of a cationic π-allylpalladium intermediate with the carbocation lying preferentially at the more substituted carbon of the π-allylpalladium species, thus favoring attack of the nucleophile on this carbon for electronic reasons. Also, when PPh_3 is added as a ligand, it increases the bulk around the palladium atom. The steric congestion that develops in the transition state for the formation of the initial product of cyclization (complex **19** or **20**) increases the energy of this transition state favoring nucleophilic attack at the more substituted carbon to form the less congested olefin-palladium π-complex (**20**).[22] In wanting to study similar reactions, but where a six-membered ring is formed during the cyclization process, the reactions of *N*-tosyl-2-iodobenzylamine with several allenes were investigated. As with compound **3**, our first reaction was run using vinylidene cyclohexane as the allene (Table 2, entries 1 and 2), since it could provide us with some answers concerning regioselectivity. Running this reaction in the presence of PPh_3 (entry 1) afforded compounds **20** and **21** in a 1:5 ratio, respectively, in 66% yield. Furthermore, when the reaction was performed in the absence of PPh_3 (entry 2), the sole product was compound **21**, which could be isolated in 84% yield. It is evident that in the absence of PPh_3, the bulky nucleophile prefers to attack at the less substituted carbon of the π-allylpalladium intermediate. However, when PPh_3 is added as a ligand, thus increasing the bulk around the palladium atom, a competition between attack at either end of the π-allylpalladium intermediate is established (see Scheme I, path a and b). The reaction of compound **19** with 1,2-cyclotridecadiene using no PPh_3 afforded two fractions after column chromatography. The first fraction ($R_f = 0.28$) was found to contain a

Table 2. Palladium-catalyzed reactions of *N*-tosyl-2-iodobenzylamine with 1,2-dienes



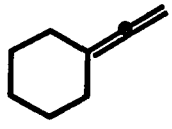
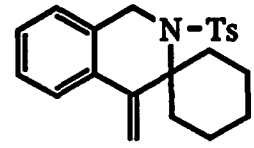
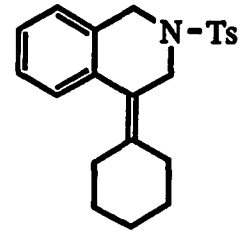
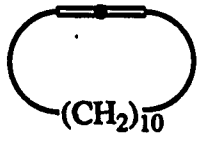
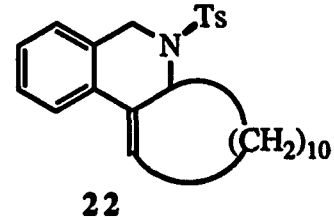
19

+ 5 allene

$\xrightarrow[n\text{-}Bu_4NCl,\ 3.5\ Na_2CO_3]{5\%\ Pd(OAc)_2,\ DMF}$

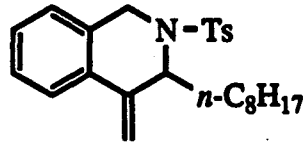
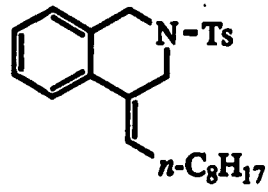
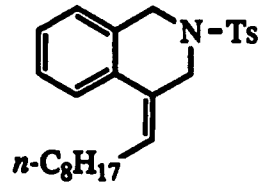
100 °C

20 - 25

Entry	Allene	Day(s)	PPh_3	Product	% Isolated Yield
1		2	+	 **20**	66 (1:5)[a]
				 **21**	
2		2	-	**21**	84
3		1	-	 **22**	51
4		1	+	Mixture	

a ^1H NMR ratio of compounds **20** to **21**.

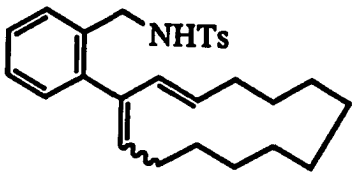
Table 2. (continued)

Entry	Allene	Day(s)	PPh_3	Product	% Isolated Yield
5		1	+	 **23**  **24**  **25**	87 (44:36:20)[b]
6		3	-	**23:24:25** (14:21:65)	77

[b] ^1H NMR ratio of compounds **23** to **24** to **25**.

51% yield of desired product **22** and it was contaminated with an impurity (ca. 3%) as indicated by the ^1H NMR and ^{13}C NMR spectra of the sample. The second fraction (R_f = 0.08, 19%) contained a complicated mixture of products and was not investigated further. On the other hand, the same reaction run in the presence of PPh_3 (entry 4) again afforded two

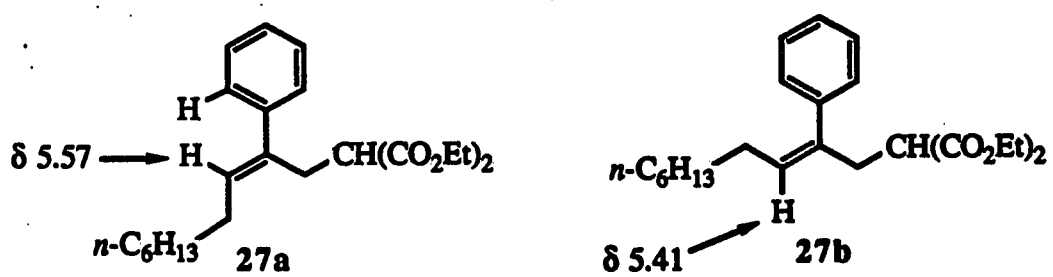
fractions (corresponding to the above fractions) after column chromatography. Contrary to the above results (entry 3), the first fraction (29%) was found to contain a mixture of compounds. Since only the desired product was isolated from the same fraction in entry 3, no effort was spent in identifying the components of this mixture. ^{1}H NMR analysis of the second fraction (41%) in entry 4 suggested a mixture of apparently two compounds in a 2:1 ratio (from ^{1}H NMR), the major component being the diene **26** expected from β-hydride elimination. The structure of the other component was not obvious from the ^{1}H NMR spectrum of the mixture, but it might be a double bond isomer of compound **26**.



26

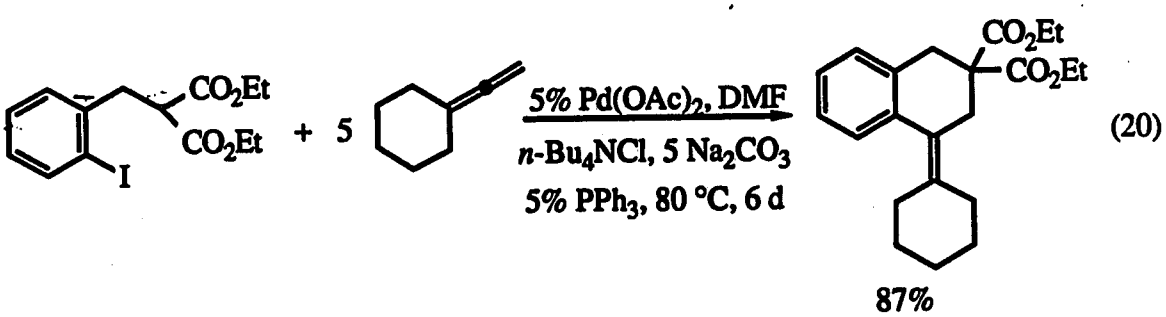
A mixture of stereoisomers and regioisomers was obtained when compound **19** was reacted with 1,2-undecadiene (entries 5 and 6). Running the reaction in the presence of PPh_3 (entry 5) afforded an 87% isolated yield of a 44:36:20 ratio of a mixture of compounds **23**, **24**, and **25**, respectively. In the absence of PPh_3, a mixture of compounds was obtained in 77% isolated yield in a 14:21:65 ratio. In entry 6, however, some starting aryl iodide was still present after 3 days. The ratio reported for these isomeric mixtures were determined by integration of the alkenyl hydrogen signals in the ^{1}H NMR spectrum of the mixture.

