1995

Synthesis of heterocycles via palladium-catalyzed coupling of vinylic halides and functionally-substituted alkenes

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Synthesis of heterocycles via palladium-catalyzed coupling of vinylic halides and functionally-substituted alkenes

by

Hoseok Yang

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1995

DEDICATION

To my family

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	acetyl
br	broad
Bu	butyl
cat	catalyst
dba	dibenzylideneacetone
DIBAH	diisobutylaluminum hydride
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
d	day; doublet (NMR)
dt	doublet of triplets
equiv	equivalent
Et	ethyl
g	gram
GC	gas chromatography
h	hour
HMPA	hexamethylphosphoramide
^{1}H NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectrometry
IR	infrared
m	multiplet
Me	methyl
mL	milliliter
mmol	millimole

mp	melting point
n	normal
PCC	pyridinium chlorochroamte
Ph	phenyl
q	quartet
s	singlet
t	triplet
TBAC	tetra-*n*-butylammonium chloride
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl
Tol	toluene

GENERAL INTRODUCTION

Nucleophilic displacement of π-allylpalladium compounds by nucleophiles has been extremely important and widely used in organic synthesis. However, relatively little work has been reported on the synthesis of heterocycles via the palladium-catalyzed coupling of vinylic halides with functionally-substituted alkenes in which π-allylpalladium intermediates are generated. In this dissertation, our successful development of this palladium-catalyzed coupling process will be discussed.

Dissertation Organization

This dissertation is divided into three papers. The focus of each paper is on the palladium-catalyzed coupling of vinylic halides with functionally-substituted alkenes for the synthesis of heterocycles. Each paper is presented with its own introduction, results and discussion, conclusion, experimental section, and references. The first author on each paper is the major professor, and the second author is the Ph. D. candidate who is primarily responsible for the research.

The first paper will discuss the synthesis of oxygen heterocycles, such as 3,4-dihydroisocoumarins, 3,4-dihydrobenzopyrans, and 2,3-dihydrobenzofurans. The establishment of optimum reaction conditions for the palladium-catalyzed coupling of vinylic halides or triflates with *o*-vinylic benzoic acids and the application of these reaction conditions to the synthesis of a variety of 3,4-dihydroisocoumarins will be discussed. The effect of the types of vinylic halides used on the outcome will also be discussed.

The synthesis of 3,4-dihydrobenzopyrans and 2,3-dihydrobenzofurans via the palladium-catalyzed coupling of vinylic halides with *o*-allylic and vinylic phenols will also be

presented. Improved procedures and their application to the reactions of *o*-allylic and vinylic phenols will be discussed.

The second paper will discuss the synthesis of nitrogen heterocycles, such as pyrrolidines, piperidines, 2,3-dihydroindoles, 2,3-dihydrobenzazepines, and 3,4-dihydroquinolines. First, the palladium-catalyzed coupling of vinylic halides or triflates with olefinic sulfonamides will be discussed as a convenient route to pyrrolidines and piperidines. Secondly, the synthesis of 2,3-dihydroindoles, 2,3-dihydrobenzazepines, and 3,4-dihydroquinolines via the palladium-catalyzed coupling of vinylic halides with *N*-tosyl-*o*-vinylic and allylic anilines will be discussed.

The third paper covers the attempted synthesis of carbocycles via the palladium-catalyzed coupling of vinylic halides with functionally-substituted alkenes.

Following the third paper is a general summary and acknowledgments.

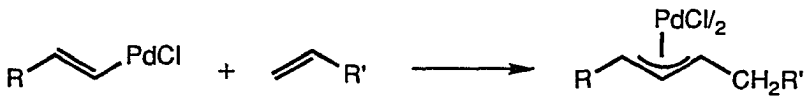
SYNTHESIS OF OXYGEN HETEROCYCLES VIA PALLADIUM-CATALYZED COUPLING OF VINYLIC HALIDES WITH FUNCTIONALLY-SUBSTITUTED ALKENES

Portions of this paper have been published or will be submitted for publication in *Synlett* and *Tetrahedron Letters*

Richard C. Larock and Hoseok Yang

Introduction

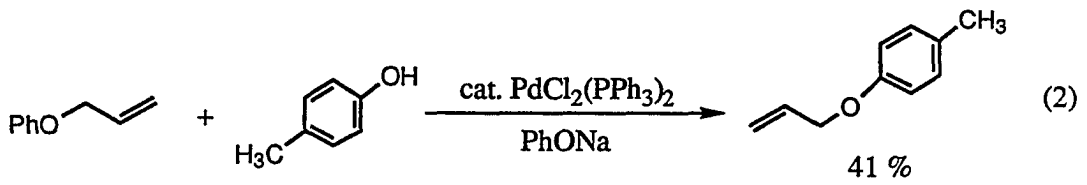
Nucleophilic displacement of π-allylpalladium compounds has proven extremely valuable in organic synthesis. Since Larock first proved in 1976 that vinylic palladium species react with simple alkenes to produce π-allylpalladium compounds via rearrangement (eq. 1),[1] π-allylpalladium compounds have become more useful and important in the synthesis of a variety of heterocycles due to their high reactivity toward nucleophiles.[2]



(1)

The majority of synthetic applications have involved displacement of the palladium moiety by either stabilized carbon nucleophiles or amines. Relatively little work has been reported on displacement by oxygen nucleophiles.

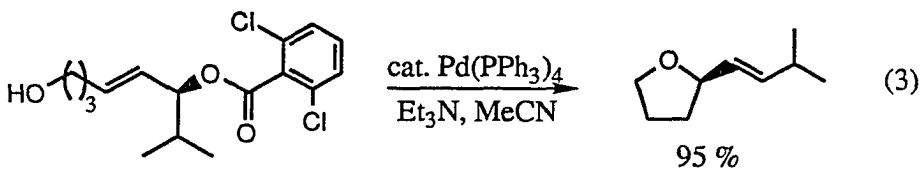
In 1972, Hata reported the use of a variety of oxygen nucleophiles, such as alcohols, phenols, phenoxides, and carboxylic acids, in π-allylpalladium chemistry, but the results were not very satisfactory (eq. 2).[3]



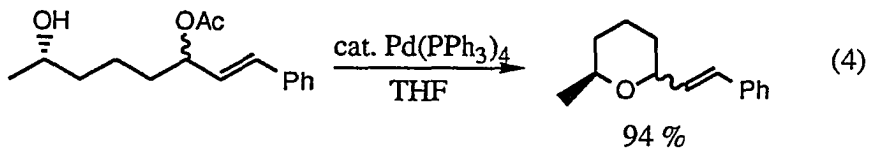
(2)

Bäckvall used acetates as the nucleophile in his study of the stereochemistry of nucleophilic attack on π-allylpalladium complexes.[4]

Stork also used an alcohol as the nucleophile in his synthesis of chiral 2-substituted tetrahydrofurans via palladium-catalyzed cyclization (eq. 3).[5] A similar approach was demonstrated by Keinan in the synthesis of tetrahydropyrans, which led to (Z)-6-methyltetrahydropyranylacetic acid, a naturally occuring heterocycle (eq. 4).[6]

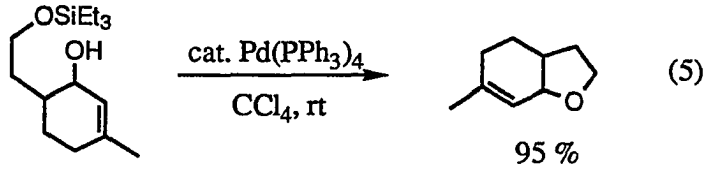


(3)



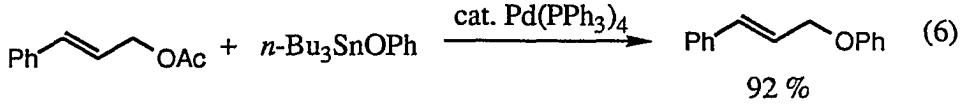
(4)

Godleski introduced the use of alkoxides which were generated *in situ* from the reaction of a triethylsilyl ether, a phosphine, and CCl4 in the palladium-catalyzed synthesis of oxygen heterocycles (eq. 5).[7]



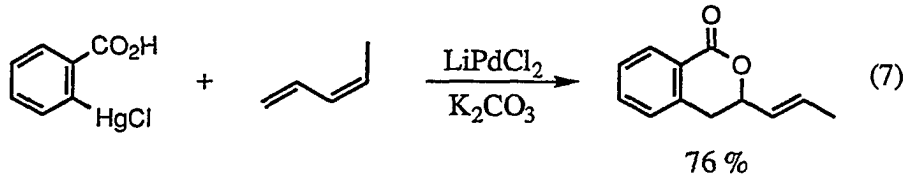
(5)

Tin alkoxides are also highly reactive nucleophiles toward π-allylpalladium intermediates. The regioselectivity of nucleophilic attack by tin alkoxides was found to follow the characteristic behavior of stabilized carbanions and amines, namely, preferred attack at the less sterically hindered position and/or at the position remote from an electron-withdrawing substituent (eq. 6).[8]



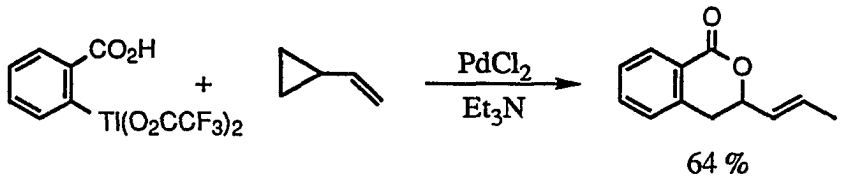
(6)

In 1984, Larock reported a one-pot approach to a wide variety of heterocycles which began with dienes or vinylic cyclopropanes and functionally-substituted organomercurials and involves formation of a π-allylpalladium species and subsequent intramolecular π-allylpalladium displacement by oxygen nucleophiles (eq. 7).[9]



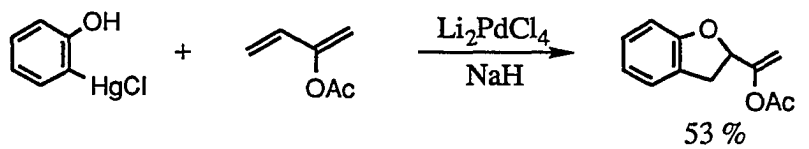
(7)

Similarly, isocoumarins and 3,4-dihydroisocoumarins were prepared from readily available benzoic acids and a variety of simple olefins and dienes by a process involving thallation and subsequent palladium-promoted olefination of benzoic acids (eq. 8).[10]



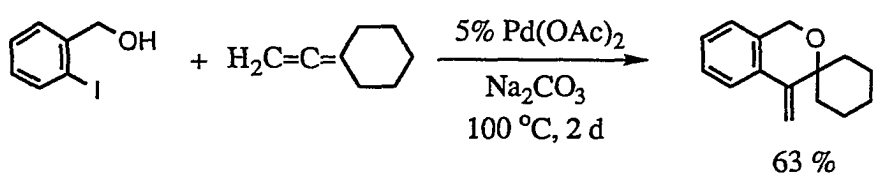
(8)

Also, it was reported that the palladium-assisted heteroannulation of dienes bearing acetoxy substitution by organomercurials proceeds smoothly, giving 2,3-dihydrobenzofurans and 3,4-dihydroisocoumarins in good yields with interesting regiochemistry (eq. 9).[11]



(9)

However, the disadvantage of having to prepare toxic aryl organometallics and in some cases employ stoichiometric amounts of expensive palladium salts brought about the search for improvements to this approach. Later, Larock and coworkers were able to report a convenient palladium-catalyzed heteroannulation of 1,2-[12] and 1,3-dienes,[13] as well as vinylic cycloalkanes,[14] by functionally-substituted aryl halides. This annulation chemistry has proven to be very useful in preparing a variety of heterocycles (eqs. 10 - 12).



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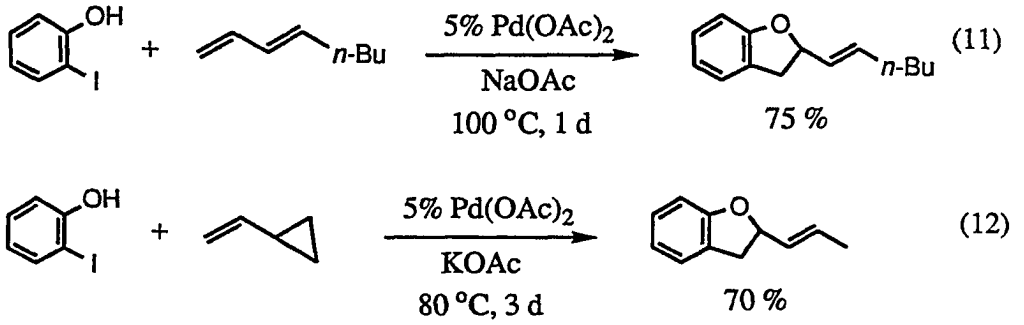
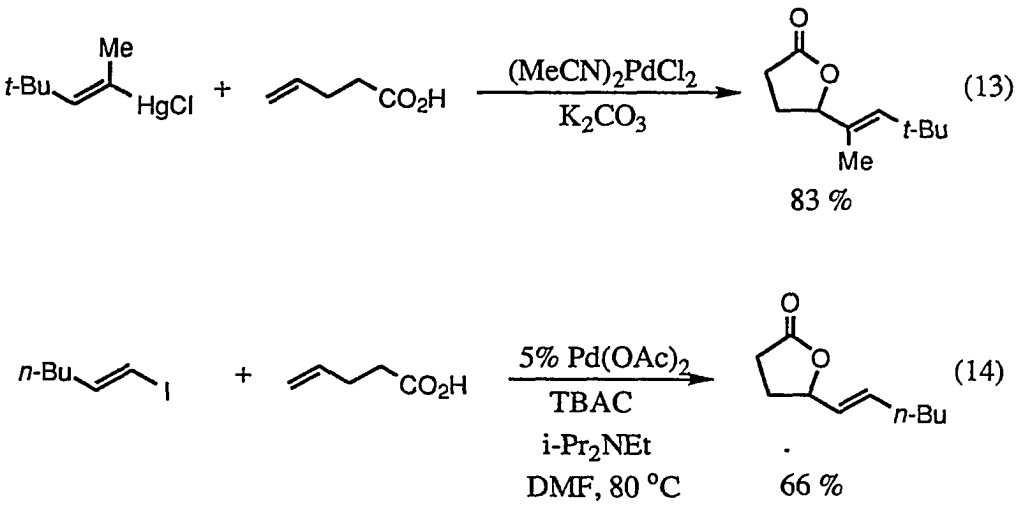


Oxygen nucleophiles were also used successfully in the synthesis of unsaturated lactones by the palladium-catalyzed cross-coupling of vinylic mercurials, halides or triflates and unsaturated carboxylic acids (eqs. 13 and 14).[15, 16]



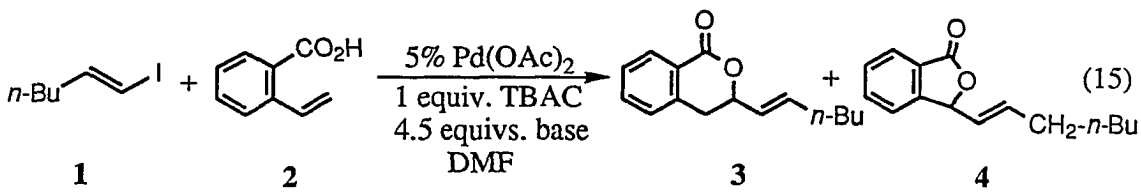
The previous literature discussion and survey indicates that little work has been reported on oxygen nucleophiles in π-allylpalladium chemistry; however, the palladium-catalyzed annulation of dienes by aryl halides has been shown to be a major route to oxygen heterocycles. In contrast, recent work on the synthesis of lactones via the palladium-catalyzed coupling of vinylic halides or triflates and alkenoic acids[15] suggests that a practical route to

oxygen heterocycles is possible. In this part of the dissertation, a successful approach to a variety of oxygen heterocycles, such as 3,4-dihydroisocoumarins, 2,3-dihydrobenzofurans, and 3,4-dihydrobenzopyrans, will be discussed.

Results and discussion

Synthesis of 3,4-dihydroisocoumarins

As the first step toward the synthesis of oxygen heterocycles via palladium-catalyzed coupling of vinylic halides with functionally-substituted alkenes, a series of reactions were performed using (*E*)-1-iodo-1-hexene (**1**) and *o*-vinylbenzoic acid (**2**) as the model system to establish optimal reaction conditions (eq. 15).



Carbonate bases, which had proven useful in the cyclization of olefinic carboxylic acids,[15] were examined first as the base for the coupling of *o*-vinylbenzoic acid and (*E*)-1-iodo-1-hexene (Table 1). In these reactions, (*E*)-1-iodo-1-hexene usually disappeared after 1 day according to TLC analysis. However, the results were not satisfactory. Regardless of the cation used, carbonate bases didn't provide the products in measurable amounts (entries 1 - 7). No improvements were seen by employing triphenylphosphine as a ligand (entries 2, 5, and 7) or LiCl as the chloride source (entry 3). The palladium-catalyzed coupling of the starting materials was also carried out using NaOAc and $NaHCO_3$ at 100 °C (entries 8 and 9). Interestingly, these bases produced not only the expected 3,4-dihydroisocoumarin, but also the

Table 1. Effect of the Base, the Ligand and the Chloride Source on the Reaction of (*E*)-1-Iodo-1-hexene (**1**) with *o*-Vinylbenzoic Acid (**2**).[a]

entry	base (4.5 equivs.)	chloride source (1.0 equiv.)	PPh_3 (5 mol %)	% isolated yield **3** and **4**	**3/4** ratio
1[b]	Na_2CO_3	TBAC	-	trace	-
2	Na_2CO_3	TBAC	+	trace	-
3	Na_2CO_3	LiCl	-	trace	-
4	K_2CO_3	TBAC	-	trace	-
5	K_2CO_3	TBAC	+	trace	-
6	Cs_2CO_3	TBAC	-	trace	-
7	Cs_2CO_3	TBAC	+	trace	-
8	NaOAc	TBAC	-	20	86:14
9	$NaHCO_3$	TBAC	-	37	86:14

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of *o*-vinylbenzoic acid, and 1 mL of DMF for 48 hours at 100 °C. [b]The reaction was run for 24 hours.

unexpected phthalide (**4**) in an 86:14 ratio in 20 % yield for NaOAc and 37 % yield for $NaHCO_3$.

Using $NaHCO_3$ as the base, the reaction temperature, the reaction time, the amount of palladium and the solvent were examined (Table 2). With regard to the reaction temperature, this coupling reaction was found to proceed well, even at room temperature, producing the products in 64 % yield after 1 day in a 78:22 ratio with the 3,4-dihydroisocoumarin being favored (entry 2). A decrease in yield was observed for reactions at higher temperatures,

Table 2. Effect of the Reaction Time, the Reaction Temperature, the Solvent, and the Amount of $Pd(OAc)_2$ on the Reaction of (*E*)-1-Iodo-1-hexene (**1**) with *o*-Vinylbenzoic Acid (**2**).[a]

entry	$Pd(OAc)_2$ (mol %)	solvent (1 mL)	time (h)	temp. (°C)	% isolated yield **3** and **4**	**3**/**4** ratio
1	5	DMF	12	25	45	78:22
2	5	DMF	24	25	64	78:22
3	5	DMF	48	25	54	77:23
4	5	DMF	6	50	52	74:26
5	5	DMF	2	80	46	73:27
6	10	DMF	24	25	66	77:23
7	10	DMF	5	50	61	76:24
8	10	DMSO	24	25	<10	-
9	10	CH_3CN	24	25	49	76:24
10	10	THF	24	25	63	75:25

[a]All reactions were run using 1 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of *o*-vinylbenzoic acid, 4.5 equivs. of $NaHCO_3$, and 1.0 equiv. of TBAC.

but the ratio of isomers didn't change significantly (entries 4 and 5). A decrease in yield at the higher temperatures is probably due to either the reaction of palladium(0) with the product, in which the allylic moiety of the product undergoes oxidative addition in the presence of the palladium catalyst or saponification of the product by the base. As far as the reaction time is concerned, a reaction time of 1 day was the best (entries 1- 3). The use of 10 mol % palladium

acetate didn't improve the yield (entry 6). Of the solvents examined, DMF gave the products in the highest yield (compare entries 6 and 8 - 10).

After establishing these preliminary reaction conditions, the effect of the base on the model reaction was investigated again (Table 3).

Table 3. Effect of the Base on the Reaction of (*E*)-1-Iodo-1-hexene (**1**) with *o*-Vinylbenzoic Acid (**2**).[a]

entry	base (4.5 equivs.)	time (h)	temp. (°C)	% isolated yield **3** and **4**	**3**/**4** ratio
1	Li_2CO_3	24	25	71	80:20
2	Na_2CO_3	48	25	17	71:29
3	$NaHCO_3$	24	25	64	78:22
4	$KHCO_3$	24	25	24	77:23
5	NaOAc	24	25	28	73:27
6	KOAc	24	25	trace	-
7	TlOAc	24	25	<10	-
8	Et_3N	24	25	trace	-
9	Et_3N	12	50	trace	-
10	*i*-Pr_2NEt	5	50	24	71:29

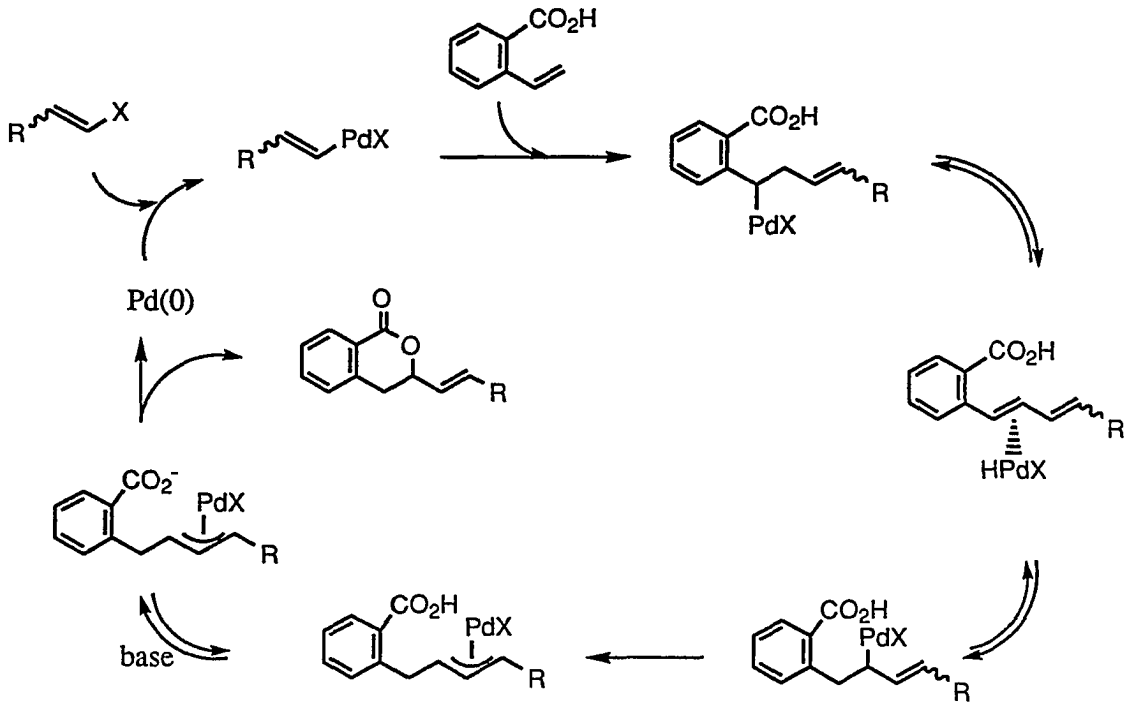
[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of *o*-vinylbenzoic acid, 1.0 equiv. of TBAC and 1 mL of DMF.

The reaction using Li_2CO_3 gave rise to products in 71 % yield in an 80:20 ratio of **3** and **4** (entry 1). In contrast, a 17 % yield of a mixture of both isomers was obtained in the analogous reaction using Na_2CO_3 (entry 2). $NaHCO_3$ also proved effective in this model system, producing a mixture of products in 64 % yield. However, other bases, such as acetates and organic amines, were not effective in this palladium-catalyzed coupling under the established reaction conditions (entries 5 - 10). From these results, the following reaction conditions were established as optimal for the palladium-catalyzed coupling of vinylic halides with *o*-vinylbenzoic acid: 5 mol % $Pd(OAc)_2$, 1.0 equiv. of the vinylic halide, 2.0 equivs. of *o*-vinylbenzoic acid, 1.1 equivs. of *n*-Bu_4NCl (TBAC), 4.5 equivs. of Li_2CO_3, and 1 mL of DMF at 25 °C for an appropriate time interval.

A mechanism which explains the formation of the 3,4-dihydroisocoumarin is presented in Scheme 1. The first step of the reaction is oxidative addition of the vinylic halide to palladium(0) to generate a vinylic palladium species. This intermediate then adds across the double bond of *o*-vinylbenzoic acid to generate a σ-homoallylpalladium intermediate. β-Hydride elimination and subsequent readdition leads to a new σ-allylpalladium intermediate, which collapses to a π-allylpalladium intermediate. Nucleophilic displacement of the palladium in the π-allylpalladium intermediate gives a 3,4-dihydroisocoumarin and regenerates palladium(0). The mechanism for formation of the phthalide product will be discussed later.

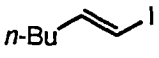
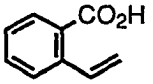
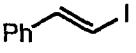
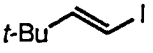
Under the optimized reaction conditions, various vinylic halides were reacted with several *o*-vinylic benzoic acids to determine the scope and limitations of this palladium-catalyzed process (Table 4). (*E*)-1-Iodo-1-hexene reacted with *o*-vinylbenzoic acid to produce a 71 % yield of a mixture of two isomers **3** and **4** in an 80:20 ratio (entry 1). The reactions of (*E*)-β-iodostyrene and (*E*)-1-iodo-3,3-dimethyl-1-butene with *o*-vinylbenzoic acid also

Scheme 1



proceeded well, giving mixtures of both isomers in high yields, but increased formation of the phthalide was observed. Ratios of of isocoumarin to phthalide of 55:45 for (*E*)-β-iodostyrene and 67:33 for (*E*)-1-iodo-3,3-dimethyl-1-butene were observed (entries 3 and 5). Similar ratios of isomers, but lower yields were obtained when the reactions of the same terminal vinylic iodides were run using Na_2CO_3, confirming that Li_2CO_3 is the better base (entries 2, 4 and 6). While phthalide side-products were observed in modest to fair amounts using (*E*)-1-iodo-1-alkenes, they were virtually eliminated when the corresponding (*Z*)-isomers were employed. As indicated in entry 7, the reaction of (*Z*)-1-iodo-1-hexene proceeded smoothly,

Table 4. Palladium-catalyzed Coupling of Vinylic Halides or Triflates with 2-Alkenylbenzoic Acids.[a]

entry	vinylic halide or triflate	benzoic acid	time (h)	temp. (°C)
1			24	25
2			24	25
3			10	25
4			12	25
5			9	25

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of the vinylic halide (0.25 mmol), 2.0 equivs. of the 2-alkenylbenzoic acid, 1.0 equiv. of TBAC, and 4.5 equivs. of Li_2CO_3 in DMF at 25 °C unless otherwise indicated.

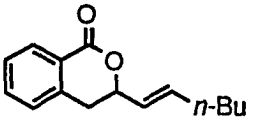
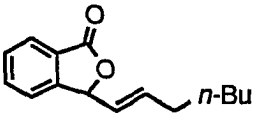
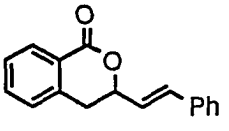
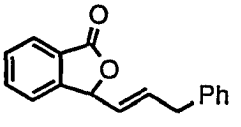
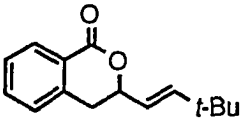
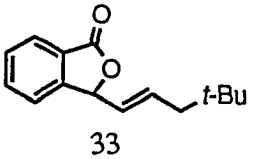
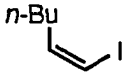
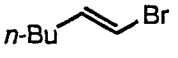
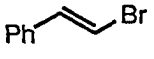
base	products (ratio)	% isolated yield
Li_2CO_3	 80 :  20	71
Na_2CO_3	78 : 22	64
Li_2CO_3	 55 :  45	94
Na_2CO_3	55 : 45	74
Li_2CO_3	 67 :  33	94

Table 4. (Continued)

entry	vinylic halide or triflate	benzoic acid	time (h)	temp. (°C)
6			13	25
7			12	25
8			19	25
9[b]			20	70
10			24	25

[b]The reaction was run for 4 hours at 25 °C before the temperature was raised to 70 °C.

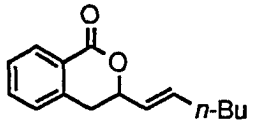
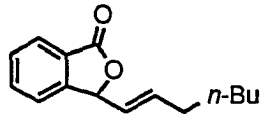
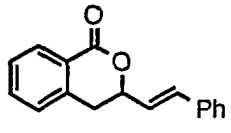
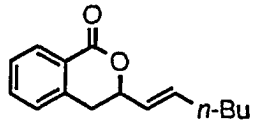
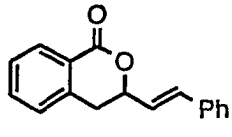
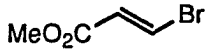
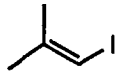
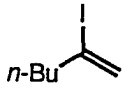
base	products (ratio)	% isolated yield
Na_2CO_3	67 : 33	68
Li_2CO_3	 94 :  6	87
Li_2CO_3		88
Li_2CO_3		34
Li_2CO_3		53

Table 4. (Continued)

entry	vinylic halide or triflate	benzoic acid	time (h)	temp. (°C)
11			24	25
12[c]			24	80
13			15	25
14			15	25
15			15	25

[c]The reaction was run in THF.

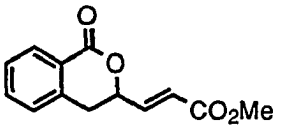
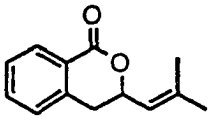
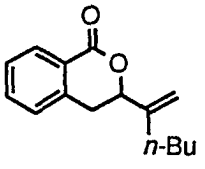
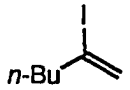
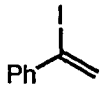
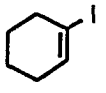
base	products (ratio)	% isolated yield
Li_2CO_3		33
Li_2CO_3		59
Li_2CO_3		75
Na_2CO_3		trace
Li_2CO_3		70

Table 4. (Continued)

entry	vinylic halide or triflate	benzoic acid	time (h)	temp. (°C)
16			15	25
17			12	25
18			14	50
19			12	25
20			19	25

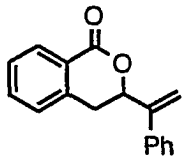
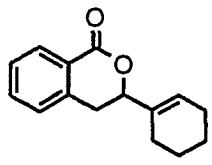
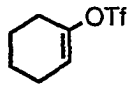
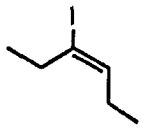
base	products (ratio)	% isolated yield
Na_2CO_3		12
Li_2CO_3		38
Li_2CO_3		54
Na_2CO_3		<5
Li_2CO_3		53

Table 4. (Continued)

entry	vinylic halide or triflate	benzoic acid	time (h)	temp. (°C)
21			10	50
22[d]			10	50
23[d]			10	50
24			14	25
25[e]			16	75

[d]Reactions were run for 12 hours at 25 °C before the temperature was raised to 50 °C.
[e]A 11:1 mixture of stereoisomers was obtained.

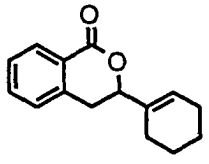
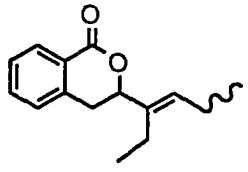
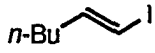
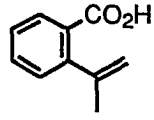
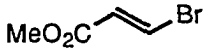
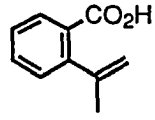
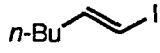
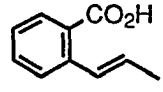
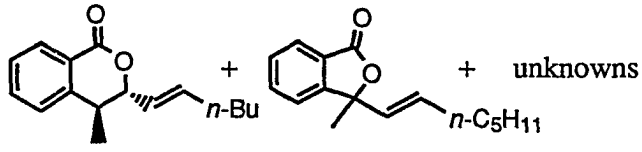
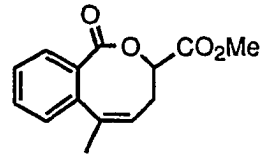
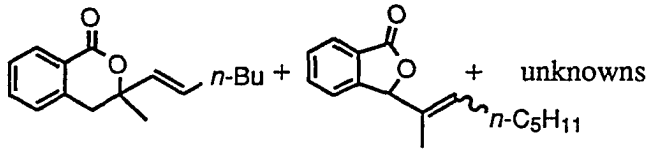
base	products (ratio)	% isolated yield
Li_2CO_3		78
Li_2CO_3		82
Na_2CO_3		12
Li_2CO_3		54
Li_2CO_3		63

Table 4. (Continued)

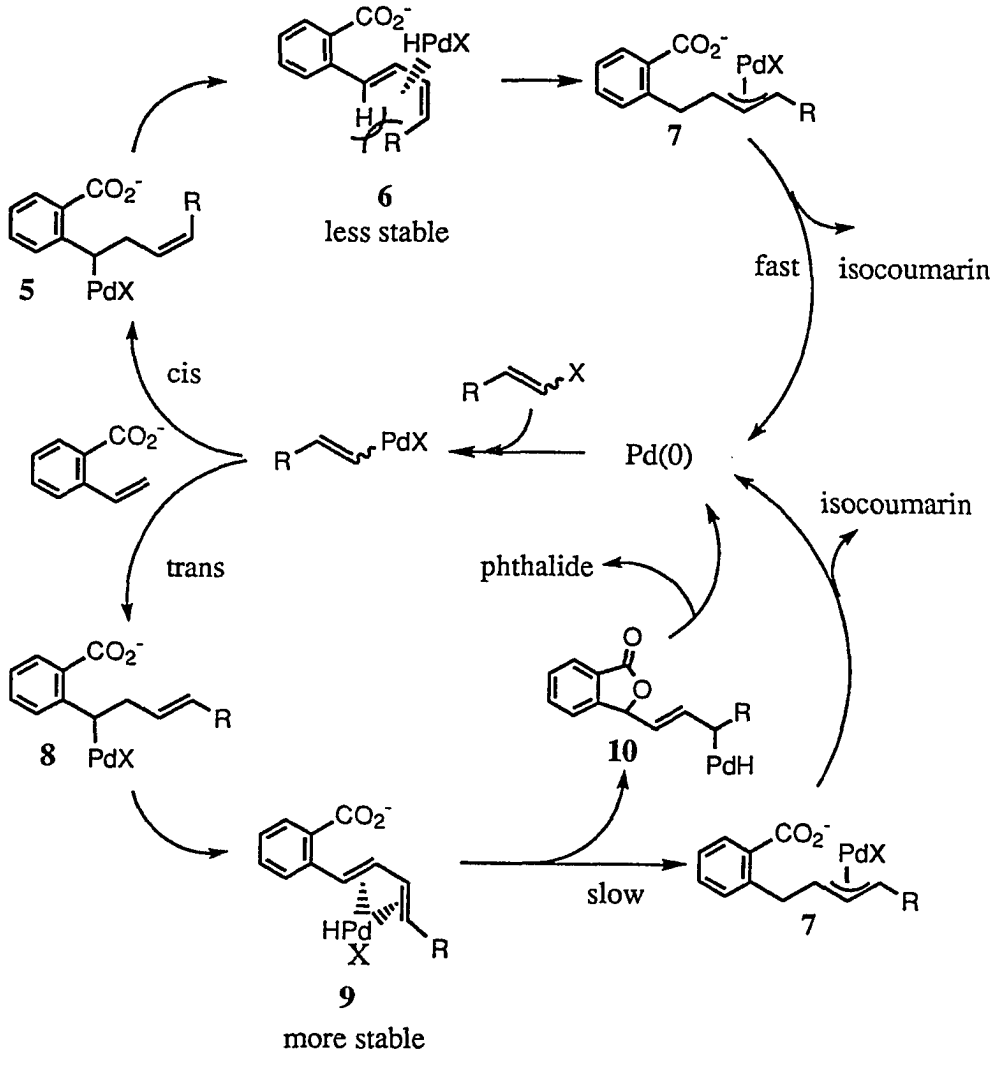
entry	vinylic halide or triflate	benzoic acid	time (h)	temp. (°C)
26			48	80
27			36	100
28[f]			18	60

[f]The reaction was run for 12 hours at 25 °C before the temperature was raised to 60 °C.

base	products (ratio)	% isolated yield
Li_2CO_3	 57 : 29 : 14	68
Li_2CO_3		63
Li_2CO_3	 9 : 77 : 14	14

producing a 94:6 mixture of isomers in 87 % yield. More surprisingly, the use of (Z)-β-iodostyrene, whose (*E*)-isomer gave virtually equal amounts of both isomers, resulted in the exclusive formation of the 3,4-dihydroisocoumarin product in 88 % yield. This phenomenon is probably due to steric hindrance as shown in Scheme 2.

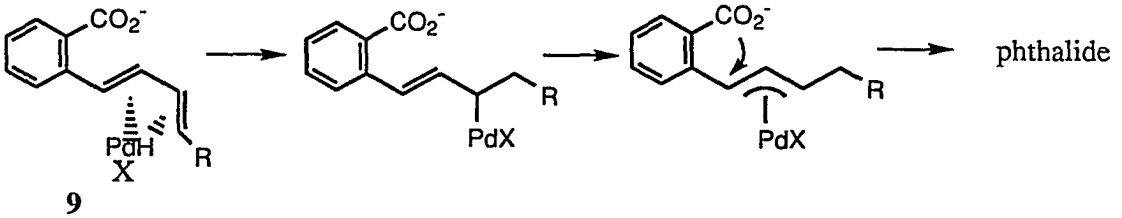
Scheme 2



σ-Homoallylpalladium intermediates **5** and **8** generated from the (Z)- and (*E*)-vinylic iodides respectively undergo β-hydride elimination to produce π-complexes **6** and **9**. Rotation of the vinylic group to form complex **6** with both double bonds coordinating the palladium hydride would seem to be very difficult due to steric hindrance. Consequently, intermediate **5** presumably collapses to a stable π-allylpalladium intermediate **7** rapidly, which eventually leads to the formation of the 3,4-dihydroisocoumarin after nucleophilic displacement. By comparison, complex **9** could be stabilized by coordination of the palladium by both double bonds. As a result of this stabilization, this complex can react further by two mechanistic pathways, nucleophilic displacement to give intermediate **10** or readdition of the palladium hydride to the diene to form the stable π-allylpalladium intermediate **7**. Intermediates **7** and **10** then lead to the corresponding dihydroisocoumarin and phthalide products respectively.

It is also conceivable that complex **9** undergoes readdition of the palladium hydride to the distal double bond and nucleophilic displacement of the resulting π-allylpalladium intermediate could produce phthalide products as shown in Scheme 3. This appears less likely to us, since this type of readdition has not been observed previously.

Scheme 3



9

The exclusive formation of 3,4-dihydroisocoumarins can also be achieved by employing the relatively less reactive vinylic bromides. As shown in entries 9 and 10, (*E*)-1-bromo-1-hexene and (*E*)-β-bromostyrene react with *o*-vinylbenzoic acid to give exclusive

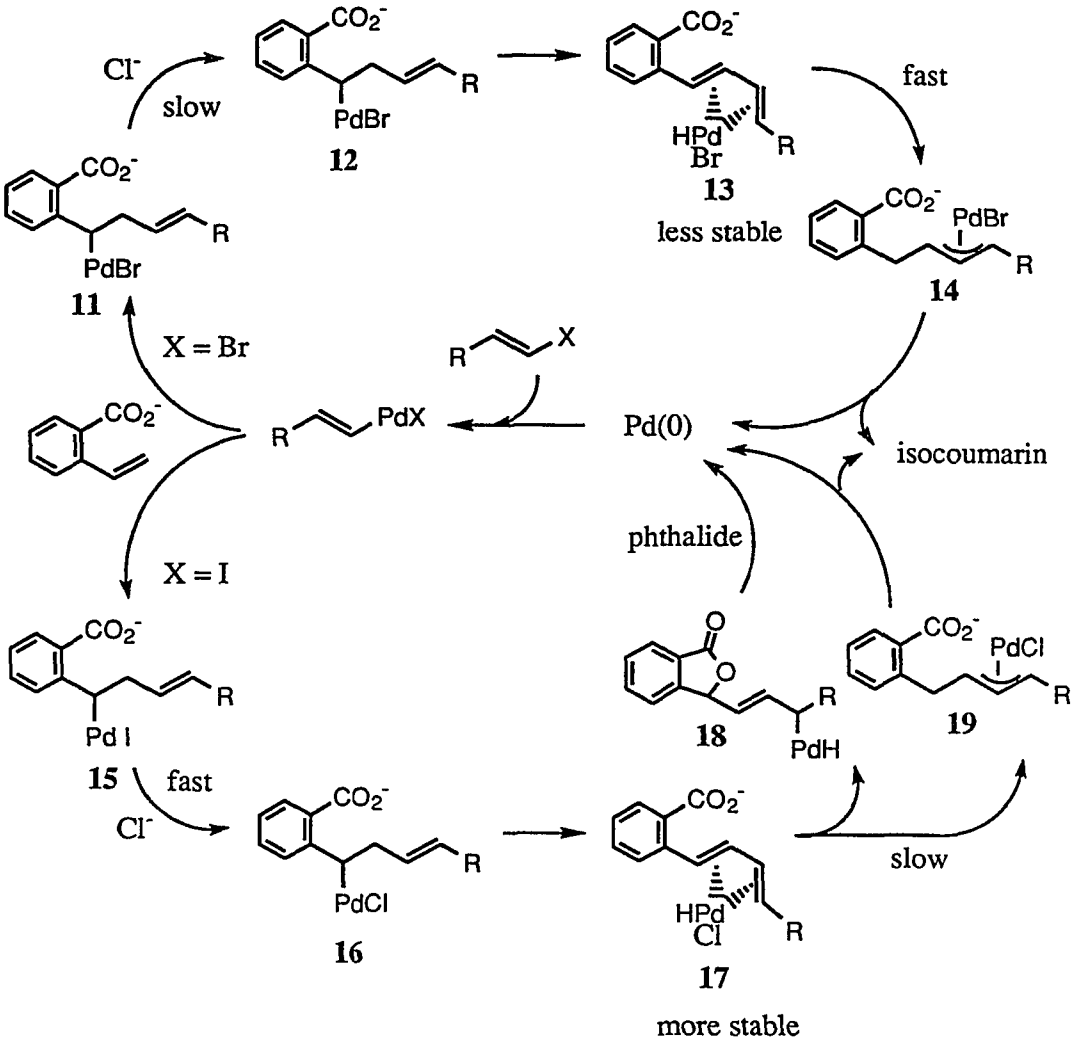
formation of the corresponding 3,4-dihydroisocoumarins. These results are rationalized in Scheme 4.

Diene complexes bearing either a chloride or a bromide may be generated by halide exchange in the initial vinylic palladium species, the allylpalladium species (**11** or **15**) or the diene complexes (**13** or **17**). Because of the difference in the ability of Br^- and I^- to act as a leaving group, ligand exchange between Cl^- and Br^- is assumed to occur slowly, while ligand exchange between Cl^- and I^- presumably takes place easily. Due to the difference in electronegativity between Cl^- and Br^-, the more electron-deficient palladium intermediate **17** presumably forms a relatively more stable π-complex through strong coordination to the two double bonds, while intermediate **13** forms a relatively less stable π-complex. By reasoning analogous to that used in Scheme 2, complex **13** forms predominantly 3,4-dihydro-isocoumarins, while complex **17** produces a mixture of both isomers. It is also conceivable that the more electron-withdrawing chloride complex (**17**) could encourage more rapid attack of the carboxylate onto the diene leading to the phthalide product.

Methyl (*E*)-β-bromoacrylate reacted slowly and not very cleanly under the established reaction conditions (entry 11). In order to improve the yield, the combination of a higher temperature and THF, which had proven useful as the solvent during the course of our optimization of the reaction conditions, was used. This change afforded a much cleaner reaction and a 59 % yield of the desired product was obtained (entry 12). In the reaction of 1-iodo-2-methylpropene, Li_2CO_3 was more effective than Na_2CO_3, as observed earlier (entries 13 and 14).

Several reactions of more substituted vinylic halides were also investigated. In general, the palladium-catalyzed coupling of internal vinylic iodides or triflates with *o*-vinylbenzoic acid proceeded as well as that of terminal vinylic halides. Interestingly, the formation of phthalides was not observed in these reactions. The reason why is not clear at this point. Thus, the

Scheme 4



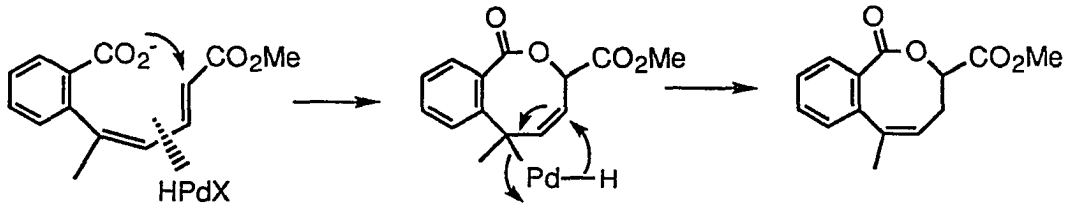
reaction of 2-iodo-1-hexene proceeded at room temperature to cleanly provide the desired 3,4-dihydroisocoumarin in 70 % yield (entry 15). A higher temperature was required to obtain the desired product in moderate yield for α-iodostyrene (entry 17 - 19).

A comparison of the reactivity between vinylic iodides and triflates was attempted and both were found to afford high yields under the optimal reaction conditions. However, higher

temperatures were required for both the vinylic iodide and triflate actually examined, namely the cyclohexenyl system (entries 21 - 23). Similarly, a higher yield of the desired product was obtained from the reaction of (*E*)-3-iodo-3-hexene at a higher temperature, 75 °C (compare entries 24 and 25).

The use of branched alkenylbenzoic acids provided some unexpected results. *o*-Isopropenylbenzoic acid coupled with (*E*)-1-iodo-1-hexene to give the anticipated dihydroisocoumarin along with a substantial amount of a product tentatively assigned as the phthalide, plus some unknown products (entry 26). The analogous reaction with methyl (*E*)-β-bromoacrylate gave exclusively an 8-membered ring lactone in 63 % yield (entry 27). This product appears to arise as depicted in Scheme 5. Nucleophile attack of oxygen on the distal end of the diene π-complex, followed by hydride transfer from the palladium to the double bond with rearrangement, explains formation of the eight-membered ring lactone with the double bond in conjugation with the aromatic ring.

Scheme 5



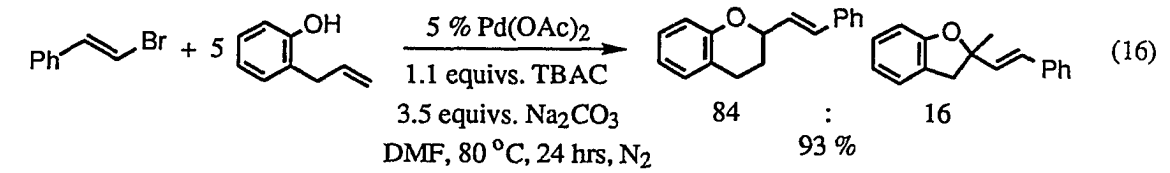
The reaction of 2-((*E*)-1-propenyl)benzoic acid was also examined (entry 28). Unlike other reactions, the phthalide product was obtained as a major isomer along with the corresponding 3,4-dihydroisocoumarin, plus some unknown products in a 77:9:14 ratio.

In summary, 3,4-dihydroisocoumarins have been prepared in high yields via the palladium-catalyzed coupling of *o*-(1-alkenyl)benzoic acids with vinylic halides or triflates. In this palladium-catalyzed process, the outcome is heavily dependent upon the starting vinylic

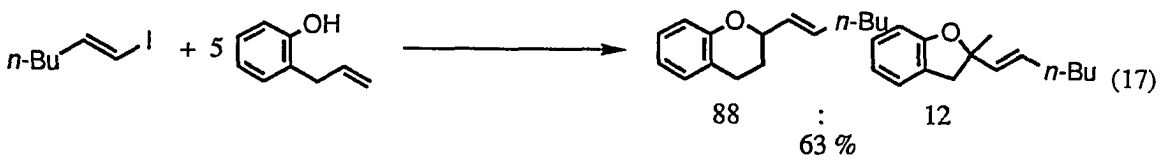
halide. Thus, the reaction of (*E*)-terminal vinylic iodides produces mixtures of 3,4-dihydroisocoumarins and phthalides, while the reaction of (*Z*)-terminal vinylic iodides and terminal vinylic bromides gives 3,4-dihydroisocoumarins exclusively. The more substituted vinylic halides and triflates afforded none of the phthalide side-products. The reaction of branched alkenylbenzoic acids was not clean and in most cases a mixture of isomers, plus unknowns, was observed.

Synthesis of 3,4-dihydrobenzopyrans and 2,3-dihydrobenzofurans

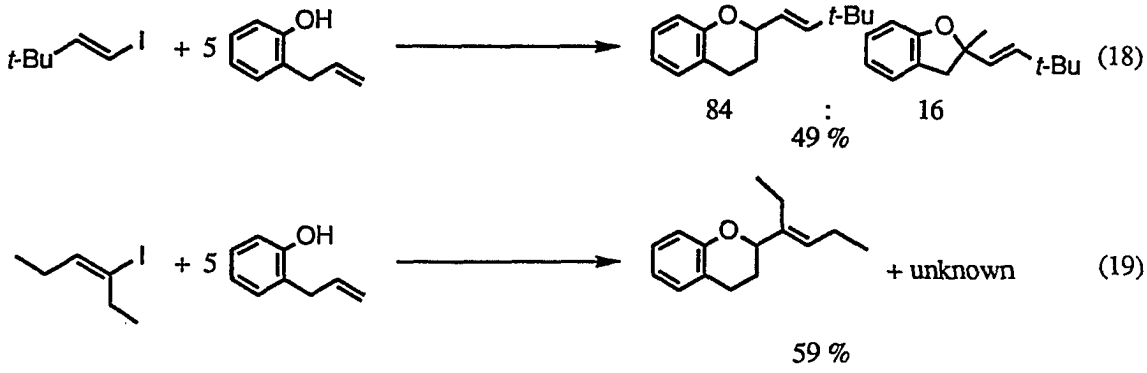
The palladium-catalyzed coupling of vinylic halides with *o*-allylphenol was initially studied by Dr. Charles E. Russell. During the course of his study, optimal reaction conditions (procedure A) involving 5 mol % $Pd(OAc)_2$, 1.0 equiv. of the vinylic halide (0.25 mmol), 5.0 equivs. of *o*-allylphenol, 3.5 equivs. of Na_2CO_3, 1.1 equivs. of TBAC at 80 °C under a nitrogen atmosphere were established for this palladium process. Using procedure A, several successful reactions were run by Dr. Russell as shown in equations 16 - 19.



(16)



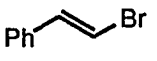
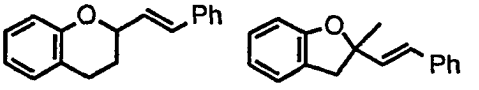
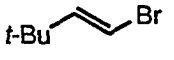
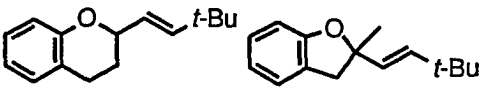
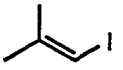
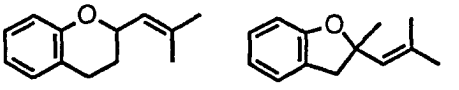
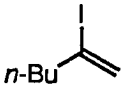
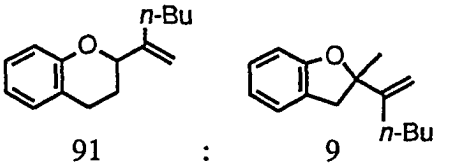
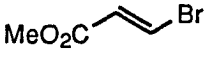
(17)



To further determine the scope and limitations of Dr. Russell's approach, more reactions were run using procedure A and the results are shown in Table 5. First, the reaction of (*E*)-β-bromostyrene was repeated under his reaction conditions and the result was very similar to that he reported (entry 1). The use of (*E*)-1-bromo-3,3-dimethyl-1-butene produced a lower yield, but a higher isomer ratio, compared with the results from the corresponding vinylic iodide (entry 2). Procedure A was also applied successfully to the reactions of 1-iodo-2-methylpropene and 2-iodo-1-hexene, producing high yields of products (entries 3 and 4). However, a complex mixture was obtained from methyl (*E*)-β-bromoacrylate (entry 5). The formation of 5-membered ring products appears to arise from internal addition of the σ-vinylic palladium species to the double bond of *o*-allylphenol.

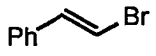
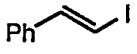
Both our results and Dr. Russell's indicate that this palladium process proceeds smoothly under the optimal conditions (procedure A) regardless of the type of vinylic halides used. Nonetheless, the fact that procedure A required 5 equivs. of *o*-allylphenol demanded further scrutiny of the reaction conditions. In an attempt to reduce the amount of *o*-allylphenol, reactions were run using three different stoichiometries of the starting materials (Table 6). The results shown in entries 1-3 strongly indicated that the use of only 2 equivs. of *o*-allylphenol is as effective as the use of 5 equivs. of *o*-allylphenol in terms of the yield. Thus, when a 1:2 ratio of (*E*)-β-bromostyrene to *o*-allylphenol was used, a 90 % yield was obtained as an

Table 5. Palladium-Catalyzed Coupling of Vinylic Halides with *o*-Allylphenol using Procedure A.[a]

entry	vinylic halide	products (ratio)	% isolated yield
1		 83 : 17	90
2		 91 : 9	35
3		 90 : 10	90
4		 91 : 9	63
5		bad mixture	-

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 5.0 equivs. of *o*-allylphenol, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 and 1.2 mL of DMF at 80 °C for 24 hours under a nitrogen atmosphere.

Table 6. Palladium-Catalyzed Coupling of Vinylic Halides with *o*-Allylphenol using Procedure B.[a]

entry	vinylic halide	time (h)	temp. (°C)
1		24	80
2[b]		24	80
3[c]		24	80
4		48	80

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of *o*-allylphenol, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 and 1.2 mL of DMF at 80 °C under a nitrogen atmosphere. [b]1.0 Equiv. of (*E*)-β-bromostyrene and 1.0 equiv. of *o*-allylphenol were used. [c]2.0 Equivs. of (*E*)-β-bromostyrene and 1.0 equiv. of *o*-allylphenol were used.

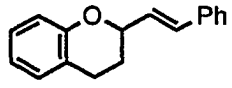
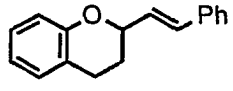
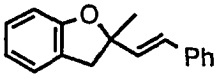
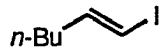
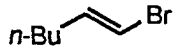
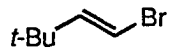
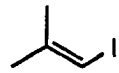
product(s) ratio			% isolated yield
	:		90
91	:	9	
91	:	9	66
91	:	9	75
	:		84
90	:	10	

Table 6. (Continued)

entry	vinylic halide	time (h)	temp. (°C)
5		36	80
6		48	80
7		48	80
8		24	100
9		36	80

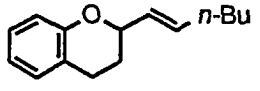
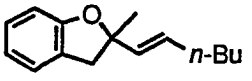
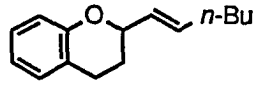
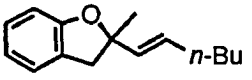
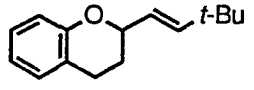
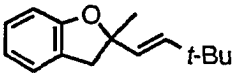
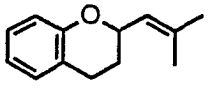
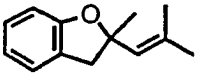
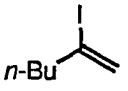
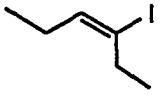
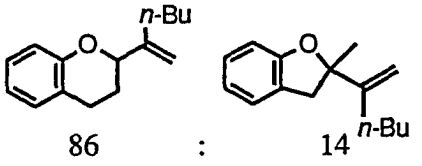
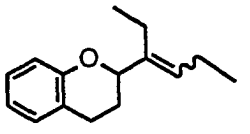
product(s) ratio	% isolated yield
 : 	72
 : 	50
 : 	15
91 : 9	10
 : 	75

Table 6. (Continued)

entry	vinylic halide	time (h)	temp. (°C)
10		36	80
11		36	80
12[d]		24	100

[d]5.0 Equivs. of 2-bromopropene and 1.0 equiv. of *o*-allylphenol were used.

product(s) ratio	% isolated yield
 86 : 14	30
 *Z* / *E* or *E* / *Z* = 83/17	44
	0

inseparable 91:9 mixture of the 6- and 5-membered ring products (entry 1). Reversing the stoichiometry of the starting materials, a significant decrease in yield was observed, but the isomer ratio remained unchanged (entry 3). A substantial decrease in yield was also observed when a 1:1 ratio of the starting materials was used. An inseparable mixture of the same two isomers was obtained in only 66 % yield (entry 2). From this study, the following modified reaction conditions (procedure B) were established: 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of *o*-allylphenol, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 and 1.2 mL of DMF at 80 °C for an appropriate time interval .

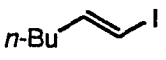
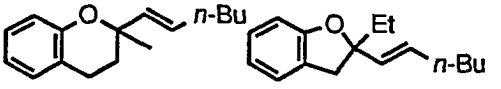
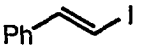
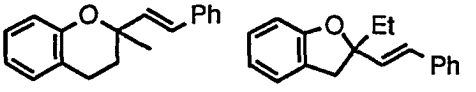
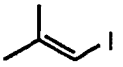
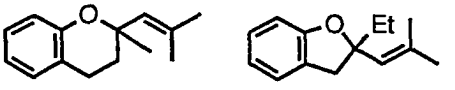
Using procedure B, the reactions of a variety of vinylic halides were run and the results are shown in Table 6. (*E*)-β-Iodostyrene reacted well with *o*-allylphenol, producing two isomeric ethers in 84 % yield (entry 4). For (*E*)-1-iodo-1-hexene, procedure B provided an 86:14 mixture of isomers in 72 % (entry 5), a slightly higher yield than procedure A, but the isomer ratio was found to be almost identical. Unlike the (*E*)-β-halostyrenes, a difference in reactivity between (*E*)-1-iodo-1-hexene and (*E*)-1-bromo-1-hexene was observed (compare entries 5 and 6). (*E*)-1-Bromo-1-hexene was less reactive and produced a lower yield. The reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene wasn't very successful, even at 100 °C (entries 7 and 8). The reaction of 1-iodo-2-methylpropene proceeded well, but the 75 % yield was lower than that using procedure A. A significant decrease in yield to 30 % was observed when 2-iodo-1-hexene was employed using procedure B (entry 10). For the more substituted vinylic halide, (*E*)-3-iodo-3-hexene, a mixture of isomers was obtained in moderate yield (entry 11). From the above results the use of 2 equivs. of *o*-allylphenol was shown to cause only slight decreases in yield, but the isomer ratio were essentially unchanged. This approach was further extended to (*E*)-*o*-crotylphenol. For comparison, both procedures A and B were employed and the results are shown in Tables 7 and 8. The palladium-catalyzed coupling of vinylic halides and *o*-crotylphenol didn't proceed as well as that of *o*-allylphenol, probably due to steric hindrance to addition of the σ-vinylic palladium species to the double bond of (*E*)-*o*-

crotylphenol. First, the reactions were run using procedure A. As indicated in Table 7, only (*E*)-β-iodostyrene gave a good yield of products, although it produced an inseparable mixture of 6- and 5-membered ring products in an 80:20 ratio (entry 2). Other vinylic halides, such as (*E*)-1-iodo-1-hexene, and 1-iodo-2-methylpropene, produced the products in low yields (entries 1 and 3). The use of 2-bromopropene didn't give any recognizable products at all (entry 4).

Mixed results were obtained when procedure B was employed (Table 8). A substantial increase in yield to 53 % of a 93:7 mixture of isomers was observed for the reaction of 1-iodo-2-methylpropene (entry 4). In contrast, the reaction of (*E*)-1-iodo-1-hexene resulted in a slightly lower yield of 31 %. For the (*E*)-β-halostyrenes, both the bromide and iodide reacted well, producing 67 % and 58 % yields, respectively, with an identical isomer ratio of 83:17. These results confirm that procedure B is as effective as procedure A. With this in mind, only procedure B was applied to the reactions of *o*-methallylphenol.

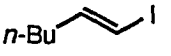
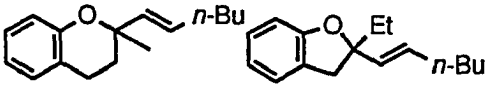
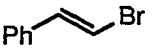
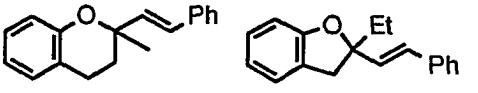
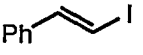
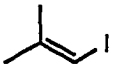
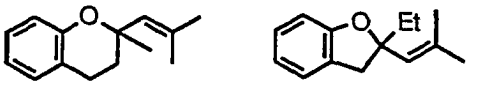
As anticipated, the reactions of vinylic halides with *o*-methallylphenol produced only 6-membered ring products in relatively high yields. These results are shown in Table 9. The reactions of both (*E*)-β-bromostyrene and (*E*)-β-iodostyrene proceeded well, giving the 6-membered ring product in 75 % yields in 77:23 and 71:29 *cis /trans* ratios respectively. Unlike the reaction with *o*-allylphenol, the reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene with *o*-methallylphenol was found to give a good yield of a mixture of stereoisomers. The reaction of 1-iodo-2-methylpropene gave a 60 % yield of a mixture of stereoisomers in equal amounts along with several unknowns. However, the more substituted vinylic halide, 2-iodo-1-hexene, didn't afford any recognizable products. The identity and ratio of the stereoisomers was determined on the basis of three references[17] indicating that the proton on C-2 of the *cis* -isomer has a higher chemical shift than that of the *trans* -isomer, which was observed in our products. Our success in the palladium-catalyzed coupling of vinylic halides with *o*-allylic phenols led to an investigation of the analogous coupling of vinylic halides with *o*-vinylic

Table 7. Palladium-Catalyzed Coupling of Vinylic Halides with (*E*)-*o*-Crotylphenol using Procedure A.[a]

entry	vinylic halide	product(s) ratio	% isolated yield
1		 88 : 12	37
2		 80 : 20	64
3		 91 : 9	28
4[b]		-	0

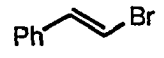
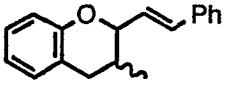
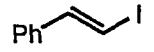
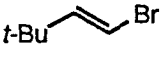
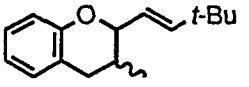
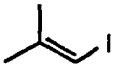
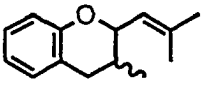
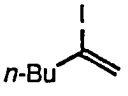
[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 5.0 equivs. of (*E*)-*o*-crotylphenol, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 and 1.2 mL of DMF at 100 °C for 24 hours under a nitrogen atmosphere. [b]5.0 Equivs. of 2-bromopropene and 1.0 equiv. of (*E*)-*o*-crotylphenol were used.