NOE experiments conducted by Ahmar et al.[9a] on compounds **27a** and **27b** have confirmed that the alkenyl hydrogen appearing at δ 5.57 in the ^{1}H NMR spectrum of **27** corresponded to that of the *E*-isomer (**27a**), since irradiation of the aromatic hydrogen shown enhanced the signal of this alkenyl hydrogen. The signal appearing at δ 5.41 was then assigned to the structure of the *Z*-isomer. Ahmar et al.[9a] have found this pattern to repeat

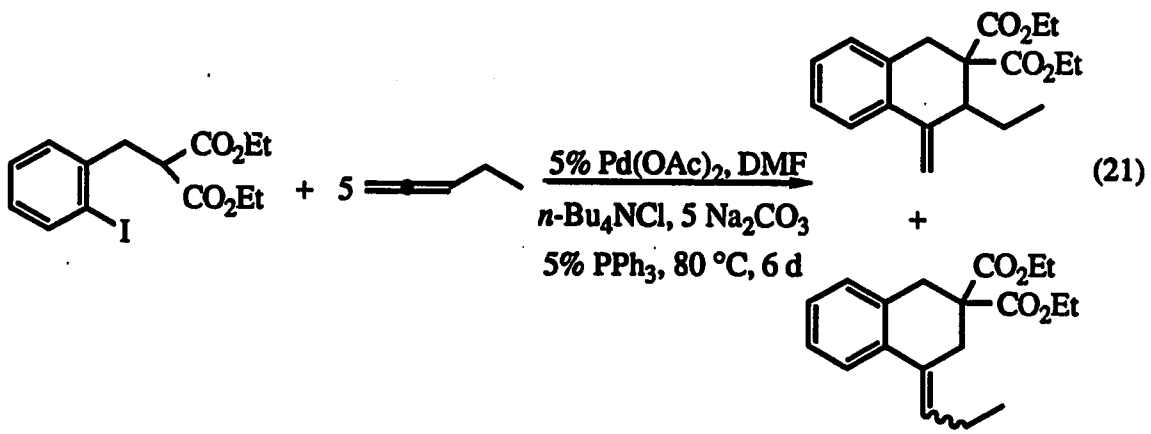


itself for a series of similar trisubstituted alkenes. The stereochemistry thus assigned to compounds **24** and **25** was based on an extrapolation of their results to our system.

Results similar to those found in Table 2 were also found by Fried[20] when carrying out carbocyclizations to generate six-membered rings. These results are shown in eqs 20 and 21.



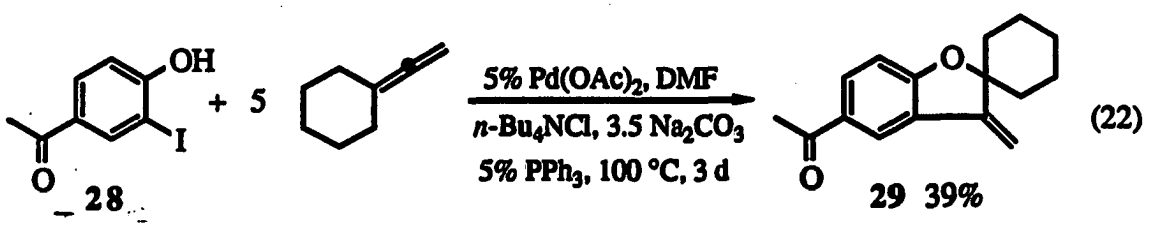
87% (20)



96% (methylene:*Z*:*E* = 10:4:1) (21)

O-Heterocycles

At this point, we wanted to explore the reactions of allenes with oxygen-containing aryl iodides. Initial studies in this area were conducted by reacting 4-hydroxy-3-iodo-acetophenone with vinylidene cyclohexane in the presence of $Pd(OAc)_2$ as the catalyst, Na_2CO_3 as the base, and PPh_3 as co-catalyst (eq 22). Unfortunately, under these conditions, only a low yield of product was obtained, thus other bases and a different catalyst were explored (Table 3).



(22)

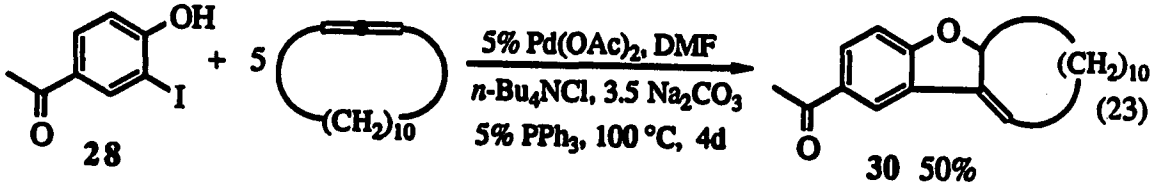
Table 3. Palladium-catalyzed reaction of 4-hydroxy-3-iodoacetophenone with vinylidene cyclohexane

Entry	Pd	Base	Day(s)	% Isolated Yield of 29
1	$Pd(OAc)_2$	Na_2CO_3	2	37
2	$Pd(OAc)_2$	K_2CO_3	2	63
3[a]	$Pd(OAc)_2$	K_2CO_3	1	65
4	$Pd(OAc)_2$	NaOAc	7	26
5[a]	$Pd(OAc)_2$	KOAc	2	54
6	$Pd(dba)_2$	NaOAc	6	42

[a]5% PPh_3 added.

Compound **28** when reacted with vinylidene cyclohexane in the absence of PPh_3 (entry 1) afforded compound **29** in 37% isolated yield. In addition to compound **29**, a 21% yield of **28** was also recovered from the reaction mixture. However, when the reaction was run in the presence or absence of PPh_3, but using K_2CO_3 as the base, good yields of product **29** were isolated (entries 2 and 3). With this base, the presence or absence of PPh_3 did not have any significant effect on the reaction, for about the same yields (63 and 65%, respectively) were obtained from both reactions. Two other bases were examined (NaOAc, KOAc) in addition to using $Pd(dba)_2$ as the catalyst. In these three cases, lower yields of product **29** were obtained than those obtained with K_2CO_3 as the base (see entries 4-6).

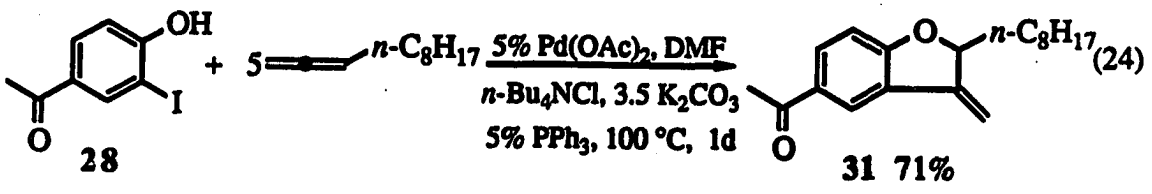
While screening the above system, the reaction of **28** with 1,2-cyclotridecadiene was performed. Running the reaction, as shown in eq 23, provided a 50% isolated yield of a mixture of compounds, compound **30** being the major component of the mixture. Analysis of the ^1H NMR spectrum of this sample showed the presence of at least 3-4 compounds in



addition to compound **30**. However, GC-MS analysis showed the presence of only two significant peaks in a 26:1 ratio with both having a molecular mass of 312. Attempted structural assignment of the second major component, from the ^1H NMR spectrum of the mixture, proved impossible. Furthermore, the ^1H NMR spectrum of the sample, four months after work up, showed that compound **30** had completely decomposed leaving behind only the above second major component and the decomposition products of **30**. Even then, the structure of this isomer was not evident. Furthermore, running the above

reaction (eq 23), in the absence of PPh_3, provided about a 1:1.5 ratio of compound **30** to the above unidentified isomer. In this case also, the ^1H NMR spectrum of this mixture after ca. four months showed none of compound **30**. This decomposition of compound **30** may account for the low yields obtained.

The reaction of **28** with 1,2-undecadiene was also investigated in an attempt to get a better understanding of the regioselectivity and stereoselectivity of these reactions (eq 24). As with the corresponding nitrogen heterocycles, this reaction proceeded regiospecifically to

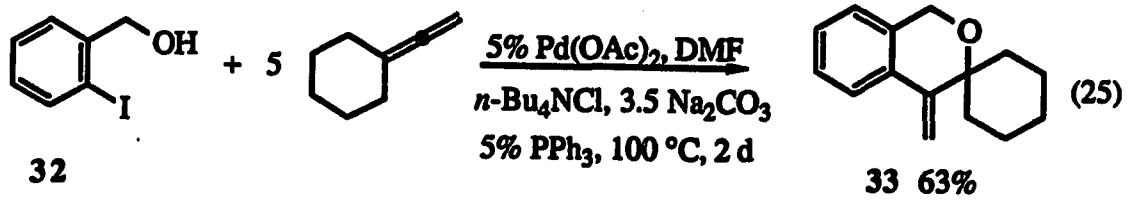


(24)

provide a 71% isolated yield of compound **31**. When the reaction was run as in eq 24, but in the absence of PPh_3, the reaction was found to proceed very sluggishly and after five days 40% of the starting aryl iodide was still present. Because of this, no isolation of the desired product was attempted from this reaction. The same reaction run in the presence of PPh_3, but using Na_2CO_3 as the base, afforded a 44% isolated yield of **31**, which was again obtained regiospecifically. Again, for the above reactions, a better yield is obtained when K_2CO_3 is used as the base.

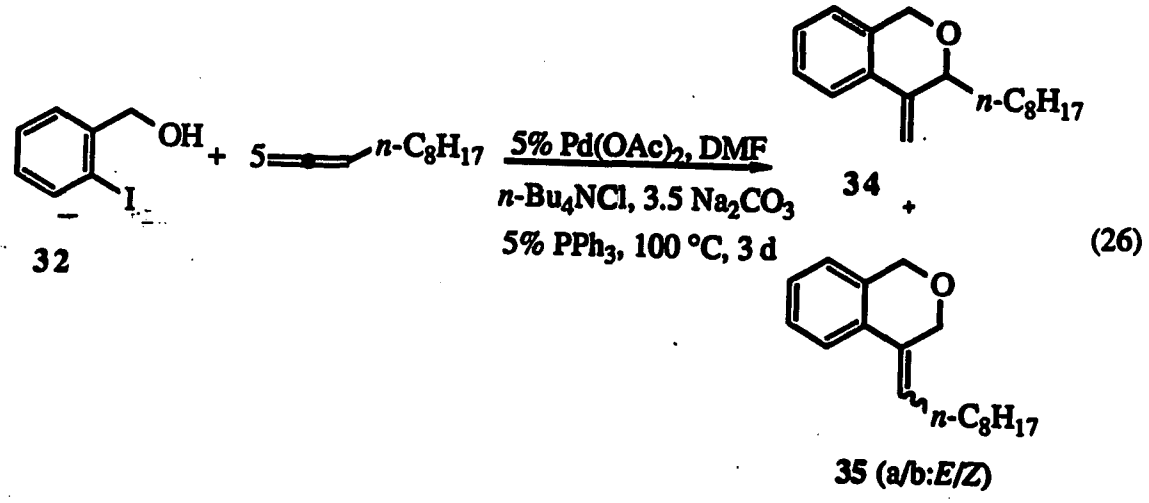
Contrary to the results shown in Table 3, the reaction of 2-iodobenzyl alcohol (**32**) with vinylidene cyclohexane provided, regiospecifically, spirocyclic ether **33** in 63% isolated yield (eq 25). The same reaction, but run in the presence of KOAc, provided compound **33** in the same yield (63%), and again the reaction was regiospecific.

Results similar to those found for the corresponding nitrogen heterocycles were obtained when **32** was reacted with 1,2-undecadiene as shown in eq 26. Purification of the



32 33 63% (25)

crude reaction mixture via flash column chromatography afforded a 68% yield of a mixture of three compounds in an 88:7:5 ^{1}H NMR ratio corresponding to structures **34**, **35a** and **35b**, respectively. The components of this mixture could not be obtained pure by using the above

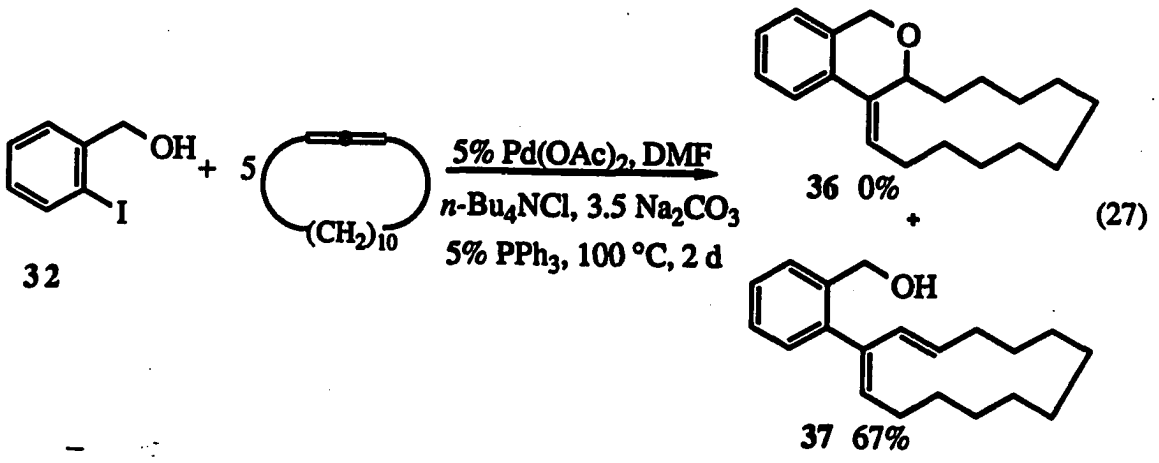


32 35 (a/b:*E*/*Z*) (26)

analytical technique. However, the use of a chromatotron to further purify this mixture provided a 44% yield of pure **34** and a 2% yield of pure **35**. Another fraction containing all three components was also isolated. The fraction containing pure **35** was found to be a 3:1 mixture (from ^{1}H NMR) of **35a** and **35b**, respectively. The purity if these samples (**34** and **35**) was established from their ^{1}H NMR spectra. The assigments of stereochemistry for **35** were based on the work of Ahmar et al.[9a] (*vide supra*).

As the last example in this series, the reaction of 1,2-cyclotridecadiene with **32** (eq 27) provided a 72% yield of a mixture of compounds. This mixture was found to contain

none of the desired product **36**, but did contain the uncyclized diene **37**, which accounted for 93% of the mixture (from GC). GC-MS analysis of this mixture showed that the other three components of the mixture were isomeric with **37**. Unfortunately, the only data available to characterize these isomers were their mass spectra, and unambiguous assignments could not



(27)

be made from them. Nevertheless, these might be double bond isomers where the double bond has migrated within the 13-membered ring. The trans stereochemistry assigned to the disubstituted double bond of **37** was based on the coupling constant (J = 15.6 Hz) obtained for the two trans hydrogens of this double bond.

Similar results were obtained when this reaction was run in the absence of PPh_3. In this case, a 74% yield of a mixture of compounds was again obtained where diene **37** was again the major component. None of the desired product **36** could be detected in the ^1H NMR spectrum of the mixture. GC analysis of the mixture showed this to be a more complicated mixture than that obtained in the presence of PPh_3, and no further efforts were spent on this system.

CONCLUSION

In this third part of this dissertation, the syntheses of a variety of nitrogen- and oxygen-containing heterocycles were accomplished from the reactions of functionalized aryl iodides with allenes in the presence of catalytic amounts of palladium. When five-membered rings were obtained during the cyclization step, the reactions were found to proceed regio-specifically, for both nitrogen- and oxygen-containing aromatic substrates.