Table 8. Palladium-Catalyzed Coupling of Vinylic Halides with (*E*)-*o*-Crotylphenol using Procedure B.[a]

entry	vinylic halide	product(s) ratio	% isolated yield
1		 83 : 17	31
2		 83 : 17	67
3		83 : 17	58
4		 93 : 7	53

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of (*E*)-*o*-crotylphenol, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 and 1.2 mL of DMF at 100 °C for 72 hours under a nitrogen atmosphere.

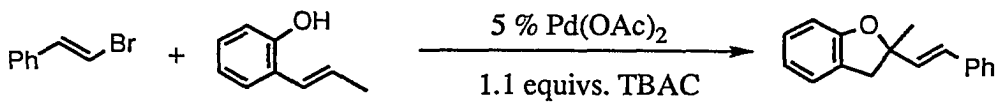
Table 9. Palladium-Catalyzed Coupling of Vinylic Halides with *o*-Methallylphenol using Procedure B.[a]

entry	vinylic halide	product(s) ratio	% isolated yield
1		 *cis /trans* = 77/23	75
2		*cis /trans* = 71/29	75[b]
3		 *cis /trans* = 70/30	83
4		 *cis /trans* = 50/50	60[b]
5			0

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of *o*-methallylphenol, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 and 1.2 mL of DMF at 100 °C for 24 hours under a nitrogen atmosphere. [b]An unknown was isolated together with the desired products in a 9:91 ratio.

phenols. The reaction of *o*-((*E*)-1-propenyl)phenol was studied using procedure B. Unlike the reactions of the *o*-allylic phenols, the *o*-vinylic phenols gave disappointing results (Table 10). First, these reactions produced many spots upon TLC analysis and consequently gave very low yields. Only traces of products were obtained from the reactions of (*E*)-1-iodo-1-hexene and (*E*)-3-iodo-3-hexene (entries 1 and 4). The use of vinylic bromides, such as (*E*)-β-bromostyrene and (*E*)-1-bromo-3,3-dimethyl-1-butene, was also ineffective, producing the corresponding products in low yields (entries 2 and 3).

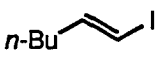
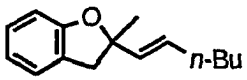
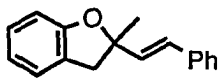
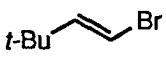
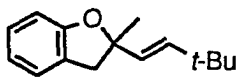
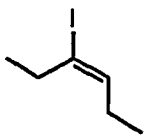
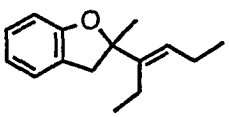
From these results, it is obvious that procedure B, the optimal procedure for the reactions of *o*-allylic phenols, is no longer applicable to *o*-vinylic phenols. Therefore, the search for new reaction conditions for *o*-vinylphenols was embarked upon using the reaction of (*E*)-β-bromostyrene and *o*-((*E*)-1-propenyl)phenol as the model system (eq. 20). The results are shown in Table 11.



20 **21** **22** (20)

Two factors, the base and the solvent, which are thought to be the most important in this palladium process were examined. Of the carbonate bases, K_2CO_3 was the best base, giving a 47 % yield (entries 1 - 3). Other bases, such as NaOAc, $NaHCO_3$, and Et_3N, afforded lower yields than K_2CO_3 (entries 4 - 6). Using K_2CO_3 as the base, the effect of the solvent was investigated and CH_3CN was found to give better results than the other solvents examined (entries 7 - 9). Despite this effort, however, these new conditions (procedure C) were found to be limited only to the reaction of (*E*)-β-bromostyrene with *o*-((*E*)-1-

Table 10. Palladium-Catalyzed Coupling of Vinylic Halides with *o*-((*E*)-1-Propenyl)phenol Using Procedure B.[a]

entry	vinylic halide	product	% isolated yield
1			trace
2			36
3			20
4			trace

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of *o*-((*E*)-1-propenyl)phenol, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 and 1.2 mL of DMF at 100 °C for 48 hours under a nitrogen atmosphere.

Table 11. Effect of the Base and the Solvent on the Reaction of (*E*)-β-Bromostyrene and *o*-((*E*)-1-Propenyl)phenol.[a]

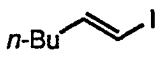
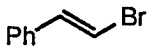
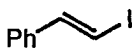
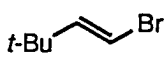
entry	base (3.5 equiv.)	solvent (1.2 mL)	% isolated yield **22**
1	Li_2CO_3	DMF	20
2	Na_2CO_3	DMF	36
3	K_2CO_3	DMF	47
4	NaOAc	DMF	34
5	$NaHCO_3$	DMF	27
6	Et_3N	DMF	35
7	K_2CO_3	THF	37
8	K_2CO_3	CH_3CN	54
9	K_2CO_3	DMA	49

[a]All reactions were run using of 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-β-bromostyrene (0.25 mmol), 2.0 equivs. of *o*-((*E*)-1-propenyl)phenol, 1.1 equivs. of TBAC, 3.5 equivs. of a base and 1.2 mL of a solvent at 100 °C for 24 hours under a nitrogen atmosphere.

propenyl)phenol. The reactions of other vinylic halides, such as (*E*)-1-iodo-1-hexene and 1-iodo-2-methylpropene, with *o*-((*E*)-1-propenyl)phenol didn't produce any recognizable products in measurable amounts.

Next, the reaction of *o*-vinylphenol itself was examined. Both procedures B and C were applied to some examples to see if any difference between them could be observed with regard to the yield. The results are shown in Table 12.

Table 12. Palladium-Catalyzed Coupling of Vinylic Halides with *o*-Vinylphenol using Procedures B and C.[a]

entry	vinylic halide	base (3.5 equiv.)	solvent (1.2 mL)
1		Na_2CO_3	DMF
2		Na_2CO_3	DMF
3		K_2CO_3	CH_3CN
4		Na_2CO_3	DMF
5		Na_2CO_3	DMF

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of *o*-vinylphenol, 1.1 equivs. of TBAC, 3.5 equivs. of base and 1.2 mL of solvent at 100 °C under a nitrogen atmosphere.

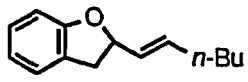
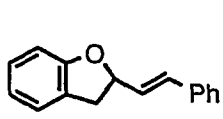
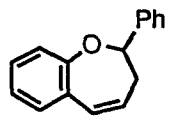
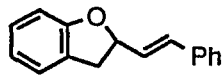
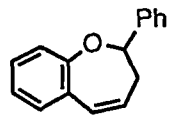
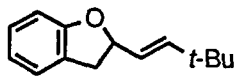
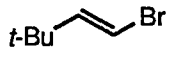
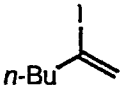
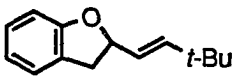
time (hr)	product(s) ratio	% isolated yield
24		0
24	 91 :  9	61
48	95 : 5	52
24	 75 :  25	72
24		40

Table 12. (Continued)

entry	vinylic halide	base (3.5 equiv.)	solvent (1.2 mL)
6		K_2CO_3	CH_3CN
7		Na_2CO_3	DMF

time (hr)	product(s) ratio	% isolated yield
48		53
24		0

Unlike the reactions of *o*-((*E*)-1-propenyl)phenol, the reactions of *o*-vinylphenol proceeded more smoothly, giving higher yields. However, these reactions afforded the desired products along with 7-membered ring products in most cases. An inseparable mixture of 5- and 7-membered ring products in a 91:9 ratio was obtained in 61 % yield from the reaction of (*E*)-β-bromostyrene (entry 2). A similar ratio, but lower yield was observed for the analogous reaction using procedure C (entry 3). (*E*)-β-Iodostyrene gave a 75:25 ratio of 5- and 7-membered ring isomers in 72 % yield (entry 4). By comparison, only 5-membered ring products were isolated from the reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene, giving a 40 % yield (entry 5). With procedure C (K_2CO_3 and CH_3CN), a higher yield, 53 %, was obtained from the reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene (entry 6). Surprisingly, (*E*)-1-iodo-1-hexene didn't give any product. Similarly, the more substituted vinylic halide, 2-iodo-1-hexene, didn't give any product (entry 7). It is not clear what caused the formation of the 7-membered ring products.

Finally, the reactions of *o*-isopropenylphenol with various vinylic halides were examined. Unlike other *o*-vinylic phenols, this phenol gave bad mixtures. Thus, (*E*)-β-bromostyrene, which usually gave good results in the reactions of other phenols, produced a mixture of the desired product and unknowns in only 27 % overall yield using procedure C. Procedure B also was ineffective and provided a similar yield, 34 %, of a mixture of the product and unknowns.

In summary, various oxygen heterocycles have been prepared in good yields via the palladium-catalyzed coupling of vinylic halides and 2-alkenylphenols. The reactions of *o*-allylphenol and *o*-crotylphenol produced a mixture of 6- and 5-membered ring products in most cases with the formation of 6-membered ring products being favored. As anticipated, only 6-membered ring products were obtained in good yields from the reactions of *o*-methallylphenol.

By comparison, the reactions of *o*-vinylic phenols didn't proceed as well as those of the *o*-allylic phenols. An inseparable mixture of 5- and 7-membered ring products was obtained from the reactions of *o*-vinylphenol in moderate yields. For the reaction of *o*-((*E*)-1-propenyl)phenol, only (*E*)-β-bromostyrene provided the desired product in good yield. *o*-Isopropenylphenol didn't give satisfactory results using either procedure B or C.

Conclusion

The palladium-catalyzed coupling of vinylic halides or triflates with 2-alkenylbenzoic acids and 2-alkenylphenols has been investigated. The reactions of vinylic halides or triflates with 2-alkenylbenzoic acids provide a convenient new route to 3,4-dihydroisocoumarins. Terminal vinylic halides, as well as internal vinylic halides, reacted smoothly with *o*-vinylbenzoic acid, giving the desired products in high yields. The relatively less reactive vinylic bromides and triflates also afford reasonable yields of products. It is noteworthy that the outcome of this palladium-catalyzed coupling is dependent upon the type of vinylic halide used. Thus, (*E*)-terminal vinylic iodides produced an inseparable mixture of 3,4-dihyroisocumarins and phthalides, while the corresponding (*Z*)-isomers and terminal vinylic bromides gave 3,4-dihydroisocoumarins exclusively.

Various oxygen heterocycles were also prepared successfully via the palladium-catalyzed coupling of vinylic halides with 2-alkenylphenols. Like the reactions of vinylic halides with 2-alkenylanilines, *o*-allylic phenols afford much better results than *o*-vinylic phenols. *o*-Allyl- and -crotylphenol produced inseparable mixtures of 6- and 5-membered ring products in good yields. As anticipated, the reactions of *o*-methallylphenol gave 6-membered ring products exclusively with moderate stereoselectivity. In contrast, the reactions of the *o*-vinylic phenols were more complex and the yields were generally lower. Moderate yields were

obtained from the reactions of vinylic halides with *o*-vinylphenol, but only (*E*)-β-bromostyrene gave a moderate yield in the reactions of *o*-((*E*)-1-propenyl)phenol.

Experimental Section

Equipment

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 at 300 and 75.5 MHz, respectively. All infrared spectra were recorded on a Beckman 4250 spectrometer and high resolution mass spectral analyses were performed on a Kratos MS-50 spectrometer. Thin-layer chromatography (TLC) was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic potassium permanganate solution.

Reagents

All reagents were used directly as obtained commercially unless otherwise noted. Palladium acetate was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. *o*-Methallyl- and -crotylphenol were prepared by Lulin Wei using a standard literature procedure.[18] Tetra-*n*- butylammonium chloride (TBAC) was purchased from Lancaster Synthesis Co. *o*-Allylphenol, azodicarbonamide, 2-bromoacetophenone, 2-bromobenzaldehyde, 1-bromo-2-methylpropene, 2-bromostyrene, catecholborane, diisobutylaluminum hydride, 3,3-dimethyl-1-butyne, ethylmagnesium bromide, 1-hexyne, 3-hexyne, 2-hydroxyacetophenone, 2-hydroxybenzaldehyde, methyllithium, methyltriphenyl-phosphonium bromide, mesyl chloride, *N*-phenyltrifluoromethanesulfonamide, 2-((*E*)-1-propenyl)phenol, chlorotrimethylsilane, and vinylmagnesium bromide were purchased from Aldrich Chemical Co. All inorganic compounds were purchased from Fisher Scientific Co.

o-Vinylbenzoic acid

2-Bromostyrene (27.3 mmol) and THF (300 mL) were placed in a 500 mL round bottom flask under nitrogen and cooled to -78 °C. *n*-Butyllithium (27.4 mmol) was then added and the mixture allowed to stir for 1 hour. This was followed by the addition of gaseous CO_2, which was bubbled through for 4 hours. The solution was then acidified using 10 % aqueous HCl solution and extracted with ether. The ether layer was then extracted with 10 % aqueous NaOH solution. The basic solution was reacidified with 10 % aqueous HCl solution to yield *o*-vinylbenzoic acid as a precipitate in approximately 60 % yield: mp 92-94 °C (lit.[19] mp 94-95 °C); ^{1}H NMR ($CDCl_3$) δ 5.40 (dd, 1 H, J = 11.1, 1.2 Hz), 5.67 (dd, 1 H, J = 17.4, 1.2 Hz), 7.35 (td, 1 H, J = 7.2, 1.5 Hz), 7.50-7.80 (m, 3 H), 8.05 (d, 1 H, J = 7.8 Hz) (CO_2H was not observed); ^{13}C NMR ($CDCl_3$) δ 116.8, 127.2, 127.5, 127.6, 131.0, 133.0, 136.0, 140.6, 173.3; IR ($CDCl_3$) 3071 (OH), 1693 (C=O), 1600 (C=C) cm^{-1}.

2-((*E*)-1-Propenyl)benzoic acid

i) 1-(2-Bromophenyl)propanol

Ethylmagnesium bromide (33 mmol) was added to 2-bromobenzaldehyde (30 mmol) in 20 mL of THF at - 30 °C and the mixture was stirred at this temperature for 90 minutes. The excess Grignard reagent was destroyed by adding 10 % aqueous HCl solution. The crude product was extracted with ether (2 x 100 mL), dried over $MgSO_4$, concentrated in vacuo, and columned to give 1-(2-bromophenyl)propanol in 65 % yield: ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7.5 Hz), 1.63-1.85 (m, 2 H), 1.93 (br s, 1 H), 4.95-5.00 (m, 1 H), 7.08 (t, 1 H, J = 7.5 Hz), 7.29 (t, 1 H, J = 6.9 Hz), 7.46-7.51 (m, 2 H).

ii) 2-((*E*)-1-Propenyl)bromobenzene

1-(2-Bromophenyl)propanol (18 mmol) was added to 2.5 mL of a mixture of conc. H_3PO_4 and H_2SO_4 (2:1 ratio) at room temperature and the mixture was stirred for 5 minutes. The mixture was diluted with ether (50 mL). The ether layer was then washed with water,

dried over $MgSO_4$, concentrated in vacuo, and columned to give the product in 38 % yield: ^1H NMR ($CDCl_3$) δ 1.92 (d, 3 H, J = 6.6 Hz), 6.13-6.25 (m, 1 H), 6.72 (d, 1 H, J = 15.6 Hz), 7.05 (t, 1 H, J = 7.2 Hz), 7.23 (t, 1 H, J = 7.5 Hz), 7.46 (d, 1 H, J = 7.8 Hz), 7.51 (d, 1 H, J = 7.8 Hz).

iii) 2-((*E*)-1-Propenyl)benzoic acid

2-((*E*)-1-Propenyl)bromobenzene (5 mmol) was added to magnesium turnings (5.5 mmol) in 10 mL of THF and the mixure was refluxed for 6 hours. The mixture was cooled to room temperature and flushed with gaseous CO_2 for 10 min. The excess Grignard reagent was destroyed by adding water. The crude product was extracted with ether (50 mL), dried over $MgSO_4$, concentrated in vacuo, and columned to give 2-((*E*)-1-propenyl)benzoic acid in 70 % yield: ^1H NMR ($CDCl_3$) δ 1.95 (dd, 3 H, J = 6.3, 1.2 Hz), 6.13-6.25 (m, 1 H), 7.18-7.33 (m, 2 H), 7.50 (t, 1 H, J = 7.2 Hz), 7.54 (t, 1 H, J = 7.5 Hz), 8.01 (d, 1 H, J = 7.2 Hz) (CO_2H was not observed); IR ($CDCl_3$) 3080 (OH), 1683 (C=O), 1598 (C=C) cm^{-1}.

2-Isopropenylbenzoic acid

i) 2-(2-Bromophenyl)-2-propanol

2-Bromoacetophenone (30 mmol) was added to MeLi (30 mmol) in 25 mL of THF at - 30 °C. The temperature was then raised to 0 °C and the mixture was stirred at this temperature for 6 hours. The mixture was washed with 10 % aqueous HCl solution. The crude product was extracted with ether (3 x 50 mL), dried over $MgSO_4$, concentrated in vacuo, and columned to give 2-(2-bromophenyl)-2-propanol in 40 % yield: ^1H NMR ($CDCl_3$) δ 1.75 (s, 6 H), 2.79 (br s, 1 H), 7.10 (t, 1 H, J = 6.9 Hz), 7.30 (t, 1 H, J = 7.5 Hz), 7.58 (d, 1 H, J = 7.8 Hz), 7.66 (d, 1 H, J = 7.2 Hz).

ii) 2-Isopropenylbenzoic acid

Mesyl chloride (24 mmol) was added to 2-(2-bromophenyl)-2-propanol (9 mmol) in 20 mL of EtOAc at 0 °C. To this mixture was added triethylamine (29 mmol) over 20 minutes

and the resulting solution was stirred for 2 hours at 0 °C. The mixure was washed with 2 N aqueous HCl solution, extracted with ether (2 x 50 mL), dried over $MgSO_4$, concentrated in vacuo, and columned to give 2-isopropenylbromobenzene in 65 % yield. 2-Isopropenyl-bromobenzene (5.5 mmol) was added to *n*-BuLi (6.0 mmol) in 10 mL of THF and the mixture was refluxed for 3.5 hours. The mixture was cooled to room temperature and flushed with gaseous CO_2 for 10 min. The excess lithium reagent was destroyed by adding water. The crude product was extracted with ether (50 mL), dried over $MgSO_4$, concentrated in vacuo, and columned to give the product in 60 % yield: ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3 H), 4.90 (s, 1 H), 5.13 (s, 1 H), 7.27 (d, 1 H, J = 6.6 Hz), 7.35 (td, 1 H, J = 7.8, 1.2 Hz), 7.50 (td, 1 H, J = 7.8, 1.2 Hz), 7.96 (d, 1 H, J = 7.8 Hz) (CO_2H was not observed); ^{13}C NMR ($CDCl_3$) δ 24.3, 113.9, 127.0, 128.0, 129.7, 130.7, 132.6, 146.3, 146.6, 173.5; IR ($CDCl_3$) 3080 (OH), 1698 (C=O), 1599 (C=C) cm^{-1}.

(*E*)-1-Iodo-1-hexene[20]

To 1-hexyne (20 mmol) in 5 mL of heptane was added diisobutylaluminum hydride (25 mmol) in heptane while maintaining the temperature below 40 °C. After the initial exothermic reaction had subsided, the reaction mixture was heated for 2 hours at 50 °C. To this mixture was added iodine (20 mmol) in 40 mL of THF at -50 °C. After allowing the reaction mixture to warm to room temperature, the excess diisobutylaluminum hydride was decomposed by the dropwise addition of 20 % H_2SO_4 solution. After the evolution of isobutane had diminished, the reaction mixture was poured into a 20 % icy aqueous H_2SO_4 solution. The product was extracted with hexane (2 x 100 mL) and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$ solution (4 x 100 mL) and then aqueous $NaHCO_3$ solution (2 x 10 mL). The organic layer was dried over $MgSO_4$ and column chromatographed with an 8:1 hexane/ethyl acetate mixture to afford the product in 35 - 50 % yield: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 6.9 Hz), 1.20-1.45 (m, 4 H), 2.02 (dq, 2 H, J = 7.2, 1.2 Hz),

5.56 (dt, 1 H, J = 14.4, 1.5 Hz), 6.47 (dt, 1 H, J = 14.0, 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 21.9, 30.5, 35.7, 74.3, 146.7; IR ($CDCl_3$) 2961(=CH), 1605 (C=C) cm^{-1}.

(*E*)-1-Bromo-1-hexene[20]

To 1-hexyne (20 mmol) in 5 mL of heptane was added DIBAH (25 mmol) while maintaining a temperature below 40 °C. After the initial reaction had subsided, the reaction mixture was heated for 4 hours at 50 °C. The heptane was then removed under reduced pressure, and the residue was diluted with THF (8 mL). To this solution was added bromine (20 mmol) in 8 mL of CH_2Cl_2 at - 50 °C. After allowing the reaction mixture to warm to room temperature, the excess DIBAH was destroyed by the dropwise addition of 20 % aqueous H_2SO_4 solution. After the evolution of isobutane had diminished, the mixture was poured into 20 % cold aqueous H_2SO_4 solution (100 mL). The product was extracted with hexane (2 x 150 mL) and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$ solution (4 x 50 mL), then with saturated $NaHCO_3$ (2 x 50 mL). After the organic layer was dried over $MgSO_4$, the product was obtained by distillation at 147 - 150 °C in 46 % yield: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6.9 Hz), 1.26-1.41 (m, 4 H), 2.04 (qd, 2 H, J = 7.2, 1.2 Hz), 6.00 (dt, 1 H, J = 13.5, 1.2 Hz), 6.17 (dt, 1 H, J = 13.2, 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.1, 30.8, 32.7, 104.0, 138.3; IR ($CDCl_3$) 2957 (=CH), 1605 (C=C) cm^{-1}.

(*E*)-1-Bromo-3,3-dimethyl-1-butene[20]

This compound was obtained from 3,3-dimethyl-1-butyne in 30 % yield using the same procedure as that used for (*E*)-1-bromo-1-hexene and distilling at 128 °C : ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H), 5.97 (d, 1 H, J = 13.8 Hz), 6.22 (d, 1 H, J = 13.8 Hz); ^{13}C NMR ($CDCl_3$) δ 29.1, 35.8, 101.9, 148.5; IR ($CDCl_3$) 2957 (=CH), 1604 (C=C) cm^{-1}.

(*E*)-β-Iodostyrene[21]

A mixture of phenylacetylene (50 mmol) and catecholborane (50 mmol) was stirred in a 100 mL round bottom flask for 2 hours under nitrogen at 70 °C to form the catechol ester. The mixture was cooled to room temperature and stirred with 50 mL of water for 2 hours at room temperature to effect the hydrolysis of the ester. The resulting mixture was cooled to 0 °C and the white solid was collected by filtration and washed to remove catechol by using ice cold water. The resulting boronic acid was then dissolved in 50 mL of ether in a 500 mL flask and cooled to 0 °C. Aqueous NaOH solution (3 N, 50 mL) was then added, followed by the addition of iodine (60 mmol) in about 150 ml of ether, while stirring at 0 °C. The mixture was stirred for 30 minutes and the excess iodine was removed with saturated aqueous $Na_2S_2O_3$ solution. The ether solution was separated, washed with water, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the product was obtained in 43 % yield by distillation at 98 °C at 10 mm Hg: ^{1}H NMR ($CDCl_3$) δ 6.80 (d, 1 H, J = 15.0 Hz), 7.20-7.30 (m. 5 H), 7.40 (d, 1 H, J = 14.7 Hz); ^{13}C NMR ($CDCl_3$) δ 125.9, 128.3, 128.7, 137.7, 144.9 (one peak is not seen due to overlap); IR ($CDCl_3$) 3057 (=CH), 1595 (C=C) cm^{-1}.

1-(Trifluoromethanesulfonyloxy)cyclohexene[22]

To a solution of diisopropylamine (15 mmol) in THF (30 mL) at -78 °C was added *n*-butyllithium (15 mmol). The solution was stirred at -78 °C for 30 minutes, warmed to 0 °C and stirred for an additional 30 minutes, and cooled to -78 °C before freshly distilled cyclohexanone (14 mmol) was introduced. The resulting solution was stirred at -78 °C for 1 hour, warmed to 0 °C and stirred for an additional 1 hour, and then cooled to -78 °C before *N*-phenyltrifluoromethanesulfonimide (15 mmol) in THF (10 mL) was added. The mixture was allowed to reach room temperature and stirred for several hours. Once analysis by thin layer chromatography indicated that all of the cyclohexanone had been consumed, the reaction

mixture was quenched by the addition of saturated NH_4Cl solution and the product was extracted with ether. The ether solution was washed with water and saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Distillation afforded the product in 45 % yield at 65 °C at 7 mm Hg: ^1H NMR ($CDCl_3$) δ 1.50-1.80 (m, 4 H), 2.10-2.40 (m, 4 H), 5.70-5.80 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.0, 22.7, 23.9, 27.6, 118.4, 149.3 (one peak is not seen due to overlap); IR ($CDCl_3$) 2942 (=CH), 1689 (C=C) cm^{-1}.

(Z)-1-Iodo-1-hexene[23]

i) 1-Iodo-1-hexyne

1-Hexyne (75 mmol) in 34 mL of ether was placed in a dry 250 mL three-necked round bottom flask equipped with a dropping funnel, a reflux condenser, and a stirring bar. The system was flushed with nitrogen and maintained under nitrogen throughout the course of the reaction. Methyllithium (85 mmol) in ether was added through the dropping funnel at such a rate as to cause gentle refluxing. After the addition, the mixture was stirred for 1 hour at room temperature. The resulting mixture was cooled to -78 °C, followed by the addition of iodine (85 mmol) in 15 mL of ether. The mixture was then allowed to warm to room temperature and the reaction was continued overnight. Water (80 mL) was added and the ether layer was separated, washed with 45 mL of saturated aqueous $Na_2S_2O_3$ solution, and dried over $MgSO_4$. The ether was removed under reduced pressure and the residue was distilled at 70 °C at 12 mm Hg, affording an 80 % yield of 1-iodo-1-hexyne: ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.2 Hz), 1.30-1.50 (m, 4 H), 2.40 (t, 2 H, J = 6.6 Hz).

ii) (Z)-1-Iodo-1-hexene

Dipotassium azodicarboxylate was prepared by adding azodicarbonamide (201 mmol) to 40 % aqueous KOH solution (70 mL) while maintaining the temperature below 10 °C. After the addition, the mixture was stirred for 45 minutes and then filtered and washed with 100 mL

of cold MeOH. The resulting solid potassium salt, MeOH (104 mL) and 1-iodo-1-hexyne (25 mmol) were placed in a 500 mL round bottom flask and to this mixture was added a mixture of glacial HOAc (20 mL) and MeOH (52 mL) slowly. After the addition, the reaction mixture was transferred to a separatory funnel containing 100 mL of water and the product was extracted with hexane (3 x 100 mL). The combined hexane solution was dried over $MgSO_4$. The hexane then was removed under reduced pressure and the residue was dissolved in 15 mL of *n*-butylamine and stirred for 1 hour to remove 1-iodohexane. After stirring, the solution was diluted with 100 mL hexane and washed with water (2 x 75 mL), 10 % cold aqueous HCl solution (75 mL), and then with water (75 mL) again. The organic layer was dried over $MgSO_4$ and the hexane was removed under reduced pressure, affording the product in 40 % yield: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.2 Hz), 1.35-1.43 (m, 4 H), 2.11-2.18 (m, 2 H), 6.14-6.17 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.3, 30.2, 34.5, 82.1, 141.5; IR ($CDCl_3$) 2955 (=CH), 1609 (C=C) cm^{-1}.

1-Iodo-2-methyl-1-propene[24]

In an oven-dried 100 mL round bottom flask equipped with an addition funnel and a stirring bar were placed magnesium turnings (44.0 mmol) and THF (50 mL). 1-Bromo-2-methylpropene (40 mmol) in THF (10 mL) was added dropwise over a 30 minute period. After the addition was complete, the contents were refluxed for 5 hours. The solution was then cooled to 0 °C and was quenched with iodine (44.0 mmol) dissolved in THF (15 mL). The resulting mixture was allowed to reach room temperature overnight before it was quenched with saturated aqueous NH_4Cl solution and the organic layer was extracted with ether. The ether layer was washed with saturated aqueous $Na_2S_2O_3$ and NaCl solutions, water, and dried over $MgSO_4$. The hexane was removed under reduced pressure and the residue was distilled at 60 °C at 100 mm Hg, producing the product in 40% yield: ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3 H),

1.90 (d, 3 H, J = 1.2 Hz), 5.80 (br t, 1 H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 25.3, 25.4, 73.9, 144.1; IR ($CDCl_3$) 1638 (C=C) cm^{-1}.

(*E*)-3-Iodo-3-hexene[20]

To a solution of 3-hexyne (60 mmol) in hexane (30 mL) was added diisobutylaluminum hydride (60 mmol) at a rate such that the temperature remained below 40 °C. The resulting solution was heated at 50 °C for 5 hours, followed by removal of the hexane under reduced pressure without contacting air. The residue was diluted with dry THF (30 mL), cooled to -50 °C, and a solution of iodine (60 mmol) in THF (30 mL) was added. The resulting mixture was allowed to reach room temperature and stirred overnight at that temperature. The reaction mixture was quenched by the dropwise addition of 25 % aqueous H_2SO_4 solution until the evolution of isobutane ceased. The mixture was then poured into cold 20 % aqueous H_2SO_4 solution (100 mL). The crude product was extracted with hexane (2 x 100 mL) and the hexane solution was washed with saturated aqueous $Na_2S_2O_3$ solution, 5 % aqueous Na_2CO_3 solution, and dried over $MgSO_4$. The hexane was removed under reduced pressure and the residue was distilled at 58-61 °C at 12 mm Hg, affording the product in 52 % yield: ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7.5 Hz), 1.00 (t, 3 H, J = 7.5 Hz), 1.95-2.55 (m, 4 H), 6.10 (t, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.4, 24.0, 32.2, 104.7, 141.8; IR ($CDCl_3$) 2996 (=CH), 1628 (C=C) cm^{-1}.

α-Iodostyrene[25]

To a solution of sodium iodide (36 mmol) in acetonitrile (60 mL) was added trimethylsilylchloride (36 mmol) and water (18 mmoL) at room temperature. After 10 minutes, phenylacetylene (30 mmol) was added and the resulting mixture was allowed to react for 1 hour. The reaction mixture was quenched with water (30 mL) and the crude product was extracted with ether (3 x 90 mL) and dried over $MgSO_4$. After removing the ether, flash

column chromatography on a silica gel column with hexane as the eluent gave the pure desired product in 60 % yield: ^{1}H NMR ($CDCl_3$) δ 6.07 (d, 1 H, J = 1.8 Hz), 6.45 (d, 1 H, J = 1.8 Hz), 7.22-7.36 (m, 3 H), 7.40-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 107.5, 127.3, 128.0, 128.2, 128.8, 141.5; IR ($CDCl_3$) 3056 (=CH), 1677 (C=C) cm^{-1}.

General procedure for the preparation of 3,4-dihydroisocoumarins

To a 1 dram vial were added $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), the vinylic halide or triflate (0.25 mmol), the 2-alkenylbenzoic acid (0.5 mmol), *n*-Bu_4NCl (0.28 mmol), Li_2CO_3 (1.125 mmol), and DMF (1 mL). The vial was capped with a screw-cap containing a teflon liner. After running the reaction at room temperature for an appropriate time interval, the reaction mixture was diluted with ether and washed with saturated NH_4Cl, followed by water. The organic layer was then dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica gel, hexane/EtOAc as eluents).