In general, the reactions cyclizing to a six-membered ring proved to be regiospecific, and provided the products coming from attack at the less substituted carbon of the π-allyl-palladium intermediates as the major regioisomers. Again, the majority of these reactions provided their best yields when $Pd(OAc)_2$ was used as the catalyst and Na_2CO_3 as the base; however, the co-catalyst PPh_3 was usually required to obtain high yields of product.

EXPERIMENTAL SECTION

Equipment

^1H NMR spectra were recorded on a Nicolet NT-300 (operating at 300 MHz for proton nuclei) spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (Me_4Si) as the internal standard. ^{13}C NMR spectra were recorded on a Nicolet NT-300 (operating at 75 MHz for carbon nuclei) spectrometer using $CDCl_3$ as both the solvent and internal standard. Infrared spectra were recorded on either an IBM IR/98 FT-IR spectrophotometer or on a Beckman-42050 spectrophotometer. High resolution mass spectral data were obtained on an MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed on an HP 5890 gas chromatograph equipped with an HP-1 Megabore column. GC-MS data were obtained on a Finnigan MS-50 mass spectrometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Thin layer analytical chromatography was performed on commercially prepared 60 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm), $KMnO_4$ solution (3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH + 300 mL H_2O), or in an iodine chamber. Flash chromatography [23] was carried out with 230-400 mesh silica gel. Purifications using a Harrison Research Chromatotron Model 7924 were carried out on 1 mm silica gel plates made with silica gel (60 PF-254, EM-Science) as described by Harrison Research, Palo Alto, CA.

Reagents

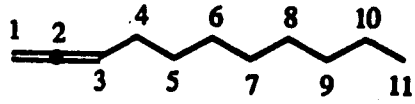
All chemicals were used directly as obtained from commercial sources unless otherwise noted. *N,N*-Dimethylformamide (DMF) (distilled at reduced pressure), diisopropylamine, and 1,4-dioxane were distilled from CaH_2. Et_3N (Eastman Kodak) was distilled from KOH pellets. The anhydrous form of Na_2CO_3 (Fisher) and K_2CO_3 (J. T. Baker), and the fused form of NaOAc (Fisher) and KOAc (Fisher) were utilized for the catalytic reactions. $Pd(OAc)_2$ and $PdCl_2$ were generously provided by Johnson Matthey, Inc. $Pd(dba)_2$ was prepared as reported by Takahashi et al.[24]

N-Tosyl-2-iodoaniline (**3**), *N*-tosyl-2-iodobenzylamine (**19**), and 4-hydroxy-3-iodoacetophenone (**28**) were prepared as reported in part I of this dissertation. 2-Iodobenzyl alcohol (**32**) was obtained from Aldrich. Dr. Richard P. Johnson of this department kindly provided the vinylidene cyclohexane, 4,5-nonadiene, and 1,2-cyclotridecadiene. Phenylallene was kindly provided by Dr. William Leong of our group. Methoxyallene was prepared as reported by Brandsma and Verkruijsse.[25] 1,2-Undecadiene was prepared as reported by Searles et al.[26]

Preparation of the starting allenes

Synthesis of methoxyallene To methyl propargyl ether (5 g, 71 mmol) was added 179 mg (1.6 mmol) of potassium *t*-butoxide, and the reaction mixture was then refluxed for 1.5 h. The reaction mixture was then distilled under reduced pressure and the distillate collected in a flask cooled to -78 °C to give 3.07 g (61%) of pure methoxyallene. IR (neat) 1960 (C=C=C) cm^{-1}; ^1H NMR δ 3.45 (s, 3H, CH_3O), 5.50 (d, 2H, J = 6.0 Hz, $=CH_2$), 6.80 (t, 1H, J = 6.0 Hz, OCH=C).

Synthesis of 1,2-undecadiene



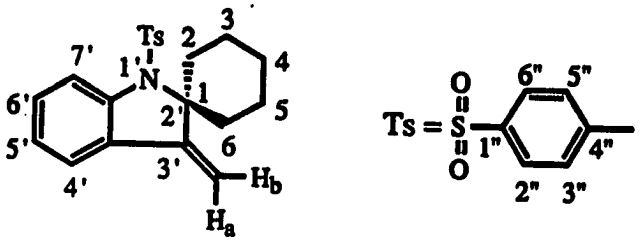
A mixture of 1-decyne (6.95 g, 50 mmol), paraformaldehyde (4.51 g, 150 mmol), diisopropylamine (14.04 mL, 10.12 g, 100 mmol), and anhydrous cuprous iodide (4.76 g, 25 mmol), was heated in dry dioxane (75 mL) under reflux for 11 h. The mixture was then cooled to room temperature and filtered through Celite. After washing the reaction flask and the precipitate with ether, the filtrate was concentrated under reduce pressure forming a gum-like residue, which was treated with 5% HCl and extracted with ether several times. The combined ether layers were dried ($MgSO_4$) and evaporated to give 2.31 g (30%) of the desired allene. IR (neat) 2923, 2850 (CH_2, CH_3), 1942 (C=C=C), 841 (=CH) cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 7.0 Hz, 11-H), 1.27 (bs, 12H, (5-10)-H), 1.99 (m, 2H, 4-H), 4.64 (dt, 2H, J = 6.0, 3.0 Hz, 1-H), 5.09 (tt, 1H, J = 6.0, 6.0 Hz, 3-H).

General procedure for the palladium-catalyzed reactions

To a 1 dram vial are added the palladium reagent (0.025 mmol, 5%), the corresponding iodo compound (0.5 mmol), a base (1.75 mmol), tetra-*n*-butylammonium chloride (0.5 mmol), DMF (1 mL), and the corresponding 1,2-diene (2.5 mmol). The vial is then flushed with nitrogen and capped with a screw-cap containing a teflon liner. After heating at the desired temperature for x number of days, the reaction mixture is diluted with ether (Et_2O) and washed with saturated ammonium chloride, followed by H_2O. The organic layer is dried ($MgSO_4$), a pinch of activated charcoal added, and the reaction mixture filtered, concentrated, and purified via "flash column chromatography"[23] (silica gel, hexanes/EtOAc as eluents).

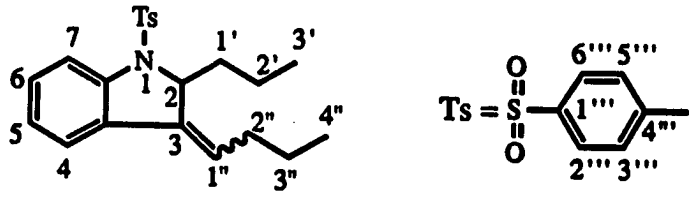
The following compounds were prepared using the above general procedure.

Cyclohexanespiro-2'-(*N*-tosyl-3'-methylene-2',3'-dihydroindole) (4)



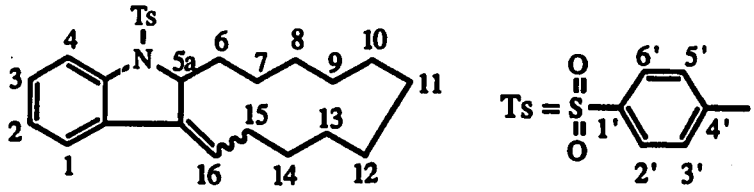
Obtained in 89% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and vinylidene cyclohexane using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 2 days at 100 °C. TLC (7.5:1 hexane/EtOAc), $R_f = 0.41$; IR (neat) 3093, 3058 (C=CH), 2930, 2860 (CH_2, CH_3), 1628 (vinylidene), 1597, 1495, 1477, 1462 (Ar), 1342, 1167 (SO_2) cm^{-1}; ^1H NMR δ 1.66-1.92 (m, 8H, (2-5)-H), 2.36 (s, 3H, 4"-CH_3), 2.75-2.9 (m, 2H, 6-H), 5.35 (s, 1H, H_b), 5.52 (s, 1H, H_a), 6.95 (ddd, 1H, J = 7.5, 7.5, 1.0 Hz, 6'-H), 7.16 (ddd, 1H, J = 7.5, 7.5, 1.0 Hz, 5'-H), 7.21 (dd, 1H, J = 7.5, 1.0 Hz, 4'-H), 7.22 (d, 2H, J = 8.1 Hz, 3"-H and 5"-H), 7.44 (d, 1H, J = 8.4 Hz, 7'-H), 7.77 (d, 2H, J = 8.4 Hz, 2"-H and 6"-H); ^{13}C NMR δ 21.11, 21.42, 23.89, 34.08, 75.79, 103.34, 114.22, 120.29, 122.57, 126.60, 127.45, 129.51, 129.74, 139.06, 142.26, 143.32, 150.70; mass spectrum m/z 353.14546 (calcd for $C_{21}H_{23}NO_2S$, 353.14496). This compound slowly decomposes, and thus it was not sent for elemental analysis.