3,4-Dihydro-3-((*E*)-3,3-dimethyl-1-butenyl)isocoumarin and 3-((*E*)-4,4-dimethyl-1-pentenyl)phthalide (Table 4, entry 5)

3,4-Dihydro-3-((*E*)-3,3-dimethyl-1-butenyl)isocoumarin was obtained in 94 % yield along with a small amount of 3-((*E*)-4,4-dimethyl-1-pentenyl)phthalide (67:33) as an inseparable mixture from the reaction of (*E*)-1-iodo-3,3-dimethyl-1-butene with *o*-vinylbenzoic acid for 9 hours at 25 °C: ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 2.97 (dd, 1 H, J = 16.2, 3.6 Hz), 3.09 (dd, 1 H, J = 16.2, 10.8 Hz), 4.80-5.05 (m, 1 H), 5.60 (dd, 1 H, J = 15.6, 6.9 Hz), 5.90 (dd, 1 H, J = 15.6, 0.6 Hz), 7.20 (d, 1 H, J = 7.5 Hz), 7.40 (t, 1 H, J = 6.9 Hz), 7.50 (td, 1 H, J = 7.5, 1.5 Hz), 8.10 (d, 1 H, J = 7.8 Hz); ^{13}C NMR of mixture ($CDCl_3$) δ 29.2, 29.5, 29.6, 31.0, 33.0, 33.9, 79.4, 82.3, 121.9, 122.5, 125.1, 125.5, 125.8, 127.3, 127.6, 129.1, 130.1, 133.7, 134.0, 135.2, 138.9, 146.3, 149.5, 165.3, 170.3 (one peak is

not seen due to overlap); IR of mixture ($CDCl_3$) 2958 (=CH), 1769 (C=O), 1608 (C=C) cm^{-1}; HRMS of mixture m/z 230.1306 (Calcd. 230.1307 for $C_{15}H_{18}O_2$).

3-((*E*)-4,4-Dimethyl-1-pentenyl)phthalide: ^1H NMR ($CDCl_3$) δ 0.93 (s, 9 H), 1.97-2.05 (m, 2 H), 5.41 (ddt, 1 H, *J* = 15.0, 8.1, 1.5 Hz), 5.82 (d, 1 H, *J* = 8.1 Hz), 6.08 (dt, 1 H, *J* = 15.0, 7.8 Hz).

3,4-Dihydro-3-((*E*)-1-hexenyl)isocoumarin and 3-((*E*)-1-heptenyl)phthalide (Table 4, entry 7)

3,4-Dihydro-3-((*E*)-1-hexenyl)isocoumarin was obtained in 87 % yield along with a small amount of 3-((*E*)-1-heptenyl)phthalide as an inseparable 94:6 mixture from the reaction of (*Z*)-1-iodo-1-hexene with *o*-vinylbenzoic acid for 12 hours at 25 °C: ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 7.2 Hz), 1.24-1.43 (m, 4 H), 2.07 (q, 2 H, *J* = 6.9 Hz), 3.00 (dd, 1 H, *J* = 16.5, 4.2 Hz), 3.07 (dd, 1 H, *J* = 16.2, 9.9 Hz), 4.87-5.10 (m, 1 H), 5.63 (ddt, 1 H, *J* = 15.6, 6.9, 1.2 Hz), 5.87 (dtd, 1 H, *J* = 14.7, 6.9, 0.6 Hz), 7.24 (d, 1 H, *J* = 7.8 Hz), 7.40 (t, 1 H, *J* = 7.8 Hz), 7.50 (td, 1 H, *J* = 7.5, 1.2 Hz), 8.07 (d, 1 H, *J* = 7.8 Hz); ^{13}C NMR of mixture ($CDCl_3$) δ 13.9, 22.2, 30.9, 31.9, 33.8, 79.0, 125.2, 126.8, 127.4, 127.6, 130.2, 133.7, 135.9, 138.8, 165.0 (peaks from the minor isomer are not seen) ; IR ($CDCl_3$) 2956 (=CH), 1733 (C=O), 1608 (C=C) cm^{-1}; HRMS of mixture m/z 230.1306 (Calcd. 230.1307 for $C_{15}H_{18}O_2$).

3-((*E*)-1-Heptenyl)phthalide: ^1H NMR ($CDCl_3$) δ 5.42 (ddt, 1 H, *J* = 15.0, 8.1, 1.2 Hz), 5.80 (d, 1 H, *J* = 8.1 Hz), 6.06 (dt, 1 H, *J* = 15.6, 7.8 Hz).

3,4-Dihydro-3-((*E*)-β-styryl)isocoumarin and 3-((*E*)-3-phenyl-1-propenyl)phthalide (Table 4, entry 8)

3,4-Dihydro-3-((*E*)-β-styryl)isocoumarin was obtained in 88 % yield from the reaction of (*Z*)-β-iodostyrene fromwith *o*-vinylbenzoic acid for 19 hours at 25 °C: ^1H NMR ($CDCl_3$) δ

3.00 (dd, 1 H, J = 16.2, 4.2 Hz), 3.10 (dd, 1 H, J = 17.1, 8.1 Hz), 4.95-5.20 (m, 1 H), 6.20 (dd, 1 H, J = 16.2, 6.3 Hz), 6.70 (d, 1 H, J = 15.9 Hz), 7.10-7.30 (m, 7 H), 7.40 (td, 1 H, J = 7.5, 1.5 Hz), 8.00 (dd, 1 H, J = 7.8, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 33.7, 78.6, 125.1, 125.8, 126.7, 127.4, 127.8, 128.3, 128.8, 130.3, 133.2, 133.8, 135.8, 138.6, 165.0 ; IR ($CDCl_3$) 3026 (=CH), 1730 (C=O), 1605 (C=C) cm^{-1}; HRMS m/z 250.0990 (Calcd. 250.0994 for $C_{17}H_{14}O_2$).

3,4-Dihydro-3-(methyl (*E*)-β-acrylyl)isocoumarin (Table 4, entry 12)

This compound was obtained in 59 % yield from the reaction of methyl (*E*)-β-bromoacrylate with *o*-vinylbenzoic acid for 24 hours at 80 °C: ^{1}H NMR ($CDCl_3$) δ 3.03-3.18 (m, 2 H), 3.76 (s, 3 H), 5.05-5.30 (m, 1 H), 6.27 (dd, 1 H, J = 15.6, 1.8 Hz), 7.01 (dd, 1 H, J = 15.9, 4.5 Hz), 7.27 (t, 1 H, J = 7.5 Hz), 7.42 (t, 1 H, J = 7.8 Hz), 7.57 (td, 1 H, J = 7.5, 1.5 Hz), 8.10 (dd, 1 H, J = 7.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 32.2, 51.9, 76.1, 122.6, 124.8, 127.4, 128.0, 130.4, 134.0, 137.8, 143.1, 164.2, 166.2; IR ($CDCl_3$) 3072 (=CH), 1727 (C=O), 1723 (C=O), 1609 (C=C) cm^{-1}; HRMS m/z 232.0736 (Calcd. 232.0736 for $C_{13}H_{12}O_4$)

3,4-Dihydro-3-(2-methyl-1-propenyl)isocoumarin (Table 4, entry 13)

This compound was obtained in 75 % yield from the reaction of 1-iodo-2-methylpropene with *o*-vinylbenzoic acid for 15 hours at 25 °C: ^{1}H NMR ($CDCl_3$) δ 1.75 (d, 3 H, J = 0.6 Hz), 1.78 (s, 3 H), 2.90 (dd, 1 H, J = 16.5, 3.0 Hz), 3.00 (dd, 1 H, J = 15.6, 10.2 Hz), 5.25-5.30 (m, 1 H), 5.40 (br d, 1 H, J = 8.7 Hz), 7.20 (d, 1 H, J = 7.5 Hz), 7.40 (t, 1 H, J = 7.5 Hz), 7.50 (td, 1 H, J = 6.9, 1.2 Hz), 8.10 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.5, 25.7, 33.7, 75.6, 122.0, 125.2, 127.4, 127.8, 130.1, 133.5, 139.1,

139.7, 165.5; IR ($CDCl_3$) 2915 (=CH), 1725 (C=O), 1609 (C=C) cm^{-1}; HRMS m/z 202.0996 (Calcd. 202.0994 for $C_{13}H_{14}O_2$).

3,4-Dihydro-3-(2-hexenyl)isocoumarin (Table 4, entry 15)

This compound was obtained in 70 % yield from the reaction of 2-iodo-1-hexene with *o*-vinylbenzoic acid for 15 hours at 25 °C: ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.2 Hz), 1.33-1.55 (m, 4 H), 2.10-2.30 (m, 2 H), 3.00 (dd, 1 H, J = 16.2, 3.3 Hz), 3.17 (dd, 1 H, J = 16.2, 11.4 Hz), 4.95 (dd, 1 H, J = 11.7, 3.0 Hz), 5.00 (s, 1 H), 5.20 (d, 1 H, J = 0.6 Hz), 7.20 (d, 1 H, J = 6.9 Hz), 7.40 (t, 1 H, J = 7.5 Hz), 7.50 (td, 1 H, J = 7.5, 1.5 Hz), 8.10 (dd, 1 H, J = 7.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 29.9, 31.6, 32.5, 80.6, 112.5, 125.0, 127.3, 127.6, 130.2, 133.7, 139.0, 146.0, 165.3; IR ($CDCl_3$) 2995 (=CH), 1723 (C=O), 1605 (C=C) cm^{-1}; HRMS m/z 230.1305 (Calcd. 230.1307 for $C_{15}H_{18}O_2$).

3,4-Dihydro-3-(α-styryl)isocoumarin (Table 4, entry 18)

This compound was obtained in 54 % yield from the reaction of α-iodostyrene with *o*-vinylbenzoic acid for 14 hours at 50 °C: ^1H NMR ($CDCl_3$) δ 2.95 (dd, 1 H, J = 16.5, 4.2 Hz), 3.00 (dd, 1 H, J = 16.2, 10.5 Hz), 5.50 (dd, 1 H, J = 10.3, 3.9 Hz), 5.40 (s, 1 H), 5.60 (s, 1 H), 7.10 (d, 1 H, J = 7.5 Hz), 7.30-7.40 (m, 6 H), 7.50 (td, 1 H, J = 7.2, 1.2 Hz), 8.10 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 33.1, 78.2, 115.8, 125.0, 127.0, 127.3, 127.8, 128.1, 128.6, 130.3, 133.8, 138.6, 138.8, 146.0, 165.2; IR ($CDCl_3$) 2915 (=CH), 1725 (C=O), 1604 (C=C) cm^{-1}; HRMS m/z 250.0990 (Calcd. 250.0994 for $C_{17}H_{14}O_2$).

3-(1-Cyclohexenyl)-3,4-dihydroisocoumarin (Table 4, entry 22)

This compound was obtained in 82 % yield from the reaction of 1-(trifluoromethanesulfonyloxy)cyclohexene with *o*-vinylbenzoic acid for 10 hours at 50 °C: ^1H

NMR ($CDCl_3$) δ 1.50-1.80 (m, 4 H), 2.00-2.30 (m, 4 H), 2.80 (dd, 1 H, J = 16.2, 3.0 Hz), 3.20 (dd, 1 H, J = 15.9, 12.3 Hz), 4.80 (d, 1 H, J = 11.7 Hz), 5.80 (d, 1 H, J = 1.5 Hz), 7.20 (d, 1 H, J = 7.5 Hz), 7.40 (t, 1 H, J = 7.8 Hz), 7.50 (td, 1 H, J = 7.5, 1.2 Hz), 8.10 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 22.2, 22.3, 24.1, 25.0, 32.0, 82.5, 125.1, 126.7, 127.3, 127.5, 130.2, 133.8, 134.6, 139.4, 165.7; IR ($CDCl_3$) 2926 (=CH), 1731 (C=O), 1606 (C=C) cm^{-1}; HRMS m/z 228.1150 (Calcd. 228.1150 for $C_{15}H_{16}O_2$).

3,4-Dihydro-3-(1-ethyl-1-butenyl)isocoumarin (Table 4, entry 25)

This compound was obtained in 59 % yield from the reaction of (*E*)-3-iodo-3-hexene with *o*-vinylbenzoic acid for 16 hours at 75 °C: ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7.5 Hz), 1.08 (t, 3 H, J = 7.5 Hz), 2.00-2.35 (m, 4 H), 2.90 (dd, 1 H, J = 16.2, 2.7 Hz), 3.20 (dd, 1 H, J = 15.9, 12.3 Hz), 4.90 (dd, 1 H, J = 12.0, 2.7 Hz), 5.60 (t, 1 H, J = 7.2 Hz), 7.20 (d, 1 H, J = 8.4 Hz), 7.30 (t, 1 H, J = 7.8 Hz), 7.50 (td, 1 H, J = 7.5, 1.2 Hz), 8.10 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 20.5, 20.8, 32.0, 82.0, 125.0, 127.3, 127.8, 130.0, 131.0, 133.0, 137.0, 139.0, 165.0; IR ($CDCl_3$) 2933 (=CH), 1723 (C=O), 1606 (C=C) cm^{-1}; HRMS m/z 230.1307 (Calcd. 230.1307 for $C_{15}H_{18}O_2$).

(*E*)-3,4-Dihydro-3-((*E*)-1-hexenyl)-4-methylisocoumarin and 3-((*E*)-1-heptenyl)-3-methylphthalide (Table 4, entry 26)

(*E*)-3,4-Dihydro-3-((*E*)-1-hexenyl)-4-methylisocoumarin was obtained in 68 % yield along with 3-((*E*)-1-heptenyl)-3-methylphthalide and unknowns (57:29:14) as an inseparable mixture from the reaction of (*E*)-1-iodo-1-hexene with *o*-isopropenylbenzoic acid for 48 hours at 80 °C: ^1H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.9 Hz), 1.37 (d, 3 H, J = 7.2 Hz), 3.03 (m, 1 H), 4.68 (t, 1 H, J = 7.2 Hz), 5.52 (dd, 1 H, J = 15.3, 7.5 Hz), 5.80 (dt, 1 H, J = 15.0, 7.8 Hz), 7.32 (d, 1 H, J = 7.8 Hz), 7.38 (t, 1 H, J = 7.5 Hz), 7.58 (td, 1 H, J = 7.5, 1.2

Hz), 8.09 (d, 1 H, J = 7.8 Hz) (several peaks can't be assigned due to overlap). ^{13}C NMR, IR, and HRMS analyses were not performed due to the presence of unknowns.

3-((*E*)-1-Heptenyl)-3-methylphthalide: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.2 Hz), 1.73 (s, 3 H), 5.65-5.62 (m, 1 H), 5.80-5.96 (m, 1 H).

3,4-Dihydro-3-methoxycarbonyl-6-methyl-1-oxobenzoxocin (Table 4, entry 27)

This compound was obtained in 63 % yield from the reaction of methyl *trans* -β-bromoacrylate with *o*-isopropenylbenzoic acid for 36 hours at 100 °C: ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3 H), 2.67-2.85 (m, 2 H), 3.64 (s, 3 H), 5.82 (dt, 1 H, J = 15.6, 0.9 Hz), 6.62-6.72 (m, 1 H), 7.34 (d, 1 H, J = 7.8 Hz), 7.48 (td, 1 H, J = 7.2, 0.9 Hz), 7.63 (td, 1 H, J = 7.8, 0.9 Hz), 7.83 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 25.8, 42.7, 51.6, 85.9, 120.9, 125.7, 125.8, 126.0, 129.4, 134.3, 140.8, 152.7, 166.0, 169.2; IR ($CDCl_3$) 2985 (=CH), 1761 (C=O), 1720 (C=O), 1648 (C=C) cm^{-1}; GC-MS 246 (M^+), 215 (M^+ - CH_3O).

3-((*E*)-1-Methyl-1-heptenyl)phthalide and 3,4-dihydro-3-((*E*)-1-hexenyl)-3-methylisocoumarin (Table 4, entry 28)

3-((*E*)-1-Methyl-1-heptenyl)phthalide was obtained in 14 % yield along with a small amount of 3,4-dihydro-3-((*E*)-1-hexenyl)-3-methylisocoumarin and unknowns (77:9:16) as an inseparable mixture from the reaction of methyl (*E*)-1-iodo-1-hexene with *o*-((*E*)-1-propenyl)benzoic acid for 18 hours at 60 °C: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 6.9 Hz), 1.30 (s, 3 H), 1.25-1.50 (m, 6 H), 2.09-2.16 (m, 2 H), 5.78 (s, 1 H), 5.91 (t, 1 H, J = 6.9 Hz), 7.35 (d, 1 H, J = 7.5 Hz), 7.54 (t, 1 H, J = 7.5 Hz), 7.67 (t, 1 H, J = 7.5 Hz), 7.92 (d, 1 H, J = 7.5 Hz). There was not enough material for ^{13}C NMR, IR, and HRMS analyses.

3,4-Dihydro-3-((*E*)-1-hexenyl)-3-methylisocoumarin: ^{1}H NMR ($CDCl_3$) δ 5.64 (d, 1 H, J = 15.6 Hz), 5.84 (dt, 1 H, J = 15.6, 6.9 Hz).

2-Vinylphenol[26]

n-BuLi (20 mmol) was added to a solution of methyltriphenylphosphonium bromide (20 mmol) in 28 mL of THF at 0 °C. After 30 minutes, a solution of 2-hydroxybenzaldehyde (10 mmol) in 10 mL of THF was added to the solution of ylide and the mixture was stirred for 2 hours at room temperature. The mixture was worked up with water and extracted with ether (2 x 100 mL), dried over $MgSO_4$, concentrated in vacuo, and columned to give the product in 67 % yield: ^{1}H NMR ($CDCl_3$) δ 5.00 (br s, 1 H), 5.36 (dd, 1 H, J = 11.1, 1.2 Hz), 5.74 (dd, 1 H, J = 17.7, 0.9 Hz), 6.79 (d, 1 H, J = 8.1 Hz), 6.91 (t, 1 H, J = 7.5 Hz), 6.93 (dd, 1 H, J = 17.7, 11.4 Hz), 7.14 (td, 1 H, J = 8.4, 1.5 Hz), 7.38 (dd, 1 H, J = 7.5, 1.2 Hz).

2-Isopropenylphenol[26]

This compound was prepared from 2-hydroxyacetophenone in 75 % yield by using the same procedure as that used for 2-vinylphenol: ^{1}H NMR ($CDCl_3$) δ 2.10 (d, 3 H, J = 1.2 Hz), 5.13 (s, 1 H), 5.37- 5.40 (m, 1 H), 5.72 (s, 1 H), 6.85-6.94 (m, 2 H), 7.12-7.18 (m, 2 H).

General procedure for the reactions of *o*-allylic phenols with vinylic halides

To a 1 dram vial were added $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), vinylic halide (0.25 mmol), the *o*-allylic phenol (0.38 mmol), *n*-Bu_4NCl (0.28 mmol), Na_2CO_3 (0.88 mmol), and DMF (1.2 mL). The vial was flushed with nitrogen gas and capped with a screw-cap containing a teflon liner. After heating at 80 °C for 1 day, the reaction mixture was diluted with ether and washed with saturated NH_4Cl, followed by water. The organic layer was then

dried over $MgSO_4$, filtered, concentrated, and purified via flash column chromatography (silica gel, hexane/EtOAc as eluents)

3,4-Dihydro-2-((*E*)-β-styryl)benzopyran and 2,3-dihydro-2-methyl-2-((*E*)-β-styryl)benzofuran (Table 5, entry 1)

3,4-Dihydro-2-((*E*)-β-styryl)benzopyran was obtained in 90 % yield along with a small amount of 2,3-dihydro-2-methyl-2-((*E*)-β-styryl)benzofuran (83:17) as an inseparable mixture from the reaction of (*E*)-β-bromostyrene with *o*-allylphenol using procedure A for 24 hours at 80 °C: ^{1}H NMR ($CDCl_3$) δ 1.88-2.01 (m, 1 H), 2.01-2.18 (m, 1 H), 2.76-2.96 (m, 2 H), 4.68-4.75 (m, 1 H), 6.34 (dd, 1 H, J = 15.9, 6.0 Hz), 6.71 (d, 1 H, J = 15.9 Hz), 6.82-6.89 (m, 2 H), 7.05-7.16 (m, 2 H), 7.22-7.43 (m, 5 H); ^{13}C NMR of mixture ($CDCl_3$) δ 24.4, 28.0, 76.2, 116.9, 120.2, 121.8, 126.6, 127.3, 127.8, 128.5, 128.7, 130.0, 131.5, 136.5, 154.5 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2952 (=CH), 1608 (C=C), 1229 (C-O) cm^{-1}; HRMS of mixture m/z 236.1199 (Calcd. 236.1201 for $C_{17}H_{16}O$).

2,3-Dihydro-2-methyl-2-((*E*)-β-styryl)benzofuran: ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 3.14 (d, 1 H, J = 15.3 Hz), 3.27 (d, 1 H, J = 15.6 Hz).

3,4-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)benzopyran and 2,3-dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)-2-methylbenzofuran (Table 5, entry 2)

3,4-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)benzopyran was obtained in 35 % yield along with a small amount of 2,3-dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)-2-methylbenzofuran as an inseparable mixture 91:9 from the reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene with *o*-allylphenol using procedure A for 24 hours at 80 °C: ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.77-1.90 (m, 1 H), 1.97-2.06 (m, 1 H), 2.71-2.93 (m, 2 H), 4.43-4.49 (m,1 H), 5.52 (dd, 1 H, J

= 15.9, 6.9 Hz), 5.82 (dd, 1 H, J = 15.6, 0.6 Hz), 6.80-6.85 (m, 2 H), 7.03-7.12 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 24.7, 28.4, 29.5, 33.0, 76.9, 116.9, 120.0, 121.9, 124.4, 127.2, 129.4, 129.5, 144.2 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2959 (=CH), 1582 (C=C), 1230 (C-O) cm^{-1}; HRMS of mixture m/z 216.1518 (Calcd. 216.1514 for $C_{15}H_{20}O$).

2,3-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)-2-methylbenzofuran: ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.52 (s, 3 H), 3.01 (d, 1 H, J = 15.3 Hz), 3.17 (d, 1 H, J = 14.7 Hz).

3,4-Dihydro-2-(2-methyl-1-propenyl)benzopyran and 2,3-dihydro-2-methyl-2-(2-methyl-1-propenyl)benzofuran (Table 5, entry 3)

3,4-Dihydro-2-(2-methyl-1-propenyl)benzopyran was obtained in 90 % yield along with a small amount of 2,3-dihydro-2-methyl-2-(2-methyl-1-propenyl)benzofuran as an inseparable 90:10 mixture from the reaction of 1-iodo-2-methylpropene with *o*-allylphenol using procedure A for 24 hours at 80 °C: ^1H NMR ($CDCl_3$) δ 1.75 (d, 3 H, J = 1.2 Hz), 1.79 (d, 3 H, J = 0.9 Hz), 1.81-2.00 (m, 2 H), 2.70-2.94 (m, 2 H), 4.69-4.77 (m, 1 H), 5.34-5.38 (m, 1 H), 6.75-6.85 (m, 2 H), 7.03- 7.10 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 18.4, 24.8, 26.0, 28.1, 73.0, 116.9, 120.0, 121.8, 124.6, 127.2, 130.0, 137.1, 154.9 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2930 (=CH), 1607 (C=C), 1232 (C-O) cm^{-1}; HRMS of mixture m/z 188.1204 (Calcd. 188.1201 for $C_{13}H_{16}O$).

2,3-Dihydro-2-methyl-2-(2-methyl-1-propenyl)benzofuran: ^1H NMR ($CDCl_3$) δ 3.10 (d, 1 H, J = 15.3 Hz), 3.29 (d, 1 H, J = 15.3 Hz), 5.53-5.57 (m, 1 H).

3,4-Dihydro-2-(2-hexenyl)benzopyran and 2,3-dihydro-2-(2-hexenyl)-2-methylbenzofuran (Table 5, entry 4)

3,4-Dihydro-2-(2-hexenyl)benzopyran was obtained in 63 % yield along with a small amount of 2,3-dihydro-2-(2-hexenyl)-2-methylbenzofuran as an inseparable 91:9 mixture from

the reaction of 2-iodo-1-hexene with *o*-allylphenol using procedure A for 24 hours at 80 °C: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.2 Hz), 1.30-1.50 (m, 4 H), 1.83-2.23 (m, 4 H), 2.71- 2.93 (m, 2 H), 4.46 (br d, 1 H, J = 7.8 Hz), 4.96 (d, 1 H, J = 1.2 Hz), 5.14 (s, 1 H), 6.80- 6.86 (m, 2 H), 7.03-7.11 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 14.2, 22.7, 24.9, 26.7, 30.2, 31.7, 78.4, 110.6, 116.8, 120.0, 121.9, 127.3, 129.4, 148.8, 155.0 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2958 (=CH), 1608 (C=C), 1234 (C-O) cm^{-1}; HRMS of mixture m/z 216.1520 (Calcd. 216.1514 for $C_{15}H_{20}O$).

2,3-Dihydro-2-(2-hexenyl)-2-methylbenzofuran: ^{1}H NMR ($CDCl_3$) δ 4.79 (s, 1 H), 5.18 (s, 1 H).

3,4-Dihydro-2-((*E*)-1-hexenyl)benzopyran and 2,3-dihydro-2-((*E*)-1-hexenyl)-2-methylbenzofuran (Table 6, entry 5)

3,4-Dihydro-2-((*E*)-1-hexenyl)benzopyran was obtained in 90 % yield along with a small amount of 2,3-dihydro-2-((*E*)-1-hexenyl)-2-methylbenzofuran as an inseparable 86:14 mixture from the reaction of (*E*)-1-iodo-1-hexene with *o*-allylphenol using procedure B for 36 hours at 80 °C: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6.9 Hz), 1.25-1.45 (m, 4 H), 1.77-2.11 (m, 4 H), 2.71-2.93 (m, 2 H), 4.44-4.50 (m, 1 H), 5.61 (ddt, 1 H, J = 15.3, 6.6, 1.2 Hz), 5.81 (dt, 1 H, J = 15.6, 6.6 Hz), 6.78-6.85 (m, 2 H), 7.02-7.13 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 14.1, 22.3, 24.5, 28.1, 31.2, 32.1, 76.5, 116.8, 120.0, 121.8, 127.2, 129.3, 129.5, 133.8, 154.7 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2955 (=CH), 1610 (C=C), 1230 (C-O) cm^{-1}; HRMS of mixture m/z 216.1518 (Calcd. 216.1514 for $C_{15}H_{20}O$).

2,3-Dihydro-2-((*E*)-1-hexenyl)-2-methylbenzofuran: ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3 H), 3.02 (d, 1 H, J = 15.6 Hz), 3.16 (d, 1 H, J = 15.6 Hz).

3,4-Dihydro-2-(1-ethyl-1-butenyl)benzopyran (Table 6, entry 11)

3,4-Dihydro-2-(3-hexenyl)benzopyran was obtained in 44 % yield as an inseparable mixture of stereoisomers (*Z* / *E* or *E* / *Z* = 83 / 17) from the reaction of (*E*)-3-iodo-3-hexene with *o*-allylphenol using procedure B for 36 hours at 80 °C: Major isomer ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3 H, *J* = 7.5 Hz), 1.07 (t, 3 H, *J* = 7.8 Hz), 1.85-2.25 (m, 6 H), 2.72-2.94 (m, 2 H), 4.39 (dd, 1 H, *J* = 9.9, 2.1 Hz), 5.51 (t, 1 H, *J* = 7.2 Hz), 6.79-6.85 (m, 2 H), 7.03-7.10 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 14.4, 20.6, 20.8, 24.0, 25.4, 25.8, 27.1, 27.2, 80.2, 116.8, 116.9, 119.9, 120.0, 127.2, 128.6, 129.4, 129.5, 139.6, 139.9, 155.3 (several peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2965 (=CH), 1609 (C=C), 1233 (C-O) cm^{-1}; HRMS of mixture m/z 216.1519 (Calcd. 216.1514 for $C_{15}H_{20}O$).

Minor isomer: ^{1}H NMR ($CDCl_3$) δ 4.88 (dd, 1 H, *J* = 11.4, 1.8 Hz), 5.33 (t, 1 H, *J* = 7.2 Hz).

3,4-Dihydro-2-((*E*)-1-hexenyl)-2-methylbenzopyran and 2,3-dihydro-2-ethyl-2-((*E*)-1-hexenyl)benzofuran (Table 7, entry 1)

3,4-Dihydro-2-((*E*)-1-hexenyl)-2-methylbenzopyran was obtained in 37 % yield along with a small amount of 2,3-dihydro-2-ethyl-2-((*E*)-1-hexenyl)benzofuran as an inseparable 88:12 mixture from the reaction of (*E*)-1-iodo-1-hexene with *o*-crotylphenol using procedure A for 24 hours at 100 °C: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H, *J* = 7.2 Hz), 1.17-1.34 (m, 4 H), 1.41 (s, 3 H), 1.75-2.10 (m, 4 H), 2.63-2.73 (m, 2 H), 5.47 (d, 1 H, *J* = 15.6 Hz), 5.58 (dt, 1 H, *J* = 15.6, 6.3 Hz), 6.76-6.84 (m, 2 H), 7.00-7.12 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 22.1, 22.6, 27.3, 29.8, 31.4, 32.0, 32.3, 76.3, 116.9, 119.6, 121.5, 127.2, 129.3, 130.0, 133.2, 154.1 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2957 (=CH), 1609 (C=C), 1240 (C-O) cm-1; HRMS of mixture m/z 230.1670 (Calcd. 230.1671 for $C_{16}H_{22}O$).

2,3-Dihydro-2-ethyl-2-((*E*)-1-hexenyl)benzofuran: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3 H, *J* = 7.5 Hz), 3.09 (br s, 2 H), 5.70 (dt, 1 H, *J* = 15.6, 6.6 Hz).

3,4-Dihydro-2-methyl-2-((*E*)-β-styryl)benzopyran and 2,3-dihydro-2-ethyl-2-((*E*)-β-styryl)benzofuran (Table 7, entry 2)

3,4-Dihydro-2-methyl-2-((*E*)-β-styryl)benzopyran was obtained in 64 % yield along with a small amount of 2,3-dihydro-2-ethyl-2-((*E*)-β-styryl)benzofuran as an inseparable 80:20 mixture from the reaction of (*E*)-β-bromostyrene with *o*-crotylphenol using procedure A for 24 hours at 100 °C: ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 3 H), 1.85-2.06 (m, 2 H), 2.65-2.76 (m, 2 H), 6.23 (d, 1 H, *J* = 16.2 Hz), 6.52 (d, 1 H, *J* = 15.9 Hz), 6.82 (td, 1 H, *J* = 7.5, 0.6 Hz), 6.91 (d, 1 H, *J* = 8.4 Hz), 7.01 (d, 1 H, *J* = 7.2 Hz), 7.12 (t, 1 H, *J* = 8.1 Hz), 7.19-7.38 (m, 5 H); ^{13}C NMR of mixture ($CDCl_3$) δ 22.7, 32.3, 40.5, 116.9, 119.9, 121.4, 126.4, 127.4, 127.5, 128.5, 128.8, 129.4, 133.1, 136.7, 153.9 (one peak is not seen due to overlap); IR of mixture ($CDCl_3$) 2973 (=CH), 1610 (C=C), 1238 (C-O) cm^{-1}; HRMS of mixture m/z 250.1362 (Calcd. 250.1358 for $C_{18}H_{18}O$).

2,3-Dihydro-2-ethyl-2-((*E*)-β-styryl)benzofuran: ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3 H, *J* = 7.5 Hz), 3.20 (br s, 2 H), 6.29 (d, 1 H, *J* = 16.2 Hz), 6.65 (d, 1 H, *J* = 15.9 Hz).