***N*-Tosyl-3-butylidene-2-*n*-propyl-2,3-dihydroindole (5)**



Obtained as a colorless oil in 78% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 4,5-nonadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 2 days at 100 °C. TLC (20:1 hexane/EtOAc), $R_f = 0.22$; IR (neat) 3060, 3030 (=CH), 2950, 2920, 2860 (CH_2, CH_3), 1650 (C=C), 1592, 1490, 1450 (Ar), 1353, 1168 (SO_2) cm^{-1}; ^1H NMR δ 0.84 (t, 3H, J = 7.5 Hz, 3'-H or 4"-H), 0.89 (t, 3H, J = 7.5 Hz, 3'-H or 4"-H), 1.31-1.45 (m, 4H, 2'-H and 3"-H), 1.60-1.74 (m, 1H, 1'-H), 1.78-1.92 (m, 1H, 1'-H), 2.21-2.27 (m, 2H, 2"-H), 2.31 (s, 3H, 4"'-CH_3), 4.53 (td, 1H, J = 5.4, 1.5 Hz, 2-H), 5.28 (td, 1H, J = 7.4, 1.5 Hz, 1"-H), 7.04 (td, 1H, J = 7.7, 0.9 Hz, 6-H), 7.11 (d, 2H, J = 8.4 Hz, 3"'-H and 5"'-H), 7.22 (td, 1H, J = 7.5, 0.9 Hz, 5-H), 7.38 (d, 1H, J = 7.5 Hz, 4-H), 7.47 (d, 2H, J = 8.4 Hz, 2"'-H and 6"'-H), 7.72 (d, 1H, J = 8.1 Hz, 7-H); ^{13}C NMR δ 13.58, 13.98, 16.80, 21.36, 22.58, 30.02, 40.16, 67.44, 117.61, 124.45, 127.04, 128.53, 129.25, 130.90, 134.60, 143.52, 144.24 (three sp^2 signals missing); mass spectrum m/z 369.17665 (calcd for $C_{22}H_{27}NO_2S$, 369.17626). Anal. Calcd for $C_{22}H_{27}NO_2S$: C, 71.51; H, 7.37. Found: C, 70.02; H, 7.40.

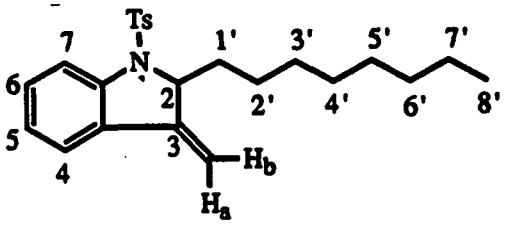
N-Tosyl-6,7,8,9,10,11,12,13,14,15-decahydrocyclotridec[*b*]indole (6)

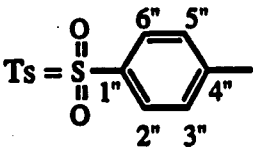


Obtained in 83% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 1,2-cyclotridecadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 2 days at 100 °C. Trituration of the oil obtained after column chromatography with hexanes followed by recrystallization from hexanes afforded square colorless crystals: mp 147-149 °C; TLC (10:1 hexane/EtOAc), $R_f = 0.30$; IR (neat) 2932, 2860 (CH_2), 1663 (C=C), 1597, 1495,

1474 (Ar), 1356, 1184 (SO_2) cm^{-1}; ^1H NMR δ 1.0-1.35 (m, 16H, (7-14)-H), 1.63-1.77 (m, 2H, 6-H), 2.08-2.23 (m, 1H, 15-H), 2.27 (s, 3H, 4'-CH_3), 2.52-2.68 (m, 1H, 15-H), 4.63 (m, 1H, 5a-H), 5.37 (dd, 1H, J = 10.4, 5.1 Hz, 16-H), 6.99 (t, 1H, J = 8.0 Hz, 3-H), 7.10 (d, 2H, J = 8.1 Hz, 3'-H and 5'-H), 7.19 (t, 1H, J = 8.0 Hz, 2-H), 7.51 (d, 1H, J = 8.0 Hz, 1-H), 7.56 (d, 2H, J = 8.1 Hz, 2'-H and 6'-H), 7.76 (d, 1H, J = 8.0 Hz, 4-H); ^{13}C NMR δ 18.46, 21.38, 24.17, 24.86, 25.20, 25.37, 26.39, 27.08, 27.80, 28.34, 36.87, 66.94, 115.94, 123.82, 123.93, 124.78, 126.93, 128.69, 129.39, 130.26, 134.56, 136.0, 143.62, 144.68; mass spectrum m/z 423.22323 (calcd for $C_{26}H_{33}NO_2S$, 423.22321). Anal. Calcd for $C_{26}H_{33}NO_2S$: C, 73.72; H, 7.85. Found: C, 73.72; H, 7.85.

***N*-Tosyl-3-methylene-2-octyl-2,3-dihydroindole (7)**

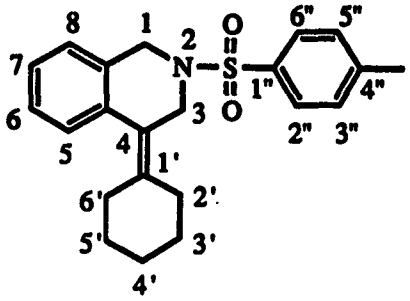




Obtained as an oil in 85% isolated yield from the reaction of *N*-tosyl-2-iodoaniline and 1,2-undecadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 1 day at 100 °C. TLC (10:1 hexane/EtOAc), R_f = 0.35; IR (neat) 2921, 2850 (CH_2), 1651 (C=C), 1600, 1541, 1452 (Ar), 1373, 1182 (SO_2) cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 6.9 Hz, 8'-H), 1.1-1.5 (m, 12H, (2'-7')-H), 1.7-1.85 (m, 1H, 1'-H), 1.95-2.15 (m, 1H, 1'-H), 2.32 (s, 3H, 4"-CH_3), 4.55-4.67 (m, 1H, 2-H), 4.85 (d, 1H, J = 2.0 Hz, H_b), 5.34 (d, 1H, J = 2.0 Hz, H_a), 7.03 (ddd, 1H, J = 7.5, 7.5, 0.6 Hz, 6-H), 7.13 (d, 2H, J = 8.1 Hz, 3"-H and 5"-H), 7.27 (t [embedded], 1H, J = 7.8 Hz, 5-H), 7.29 (d, 1H, J = 7.8 Hz, 4-H), 7.53 (d, 2H, J = 8.1 Hz, 2"-H and 6"-H), 7.74 (d, 1H, J = 7.8 Hz, 7-H); ^{13}C NMR δ 14.12, 21.46, 22.62,

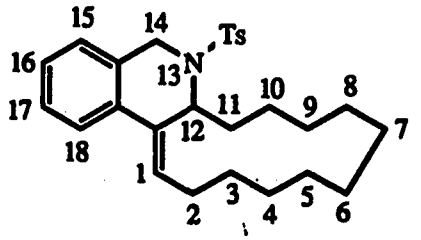
22.81, 29.26, 29.41, 29.59, 31.81, 37.18, 66.65, 102.61, 116.89, 120.71, 124.33, 127.06, 129.44, 129.84, 130.29, 134.36, 143.78, 143.87, 145.07; mass spectrum m/z 397.20690 (calcd for $C_{24}H_{31}NO_2S$, 397.20756). Anal. Calcd for $C_{24}H_{31}NO_2S$: C, 72.51; H, 7.86. Found: C, 70.70; H, 7.80.

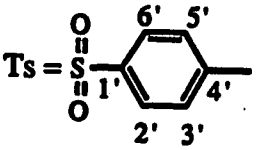
_N_-Tosyl-4-cyclohexylidene-1,2,3,4-tetrahydroisoquinoline (21)



Obtained as a colorless oil in 84% isolated yield from the reaction of *N*-tosyl-2-iodobenzylamine and vinylidene cyclohexane using $Pd(OAc)_2$, Na_2CO_3, DMF, and stirring for 3 days at 100 °C. Trituration with hexanes followed by recrystallization provided colorless needles: mp 113-114 °C; TLC (10:1 hexane/EtOAc), $R_f = 0.22$; IR (neat) 2932, 2856 (CH_2), 1599, 1454 (Ar), 1346, 1159 (SO_2) cm^{-1}; ^1H NMR δ 1.5-1.65 (m, 6H, (3'-5')-H), 2.25-2.33 (m, 2H, 2'-H), 2.33-2.40 (m, 2H, 4'-H), 2.37 (s, 3H, 4"-CH_3), 4.07 (s, 2H, 3-H), 4.31 (s, 2H, 1-H), 7.04-7.16 (m, 4H, Ar from isoquinoline), 7.2 (d, 2H, $J = 8.4$ Hz, 3"-H and 5"-H), 7.61 (d, 2H, $J = 8.4$ Hz, 2"-H and 6"-H); ^{13}C NMR δ 21.41, 26.52, 28.05, 28.34, 31.15, 31.77, 45.98, 47.75, 121.03, 125.99, 126.24, 126.45, 127.29, 128.60, 129.38, 133.88, 134.67, 135.36, 139.60, 143.04. Anal. Calcd for $C_{22}H_{25}NO_2S$: C, 71.94; H, 6.87. Found: C, 72.06; H, 6.96.

Isoquinoline 22

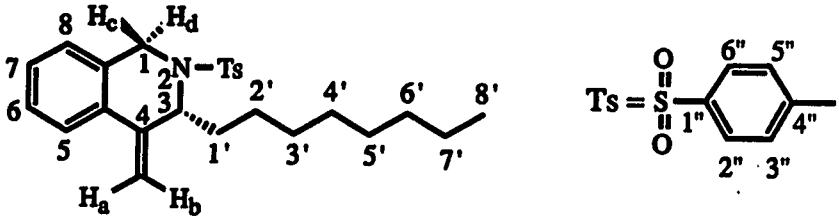




Obtained in 51% isolated yield from the reaction of *N*-tosyl-2-iodobenzylamine and 1,2-cyclotridecadiene using $Pd(OAc)_2$, Na_2CO_3, and DMF, and stirring for 1 day at 100 °C. Recrystallization from hexane/EtOAc afforded amorphous crystals: mp 142-146 °C; TLC (10:1 hexane/EtOAc), $R_f = 0.28$; IR (neat) 2858, 2877 (CH_2), 1625 (C=C), 1382, 1166 (SO_2) cm^{-1}; ^1H NMR δ 1.0-1.5 (m, 20H, CH_2's), 2.36 (s, 3H, $ArCH_3$), 4.43 (dd, 1H, J = 11.4, 4.2 Hz, NCH), 4.44 (d, 1H, J = 16.2 Hz, $ArCH_2$), 4.54 (d, 1H, J = 16.2 Hz, $ArCH_2$), 5.47 (dd, 1H, J = 11.4, 4.5 Hz, C=CH), 7.08-7.13 (m, 1H, Ar), 7.16-7.22 (m, 4H, Ar), 7.38-7.43 (m, 1H, Ar), 7.65 (d, 2H, J = 8.4 Hz, Ar); ^{13}C NMR δ 21.31, 24.26, 24.42, 24.62, 24.84, 25.00, 25.38, 27.39, 27.51, 27.78, 31.64, 45.19, 61.50, 125.94, 126.46, 127.09, 127.18, 127.46, 129.15, 130.35, 131.52, 131.71, 132.12, 136.27, 142.78; mass spectrum m/z 437.23842 (calcd for $C_{27}H_{35}NO_2S$, 437.23886). Anal. Calcd for $C_{27}H_{35}NO_2S$: C, 74.10; H, 8.06. Found: C, 72.27; H, 8.01.

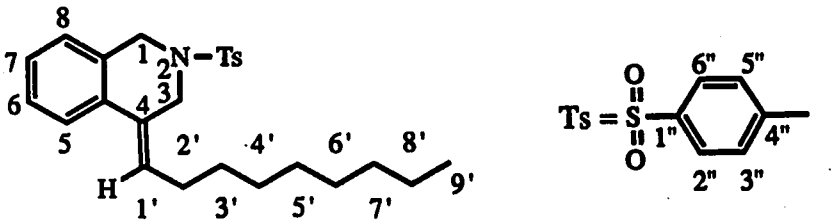
The following compounds were obtained as a light yellow oil in 87% isolated yield as a mixture, in a 44:36:20 GC ratio, in the order shown, from the reaction of *N*-tosyl-2-iodoaniline and 1,2-undecadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 3 days at 100 °C. TLC (7.5:1 hexane/EtOAc), $R_f = 0.24$; IR of the mixture: (neat) 2928, 2856 (CH_2), 1695, 1651 (C=C), 1598, 1489, 1458 (Ar), 1350, 1183 (SO_2) cm^{-1}. The ^1H NMR spectrum of each component of the mixture follows as extracted from the ^1H NMR spectrum of the mixture.

***N*-Tosyl-4-methylene-3-octyl-1,2,3,4-tetrahydroisoquinoline (23)**



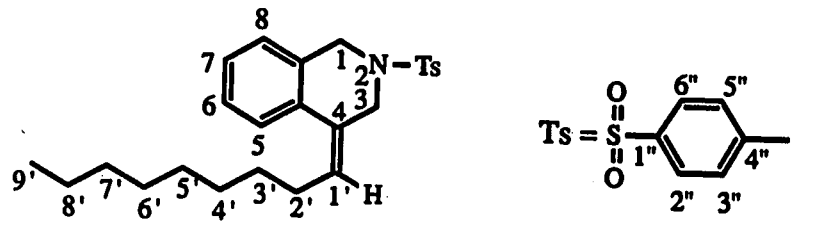
^{1}H NMR δ 0.87 (t, 3H, *J* = 7.0 Hz, 8'-H), 1.0-1.7 (m, 14H, (1'-7')-H), 2.37 (s, 3H, 4"-CH_3), 4.43 (d, 1H, *J* = 18.0 Hz, H_c), 4.6 (m, 1H, 3-H), 4.79 (d, 1H, *J* = 18.0 Hz, H_d), 4.92 (s, 1H, H_b), 5.36 (s, 1H, H_a), 6.95-7.70 (m, 8H, Ar).

***N*-Tosyl-4-[(*Z*)-nonylidene]-1,2,3,4-tetrahydroisoquinoline (24)**



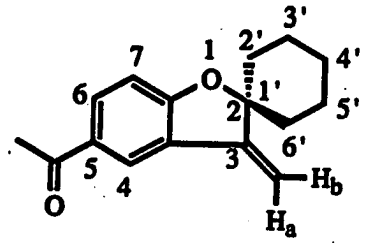
^{1}H NMR δ 0.89 (t, 3H, *J* = 7.0 Hz, 9'-H), 1.0-1.5 (m, 12H, (3'-8')-H), 2.18 (m, 2H, 2'-H), 2.28 (s, 3H, 4"-CH_3), 4.06 (s, 2H, 3-H), 4.33 (s, 2H, 1-H), 6.04 (t, 1H, *J* = 7.0 Hz, 1'-H), 6.95-7.70 (m, 8H, Ar).