3,4-Dihydro-2-methyl-2-(2-methyl-1-propenyl)benzopyran and 2,3-dihydro-2-ethyl-2-(2-methyl-1-propenyl)benzofuran (Table 8, entry 4)

3,4-Dihydro-2-methyl-2-(2-methyl-1-propenyl)benzopyran was obtained in 53 % yield along with a small amount of 2,3-dihydro-2-ethyl-2-(2-methyl-1-propenyl)benzofuran (93:7) as an inseparable mixture from the reaction of 1-iodo-2-methylpropene with *o*-crotylphenol using procedure B for 72 hours at 100 °C: ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3 H), 1.64 (d, 3 H, *J* = 0.9 Hz), 1.79 (d, 3 H, *J* = 1.2 Hz), 1.71-1.81 (m, 1 H), 1.93-2.05 (m, 1 H), 2.64-2.87

(m, 2 H), 5.15-5.18 (m, 1 H), 6.77-6.84 (m, 2 H), 7.01-7.10 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 18.6, 22.6, 27.3, 27.5, 33.4, 76.4, 117.1, 119.7, 121.8, 127.0, 128.0, 129.3, 135.5, 154.0 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 1219 (C-O) cm^{-1}; HRMS of mixture m/z 202.1359 (Calcd. 202.1358 for $C_{14}H_{18}O$).

2,3-Dihydro-2-ethyl-2-(2-methyl-1-propenyl)benzofuran: ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.2 Hz), 3.10-3.30 (m, 2 H), 5.47 (s, 1 H).

3,4-Dihydro-3-methyl-2-((*E*)-β-styryl)benzopyran (Table 9, entry 1)

3,4-Dihydro-3-methyl-2-((*E*)-β-styryl)benzopyran was obtained in 75 % yield as an inseparable mixture of stereoisomers (*cis* / *trans* = 77 / 23) from the reaction of (*E*)-β-bromostyrene with *o*-methallylphenol using procedure B for 24 hours at 100 °C: *cis* -isomer ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 6.9 Hz), 2.20-2.35 (m, 1 H), 2.54 (dd, 1 H, J = 16.5, 7.2 Hz), 2.94 (dd, 1 H, J = 16.2, 5.4 Hz), 4.70-4.76 (m, 1 H), 6.27 (dd, 1 H, J = 15.9, 6.6 Hz), 6.69 (d, 1 H, J = 16.2 Hz), 6.83-6.89 (m, 2 H), 7.04 (d, 1 H, J = 7.5 Hz) (several peaks can't be assigned due to overlap); ^{13}C NMR of mixture ($CDCl_3$) δ 30.9, 31.7, 116.5, 116.6, 116.9, 120.3, 121.0, 121.8, 125.9, 126.5, 126.6, 127.3, 127.4, 127.9, 128.5, 129.3, 130.0, 132.5, 133.4, 136.6, 153.7 (several peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2969 (=CH), 1608 (C=C), 1230 (C-O) cm^{-1}; HRMS of mixture m/z 250.1365 (Calcd. 250.1358 for $C_{18}H_{18}O$).

trans -3,4-Dihydro-3-methyl-2-((*E*)-β-styryl)benzopyran: ^1H NMR ($CDCl_3$) δ 1.75-2.08 (m, 1 H), 2.85 (dd, 1 H, J = 15.9, 4.8 Hz), 4.28 (t, 1 H, J = 8.1 Hz).

3,4-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)-3-methylbenzopyran (Table 9, entry 3)

3,4-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)-3-methylbenzopyran was obtained in 83 % yield as an inseparable mixture of stereoisomers (*cis* / *trans* = 70 / 30) from the reaction of

(*E*)-1-bromo-3,3-dimethyl-1-butene with *o*-methallylphenol using procedure B for 24 hours at 100 °C: *cis* -isomer ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3 H, *J* = 7.2 Hz), 1.03 (s, 9 H), 2.11-2.22 (m, 1 H), 2.48-2.54 (m, 1 H), 2.90 (dd, 1 H, *J* = 16.2, 5.4 Hz), 4.51 (dd, 1 H, *J* = 6.9, 2.7 Hz), 5.44 (dd, 1 H, *J* = 15.6, 6.9 Hz), 5.79 (dd, 1 H, *J* = 15.6, 0.6 Hz), 6.80-6.88 (m, 2 H), 7.00 - 7.15 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 29.4, 29.5, 29.6, 30.7, 31.8, 33.2, 33.5, 79.7, 83.3, 116.5, 116.7, 120.0, 121.1, 122.1, 123.4, 127.2, 129.2, 129.9, 145.3, 146.3, 153.9, 154.4 (several peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2962 (=CH), 1610 (C=C), 1232 (C-O) cm^{-1}; HRMS of mixture m/z 230.1677 (Calcd. 230.1358 for $C_{16}H_{22}O$).

trans -3,4-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)-3-methylbenzopyran: ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 6.9 Hz), 1.07 (s, 9 H), 1.80-1.93 (m, 1 H), 2.80 (dd, 1 H, *J* = 16.5, 5.1 Hz), 4.03 (t, 1 H, *J* = 8.7 Hz), 5.81 (d, 1 H, *J* = 15.6 Hz).

3,4-Dihydro-3-methyl-2-(2-methyl-1-propenyl)benzopyran (Table 9, entry 4)

3,4-Dihydro-3-methyl-2-(2-methyl-1-propenyl)benzopyran was obtained in 60 % yield as an inseparable mixture of stereoisomers (*cis* / *trans* = 50 / 50) and unknowns in a 10:1 ratio from the reaction of 1-iodo-2-methylpropene with *o*-methallylphenol for 24 hours at 100 °C: *cis* -isomer ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 7.2 Hz), 1.77 (s, 3 H), 2.10-2.21 (m, 1 H), 2.53-2.58 (m, 1 H), 2.90 (dd, 1 H, *J* = 16.2, 5.7 Hz), 4.37 (t, 1 H, *J* = 9.0 Hz), 5.34 (dt, 1 H, *J* = 9.0, 1.5 Hz), 6.78-6.86 (m, 2 H), 7.01-7.14 (m, 2 H); ^{13}C NMR of mixture ($CDCl_3$) δ 18.7, 18.8, 26.1, 26.2, 30.6, 30.7, 31.7, 31.8, 33.6, 33.7, 75.4, 78.2, 116.5, 116.8, 120.0, 121.1, 121.2, 122.1, 123.8, 127.1, 129.2, 129.9, 130.7, 136.2, 137.6, 138.3, 153.9, 154.6; IR of mixture ($CDCl_3$) 2969 (=CH), 1610 (C=C), 1234 (C-O) cm^{-1}; HRMS of mixture m/z 202.1359 (Calcd. 202.1358 for $C_{14}H_{18}O$).

trans -3,4-Dihydro-3-methyl-2-(2-methyl-1-propenyl)benzopyran: ^{1}H NMR ($CDCl_3$) δ 1.73 (d, 3 H, J = 0.9 Hz), 2.48-2.53 (m, 1 H), 2.82 (dd, 1 H, J = 16.5, 5.1 Hz), 4.82 (dd, 1 H, J = 9.0, 3.0 Hz), 5.28 (dt, 1 H, J = 9.3, 1.2 Hz).

2,3-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)-2-methylbenzofuran (Table 10, entry 3)

This compound was obtained in 20 % yield from the reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene with *o*-((*E*)-1-propenyl)phenol using procedure B for 48 hours at 100 °C: ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.52 (s, 3 H), 3.02 (d, 1 H, J = 15.3 Hz), 3.17 (d, 1 H, J = 15.6 Hz), 5.61 (d, 1 H, J = 15.9 Hz), 5.75 (d, 1 H, J = 15.9 Hz), 6.74-6.85 (m, 2 H), 7.08-7.14 (m, 2 H); IR ($CDCl_3$) 2930 (=CH), 1597 (C=C), 1245 (C-O) cm^{-1}; HRMS m/z 216.1520 (Calcd. 216.1514 for $C_{15}H_{20}O$). There was not enough material for ^{13}C NMR spectral analysis.

2,3-Dihydro-2-methyl-2-((*E*)-β-styryl)benzofuran (Table 11, entry 8)

This compound was obtained in 54 % yield from the reaction of (*E*)-β-bromostyrene with *o*-((*E*)-1-propenyl)phenol using procedure C for 24 hours at 100 °C: ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3 H), 3.30 (d, 1 H, J = 15.6 Hz), 3.44 (d, 2 H, J = 15.6 Hz), 6.56 (d, 1 H, J = 16.2 Hz), 6.82 (d, 1 H, J = 15.9 Hz), 6.98 (m, 2 H), 7.27-7.55 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 26.7, 42.7, 87.6, 109.6, 120.3, 125.1, 126.5, 126.6, 127.7, 128.0, 128.2, 128.6, 133.2, 136.6, 158.8; IR ($CDCl_3$) 2930 (=CH), 1597 (C=C), 1244 (C-O) cm^{-1}; HRMS m/z 236.1208 (Calcd. 236.1201 for $C_{17}H_{16}O$).

2,3-Dihydro-2-((*E*)-β-styryl)benzofuran and 2,3-dihydro-2-phenylbenzoxepin (Table 12, entry 2)

2,3-Dihydro-2-((*E*)-β-styryl)benzofuran was obtained in 61 % yield along with a small amount of 2,3-dihydro-2-phenylbenzoxepin as an inseparable 91:9 mixture from the reaction of (*E*)-β-bromostyrene with *o*-vinylphenol using procedure B for 24 hours at 100 °C : ^{1}H NMR ($CDCl_3$) δ 3.09 (dd,1 H, J = 15.6, 7.8 Hz), 3.44 (dd, 1 H, J = 16.2, 8.4 Hz), 5.36 (dtd, 1 H, J = 15.3, 8.1, 0.6 Hz), 6.36 (dd, 1 H, J = 15.6, 7.2 Hz), 6.71 (d, 1 H, J = 15.6 Hz), 6.81-6.89 (m, 2 H), 7.10-7.20 (m, 2 H), 7.24-7.42 (m, 5 H); ^{13}C NMR of mixture ($CDCl_3$) δ 36.4, 83.5, 109.5, 120.5, 124.9, 126.5, 126.7, 128.0, 128.1, 128.4, 128.6, 132.3, 136.3, 159.4 (peaks from the minor isomer are not seen); IR of mixture ($CDCl_3$) 2954 (=CH), 1598 (C=C), 1229 (C-O) cm^{-1}; HRMS of mixture m/z 222.1051 (Calcd. 222.1045 for $C_{16}H_{14}O$).

2,3-Dihydro-2-phenylbenzoxepin: ^{1}H NMR ($CDCl_3$) δ 2.91 (dd, 1 H, J = 13.8, 6.3 Hz), 4.96-5.08 (m, 1 H), 5.68 (dd, 1 H, J = 9.9, 3.6 Hz), 6.41 (d, 1 H, J = 9.6 Hz).

2,3-Dihydro-2-((*E*)-3,3-dimethyl-1-butenyl)benzofuran (Table 12, entry 6)

This compound was obtained in 53 % yield from the reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene with *o*-vinylphenol using procedure C for 48 hours at 100 °C : ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H), 2.97 (dd, 1 H, J = 15.6, 8.4 Hz), 3.32 (dd, 1 H, J = 15.6, 9.0 Hz), 5.13 (q, 1 H, J = 8.4 Hz), 5.57 (dd, 1 H, J = 15.3, 7.8 Hz), 5.84 (dd, 1 H, J = 15.0, 0.9 Hz), 6.78 (d, 1 H, J = 7.8 Hz), 6.83 (td, 1 H, J = 7.5, 0.6 Hz), 7.08-7.16 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.4, 33.0, 36.5, 84.5, 109.4, 120.3, 124.1, 124.8, 127.0, 128.0, 145.6, 159.4; IR ($CDCl_3$) 2961 (=CH), 1598 (C=C), 1230 (C-O) cm^{-1}; HRMS m/z 202.1362 (Calcd. 202.1358 for $C_{14}H_{18}O$).

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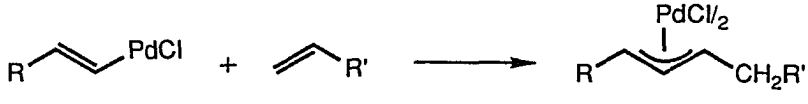
SYNTHESIS OF NITROGEN HETEROCYCLES VIA PALLADIUM-CATALYZED COUPLING OF VINYLIC HALIDES WITH FUNCTIONALLY-SUBSTITUTED ALKENES

Portions of this paper have been published or will be submitted for publication in the *Journal of Organic Chemistry* and *Tetrahedron Letters*

Richard C. Larock and Hoseok Yang

Introduction

Since Larock first demonstrated in 1976 that π-allylpalladium compounds are readily formed by the reaction of vinylpalladium compounds and alkenes (eq. 1),[1] π-allylpalladium species have become important intermediates in organic synthesis due to their easy availability, their ability to accommodate many functional groups, and their high reactivity toward a variety of nucleophiles.

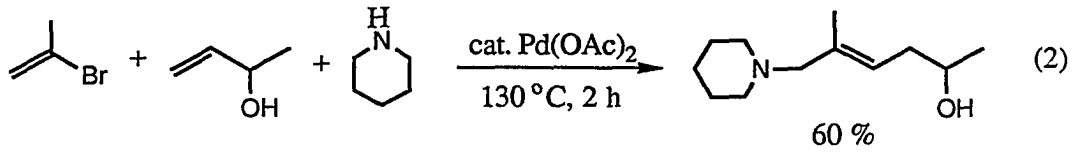


(1)

The most important property of π-allylpalladium species is their reaction with nucleophiles, which results in a new carbon-carbon or carbon-heteroatom bond, depending on the nature of the nucleophile. Various nucleophiles have been used in the displacement reactions of π-allylpalladium species and several reviews of π-allylpalladium chemistry have been written.[2]

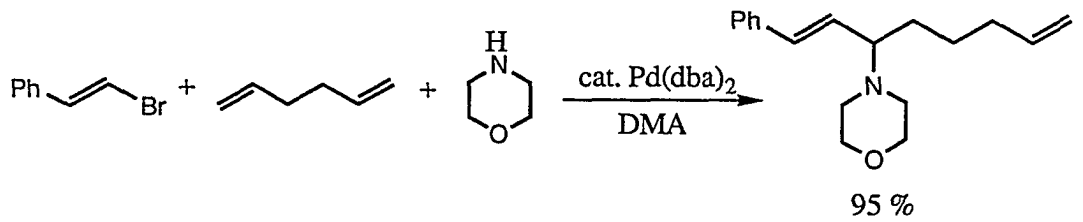
In 1978, Heck reported the palladium-catalyzed synthesis of allylic tertiary amines from vinylic bromides and olefins using secondary amines as the nucleophiles,[3] but this process

provided an isomeric mixture of products, as well as dienes, in significant amounts in some examples (eq. 2).



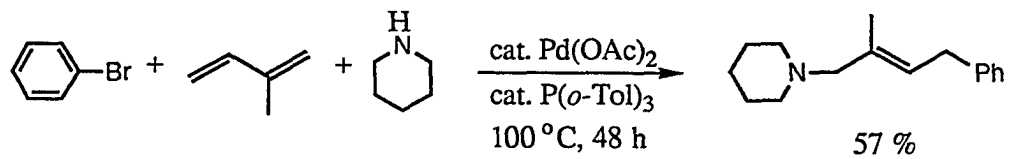
(2)

A similar process has recently been investigated extensively by Larock and Tu.[4] This study revealed that the cross-coupling of three components generally produces a mixture of regioisomers due to external and internal addition of the σ-palladium species to the double bond and attack of the nucleophile at either end of the π-allylpalladium system. The ratio of isomers and the yields were found to be dependent upon the substrates used (eq. 3).



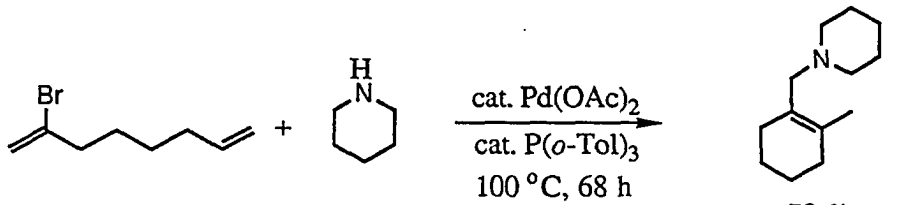
(3)

π-Allylpalladium species can be also prepared from the reaction of σ-palladium species and dienes. This approach has been used in the synthesis of allylic amines from the reaction of conjugated and non-conjugated dienes with vinylic and aryl halides (eq. 4).[5]



(4)

Heck also introduced the palladium-catalyzed cyclization of bromodienes in the presence of piperidine as the nucleophile to form 5- and 6-membered ring products (eq. 5).[6] This approach has been further explored in the synthesis of heterocycles from the reaction of bromodialkenylethers or amines in the presence of an amine nucleophile (eq. 6).[7] In this report, however, an attempt to form heterocycles by intramolecular nucleophilic attack of



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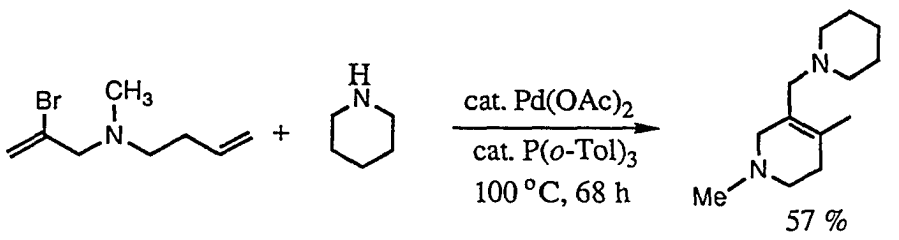
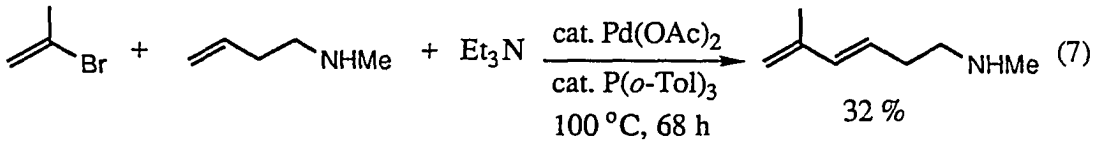


(6)

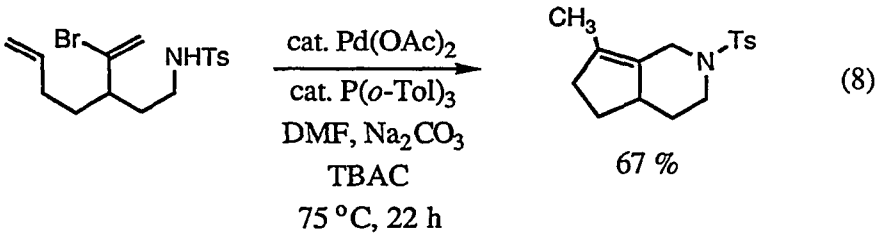
a secondary amine moiety upon a π-allylpalladium intermediate was not successful and only elimination occurred to form the dienylamine (eq. 7).



(7)

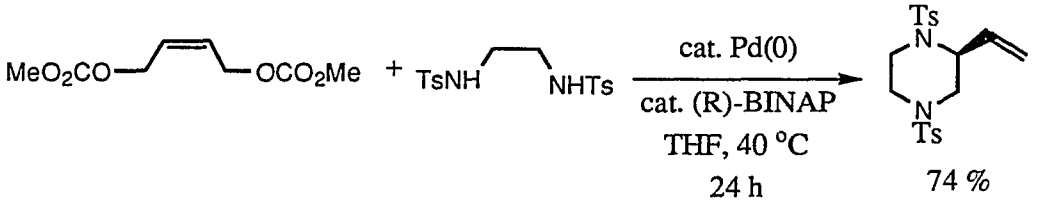
Recently, the success of the intramolecular palladium-catalyzed three-component cyclization of substrates containing vinylic halide, olefin, and sulfonamide moieties to generate

a diverse group of nitrogen heterocycles has been reported by Weinreb.[8] This methodology has been applied to the construction of both fused and bridged bicyclic systems (eq. 8).



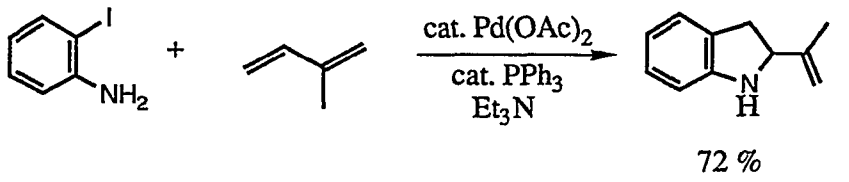
(8)

The use of allylic substrates[9] for the palladium-catalyzed process is another convenient route to nitrogen heterocyles and Hayashi was able to achieve catalytic asymmetric construction of morpholines and piperazines by palladium-catalyzed tandem allylic substitution reactions (eq. 9).[10]



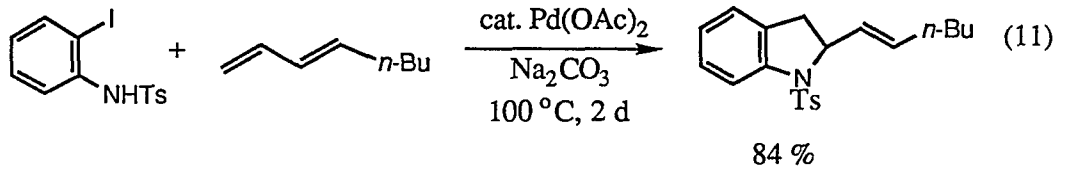
(9)

One of the useful methodologies for preparing nitrogen heterocycles is palladium-catalyzed annulation and various methods have been introduced in this area. In 1983, Dieck reported two examples of the palladium-catalyzed annulation of 1,3-dienes by *o*-iodoaniline. The corresponding 2,3-dihydroindoles were obtained in good yields (eq. 10).[11]



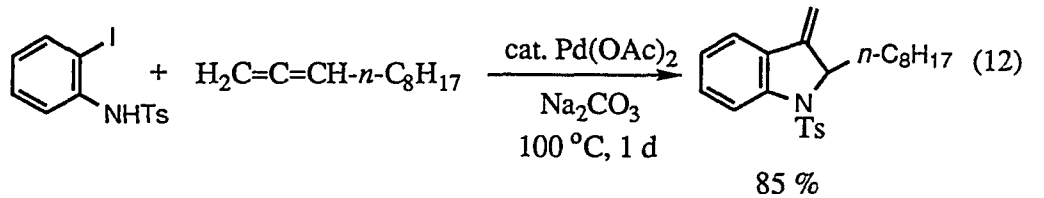
(10)

Larock also introduced a procedure for the preparation of nitrogen-containing heterocycles via palladium-assisted heteroannulation of simple 1,3- and 1,4-dienes, as well as vinylic cyclopropanes and cyclobutanes.[12] The disadvantage of having to prepare toxic arylmercury intermediates, however, has brought about an improved procedure. In this modified process, Larock was able to prepare a variety of heterocyclic compounds, including nitrogen heterocyles (eq. 11).[13]

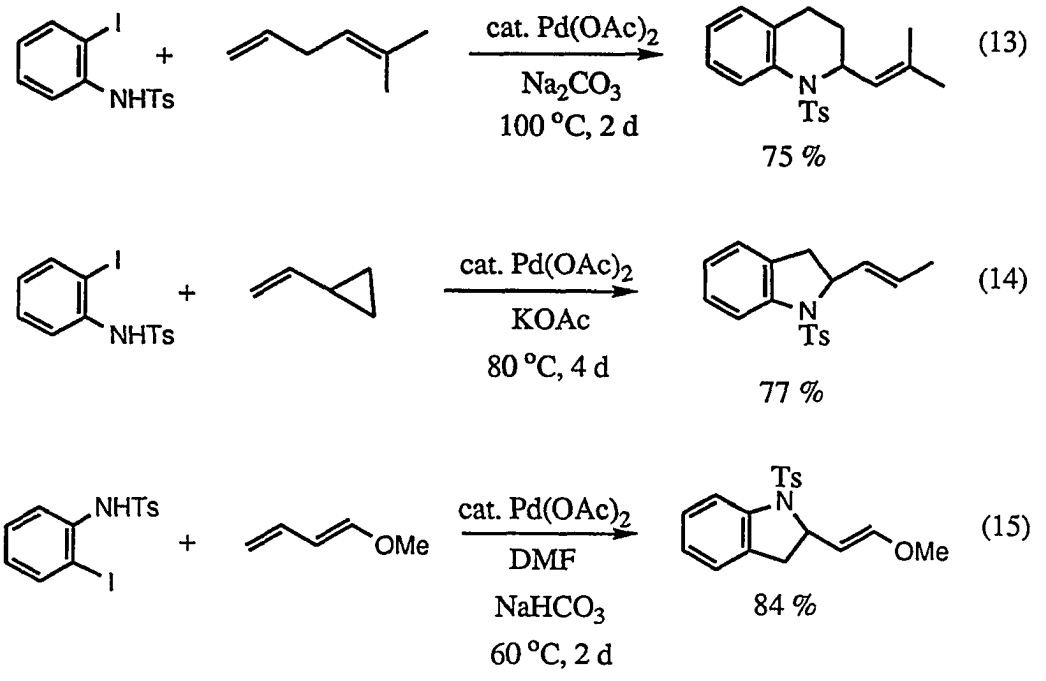


(11)

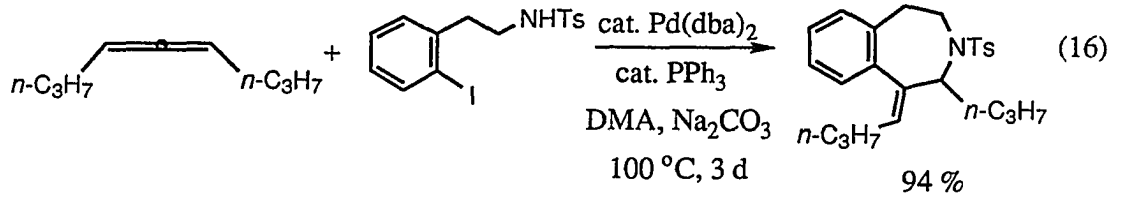
This approach has been further extended to analogous palladium-catalyzed annulations using 1,2-dienes,[14] non-conjugated dienes,[15] and vinylic cycloalkanes[16] and these methods have proven to be very useful in preparing various heterocycles (eqs. 12 - 14). In addition, both electronic and steric effects on the palladium-catalyzed annulation of 1,3-dienes have been explored by introducing an acetoxy or methoxy group on the double bond (eq. 15).[17]



(12)



Seven- and larger-membered nitrogen heterocycles have been synthesized successfully from the annulation of 1,2-dienes using vinylic or aryl halides containing a nitrogen nucleophile (eq. 16).[18]



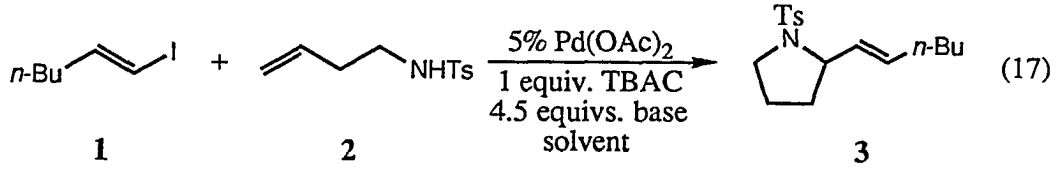
As discussed above, various methods have been developed for the synthesis of nitrogen heterocycles. However, in most cases these methods rely on the palladium-catalyzed annulation of aryl halides and alkenes or the coupling of three components with relatively little

attention being paid to the palladium-catalyzed coupling of vinylic halides and functional alkenes as an alternative to the synthesis of nitrogen heterocycles. Our prior experience with the palladium-catalyzed coupling of vinylic halides with alkenoic acids[19] and recent intramolecular versions of this type of process using olefinic sulfonamides by Weinreb and Herr[8] suggested that the analogous coupling of vinylic halides and olefinic sulfonamides should provide a convenient new route to nitrogen heterocycles. In this part of the dissertation, the successful palladium-catalyzed coupling of vinylic halides and olefinic sulfonamides will be discussed.

Results and Discussion

Synthesis of pyrrolidines and piperidines

Initial studies were aimed at finding the best reaction conditions for the palladium-catalyzed coupling of vinylic halides or triflates and olefinic sulfonamides. The reaction between (*E*)-1-iodo-1-hexene (**1**) and *N*-(3-butenyl)-*p*-toluenesulfonamide (**2**) was chosen as a model reaction for the synthesis of pyrrolidines (eq. 17). In the search for a set of reaction conditions that would maximize the yield of this reaction, important variables such as the base, the reaction temperature, the solvent, and the substituent on the nitrogen atom were explored extensively.



1 **2** **3** (17)

The reaction of (*E*)-1-iodo-1-hexene and *N*-(3-butenyl)-*p*-toluenesulfonamide in DMF was first attempted at 80 °C using a variety of bases and the results are summarized in Table 1. All of the reactions in Table 1 were initially run at 25 °C, but there was no significant

Table 1. Effect of Bases on the Palladium-catalyzed Coupling of (*E*)-1-Iodo-1-hexene (**1**) and *N*-(3-Butenyl)-*p*-toluenesulfonamide (**2**).[a]

entry	base (4.5 equivs.)	time (h)	% isolated yield **3**
1	Li_2CO_3	8[b]	4
2	Na_2CO_3	8[b]	38
3	K_2CO_3	8[b]	4
4	Cs_2CO_3	12[c]	5
5	$NaHCO_3$	8[b]	39
6	NaOAc	24[c]	29
7	KOAc	8[b]	36
8	CsOAc	12[c]	36
9	Et_3N	24[c]	16

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of *N*-(3-butenyl)-*p*-toluenesulfonamide, 1.0 equiv. of TBAC in 1 mL of DMF. [b]Reactions times after running the reaction for 12 hours at 25 °C. [c]Reaction times after running the reaction for 9 hours at 25 °C.

progress according to TLC analysis. Therefore, the temperature was raised to 80 °C. Among carbonate bases examined, Na_2CO_3 afforded the best yield, 38 %. Other carbonate bases provided small amounts of the product after the appropriate time intervals according to TLC analysis (entries 1- 4). In most cases, unreacted (*E*)-1-iodo-1-hexene still remained. $NaHCO_3$ also proved to be useful and the desired product was obtained in 39 % yield (entry 5). On the other hand, (entries 6 - 8). It is apparent that both the cation and the anion in the

base used play a role in acetate bases afforded the desired product in 29 to 36 % yields, regardless of the cation used this palladium process and it is not clear which one is more important at this point. Finally, an organic amine, Et3N, was investigated and it was found that a longer reaction time was required and the yield was not satisfactory (entry 9). From the results shown in Table 1, Na_2CO_3 and $NaHCO_3$ seemed to be better than other bases and the effects of other factors on the model reaction were examined by using these two bases (Table 2). Before the effect of the solvent was explored, the temperature was increased to 100 °C, because the reactions run at 80 °C were not complete in most cases. With regard to the solvent, it was found that moderately polar solvents, such as CH_3CN and DMF, are more effective than nonpolar solvents like THF and polar solvents, such as DMSO and HMPA. It appears that polar solvents lessen the activity of the catalyst by strong coordination. THF and DMA provided the desired product in 48 % yield (entries 1 and 4) and lower yields were obtained when DMSO and HMPA were employed in the presence of Na_2CO_3 (entries 5 and 6). The use of DMF increased the yield to 57 % (entry 3) and CH_3CN proved to be the best solvent. The desired product was obtained in 61% yield (entry 2). When the reactions were run using different solvents in the presence of $NaHCO_3$, similar results were obtained and CH_3CN remained the best solvent (entries 7 - 10). Based on the results shown in entries 1 - 10, two bases, Na_2CO_3 and $NaHCO_3$, are equally effective in the palladium-catalyzed coupling reaction of (*E*)-1-iodo-1-hexene and *N*-(3-butenyl)-*p*-toluenesulfonamide. Nonetheless, Na_2CO_3 was selected as the best base for this model system, because the use of Na_2CO_3 seemed to give cleaner reactions according to TLC analysis and it was proven later that Na_2CO_3 indeed is more effective.