***N*-Tosyl-4-[(*E*)-nonylidene]-1,2,3,4-tetrahydroisoquinoline (25)**



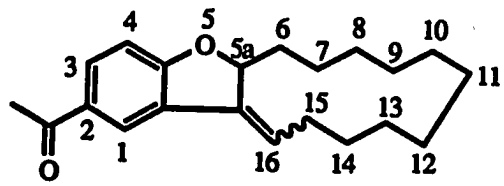
^{1}H NMR δ 0.88 (t, 3H, *J* = 7.0 Hz, 9'-H), 1.1-1.5 (m, 12H, (3'-8')-H), 2.27 (q, 2H, *J* = 7.0 Hz, 2'-H), 2.36 (s, 3H, 4"-CH_3), 3.88 (s, 2H, 3-H), 4.38 (s, 2H, 1-H), 5.59 (t, 1H, *J* = 7.0 Hz, 1'-H), 6.98-7.20 (m, 4H, Ar), 7.22 (d, 2H, *J* = 8.0 Hz, 3'-H and 5'-H), 7.65 (d, 2H, *J* = 8.0 Hz, 2'-H and 6'-H).

5-Acetyl-3-methylenespiro[benzofuran-2(3*H*),1'-cyclohexane] (29)



Obtained as a light yellow oil in 65% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and vinylidene cyclohexane using $Pd(OAc)_2$, K_2CO_3, DMF, and PPh_3, and stirring for 2 days at 100 °C. TLC (10:1 hexane/EtOAc), $R_f = 0.27$; IR (neat) 2934, 2860 (CH_2), 1678 (C=O), 1643 (vinylic), 1609, 1587, 1483, 1448 (Ar), 1279 (C-O-C) cm^{-1}; ^1H NMR δ 1.4-1.9 (m, 10H, (2'-6')-H), 2.57 (s, 3H, CH_3CO), 4.87 (s, 1H, H_b), 5.49 (s, 1H, H_a), 6.87 (d, 1H, J = 8.4 Hz, 7-H), 7.89 (dd, 1H, J = 8.7, 1.8 Hz, 6-H), 8.03 (d, 1H, J = 1.8 Hz, 4-H); ^{13}C NMR δ 21.96, 24.80, 26.27, 37.07, 91.98, 100.88, 110.28, 122.01, 125.91, 130.12, 131.89, 150.93, 164.39, 196.42; mass spectrum m/z 242.13105 (calcd for $C_{16}H_{18}O_2$, 242.13068). This compound slowly decomposes, and thus it was not sent for elemental analysis.

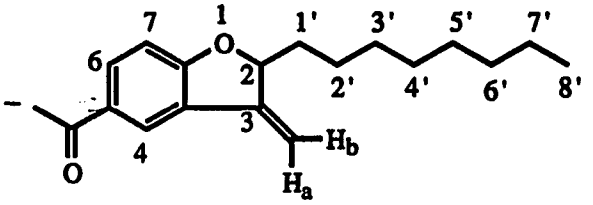
2-Acetyl-6,7,8,9,10,11,12,13,14,15-decahydrocyclotrideca[*b*]benzofuran (30)



Obtained as a light yellow oil as a mixture of compounds in 50% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and 1,2-cyclotridecadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 4 days at 100 °C. Filtration through a plug of

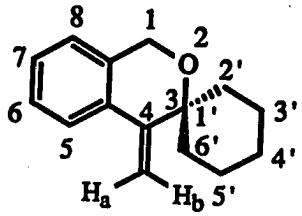
neutral Al_2O_3 and elution with 7.5:1 hexane/EtOAc provided a colorless oil. TLC (10:1 hexane/EtOAc), R_f = 0.30; IR (neat) 2950, 2880 (CH_2), 1680 (C=O), 1660 (C=C), 1600, 1580 (Ar), 1255 (C-O-C) cm^{-1}; ^1H NMR δ 1.1-1.5 (m, 16H, (7-14)-H), 1.72-1.92 (m, 2H, 15-H), 1.95-2.17 (m, 1H, 6-H), 2.2-2.4 (m, 1H, 6-H), 2.54 (s, 3H, 2-CH_3CO), 5.30-5.38 (m, 1H, 5a-H), 5.43 (ddd, 1H, J = 11.0, 5.0, 2.0 Hz, 16-H), 6.80 (d, 1H, J = 8.4 Hz, 4-H), 7.80 (dd, 1H, J = 8.4, 1.5 Hz, 3-H), 8.17 (d, 1H, J = 1.5 Hz, 1-H); mass spectrum m/z 312.20858 (calcd for $C_{12}H_{28}O_2$, 312.20894). This compound slowly decomposes, and thus it was not sent for elemental analysis.

5-Acetyl-3-methylene-2-octyl-2,3-dihydrobenzofuran (31)



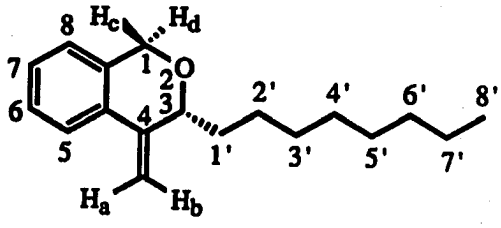
Obtained as a light yellow oil in 71% isolated yield from the reaction of 4-hydroxy-3-iodoacetophenone and 1,2-undecadiene using $Pd(OAc)_2$, K_2CO_3, DMF, and PPh_3, and stirring for 1 day at 100 °C. TLC (10:1 hexane/EtOAc), R_f = 0.29; IR (neat) 2931, 2822 (CH_2, CH_3), 1681 (C=O), 1609 (C=C), 1202 (C-O-C) cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.9 Hz, 8'-H), 1.15-1.60 (m, 12H, (2'-7')-H), 1.65-1.90 (m, 2H, 1'-H), 2.56 (s, 3H, CH_3CO), 4.98 (d, 1H, J = 2.1 Hz, H_b), 5.2-5.3 (m, 1H, 2-H), 5.54 (d, 1H, J = 2.1 Hz, H_a), 6.85 (d, 1H, J = 8.4 Hz, 7-H), 7.87 (dd, 1H, J = 8.4, 1.8 Hz, 6-H), 8.05 (d, 1H, J = 1.5 Hz, 4-H); ^{13}C NMR δ 14.04, 22.58, 24.33, 26.34, 29.17, 29.26, 29.38, 31.77, 36.13, 87.42, 101.56, 110.03, 121.62, 126.44, 130.45, 131.99, 146.01, 166.04, 196.41; mass spectrum m/z 286.19292 (calcd for $C_{19}H_{26}O_2$, 286.19329). This compound slowly decomposes, and thus it was not sent for elemental analysis.

1,4-Dihydro-4-methylenespiro[3*H*-2-benzopyran-3,1'-cyclohexane] (33)



Obtained as a colorless oil in 63% isolated yield from the reaction of 2-iodobenzyl alcohol and vinylidene cyclohexane using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 2 days at 100 °C. TLC (60:1 hexane/EtOAc), $R_f = 0.37$; IR (neat) 3066, 3022 (C=CH), 2934, 2853 (CH_2), 1627 (vinylidene), 1576, 1487, 1445 (Ar), 1088 (C-O-C) cm^{-1}; ^1H NMR δ 1.15-2.0 (m, 10H, (2'-6')-H), 4.73 (s, 2H, 1-H), 5.07 (s, 1H, H_b), 5.54 (s, 1H, H_a), 6.96-7.03 (m, 1H, Ar), 7.14-7.24 (m, 2H, Ar), 7.56-7.64 (m, 1H, Ar); ^{13}C NMR δ 21.80, 25.84, 33.98, 61.73, 74.22, 106.10, 123.99, 124.35, 126.69, 127.30, 131.61, 134.17, 146.98; mass spectrum m/z 214.13569 (calcd for $C_{15}H_{18}O$, 214.13577). This compound slowly decomposes, and thus it was not sent for elemental analysis.

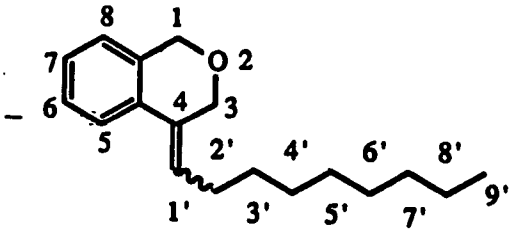
3,4-Dihydro-4-methylene-3-octyl-1*H*-2-benzopyran (34)



Obtained as a colorless oil in 44% isolated yield from the reaction of 2-iodobenzyl alcohol and 1,2-undecadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 3 days at 100 °C. Obtained pure after flash column chromatography on silica gel, followed by purification with a chromatotron (1 mm plate). TLC (35:1 hexane/EtOAc), $R_f = 0.20$; IR (neat) 2926, 2854 (CH_2), 1634 (C=C), 1576, 1487, 1456 (Ar), 1103 (C-O-C) cm^{-1};

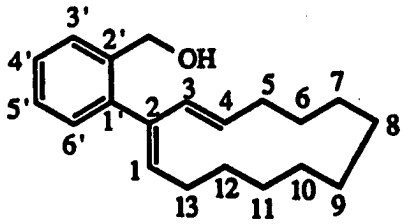
^{1}H NMR δ 0.88 (t, 3H, *J* = 7.0 Hz, 8'-H), 1.2-1.4 (m, 12H, (2'-7')-H), 1.70-1.80 (m, 2H, 1'-H), 4.27 (dd, 1H, *J* = 7.2, 6.6 Hz, 3-H), 4.73 (d, 1H, *J* = 15.0 Hz, H_c), 4.84 (d, 1H, *J* = 15.0 Hz, H_d), 5.02 (d, 1H, *J* = 1.0 Hz, H_b), 5.59 (s, 1H, H_a), 6.96-7.04 (m, 1H, Ar), 7.17-7.15 (m, 2H, Ar), 7.58-7.66 (m, 1H, Ar); ^{13}C NMR δ 14.12, 22.68, 25.59, 29.31, 29.48, 29.62, 31.90, 32.56, 65.70, 77.23, 106.89, 123.87, 124.29, 126.82, 127.64, 131.61, 134.42, 142.01; mass spectrum m/z 258.19798 (calcd for $C_{18}H_{26}O$, 258.19837). Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.23; H, 10.16.

3,4-Dihydro-4-nonylidene-1*H*-2-benzopyran (35)



Obtained as a colorless oil in a 3:1 ^{1}H NMR ratio of *E*:*Z* stereoisomers in 2% isolated yield from the reaction of 2-iodobenzyl alcohol and 1,2-undecadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 3 days at 100 °C. Obtained pure after purification by flash column chromatography on silica gel, followed by purification with a chromatotron (1 mm plate). IR of the mixture: (neat) 2955, 2926, 2854 (CH_2, CH_3), 1730 (C=C), 1485, 1458 (Ar), 1105 (C-O-C) cm^{-1}; ^{1}H NMR of *E*-isomer (35a): δ 0.86 (t, 3H, *J* = 7.0 Hz, 9'-H), 1.15-1.40 (m, 12H, (3'-8')-H), 2.29 (td, 2H, *J* = 7.0, 7.0 Hz, 2'-H), 4.28 (s, 2H, 3-H), 4.85 (s, 2H, 1-H), 5.55 (t, 1H, *J* = 7.0 Hz, 1'-H), 7.0-7.7 (m, 4H, Ar); ^{1}H NMR of *Z*-isomer (35b): δ 0.88 (t, 3H, *J* = 7.0 Hz, 9'-H), 1.15-1.40 (m, 12H, (3'-8')-H), 2.14 (td, 2H, *J* = 7.0, 7.0 Hz, 2'-H), 4.54 (s, 2H, 3-H), 4.73 (s, 2H, 1-H), 6.10 (t, 1H, *J* = 7.0 Hz, 1'-H), 7.0-7.7 (m, 4H, Ar).

(1*E*,3*E*)-2-[2-(Hydroxymethyl)phenyl]-1,3-cyclotridecadiene (36)



Obtained as a colorless oil in 78% isolated yield as a 1.6:28:1:1.1 GC ratio of a mixture of compounds. Prepared from the reaction of 2-iodobenzyl alcohol and 1,2-cyclotridecadiene using $Pd(OAc)_2$, Na_2CO_3, DMF, and PPh_3, and stirring for 2 days at 100 °C. The spectral data of the major component follows: TLC (10:1 hexane/EtOAc), R_f = 0.17; IR (neat) 3370 (OH), 3070, 3040 (C=CH), 2940, 2860 (CH_2), 1490, 1460, 1450 (Ar) cm^{-1}; ^1H NMR δ 1.2-1.5 (m, 14H, (6-12)-H), 1.77 (bs, 1H, OH), 2.05-2.15 (m, 2H, 5-H), 2.25-2.4 (m, 2H, 13-H), 4.58 (s, 2H, CH_2OH), 5.126 (dt, 1H, J = 15.6, 7.8 Hz, 4-H), 5.30 (t, 1H, J = 8.4 Hz, 1-H), 6.69 (d, 1H, J = 15.6 Hz, 3-H), 7.12 (dd, 1H, J = 7.0, 1.7 Hz, 6'-H), 7.25 (ddd, 1H, J = 7.0, 7.0, 1.7 Hz, 4'-H), 7.30 (ddd, 1H, J = 7.0, 7.0, 1.7 Hz, 5'-H), 7.44 (dd, 1H, J = 7.0, 1.7 Hz, 3'-H); mass spectrum m/z 284.21439 (calcd for $C_{20}H_{28}O$, 284.21402).

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GENERAL SUMMARY

In this dissertation, the syntheses of a variety of nitrogen- and oxygen-containing heterocycles were accomplished from the reactions of functionalized aryl iodides with 1,2-, 1,3-, and 1,4-dienes in the presence of catalytic amounts of palladium. In the first part of this dissertation, it was shown that benzofuran, dibenzofuran, dibenzopyran, indole, tetrahydrocarbazole, tetrahydroisoquinoline, and phenanthridine derivatives can be prepared using this methodology. The reactions with the oxygen-containing aryl iodides were found to give higher yields when an electron-withdrawing group was attached to the aromatic ring. With the nitrogen-containing aryl iodides better yields were obtained when an electron-withdrawing group was attached to the nitrogen atom. Best yields were obtained when a tosyl group was attached to this nitrogen atom.

In the second part of this dissertation, it was shown that benzopyran, tetrahydroquinoline, and benzoxocin derivatives can be prepared, while in the third part of this dissertation, the syntheses of a variety of nitrogen- and oxygen-containing heterocycles were accomplished using this methodology. The reactions with the 1,2-dienes were found to proceed regiospecifically for both nitrogen- and oxygen-containing aromatic substrates when five-membered rings were obtained during the cyclization step. In addition, the reactions cyclizing to a six-membered ring proved to be regiospecific, and provided as the major regioisomers the products coming from attack at the less substituted carbon of the π-allylpalladium intermediates.

In general, the reactions were found to be regioselective providing the products coming from attack of the intermediate arylpalladium species on the less substituted carbon of the diene (except for the 1,2-dienes were all aryl additions occurred at the center carbon of the diene moiety). Best results were found to be obtained when Na_2CO_3 was used as the base

and $Pd(OAc)_2$ as the catalyst. However, in some instances, the use of $Pd(dba)_2$ as the catalyst, DMA as the solvent, or the addition of PPh_3 provided even better yields of products.

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