With the best base and solvent at hand, other factors were also examined. First, the reactions were run at 120 °C in DMF and CH_3CN in order to decrease the reaction time. For the reaction using DMF, it took only 36 hours to reach completion, but a lower yield was

Table 2. Effects of the Solvent, the Ligand, the Temperature, the Stoichiometries, and the Source of Chloride on the Palladium-catalyzed Coupling of (*E*)-1-Iodo-1-hexene (**1**) and *N*-(3-Butenyl)-*p*-toluenesulfonamide (**2**).

entry	base (4.5 equivs.)	solvent (1 mL)	time (h)	% isolated yield **3**
1	Na_2CO_3	THF	58	48
2	Na_2CO_3	CH_3CN	60	61
3	Na_2CO_3	DMF	48	57
4	Na_2CO_3	DMA	36	48
5	Na_2CO_3	DMSO	60	39
6	Na_2CO_3	HMPA	48	44
7	$NaHCO_3$	THF	60	39
8	$NaHCO_3$	CH_3CN	60	60
9	$NaHCO_3$	DMF	36	57
10	$NaHCO_3$	DMSO	60	40
11[b]	Na_2CO_3	DMF	36	39
12[b]	Na_2CO_3	CH_3CN	56	57

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of *N*-(3-butenyl)-*p*-toluenesulfonamide, 1.0 equiv. of TBAC at 100 °C.
[b]Reactions were run at 120 °C.

Table 2. (Continued)

entry	base (4.5 equivs.)	solvent (1 mL)	time (h)	% isolated yield **3**
13[c]	Na_2CO_3	CH_3CN	48	46
14[d]	Na_2CO_3	CH_3CN	48	36
15[e]	Na_2CO_3	CH_3CN	60	56
16	Na_2CO_3	DMF	96	57
17	Na_2CO_3	CH_3CN	96	64
18	Na_2CO_3	CH_3CN	48	47
19[f]	Na_2CO_3	CH_3CN	120	22

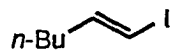
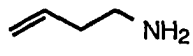
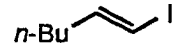
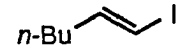
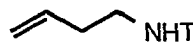
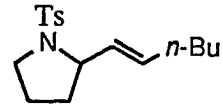
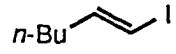
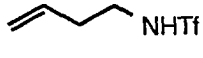
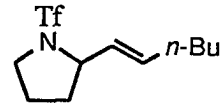
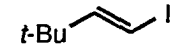
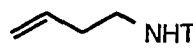
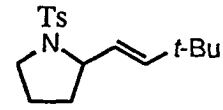
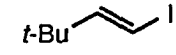
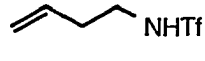
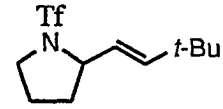
[c]5 Mol % PPh_3 was used. [d]10 Mol % PPh_3 was used. [e]5 Mol % $Ph_2P(CH_2)_2PPh_2$ was used. [f]1 Equiv. of LiCl was used instead of TBAC.

obtained (entry 11). For the reaction using CH_3CN, no significant change in the yield was noted (entry 12). It was found that ligands didn't have a positive effect on the model reaction. As indicated in entries 13 to 15, the yields were usually lower than those obtained without ligands. Finally, the use of a 1:1 ratio of starting materials and LiCl as a chloride source didn't improve the yield at all (entry 19). In fact, the yield dropped substantially. From the results discussed, the following reaction conditions appeared to be optimal for the palladium-catalyzed coupling of vinylic halides or triflates and olefinic sulfonamides: 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide or triflate (0.25 mmol), 2.0 equivs. of olefinic sulfonamide, 1.1 equivs. of TBAC, 4.5 equivs. of Na_2CO_3, and 1 mL of CH_3CN at 100 ^oC for an appropriate time interval.

Once the optimal reaction conditions were established, a variety of vinylic halides or triflates were employed to determine the scope and limitations of this palladium-catalyzed coupling reaction (Table 3). Prior to that, four reactions were run using (*E*)-1-iodo-1-hexene and olefinic amines with different substituents on the nitrogen atom in order to examine the effect of the basicity (or nucleophilicity) of the nitrogen. As shown in entries 1 and 2, 3-butenylamine and *N*-(3-butenyl)benzamide didn't afford any product under the optimal reaction conditions. For the reaction of 3-butenylamine, problems seem to be caused by strong coordination between the NH_2 group and the catalyst, which reduces the activity of the catalyst dramatically. The amide presumably gives a lower yield, because the hydrogen on the nitrogen is less acidic than that of a tosylamide and the nucleophile is generated in insufficient amounts to affect cyclization. On the other hand, an increase in the yield and a decrease in the reaction time were observed when the trifluoromethanesulfonyl group was introduced (entry 4). Thus, the desired product was obtained in 68 % yield, which is 7 % higher than that obtained from the reaction of a tosylamide. This result seemed to indicate that the trifluoromethanesulfonyl group is better than the *p*-toluenesulfonyl group. After further examination, as shown in entries 5, 6, 15, and 16, however, it was proven that the *p*-toluenesulfonyl group was generally more effective than the trifluoromethanesulfonyl group in promoting heterocycle formation. The reactions of (*E*)-3,3-dimethyl-1-iodo-1-butene and (*E*)-β-iodostyrene with *N*-(3-butenyl)-*p*-toluenesulfonamide proceeded well, resulting in the desired products in 63 % and 66 % yields respectively (entries 5 and 7).

As anticipated, (*Z*)-1-iodo-1-hexene and (*Z*)-β-iodostyrene both gave exclusively the *trans* -substituted products (entries 7 and 8), which strongly indicates the palladium process proceeds through the thermodynamically more stable *syn, syn*-π–allylpalladium intermediate. Analogous reactions using relatively less reactive vinylic bromides also provided the

Table 3. Palladium-catalyzed Coupling of Vinylic Halides and Triflates with *N*-(3-Butenyl)-*p*-toluenesulfonamide. [a]

entry	vinylic halide or triflate	amine	time (h)	product	% isolated yield
1			60	—	0
2			60	—	0
3			60		61
4			48		68
5			42		63
6			48		52

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of sulfonamide, 1.0 equiv. of TBAC, 4.5 equivs. of Na_2CO_3 and 1 mL of CH_3CN at 100 °C.

Table 3. (Continued)

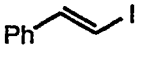
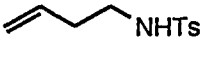
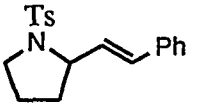
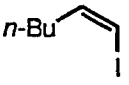
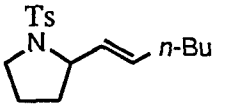
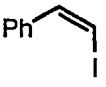
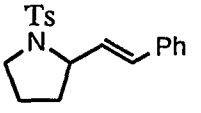
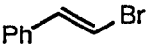
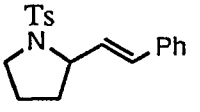
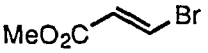
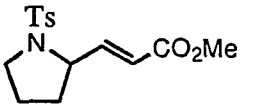
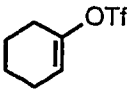
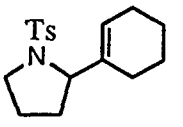
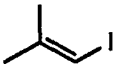
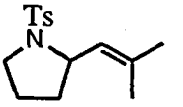
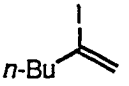
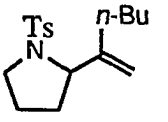
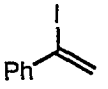
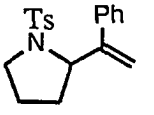
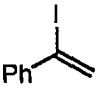
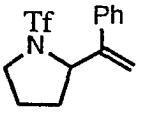
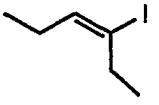
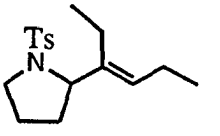
entry	vinylic halide or triflate	amine	time (h)	product	% isolated yield
7			26		66
8			42		61
9			48		61
10			60		69
11			48		60
12			72		40

Table 3. (Continued)

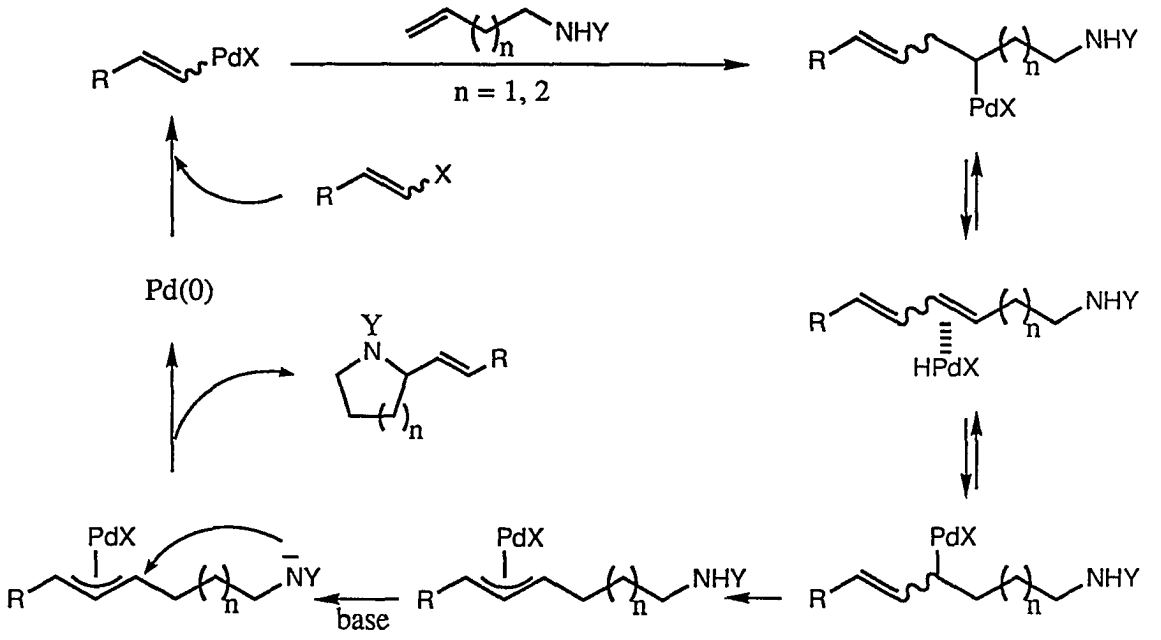
entry	vinylic halide or triflate	amine	time (h)	product	% isolated yield
13			26		57
14			36		48
15			72		33
16			48		22
17			26		50

desired products in good yields (entries 10 and 11). A 57 % yield of the product was obtained from the reaction of 2-methyl-1-iodopropene (entry 13). Reactions using more substituted vinylic halides and a triflate generally provided lower yields (entries 14, 15, and 17). This is

probably due to the steric hindrance which makes the initial oxidative addition of palladium more difficult. Furthermore, it seems that the instability of α-iodostyrene under the reaction conditions resulted in the very low yield observed.

These reactions undoubtedly proceed according to the mechanism outlined in Scheme 1.

Scheme 1

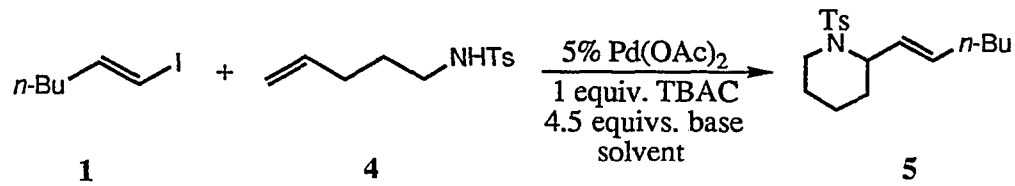


syn, syn π-allylpalladium complex

The individual steps in the process are well known. The exclusive formation of *trans* -substituted products from either (*Z*)- or (*E*)-vinylic halides is the result of the thermodynamic preference for *syn, syn*-π-allylpalladium formation.

Next, several reactions were run to establish the optimal conditions for the synthesis of piperidines via the palladium-catalyzed coupling of vinylic halides or triflates with *N*-(4-

pentenyl)sulfonamides. First, the base was examined in the reaction of (*E*)-1-iodo-1-hexene and *N*-(4-pentenyl)-*p*-toluenesulfonamide as the model reaction and the results are summarized in Table 4.



1 **4** **5** (18)

Regardless of the cation used, the carbonate bases didn't afford satisfactory results and only a 20% yield was obtained in the reaction using K_2CO_3 (entries 1- 4). Analogous reactions using bicarbonate bases appeared to be better and the reaction using $KHCO_3$ produced the desired product in 33 % yield (entries 5 and 6). By comparison, acetates and organic amines proved not to be effective at all for this model reaction (entries 7 - 11).

With $KHCO_3$ as the best base, the reactions were run in order to see the effects of the solvent, the palladium source, the ligand, the chloride source and the stoichiometry (Table 5). As indicated in entries 1- 3, a moderately polar solvent, CH_3CN, was again the best solvent as seen previously in the synthesis of pyrrolidines, and the yield was improved by 11% simply by changing the solvent from DMF to CH_3CN. For the polar solvent DMSO, no significant product-like spot was observed according to TLC analysis. The reactions using $KHCO_3$ and CH_3CN in the presence of $Pd(dba)_2$ or $Pd(PPh_3)_4$ as the catalyst were not as good as the reaction using $Pd(OAc)_2$. As anticipated from the result of the reaction using $Pd(PPh_3)_4$, the addition of various ligands proved detrimental to the model reaction (entries 6 - 9). The replacement of TBAC by LiCl produced worse results and the use of a 1:1 ratio of starting materials provided the product in a slightly lower yield (entries 10 and 11). This investigation

Table 4. Effect of Bases on the Palladium-catalyzed Coupling of (*E*)-1-Iodo-1-hexene (**1**) and *N*-(4-Pentenyl)-*p*-toluenesulfonamide (**4**).[a]

entry	base (4.5 equivs.)	% isolated yield **5**
1	Li_2CO_3	0
2	Na_2CO_3	19
3	K_2CO_3	20
4	Cs_2CO_3	11
5	$NaHCO_3$	25
6	$KHCO_3$	33
7	NaOAc	<10
8	KOAc	9
9	CsOAc	12
10	Et_3N	<5
11	*i*-Pr_2NEt	<5

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of *N*-(4-pentenyl)-*p*-toluenesulfonamide, 1.0 equiv. of TBAC, and 1 mL of DMF at 100 °C.

Table 5. Effects of the Solvent, the Palladium source, the Ligand, the Chloride source, and the Stoichiometry on the Palladium-catalyzed Coupling of (*E*)-1-Iodo-1-hexene (**1**) and *N*-(4-Pentenyl)-*p*-toluenesulfonamide (**4**).[a]

entry	Pd (5 mol %)	ligand (5 mol %)	solvent (1 mL)	% isolated yield **5**
1	$Pd(OAc)_2$	-	THF	37
2	$Pd(OAc)_2$	-	CH_3CN	44
3	$Pd(OAc)_2$	-	DMSO	0
4	$Pd(dba)_2$	-	CH_3CN	37
5	$Pd(PPh_3)_4$	-	CH_3CN	12
6	$Pd(OAc)_2$	PPh_3	CH_3CN	26
7	$Pd(OAc)_2$	$Ph_2P(CH_2)_2PPh_2$	CH_3CN	36
8	$Pd(OAc)_2$	$Ph_2P(CH_2)_3PPh_2$	CH_3CN	31
9	$Pd(OAc)_2$	P(*o*-Tol)$_3$	CH_3CN	31
10[b]	$Pd(OAc)_2$	-	CH_3CN	16
11[c]	$Pd(OAc)_2$	-	CH_3CN	39

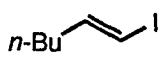
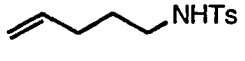
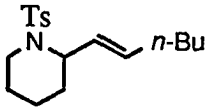
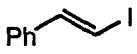
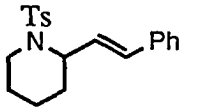
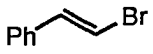
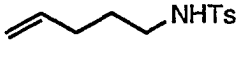
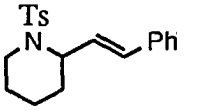
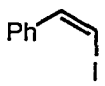
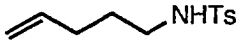
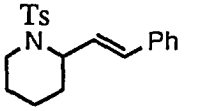
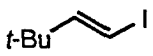
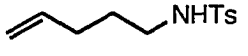
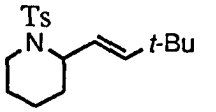
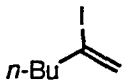
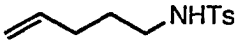
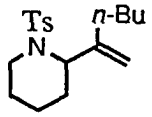
[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of *N*-(4-pentenyl)-*p*-toluenesulfonamide, 1.0 equiv. of TBAC, 4.5 equivs. of $KHCO_3$ and 1 mL of DMF for 24 hours at 100 °C. [b]1.0 Equiv. of LiCl was used instead of TBAC. [c]1.0 Equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol) and 1.0 equiv. of *N*-(4-pentenyl)-*p*-toluenesulfonamide were used.

showed the following reaction conditions to be optimal: 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of *N*-(4-pentenyl)-*p*-toluenesulfonamide, 1.0 equiv. of TBAC, 4.5 equivs. of $KHCO_3$, and 1 mL of CH_3CN at 100 °C for an appropriate time interval.

Once the best reaction conditions were established, the reactions of various vinylic halides with *N*-(4-pentenyl)-*p*-toluenesulfonamide were run, but the results were not satisfactory. As shown in Table 6, the yields generally were less than 50 %. For the (*E*)-terminal vinylic halides, the desired products were obtained in 36 to 57 % yields (entries 1, 2 and 5). The relatively less reactive (*E*)-β-bromostyrene produced a still lower yield (entry 3) and surprisingly, (*Z*)-β-iodostyrene gave only an 18 % yield, although it was expected to give a similar result to that obtained from the reaction using the corresponding (*E*)-isomer (entry 4). Analogous reactions using the internal vinylic iodides didn't provide the products in measurable amounts (entries 6 and 7). These frustrating results and prior experience with the palladium-catalyzed coupling of vinylic halides or triflates with *N*-(3-butenyl)-*p*-toluenesulfonamide which showed the importance of the basicity (or nucleophilicity) of the nitrogen atom led to replacement of the *p*-toluenesulfonyl group by the trifluoromethane-sulfonyl group to see if any improvement could be made.

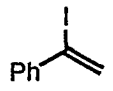
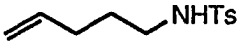
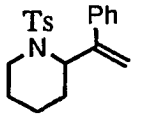
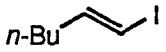
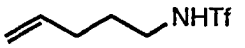
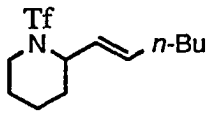
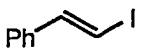
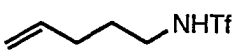
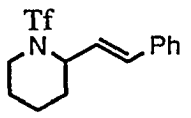
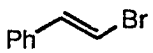
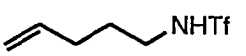
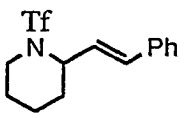
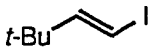
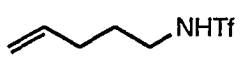
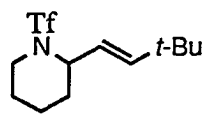
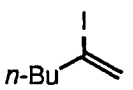
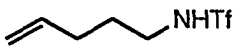
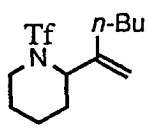
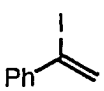
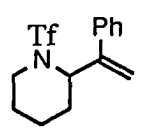
It was found that the trifluoromethanesulfonyl group was much more effective. This indicated that this palladium-catalyzed process is very sensitive to the basicity (or nucleophilicity) of the nitrogen moiety, probably due to the ability of the nitrogen atom to chelate or coordinate the palladium. As shown in entries 8 - 13, much higher yields were obtained simply by changing the substituent on the nitrogen atom. Thus, the reactions of (*E*)-1-iodo-1-hexene, (*E*)-β-iodostyrene, and (*E*)-3,3-dimethyl-1-iodo-1-butene afforded the

Table 6. Palladium-catalyzed Coupling of Vinylic Halides with Sulfonamides.[a]

entry	vinylic halide	amine	product	% isolated yield
1				44
2				57[b]
3				38
4				18
5				36
6				<10

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 2.0 equivs. of sulfonamide, 1.0 equiv. of TBAC, 4.5 equivs. of $KHCO_3$, and 1 mL of CH_3CN for 24 hours at 100 °C. [b]Purity was 85 % on GC analysis.

Table 6. (Continued)

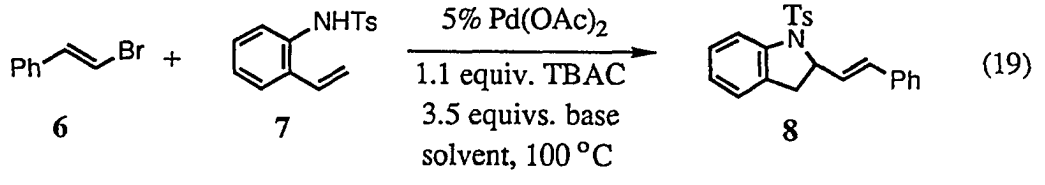
entry	vinylic halide	amine	product	% isolated yield
7				trace
8				77
9				69
10				63
11				69
12				43
13				31

corresponding piperidines in 77, 69, and 69 % yields respectively (entries 8, 9 and 11). The relatively less reactive (*E*)-β-bromostyrene also proceeded well, producing the desired product in 69 % yield (entry 10). However, internal vinylic iodides, such as 2-iodo-1-hexene, gave only modest yields, probably due to the increased difficulty in undergoing oxidative addition to palladium (entry 10). However, internal vinylic iodides, such as 2-iodo-1-hexene, gave only modest yields, probably due to the increased difficulty in undergoing oxidative addition to palladium caused by steric hindrance (entries 12 - 14). The low yield in the reaction using α-bromostyrene appeared to arise as a result of the instability of α-bromostyrene under the reaction conditions.

In summary, the palladium-catalyzed coupling of vinylic halides and olefinic sulfonamides affords good yields of 2-(1-alkenyl)-pyrrolidine and -piperidine sulfonamides and provides a convenient new route to nitrogen heterocycles.

Synthesis of 2,3-dihydroindoles, 2,3-dihydrobenzazepines, and 1,2,3,4-tetrahydroquinolines

Our prior experience with the palladium-catalyzed coupling of vinylic halides or triflates with olefinic sulfonamides in the synthesis of pyrrolidines and piperidines suggested that analogous coupling of vinylic halides and *N*-tosyl-2-alkenylanilines should also provide a convenient new route to nitrogen heterocycles, such as 2,3-dihydroindoles and 1,2,3,4-tetrahydroquinolines. In order to determine if the previous approach could be applied to this new objective, the reaction of *N*-tosyl-2-vinylaniline and (*E*)-β-bromostyrene was chosen as the model reaction and various reaction conditions were studied as shown in Table 7 (eq. 19).



6 7 8 (19)

Table 7. Palladium-catalyzed Coupling of (*E*)-β-Bromostyrene (**6**) and *N*-Tosyl-*o*-vinylaniline (**7**).[a]

entry	base (3.5 equivs.)	solvent (1 mL)	% isolated yield **8**
1	Li_2CO_3	CH_3CN	19
2	Na_2CO_3	CH_3CN	36
3	K_2CO_3	CH_3CN	60
4	$NaHCO_3$	CH_3CN	12
5	$KHCO_3$	CH_3CN	0
6	NaOAc	CH_3CN	12
7	Et_3N	CH_3CN	0
8	K_2CO_3	THF	21
9	K_2CO_3	DMF	0
10	K_2CO_3	DMA	43

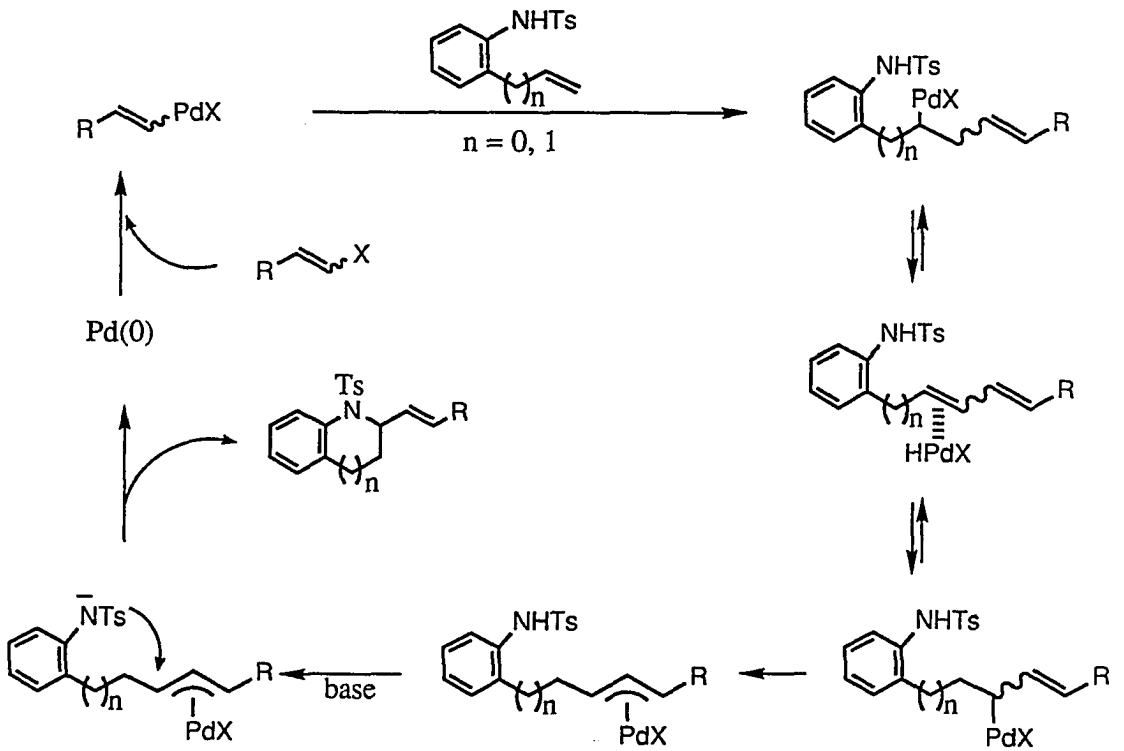
[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-β-bromostyrene (0.2 mmol), 1.5 equivs. of *N*-tosyl-*o*-vinylaniline, 1.1 equivs. of TBAC for 24 hours at 100 °C.

The yield of the reaction was significantly altered by changing the base. Of the carbonate bases examined, K_2CO_3 provided the desired product in 60 % yield and the other carbonate bases, namely Li_2CO_3 and Na_2CO_3, gave much lower yields (entries 1 - 3). It is noteworthy that significant amounts of diene side-products were observed in most of the reactions shown in Table 7. Other bases were also investigated. Bicarbonate, acetate and organic amine bases were found not to be effective in this model reaction as indicated in entries

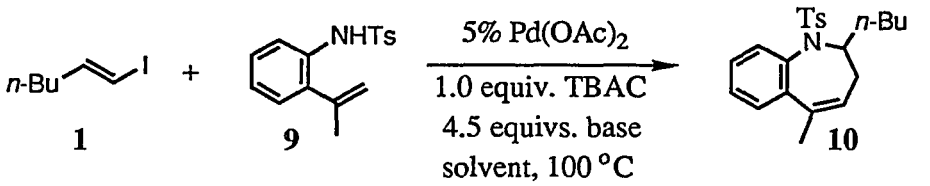
4 - 7. With regard to the effect of the solvent, CH_3CN proved to be the most useful (entries 1 and 8 - 10).

Under the optimal reaction conditions using K_2CO_3 and CH_3CN, *N*-tosyl-2-vinylaniline was reacted with other vinylic halides. Unfortunately, none of the reactions afforded the desired products in measurable amounts. Instead, the reactions were not clean at all and gave significant amounts of diene side-products according to TLC analysis. The proposed mechanism which is applicable to the coupling of both vinylic halides with *N*-tosyl-2-vinylanilines and vinylic halides with *N*-tosyl-2-allylanilines is shown in Scheme 2.

Scheme 2



Next, the reaction of *N*-tosyl-2-isopropenylaniline was investigated. Based on the fact that the analogous reaction of *N*-tosyl-2-vinylaniline was not successful despite the establishment of optimal reaction conditions, the effects of variables on the palladium-catalyzed coupling of (*E*)-1-iodo-1-hexene with *N*-tosyl-2-isopropenylaniline were again investigated in a similar manner (eq. 20). The results of this investigation are shown in Table 8.



(20)

First, the effect of bases on the reaction of *N*-tosyl-2-isopropenylaniline and (*E*)-1-iodo-1-hexene was examined. Surprisingly, the product was not the expected 2,3-dihydroindole. Instead, the product obtained from the model reaction was a 7-membered ring product, a benzazepine. Regardless of the bases used, the major product consistently was the benzazepine with the exception of Li_2CO_3 which didn't give a significant spot by TLC analysis (entries 1 - 8). These results showed that Na_2CO_3 was the best base for the reaction. Using Na_2CO_3 as the base, the reactions were run in different solvents and an improvement in the yield was observed when the solvents THF, DMF, and DMA, were employed (entries 9 - 11). The reaction using DMA resulted in a 65 % yield of the benzazepine. In contrast, a decrease in yield was observed in the reaction using DMSO (entry 12). The model reaction was not positively affected by the use of various ligands as observed in the synthesis of pyrrolines and piperidines and the replacement of TBAC by LiCl resulted in a lower yield (entries 13 - 16). Finally, it was found that the yield could be further improved by using a 1:1 ratio of starting materials as shown in entry 17. A 72 % yield of the benzazepine was obtained from the

Table 8. Palladium-catalyzed Coupling of (*E*)-1-Iodo-1-hexene (**1**) and *N*-Tosyl-2-isopropenylaniline (**9**).[a]

entry	base (4.5 equivs.)	solvent (1 mL)	% isolated yield **10**
1	Li_2CO_3	CH_3CN	0
2[b]	Na_2CO_3	CH_3CN	41
3	K_2CO_3	CH_3CN	27
4	$NaHCO_3$	CH_3CN	35
5	$KHCO_3$	CH_3CN	31
6	NaOAc	CH_3CN	33
7	KOAc	CH_3CN	37
8	Et_3N	CH_3CN	34
9	Na_2CO_3	THF	56
10	Na_2CO_3	DMF	59
11	Na_2CO_3	DMA	65
12	Na_2CO_3	DMSO	16

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.2 mmol), 2.0 equivs. of *N*-tosyl-2-isopropenylaniline, 1.0 equiv. of TBAC, 4.5 equivs. of a base, and 1 mL of a solvent for 24 hours at 100 °C. [b]The reaction was run for 30 hours.

Table 8. (Continued)

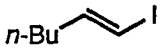
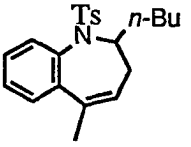
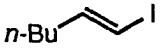
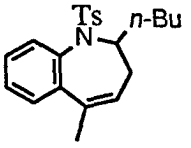
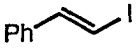
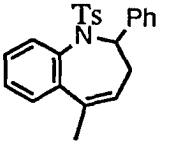
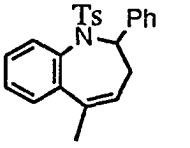
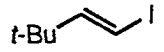
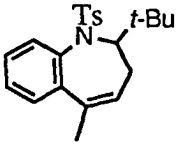
entry	base (4.5 equivs.)	solvent (1 mL)	% isolated yield **10**
13[c]	Na_2CO_3	DMA	35
14[d]	Na_2CO_3	DMA	60
15[e]	Na_2CO_3	DMA	57
16[f]	Na_2CO_3	DMA	49
17[g]	Na_2CO_3	DMA	72

[c]5 Mol % PPh_3 was used. [d]5 Mol % $Ph_2P(CH_2)_2PPh_2$ was used. [e]5 Mol % $Ph_2P(CH_2)_3PPh_2$ was used. [f]1.0 Equiv. of LiCl was used instead of TBAC. [g]1.0 Equiv. of (*E*)-1-Iodo-1-hexene (0.2 mmol) and 1.0 equivs. of *N*-tosyl-2-isopropenylaniline were used.

reaction using a 1:1 ratio of starting materials, Na_2CO_3 as the base and DMA as the solvent.

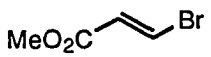
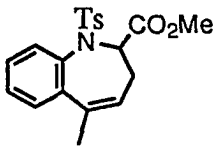
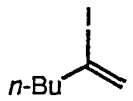
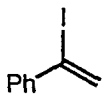
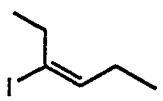
Once the best reaction conditions were established, the reactions of various vinylic halides were run and the results are shown in Table 9. It is noteworthy that the spots corresponding to the 7-membered ring products were always major according to TLC analysis along with other small spots which were not isolated. The result of entry 2 showed that $NaHCO_3$, which had proven useful in the preliminary study, was not as good as Na_2CO_3, confirming that Na_2CO_3 indeed was the best base for this palladium-catalyzed coupling. (*E*)-β-Bromostyrene was more effective than (*E*)-β-iodostyrene, producing the product in 39 % yield (entries 3 and 4). Other terminal vinylic halides, such as (*E*)-3,3-dimethyl-1-iodo-1-butene and methyl (*E*)-β-bromoacrylate, proceeded well, giving 67 % and 44 % yields

Table 9. Palladium-catalyzed Coupling of Vinylic Halides and *N*-Tosyl-2-isopropenylaniline.[a]

entry	vinylic halide	product	% isolated yield
1			72
2			22[b]
3			26[c]
4			39
5			67

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 1.0 equiv. of *N*-tosyl-2-isopropenylaniline, 1.0 equiv. of TBAC, 4.5 equivs. of Na_2CO_3 and 1 mL of DMA at 100 °C for 24 hours. [b]$NaHCO_3$was used. [c]GC purity was 80 %.

Table 9. (Continued).

entry	vinylic halide	product	% isolated yield
6			44
7		–	bad mixture
8		–	bad mixture
9		–	bad mixture

respectively (entries 5 and 6). Unfortunately, the reactions of internal vinylic halides were so messy that products couldn't be identified.

Considering the fact that many biological compounds and alkaloids, such as apo-β-erythroidine (Figure 1), are benzazepine derivatives and that lengthy procedures are usually

required for the synthesis of such benzazepines,[20] this palladium process really provides a convenient alternative for the synthesis of benzazepines.

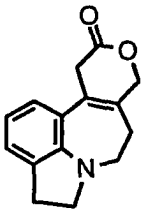
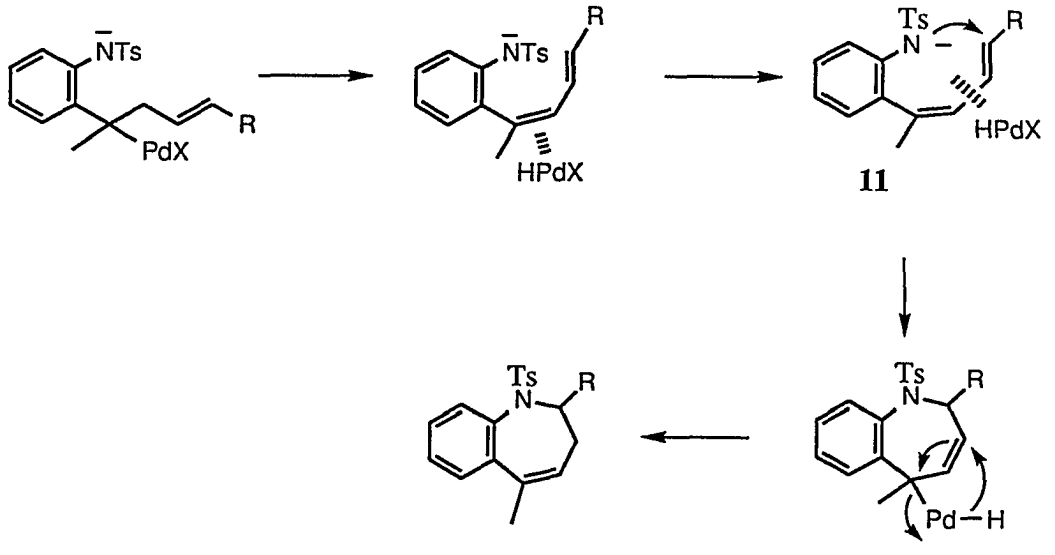


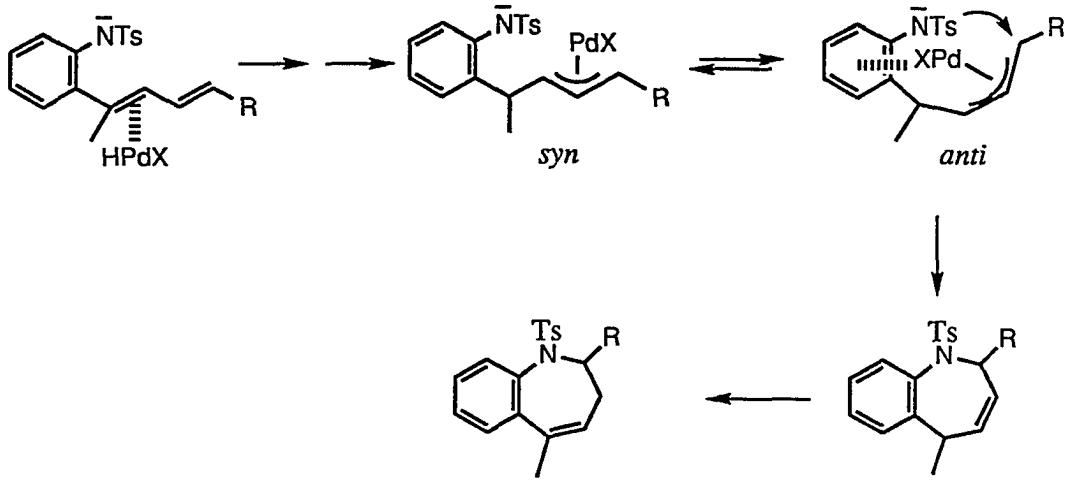
Figure 1. apo-β-erythroidine

Based on the structure of the product and the location of the double bond, it seems that complex **11**, as shown in Scheme 3, is involved in this process rather than a π-allylpalladium complex. Subsequent nucleophilic attack of nitrogen on the diene π-complex, followed by hydride transfer from the palladium to the double bond with rearrangement, affords the observed product.

Scheme 3

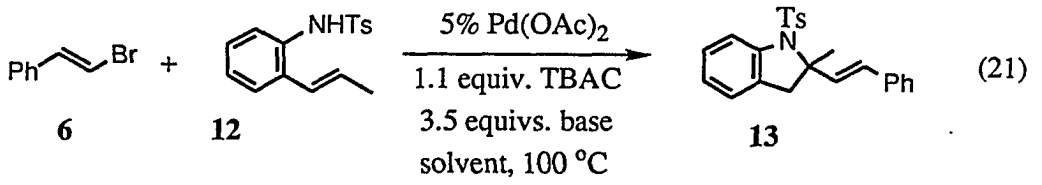


Scheme 4



Another possibility is the involvement of an *anti* -π-allylpalladium intermediate which is usually less stable than the corresponding *syn*-π-allylpalladium complex, though it is conceivable that coordination of the aryl group with the palladium could stabilize the *anti* -intermediate (Scheme 4). After ring closure, the double bond must isomerize to give the thermodynamically more stable compound. It is not obvious, however, how that isomerization occurs under our reaction conditions. It is not clear at this point why predominant formation of the larger ring compounds occurs.

The reaction of *N*-tosyl-2-((*E*)-1-propenyl)aniline was also examined and the results are shown in Table 10 (eq. 21).



6 **12** **13** (21)

Table 10. Palladium-catalyzed Coupling of (*E*)-β-Bromostyrene (**6**) and *N*-Tosyl-2-((*E*)-1-propenyl)aniline (**12**).[a]

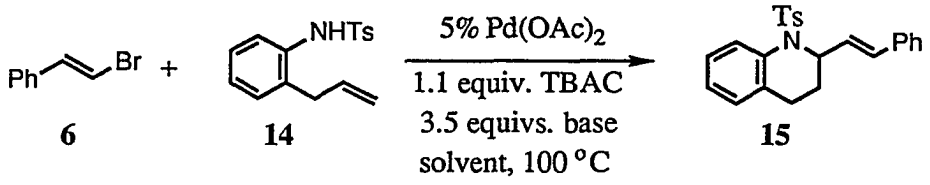
entry	base (3.5 equivs.)	solvent (1 mL)	% isolated yield **13**
1	Li_2CO_3	DMF	20
2	Na_2CO_3	DMF	trace
3	K_2CO_3	DMF	47
4	$NaHCO_3$	DMF	27
5	NaOAc	DMF	34
6	Et_3N	DMF	35
7	K_2CO_3	DMF	37
8	K_2CO_3	CH_3CN	54
9	K_2CO_3	DMA	49

[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-β-bromostyrene (0.2 mmol), 1.5 equivs. of *N*-tosyl-2-((*E*)-1-propenyl)aniline, 1.0 equiv. of TBAC for 24 hours at 100 °C.

Of the bases examined, K_2CO_3 seemed to be the best (entry 3) and subsequent investigation revealed that CH_3CN remained the best solvent. Unfortunately, attempts to utilize these reaction conditions for the reactions of other terminal and internal vinylic halides were not successful and the cyclized products couldn't be obtained.

After our attempts to effect the palladium-catalyzed coupling of *N*-tosyl-2-vinylic anilines with vinylic halides, it seemed natural to explore the reactions of *N*-tosyl-2-allylic

anilines with vinylic halides. In order to do that, the reaction of *N*-tosyl-2-allylaniline and (*E*)-β-bromostyrene was chosen as the model system and reaction conditions were optimized (eq. 22).



6 **14** **15** (22)

Two important variables were explored, the base and the solvent. As shown in Table 11, investigation of the solvent revealed that CH_3CN still remained the best for the model reaction (entries 1 - 4). Using CH_3CN as the solvent, different bases were also examined. Li_2CO_3 didn't give a significant spot corresponding to the product (entry 5). In contrast, other bases, such as K_2CO_3, $NaHCO_3$, and NaOAc, afforded the product in 72 %, 70 %, and 72 % yields, respectively. However, the yields were not as high as that obtained from the reaction using Na_2CO_3 (entries 5 - 8). As observed in the previous reactions using 2-vinylanilines, the organic amine Et_3N wasn't very useful. As a result of this investigation, the best reaction conditions for the model system are 5 mol % $Pd(OAc)_2$, 1 equiv. of vinylic halide (0.25 mmol), 1.5 equivs. of *N*-tosyl-2-allylaniline, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 at 100 °C for 24 hours under a nitrogen atmosphere.

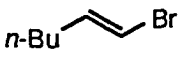
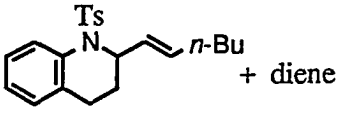
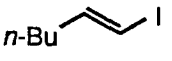
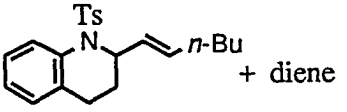
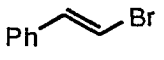
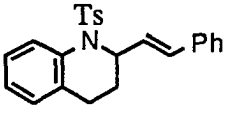
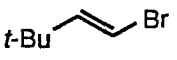
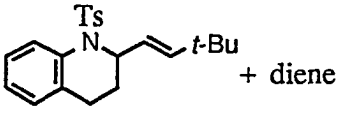
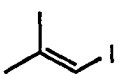
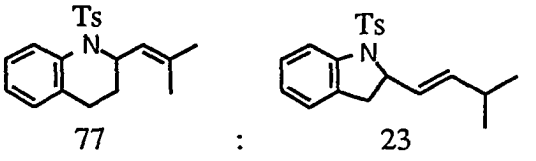
With these reaction conditions at hand, the reactions of a variety of vinylic halides were run and the results are shown in Table 12. The reactions using the relatively less reactive (*E*)-1-bromo-1-hexene, as well as the corresponding iodide, proceeded well, but the products were obtained as an inseparable mixture of the desired product and a diene side-product in 95:5

Table 11. Palladium-catalyzed Coupling of (*E*)-β-Bromostyrene (**6**) and *N*-Tosyl-2-allylaniline (**14**).[a]

entry	base (3.5 equivs.)	solvent (1 mL)	% isolated yield **15**
1	Na_2CO_3	THF	64
2	Na_2CO_3	CH_3CN	80
3	Na_2CO_3	DMF	59
4	Na_2CO_3	DMA	51
5	Li_2CO_3	CH_3CN	0
6	K_2CO_3	CH_3CN	72
7	$NaHCO_3$	CH_3CN	70
8	NaOAc	CH_3CN	72
9	Et_3N	CH_3CN	51

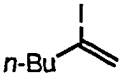
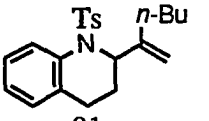
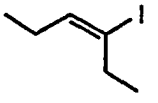
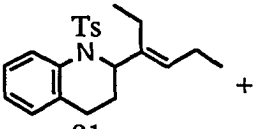
[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of (*E*)-β-bromostyrene (0.2 mmol), 1.5 equivs. of *N*-tosyl-2-allylaniline, 1.0 equiv. of TBAC for 24 hours at 100 °C.

Table 12. Palladium-catalyzed Coupling of Various Vinylic Halides and *N*-Tosyl-2-allylaniline. [a]

entry	vinylic halide	product(s)	% isolated yield
1		 + diene 95 : 5	74
2		 + diene 88 : 12	85
3			80
4		 + diene 95 : 5	72
5		 77 : 23	66

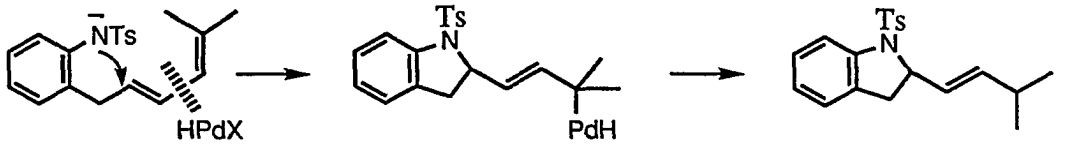
[a]All reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 1.5 equivs. of *N*-tosyl-2-allylaniline, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 in CH_3CN at 100 °C for 24 hours under a nitrogen atmosphere.

Table 12. (Continued)

entry	vinylic halide	product(s)	% isolated yield
6		 + diene 91 : 9	52
7		 + diene 91 : 9	31

and 88:12 ratios in 74 % and 85 % yields, respectively (entries 1 and 2). (*E*)-1-Bromo-3,3-dimethyl-1-butene also produced a mixture in 72 % yield (entry 4). An interesting result was obtained when 1-iodo-2-methylpropene was employed. In this reaction, an inseparable mixture of the desired product and a 5-membered ring isomer, a 2,3-dihydroindole, was obtained in a ratio of 77:23 and 66 % yield (entry 5). Formation of the 2,3-dihydroindole seems to indicate the involvement of an intermediate similar to that discussed earlier in the reaction of *N*-tosyl-2-isopropenylaniline. The difference is that nucleophilic attack at the benzylic position occurs this time to give the 5-membered ring compound rather than at the remote carbon to give the larger ring size (Scheme 5). Now, however, it appears that reductive elimination of the intermediate palladium hydride proceeds without rearrangement.

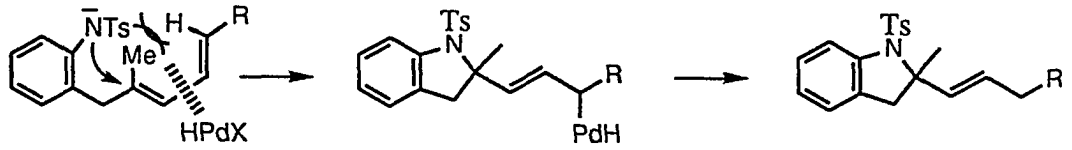
Scheme 5



The use of internal vinylic iodides resulted in lower yields as expected. Thus, 52 % and 31 % yields were obtained as mixtures from the reaction of 2-iodo-1-hexene and (*E*)-3-iodo-3-hexene (entries 6 and 7).

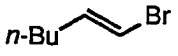
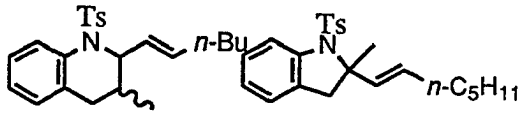
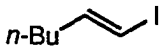
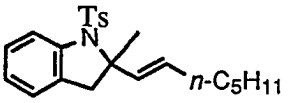
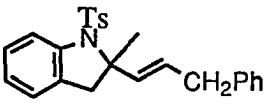
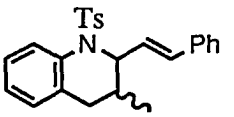
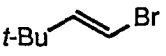
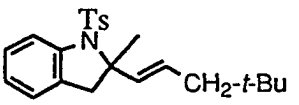
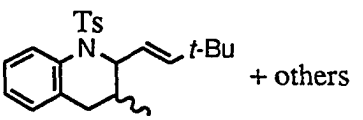
Analogous reactions using *N*-tosyl-2-methallylaniline were also conducted under the same reaction conditions. Those reactions were more complicated and significant amounts of diene side-products were observed in most cases. In addition, the main products obtained from these reactions were the unexpected dihydroindoles which appeared to arise from the intermediate shown in Scheme 6 despite the fact that a methyl group on the double bond woulld seem to cause steric hindrance and consequently destablize the intermediate. The results are shown in Table 13.

Scheme 6



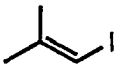
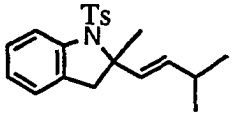
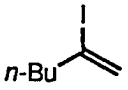
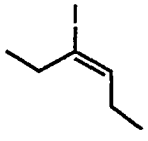
As indicated in entries 1, 3 and 4, the reactions of terminal vinylic bromides provided a mixture of the 5- and 6-membered ring products with formation of the 5-membered ring isomer

Table 13. Palladium-catalyzed Coupling of *N*-Tosyl-2-methallylaniline and Various Vinylic Halides.[a]

entry	vinylic halide	product(s)	% isolated yield
1		 *cis /trans* = 66 / 34	66
		19 : 81	
2			31
3			48
		 *cis /trans* = 67 / 33	24
4			27
		 *cis /trans* = 67 / 33	25

[a]Reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 1.5 equivs. of *N*-tosyl-2-methallylaniline, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3, and 1.2 mL of CH_3CN at 100 °C for 24 hours under a nitrogen atmosphere.

Table 13. (Continued)

entry	vinylic halide	product(s)	% isolated yield
5			61
6		diene	54
7[b]		diene	20
8[c]		diene	56
9[d]		diene	31
10		diene	54

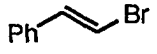
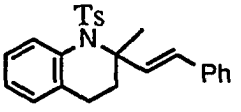
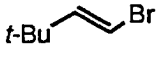
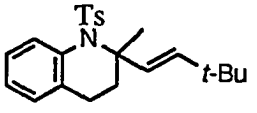
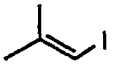
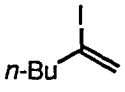
[b]1.0 Equiv. of Na_2CO_3 was used. [c]1.0 Equiv. of NaOAc was used. [d]1.0 Equiv. of $NaHCO_3$ was used.

being favored. Thus, (*E*)-1-bromo-1-hexene afforded an inseparable mixture of the 5- and 6-ring isomers in 66 % overall yield in an 81:19 ratio. For the 6-membered ring isomer, it was not possible to determine the ratio of stereoisomers due to the complexity of the proton NMR spectrum. The reaction of (*E*)-β-bromostyrene also provided both isomers, but they were separable. Thus, a 48 % yield of the 2,3-dihydroindole and a 24 % yield of the 1,2,3,4-tetrahydroquinoline in a 67:33 *cis /trans* ratio were obtained. Similarly, (*E*)-1-bromo-3,3-dimethyl-1-butene also produced both isomers in almost equal amounts. For (*E*)-1-iodo-1-hexene, only the dihydroindole was obtained, but the yield was low (entry 2). By comparison, a 61 % yield of the 2,3-dihydroindole isomer was obtained when 1-iodo-2-methylpropene was used (entry 5). The reactions using internal vinylic iodides were not successful and the only products obtained in measurable amounts were dienes (entries 6 and 10). Attempts to reduce the formation of diene side-products by lessening the amount of various bases to 1.0 equivalent were not successful (entries 7 - 9).

Finally, the reactions of *N*-tosyl-2-crotylaniline were investigated (Table 14). Like the reactions of *N*-tosyl-2-methallylaniline, these reactions were also very complicated and heavy spots corresponding to the diene side-products were observed by TLC analysis. As a result, the yields were relatively low and in some cases, the diene side-products were obtained predominantly.

In summary, the palladium-catalyzed coupling of vinylic halides with *N*-tosyl-2-alkenylanilines produces a variety of nitrogen heterocycles. It is very significant that the reactions of *N*-tosyl-2-isopropenylaniline afford benzazepines exclusively. The reactions of *N*-tosyl-2-vinylaniline and *N*-tosyl-2-((*E*)-1-propenyl)aniline were not successful with the exception of the reactions with (*E*)-β-bromostyrene. The reactions of *N*-tosyl-2-allylic anilines proceeded better and both 5- and 6-membered ring products were obtained in most cases. It is noteworthy that the 5-membered ring compounds were formed predominantly, rather than the 6-membered ring isomers, for the reactions of *N*-tosyl-2-methallylaniline.

Table 14. Palladium-catalyzed Coupling of *N*-Tosyl-2-crotylaniline and Vinylic Halides.[a]

entry	vinylic halide	product	% isolated yield
1			32
2			22
3		diene	34
4		diene	52

[a]Reactions were run using 5 mol % $Pd(OAc)_2$, 1.0 equiv. of vinylic halide (0.25 mmol), 1.5 equivs. of *N*-tosyl-2-crotylaniline, 1.1 equivs. of TBAC, 3.5 equivs. of Na_2CO_3 in CH_3CN at 100 °C for 24 hours under a nitrogen atmosphere.

Conclusion

The palladium-catalyzed coupling of vinylic halides or triflates with olefinic sulfonamides has been investigated. For the reactions of vinylic halides with *N*-3-butenyl- and 4-pentenylsulfonamides, the corresponding pyrrolidines and piperidines were obtained in moderate to good yields. Generally, terminal vinylic halides produced products in higher yields than internal vinylic halides and vinylic bromides proceeded as well as the corresponding iodides.

With regard to the reactions of vinylic halides with *N*-tosyl-2-alkenylanilines, they are more complicated and diene side-products were observed in most cases, which seemed to be the major cause for the lower yields observed. Nonetheless, interesting results were obtained from the reactions of *N*-tosyl-2-isopropenylaniline, in which benzazepines were formed exclusively in moderate to good yields. In contrast, the reactions of *N*-tosyl-2-vinylaniline and *N*-tosyl-2-(1-propenyl)aniline were not successful with the exception of the reaction with (*E*)-β-bromostyrene. The reactions of *N*-tosyl-2-allylaniline proceeded well , producing products in high yields along with a small amount of diene side-products. Interestingly, 5-membered ring compounds, rather than the expected 6-membered ring isomers, were obtained as major products for the reactions of *N*-tosyl-2-methallylaniline. Again, terminal vinylic halides produce better results in most cases than internal vinylic halides.

In conclusion, the palladium-catalyzed coupling of vinylic halides or triflates with olefinic sulfonamides provides a convenient route to a variety of useful nitrogen heterocyles.

Experimental Section

Equipment

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 at 300 and 75.5 MHz, respectively. All infrared spectra were recorded on a Beckman 4250 spectrometer and high resolution mass spectral analyses were performed on a Kratos MS-50 spectrometer. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic potassium permanganate solution.

Reagents

All reagents were used directly as obtained commercially unless otherwise noted. Palladium acetate was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride (TBAC) was purchased from Lancaster Synthesis Co. and *p*-toluenesulfonyl chloride was obtained from Eastman Kodak Co. Allyl cyanide, 4-bromo-1-butene, 5-bromo-1-pentene, diisobutylaluminum hydride, trifluoromethanesulfonic anhydride, 2-aminobenzyl alcohol, 1-bromopropene, 2-bromopropene, chlorotrimethylsilane, ethyltriphenylphosphonium bromide, 2-isopropenylaniline, methyltriphenylphosphonium bromide, PCC, and vinylmagnesium bromide were purchased from Aldrich Chemical Co. Sodium iodide, florisil and other inorganic compounds were purchased from Fischer Scientific Co.

Preparation of *N*-(3-butenyl)-*p*-toluenesulfonamide

i) Preparation of 3-butenylamine[21]

In an oven-dried, three-neck round bottom flask, $LiAlH_4$ (80 mmol) and 40 mL of THF were added. The mixture was cooled down in an ice-bath and conc. sulfuric acid (40 mmol) was slowly added through a dropping funnel over 20 minutes while the solution was vigorously stirred. The stirring was continued for an additional hour. To this solution, allyl cyanide (75 mmol) in THF (15 mL) was slowly added. After 2 hours, a 1:1 mixture of water and THF was added to destroy any excess hydride and 45 mL of aqueous sodium hydroxide (4.5 g) was introduced to coagulate the aluminum hydroxide precipitate. The clear THF solution was decanted and the remaining mass was extracted with ether (30 mL), and acidified with 2 N aqueous hydrochloric acid (50 mL). The water layer was concentrated to a viscous mass. The mass was diluted with ether (50 mL) and made basic with a saturated potassium hydroxide solution. The ether layer was separated and dried over anhydrous potassium carbonate. The product was obtained by distillation at 84 °C in 65 % yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br s, 2 H), 2.19 (q, 2 H, J = 6.6 Hz), 2.75 (t, 2 H, J = 6.6 Hz), 5.03-5.11 (m, 2 H), 5.76 (ddt, 1 H, J = 17.1, 10.2, 6.9 Hz).

ii) Preparation of *N*-(3-butenyl)-*p*-toluenesulfonamide

Tosyl chloride (20 mmol) was slowly added to a solution of 3-butenylamine (20 mmol) and pyridine (6.4 mL) at 0 °C. The reaction mixture was heated for 2 hours at 60 °C. After heating, the mixture was cooled down to room temperature, diluted with ether (150 mL) and washed with cold 10 % aqueous hydrochloric acid. The organic layer was dried over anhydrous potassium carbonate and concentrated in vacuo to afford the desired product in 75% yield: ^{1}H NMR ($CDCl_3$) δ 2.00 (qt, 2 H, J = 6.9, 0.9 Hz), 2.43 (s, 3 H), 2.98-3.05 (m, 2 H), 4.43 (s, 1 H), 5.00-5.10 (m, 2 H), 5.62 (ddt, 1 H, J = 17.1, 10.5, 6.9 Hz), 7.31 (d, 2 H, J = 8.1 Hz), 7.74 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 33.6, 42.1, 118.0,

127.1, 129.7, 134.1, 136.9, 143.4; IR ($CDCl_3$) 3283 (NH), 1599 (C=C), 1161 (SO_2) cm^{-1}; HRMS m/z 225.0829 (Calcd. 225.0824 for $C_{11}H_{15}NO_2S$).

Preparation of *N*-(4-pentenyl)-*p*-toluenesulfonamide

i) Preparation of 4-pentenylamine[22]

A mixture of 5-bromo-1-pentene (35 mmol), potassium phthalimide (38 mmol), and potassium iodide (51 mg) in DMF (25 mL) was heated at 120 °C for 1 hour and then at 160 °C for 4 hours. The hot mixture was poured into 100 g of ice and the organic layer was extracted with three 100 mL portions of chloroform. The combined extract was washed successively with 1 N aqueous potassium hydroxide, water, 0.5 N aqueous hydrochloric acid and water again. The chloroform solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Crude *N*-4-pentenylphthalimide was treated with hydrazine monohydrate (2.5 mL) in 50 mL of 95 % ethanol and the mixture was refluxed for 10 hours. The mixture was cooled down, treated with 7 mL of conc. hydrochloric acid and the resulting solid was filtered. The solid phthalhydrazide was washed with water (150 mL) and the combined solution of filtrate was evaporated to dryness under reduced pressure. The residue was diluted with ether (50 mL) and made basic with aqueous potassium hydroxide. The ether layer was separated and dried over anhydrous potassium carbonate. Then the pure product was obtained by distillation at 105-106 °C in 67 % yield: ^1H NMR ($CDCl_3$) δ 1.27 (s, 2 H), 1.54 (m, 2 H), 2.10 (qt, 2 H, J = 7.2, 1.5 Hz), 2.71 (t, 2 H, J = 6.9 Hz), 4.93-5.06 (m, 2 H), 5.82 (ddt, 1 H, J = 17.1, 10.2, 6.6 Hz).

ii) Preparation of *N*-(4-pentenyl)-*p*-toluenesulfonamide

Tosyl chloride (20 mmol) was slowly added to a solution of 4-pentylamine (20 mmol) and pyridine (6.4 mL) at 0 °C. The reaction mixture was heated for 4 hours at 60 °C. After heating, the mixture was cooled down to room temperature, diluted with ether (150 mL), and washed with cold 10 % aqueous hydrochloric acid. The organic layer was dried over

anhydrous potassium carbonate and concentrated in vacuo to afford the desired product in 70 % yield: ^{1}H NMR ($CDCl_3$) δ 1.51-1.61 (m, 2 H), 2.02 (q, 2 H, *J* = 6.9 Hz), 2.41 (s, 3 H), 2.91 (q, 2 H, *J* = 6.9 Hz), 4.90-4.98 (m, 2 H), 5.24 (t, 1 H, *J* = 6.0 Hz), 5.68 (ddt, 1 H, *J* = 17.1, 10.2, 6.6 Hz), 7.30 (d, 2 H, *J* = 7.8 Hz), 7.77 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 28.6, 30.6, 42.5, 115.4, 127.0, 129.6, 136.9, 137.2, 143.2; IR ($CDCl_3$) 3282 (NH), 1598 (C=C), 1159 (SO_2) cm^{-1}; HRMS m/z 239.0987 (Calcd. 239.0980 for $C_{12}H_{17}NO_2S$).

_N_-(4-Pentenyl)trifluoromethanesulfonamide

This compound was prepared in 45 % yield by the same procedure as that used for *N*-(4-pentenyl)-*p*-toluenesulfonamide, except for using trifluoromethanesulfonic anhydride instead of *p*-toluenesulfonyl chloride: ^{1}H NMR ($CDCl_3$) δ 1.68-1.77 (m, 2 H), 2.15 (q, 2 H, *J* = 7.2 Hz), 3.32 (q, 2 H, *J* = 6.9 Hz), 4.88 (br s, 1 H), 5.03-5.12 (m, 2 H), 5.78 (ddt, 1 H, *J* = 17.1, 10.2, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 29.2, 30.4, 44.0, 116.2, 117.0, 136.7; IR ($CDCl_3$) 3317 (NH), 1598 (C=C), 1189 (SO_2) cm^{-1}; HRMS m/z 217.0379 (Calcd. 217.0384 for $C_6H_{10}F_3NO_2S$).

General procedure for the preparation of pyrrolidines

To a 1 dram vial were added $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), the vinylic halide (0.25 mmol), Na_2CO_3 (1.125 mmol), *n*-Bu_4NCl (0.25 mmol), CH_3CN (1 mL), and *N*-(3-butenyl)-*p*-toluenesulfonamide (0.5 mmol). The vial was capped with a screw-cap containing a teflon liner. After heating at 100 °C for an appropriate time interval, the reaction mixture was diluted with ether (Et_2O) and washed with saturated NH_4Cl, followed by water. The organic layer was then dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica gel, hexane/EtOAc as eluents).

General procedure for the preparation of piperidines

To a 1 dram vial were added $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), the vinylic halide (0.25 mmol), $KHCO_3$ (1.125 mmol), *n*-Bu_4NCl (0.25 mmol), CH_3CN (1 mL), and *N*-(4-pentenyl)trifluoromethanesulfonamide (0.5 mmol). The vial was capped with a screw-cap containing a teflon liner. After heating at 100 °C for 24 hours, the reaction mixture was diluted with ether (Et_2O) and washed with saturated NH_4Cl, followed by water. The organic layer was then dried over $MgSO_4$, filtered, concentrated, and purified via flash column chromatography (silica gel, hexane/EtOAc as eluents).

***N*-Tosyl-2-((*E*)-1-hexenyl)pyrrolidine (Table 3, entry 3)**

This compound was obtained in 61 % yield from the reaction of (*E*)-1-iodo-1-hexene and *N*-(3-butenyl)-*p*-toluenesulfonamide at 100 °C for 60 hours: ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.6 Hz), 1.20-1.40 (m, 4 H), 1.55-1.85 (m, 4 H), 2.00 (q, 2 H, J = 7.2 Hz), 2.42 (s, 3 H), 3.20-3.45 (m, 2 H), 4.05-4.15 (m, 1 H), 5.33 (ddt, 1 H, J = 15.3, 6.6, 1.2 Hz), 5.63 (dt, 1 H, J = 15.0, 6.9 Hz), 7.29 (d, 2 H, J = 8.1 Hz), 7.70 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.5, 22.3, 23.9, 31.3, 31.7, 32.8, 48.6, 61.6, 127.5, 129.4, 130.1, 131.9, 135.6, 143.0; IR ($CDCl_3$) 3060 (=CH), 1597 (C=C), 1161 (SO_2) cm^{-1}; HRMS m/z 307.1599 (Calcd. 307.1606 for $C_{17}H_{25}NO_2S$).

***N*-Trifluoromethanesulfonyl-2-((*E*)-1-hexenyl)pyrrolidine (Table 3, entry 4)**

This compound was obtained in 61 % yield from the reaction of (*E*)-1-iodo-1-hexene and *N*-(3-butenyl)trifluoromethanesulfonamide at 100 °C for 60 hours: ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.9 Hz), 1.20-1.40 (m, 4 H), 1.80-2.20 (m, 6 H), 3.47-3.67 (m, 2 H), 4.46 (m, 1 H), 5.63 (dd, 1 H, J = 15.0, 7.2 Hz), 5.66 (dt, 1 H, J = 15.3, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.2, 24.4, 31.1, 31.8, 33.1, 49.2, 63.8, 129.1, 134.8; IR ($CDCl_3$) 2957 (=CH) cm^{-1}; HRMS m/z 285.1010 (Calcd. 285.1002 for $C_{11}H_{18}F_3NO_2S$).

_N_-Tosyl-2-((_E_)-3,3-dimethyl-1-butenyl)pyrrolidine (Table 3, entry 5)

This compound was obtained in 63 % yield from the reaction of (_E_)-1-iodo-3,3-dimethyl-1-butene and _N_-(3-butenyl)-_p_-toluenesulfonamide at 100 °C for 42 hours: ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 9 H), 1.60-1.90 (m, 4 H), 2.42 (s, 3 H), 3.28-3.45 (m, 2 H), 4.13 (m, 1 H), 5.21 (dd, 1 H, J = 15.6, 6.6 Hz), 5.61 (dd, 1 H, J = 15.6, 1.2 Hz), 7.28 (d, 2 H, J = 8.4 Hz), 7.71 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 23.9, 29.4, 32.7, 33.0, 48.6, 61.8, 125.0, 127.5, 129.4, 136.0, 142.6, 143.0; IR ($CDCl_3$) 3025 (=CH), 1596 (C=C), 1160 (SO_2) cm^{-1}; HRMS m/z 307.1611 (Calcd. 307.1606 for $C_{17}H_{25}NO_2S$).

_N_-Trifluoromethanesulfonyl-2-((_E_)-3,3-dimethyl-1-butenyl)pyrrolidine (Table 3, entry 6)

This compound was obtained in 63 % yield from the reaction of (_E_)-1-iodo-3,3-dimethyl-1-butene and _N_-(3-butenyl)trifluoromethanesulfonamide at 100 °C for 42 hours: ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.79-2.19 (m, 4 H), 3.45-3.70 (m, 2 H), 4.46 (m, 1 H), 5.24 (dd, 1 H, J = 15.6, 7.8 Hz), 5.65 (dd, 1 H, J = 15.3, 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5, 29.3, 32.9, 33.2, 49.3, 63.7, 123.0, 144.9; IR ($CDCl_3$) 2960 (=CH), 1224 (SO_2) cm^{-1}; HRMS m/z 285.1008 (Calcd. 285.1002 for $C_{11}H_{18}F_3NO_2S$).

_N_-Tosyl-2-((_E_)-β-styryl)pyrrolidine (Table 3, entry 10)

This compound was obtained in 69 % yield from the reaction of (_E_)-β-bromostyrene and _N_-(3-butenyl)-_p_-toluenesulfonamide at 100 °C for 60 hours: mp 113-116 °C; ^{1}H NMR ($CDCl_3$) δ 1.58-1.96 (m, 4 H), 2.39 (s, 3 H), 3.29-3.55 (m, 2 H), 4.34 (q, 1 H, J = 3.9 Hz), 6.05 (dd, 1 H, J = 15.9, 7.2 Hz), 6.54 (dd, 1 H, J = 15.9, 0.9 Hz), 7.24-7.30 (m, 7 H), 7.72 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.0, 32.8, 48.7, 61.7, 126.5, 127.6, 128.4, 129.5, 130.0, 130.2, 135.6, 136.6, 143.1; IR ($CDCl_3$) 3080 (=CH), 1597 (C=C), 1159 (SO_2) cm^{-1}; HRMS m/z 327.1287 (Calcd. 327.1293 for $C_{15}H_{21}NO_2S$).

Methyl-(*E*)-β-(2-(*N*-tosylpyrrolidinyl))acrylate (Table 3, entry 11)

This compound was obtained in 60 % yield from the reaction of methyl (*E*)-β-bromoacrylate and *N*-(3-butenyl)-*p*-toluenesulfonamide at 100 °C for 48 hours: mp 101-102 °C; ^{1}H NMR ($CDCl_3$) δ 1.56-1.87 (m, 4 H), 2.43 (s, 3 H), 3.19-3.52 (m, 2 H), 3.73 (s, 3 H), 4.26-4.32 (m, 1 H), 6.07 (dd, 1 H, J = 15.3, 0.9 Hz), 6.85 (dd, 1 H, J = 15.6, 5.7 Hz), 7.32 (d, 2 H, J = 8.1 Hz), 7.71 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.9, 31.9, 48.9, 51.6, 60.1, 121.5, 127.5, 129.7, 134.6, 143.6, 147.9, 166.7; IR ($CDCl_3$) 3023 (=CH), 1724 (C=O), 1595 (C=C), 1161 (SO_2) cm^{-1}; HRMS m/z 309.1032 (Calcd. 309.1035 for $C_{15}H_{19}NO_4S$).

***N*-Tosyl-2-(1-cyclohexenyl)pyrrolidine (Table 3, entry 12)**

This compound was obtained in 40 % yield from the reaction of 1-trifluoromethanesulfonyloxycyclohexene and *N*-(3-butenyl)-*p*-toluenesulfonamide at 100 °C for 72 hours: mp 116-117 °C; ^{1}H NMR ($CDCl_3$) δ 1.50-1.98 (m, 12 H), 2.42 (s, 3 H), 3.26-3.43 (m, 2 H), 3.99 (t, 1 H, J = 6.0 Hz), 5.62 (br d, 1 H, J = 0.9 Hz), 7.29 (d, 2 H, J = 8.1 Hz), 7.70 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.4, 22.5, 24.2, 24.4, 24.9, 31.4, 49.2, 66.4, 123.2, 129.4, 135.4, 137.1, 143.0; IR ($CDCl_3$) 2969 (=CH), 1596 (C=C), 1159 (SO_2) cm^{-1}; HRMS m/z 305.1447 (Calcd. 305.1449 for $C_{17}H_{23}NO_2S$).

***N*-Tosyl-2-(2-methyl-1-propenyl)pyrrolidine (Table 3, entry 13)**

This compound was obtained in 57 % yield from the reaction of 1-iodo-2-methylpropene and *N*-(3-butenyl)-*p*-toluenesulfonamide at 100 °C for 26 hours: mp 68-69 °C; ^{1}H NMR ($CDCl_3$) δ 1.53-1.61 (m, 2 H), 1.65 (d, 3 H, J = 0.9 Hz), 1.70 (d, 3 H, J = 0.9 Hz), 1.79-1.90 (m, 2 H), 2.42 (s, 3 H), 3.28-3.42 (m, 2 H), 4.30-4.38 (m, 1 H), 5.02-5.07 (m, 1 H), 7.28 (d, 2 H, J = 8.7 Hz), 7.68 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 18.1,

21.5, 24.2, 25.8, 33.5, 48.5, 58.0, 125.8, 127.5, 129.3, 133.0, 136.0, 142.9; IR ($CDCl_3$) 2970 (=CH), 1596 (C=C), 1159 (SO_2) cm^{-1}; HRMS m/z 279.1288 (Calcd. 279.1293 for $C_{15}H_{21}NO_2S$).

_N_-Tosyl-2-(2-hexenyl)pyrrolidine (Table 3, entry 14)

This compound was obtained in 48 % yield from the reaction of 2-iodo-1-hexene and _N_-(3-butenyl)-_p_-toluenesulfonamide at 100 °C for 36 hours: ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 7.2 Hz), 1.10-2.10 (m, 10 H), 2.40 (s, 3 H), 3.20-3.47 (m, 2 H), 4.07 (t, 1 H, J = 5.7 Hz), 4.83 (s, 1 H), 5.02 (s, 1 H), 7.27 (d, 2 H, J = 8.1 Hz), 7.68 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.6, 22.6, 23.9, 29.9, 31.6, 32.0, 49.1, 64.2, 109.8, 127.5, 129.5, 136.1, 143.2, 149.3; IR ($CDCl_3$) 3082 (=CH), 1595 (C=C), 1160 (SO_2) cm^{-1}; HRMS m/z 307.1613 (Calcd. 307.1606 for $C_{17}H_{25}NO_2S$).

_N_-Tosyl-2-(α-styryl)pyrrolidine (Table 3, entry 15)

This compound was obtained in 33 % yield from the reaction of α-iodostyrene and _N_-(3-butenyl)-_p_-toluenesulfonamide at 100 °C for 48 hours: ^1H NMR ($CDCl_3$) δ 1.40-1.80 (m, 4 H), 2.44 (s, 3 H), 3.20-3.35 (m, 1 H), 3.40-3.60 (m, 1 H), 4.70-4.78 (m, 1 H), 5.35 (br s, 1 H), 5.39 (t, 1 H, J = 0.9 Hz), 7.20-7.40 (m, 7 H), 7.80 (d, 2 H, J = 8.1 Hz); HRMS m/z 327.1287 (Calcd. 327.1293 for $C_{15}H_{21}NO_2S$). There was not enough material for ^{13}C NMR and IR analysis.

_N_-Trifluoromethanesulfonyl-2-(α-styryl)pyrrolidine (Table 3, entry 16)

This compound was obtained in 22 % yield from the reaction of α-iodostyrene and _N_-(3-butenyl)trifluoromethanesulfonamide at 100 °C for 48 hours: mp 54-58 °C; ^1H NMR ($CDCl_3$) δ 1.76-1.85 (m, 1 H), 1.96-2.15 (m, 3 H), 3.60-3.75 (m, 2 H), 5.25 (d, 1 H, J = 6.9 Hz), 5.28 (s, 1 H), 5.41 (s, 1 H), 7.20-7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.4, 32.0,

49.6, 64.4, 113.6, 126.1, 126.8, 128.6, 138.9, 147.8; IR ($CDCl_3$) 2928 (=CH), 1186 (SO_2) cm^{-1}; HRMS m/z 305.0697 (Calcd. 305.0697 for $C_{13}H_{14}F_3NO_2S$).

_N_-Tosyl-2-((_E_)-1-ethyl-1-butenyl)pyrrolidine (Table 3, entry 17)

This compound was obtained in 50 % yield from the reaction of (*E*)-3-iodo-3-hexene and *N*-(3-butenyl)-*p*-toluenesulfonamide at 100 °C for 26 hours: mp 62-64 °C; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.5 Hz), 1.02 (t, 3 H, J = 7.5 Hz), 1.44-2.19 (m, 8 H), 2.42 (s, 3 H), 3.26-3.50 (m, 2 H), 4.11 (t, 1 H, J = 5.7 Hz), 5.29 (t, 1 H, J = 7.2 Hz), 7.29 (d, 2 H, J = 8.1 Hz), 7.70 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.4, 20.8, 21.4, 21.5, 23.7, 31.8, 49.1, 64.5, 127.5, 127.7, 129.4, 135.5, 139.4, 143.0; IR ($CDCl_3$) 2965 (=CH), 1597 (C=C) cm^{-1}; HRMS m/z 307.1601 (Calcd. 307.1606 for $C_{17}H_{25}NO_2S$). This compound is assigned to be the (*E*)-isomer, although this has not been proven.

_N_-Tosyl-2-((_E_)-1-hexenyl)piperidine (Table 6, entry 1)

This compound was obtained in 44 % yield from the reaction of (*E*)-1-iodo-1-hexene and *N*-(4-pentenyl)-*p*-toluenesulfonamide at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.9 Hz), 1.21-1.68 (m, 12 H), 1.90 (q, 2 H, J = 6.3 Hz), 2.40 (s, 3 H), 2.94 (m, 1 H), 3.68 (br d, 1 H, J = 13.2 Hz), 4.55 (br s, 1 H), 5.30 (ddt, 1 H, J = 15.6, 6.3, 1.2 Hz), 5.51 (ddt, 1 H, J = 15.6, 6.3, 1.2 Hz), 7.24 (d, 2 H, J = 8.4 Hz), 7.66 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.1, 21.5, 22.3, 25.3, 30.6, 31.1, 32.0, 41.6, 54.7, 126.1, 127.4, 129.3, 133.5, 137.9, 142.6; IR ($CDCl_3$) 3060 (=CH), 1597 (C=C), 1184 (SO_2) cm^{-1}; HRMS m/z 321.1768 (Calcd. 321.1763 for $C_{18}H_{27}NO_2S$).

_N_-Tosyl-2-((_E_)-β-styryl)piperidine (Table 6, entry 3)

This compound was obtained in 38 % yield from the reaction of (_E_)-β-bromostyrene and _N_-(4-pentenyl)-_p_-toluenesulfonamide at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 1.46-1.79 (m, 6 H), 3.00 (m, 1 H), 3.75 (br d, 1 H, J = 12.9 Hz), 4.74 (br s, 1 H), 5.97 (dd, 1 H, J = 16.2, 6.3 Hz), 6.39 (dd, 1 H, J = 15.9, 1.2 Hz), 7.15-7.30 (m, 7 H), 7.67 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.3, 21.5, 25.2, 30.7, 42.0, 55.2, 126.3, 127.4, 127.6, 128.4, 129.4, 132.1, 136.6, 137.4, 142.9; IR ($CDCl_3$) 2939 (=CH), 1597 (C=C), 1184 (SO_2) cm^{-1}; HRMS m/z 319.0844 (Calcd. 319.0854 for $C_{20}H_{21}NO_2S$).

_N_-Tosyl-2-((_E_)-3,3-dimethyl-1-butenyl)piperidine (Table 6, entry 5)

This compound was obtained in 36 % yield from the reaction of (_E_)-3,3-dimethyl-1-iodo-1-butene and _N_-(4-pentenyl)-_p_-toluenesulfonamide at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9 H), 1.43-1.72 (m, 6 H), 2.40 (s, 3 H), 2.94 (m, 1 H), 3.70 (br d, 1 H, J = 12.9 Hz), 4.55 (br s, 1 H), 5.19 (dd, 1 H, J = 15.6, 0.6 Hz), 5.50 (dd, 1 H, J = 15.9, 1.2), 7.24 (d, 2 H, J = 8.1 Hz), 7.66 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.1, 21.5, 25.3, 29.4, 30.9, 32.9, 41.7, 54.8, 121.1, 127.4, 129.4, 138.0, 142.7, 144.0; IR ($CDCl_3$) 3062 (=CH), 1598 (C=C), 1182 (SO_2) cm^{-1}; HRMS m/z 321.1772 (Calcd. 321.1762 for $C_{20}H_{21}NO_2S$).

_N_-Tosyl-2-(2-hexenyl)piperidine (Table 6, entry 6)

This compound was obtained in less than 10 % yield from the reaction of 2-iodo-1-hexene and _N_-(4-pentenyl)-_p_-toluenesulfonamide at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.2 Hz), 1.26-1.97 (m, 12 H), 2.42 (s, 3 H), 3.02 (m, 1 H), 3.72 (m, 1 H), 4.56 (m, 1 H), 4.92 (s, 1 H), 5.00 (s, 1 H), 7.27 (d, 2 H, J = 8.4 Hz), 7.73 (d, 2 H, J = 8.4 Hz). There was not enough material for ^{13}C NMR, IR and HRMS analysis.

_N_-Trifluoromethanesulfonyl-2-((_E_)-1-hexenyl)piperidine (Table 6, entry 8)

This compound was obtained in 77 % yield from the reaction of (_E_)-1-iodo-1-hexene and _N_-(4-pentenyl)trifluoromethanesulfonamide at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6.6 Hz), 1.25-1.82 (m, 12 H), 2.08 (q, 2 H, J = 6.9 Hz), 3.22 (t, 1 H, J = 12.3 Hz), 3.76 (d, 1 H, J = 13.8 Hz), 4.61 (br s, 1 H), 5.49 (dd, 1 H, J = 15.3, 4.2 Hz), 5.69 (dtd, 1 H, J = 15.3, 6.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 18.6, 22.2, 25.6, 29.8, 31.2, 32.1, 43.0, 56.1, 135.0; IR ($CDCl_3$) 2981(=CH), 1184 (SO_2) cm^{-1}; HRMS m/z 299.1166 (Calcd. 299.1167 for $C_{12}H_{20}F_3NO_2S$).

_N_-Trifluoromethanesulfonyl-2-((_E_)-β-styryl)piperidine (Table 6, entry 9)

This compound was obtained in 69 % yield from the reaction of (_E_)-β-iodostyrene and _N_-(4-pentenyl)trifluoromethanesulfonamide at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 1.56 -2.01 (m, 6 H), 3.30 (t, 1 H, J = 12.3 Hz), 3.83 (d, 1 H, J = 13.8 Hz), 4.83 (br s, 1 H), 6.22 (dd, 1 H, J = 15.9, 5.1 Hz), 6.59 (dd, 1 H, J = 16.2, 1.5 Hz), 7.25-7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.8, 25.4, 29.7, 43.3, 56.3, 126.6, 128.1, 128.7, 133.4, 136.1; IR ($CDCl_3$) 2947 (=CH), 1184 (SO_2) cm^{-1}; HRMS m/z 319.0845 (Calcd. 319.0854 for $C_{14}H_{16}F_3NO_2S$).

_N_-Trifluoromethanesulfonyl-2-((_E_)-3,3-dimethyl-1-butenyl)piperidine (Table 6, entry 11)

This compound was obtained in 69 % yield from the reaction of (_E_)-3,3-dimethyl-1-iodo-1-butene and _N_-(4-pentenyl)trifluoromethanesulfonamide at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 9 H), 1.45-1.80 (m, 6 H), 3.14 (br t, 1 H, J = 12.3 Hz), 3.70 (br d, 1 H, J = 14.4 Hz), 4.55 (br d, 1 H, J = 2.7 Hz), 5.25-5.45 (m, 1 H), 5.64 (dd, 1 H, J = 15.9, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.6, 25.7, 29.4, 30.3, 33.2, 43.0, 56.3, 145.7; IR

($CDCl_3$) 2981 (=CH), 1185 (SO_2) cm^{-1}; HRMS m/z 299.1170 (Calcd. 299.1167 for $C_{12}H_{20}F_3NO_2S$).

_N_-Trifluoromethanesulfonyl-2-(2-hexenyl)piperidine (Table 6, entry 12)

This compound was obtained in 43 % yield from the reaction of 2-iodo-1-hexene and _N_-(4-pentenyl)trifluoromethanesulfonamide at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.2 Hz), 1.28-1.80 (m, 10 H), 1.90-2.14 (m, 2 H), 3.23 (td, 1 H, J = 12.0, 2.1 Hz), 3.79 (d, 1 H, J = 14.7 Hz), 4.55 (br s, 1 H), 5.04 (s, 1 H), 5.15 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.8, 22.5, 25.2, 26.7, 30.0, 33.3, 43.7, 58.3, 112.8, 144.2; IR ($CDCl_3$) 2954 (=CH), 1196 (SO_2) cm^{-1}; HRMS m/z 299.1165 (Calcd. 299.1167 for $C_{12}H_{20}F_3NO_2S$).

_N_-Trifluoromethanesulfonyl-2-(α-styryl)piperidine (Table 6, entry 13)

This compound was obtained in 31 % yield from the reaction of α-iodostyrene and _N_-(4-pentenyl)trifluoromethanesulfonamide at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 1.20 -1.90 (m, 6 H), 3.44 (td, 1 H, J = 13.2, 2.1 Hz), 3.87 (dd, 1 H, J = 14.1, 2.7 Hz), 5.13 (br s, 1 H), 5.32 (d, 1 H, J = 2.1 Hz), 5.40 (d, 1 H, J = 2.1 Hz), 7.25-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.4, 25.2, 27.5, 43.7, 57.9, 116.2, 127.1, 127.9, 128.5, 140.1, 145.8; IR ($CDCl_3$) 2958 (=CH), 1194 (SO_2) cm^{-1}; HRMS m/z 319.0858 (Calcd. 319.0854 for $C_{14}H_{16}F_3NO_2S$).

Preparation of _N_-tosyl-2-vinylaniline

i) Preparation of 2-(_N_-tosylamino)benzaldehyde[23]

To a solution of 2-(_N_-tosylamino)benzyl alcohol (10 mmol), which was prepared from 2-aminobenzyl alcohol in 78 % yield using the same procedure as that used for _N_-tosyl-2-isopropenylaniline, in CH_2Cl_2 (25 mL) was added PCC (15 mmol) at room temperature and

the mixture was stirred for 1 hour. Upon completion of the reaction, the mixture was diluted with ethyl ether (50 mL) and filtered through the short column packed with florisil to remove excess chromium. The ether solution was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography using 5:1 hexane/THF to afford the product in 91 % yield: ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 7.15 (t, 1 H, J = 7.5 Hz), 7.23 (d, 2 H, J = 7.8 Hz), 7.50 (t, 1 H, J = 7.5 Hz), 7.58 (d, 1 H, J = 7.5 Hz), 7.67 (d, 1 H, J = 7.5 Hz), 7.76 (d, 2 H, J = 8.1 Hz), 9.81 (s, 1 H), 10.8 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 117.8, 121.9, 123.1, 127.2, 129.8, 135.8, 136.2, 136.3, 139.9, 144.3, 195.1; IR ($CDCl_3$) 3186 (NH), 1676 (C=O), 1606 (C=C), 1170 (SO_2) cm^{-1}.

ii) Preparation of *N*-tosyl-2-vinylaniline[24]

A solution of *n*-BuLi (10 mmol) was added to a solution of methyl-triphenylphosphonium bromide (10 mmol) in THF (14 mL) at 0 °C. After 30 minutes, a solution of 2-(*N*-tosylamino)benzaldehyde (5 mmol) was added slowly to the solution and the mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water (15 mL) and the crude product was extracted with ethyl ether (100 mL). The ether solution was dried over $MgSO_4$ and the ether was removed under reduced pressure. The resulting residue was purified by flash column chromatography using 5:1 hexane/THF to afford the product in 60 % yield: mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3 H), 5.26 (dd, 1 H, J = 11.1, 0.9 Hz), 5.50 (dd, 1 H, J = 17.1, 0.9 Hz), 6.41 (s, 1 H), 6.51 (dd, 1 H, J = 17.4, 11.1 Hz), 7.15-7.25 (m, 4 H), 7.31 - 7.36 (m, 2 H), 7.60 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 118.4, 124.8, 126.4, 127.0, 127.2, 128.6, 129.6, 131.5, 132.7, 133.2, 136.4, 143.9; IR ($CDCl_3$) 3269 (NH), 1598 (C=C), 1163 (SO_2) cm^{-1}.

Preparation of *N*-tosyl-2-isopropenylaniline

p-Toluenesulfonyl chloride (20 mmol) was added to the solution of 2-isopropenylaniline (20 mmol) and pyridine (6.4 mL) at 0 °C. The reaction mixture was heated

for 2 hours at 65 °C. Then, the mixture was cooled down to room temperature, diluted with ethyl ether (150 mL) and washed with cold 10 % aqueous hydrochloric acid (6 x 50 mL). The organic layer was dried over anhydrous K_2CO_3 and concentrated in vacuo to afford the desired product in 75 % yield: mp 77-79 °C; ^{1}H NMR ($CDCl_3$) δ 1.69 (d, 3 H, J = 0.9 Hz), 2.36 (s, 3 H), 4.68 (t, 1 H, J = 0.6 Hz), 5.26 (t, 1 H, J = 1.5 Hz), 7.00-7.80 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.4, 117.1, 120.5, 124.4, 127.2, 127.9, 128.0, 129.6, 132.8, 134.7, 136.4, 142.0, 143.8; IR ($CDCl_3$) 3270 (NH), 1599 (C=C), 1164 (SO_2) cm^{-1}.

Preparation of *N*-Tosyl-2-((*E*)-1-propenyl)aniline

This compound was obtained in 72 % yield using the same procedure as that used for *N*-tosyl-2-vinylaniline: mp 135-136 °C (lit. mp 134-134.5 °C)[25]; ^{1}H NMR ($CDCl_3$) δ 1.77 (dd, 3 H, J = 6.6, 1.5 Hz), 2.37 (s, 3 H), 5.89 (dq, 1 H, J = 15.6, 6.6 Hz), 6.17 (dd, 1 H, J = 15.9, 1.2 Hz), 6.77 (s, 1 H), 7.07-7.26 (m, 5 H), 7.32 (dd, 1 H, J = 7.5, 1.5 Hz), 7.60 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 18.7, 21.5, 124.7, 125.3, 126.3, 127.0, 127.2, 127.6, 129.5, 130.2, 132.7, 132.8, 136.5, 143.7; IR ($CDCl_3$) 3269 (NH), 1599 (C=C), 1162 (SO_2) cm^{-1}.

Preparation of *N*-tosyl-2-methallylaniline

i) Preparation of *N*-tosyl-2-iodomethylaniline[26]

To a solution of 2-(*N*-tosylamino)benzyl alcohol (10 mmol) and sodium iodide (20 mmol) in CH_3CN (20 mL) was added slowly chlorotrimethylsilane (20 mmol) with good stirring. The reaction was completed within 30 minutes. Upon completion of the reaction, the reaction mixture was diluted with ethyl ether (100 mL) and the ether solution was washed successively with water (100 mL), sat'd aqueous sodium thiosulfate (5 x 100 mL) and water (100 mL). The ether layer then was dried over $MgSO_4$ and concentrated in vacuo. The addition of a small amount of THF to the resulting residue followed by the addition of hexane

afforded the product as a white solid in 85 - 90 % yield: ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 4.11 (s, 2 H), 6.50 (s, 1 H), 7.08-7.14 (m, 1 H), 7.18-7.26 (m, 5 H), 7.67 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 2.1, 21.6, 125.6, 126.7, 127.2, 129.4, 129.8, 130.1, 132.7, 134.3, 136.3, 144.1.

ii) Preparation of *N*-tosyl-2-methallylaniline

In an oven-dried, 50 mL round bottom flask equipped with a condenser and a stirring bar were placed magnesium turnings (9 mmol) and THF (3 mL) under a nitrogen atmosphere. A solution of 2-bromopropene (9 mmol) in 1 mL of THF was introduced slowly into the flask at room temperature with good stirring. After the formation of the Grignard reagent (about 30 min.) a solution of *N*-tosyl-2-iodomethylaniline (3 mmol) in THF (5 mL) was added slowly at room temperature and the mixture was stirred for 1 hour. The excess Grignard reagent was destroyed by adding water and the crude product was extracted with ethyl ether (100 mL). The ether solution then was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography using 5:1 hexane/THF to afford the product in 62 % yield: mp 51-52 °C; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3 H), 2.39 (s, 3 H), 2.91 (s, 2 H), 4.61 (s, 1 H), 4.89 (s, 1 H), 6.67 (s, 1 H), 7.03 (dd, 1 H, J = 7.5, 1.5 Hz), 7.09 (td, 1 H, J = 7.2, 0.9 Hz), 7.18-7.24 (m, 3 H), 7.46 (d, 1 H, J = 8.1 Hz), 7.59 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.2, 41.0, 112.9, 124.1, 125.9, 127.1, 127.8, 129.6, 131.0, 131.3, 135.5, 136.9, 143.6, 143.8; IR ($CDCl_3$) 3308 (NH), 1599 (C=C), 1164 (SO_2) cm^{-1}.

Preparation of *N*-tosyl-2-allylaniline

N-Tosyl-2-allylaniline was obtained in 55 % yield using the same procedure as that used for *N*-tosyl-2-methallylaniline except vinylmagnesium bromide was used instead of 2-propenylmagnesium bromide: mp 69-70 °C (lit.[25] mp 70.5-71 °C); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3 H), 3.01 (d, 2 H, J = 5.7 Hz), 4.94 (dd, 1 H, J = 17.4, 1.5 Hz), 5.11 (dd, 1 H, J = 9.9, 1.5 Hz), 5.78 (ddt, 1 H, J = 17.1, 10.2, 5.7 Hz), 6.49 (s, 1 H), 7.04-7.23 (m, 5 H),

7.40 (d, 1 H, J = 7.8 Hz), 7.59 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 36.2, 117.0, 124.5, 126.3, 127.1, 127.7, 129.6, 130.5, 132.1, 134.9, 135.6, 136.7, 143.8; IR ($CDCl_3$) 3285 (NH), 1599 (C=C), 1163 (SO_2) cm^{-1}.

Preparation of *N*-tosyl-2-crotylaniline

N-Tosyl-2-crotylaniline was obtained as a mixture of *cis* - and *trans* -isomers in a 56:44 ratio in 52 % overall yield using the same procedure as that used for *N*-tosyl-2-methallylaniline except 1-propenylmagnesium bromide was used instead of 2-propenylmagnesium bromide. *cis* -isomer: ^{1}H NMR ($CDCl_3$) δ 1.70 (d, 2 H, J = 6.9 Hz), 2.39 (s, 3 H), 3.02 (d, 2 H, J = 6.9 Hz), 5.20-5.30 (m, 1 H), 5.60-5.73 (m, 1 H), 6.48 (s, 1 H), 7.00-7.28 (m, 5 H), 7.41 (d, 1 H, J = 8.4 Hz), 7.58 (d, 2 H, J = 8.4 Hz); ^{13}C NMR of mixture ($CDCl_3$) δ 12.7, 17.7, 21.4, 29.3, 34.8, 124.1, 124.3, 125.9, 126.1, 126.4, 126.9, 127.0, 127.2, 127.4, 128.2, 129.4, 129.7, 130.1, 132.9, 133.3, 134.7, 134.9, 136.6, 143.6 (several peaks are not seen due to overlap); IR ($CDCl_3$) 3301 (NH), 1599 (C=C), 1164 (SO_2) cm^{-1}.

trans -isomer: ^{1}H NMR ($CDCl_3$) δ 1.65-1.68 (m, 2 H), 2.91 (br s, 2 H), 5.35-5.41 (m, 2 H), 6.60 (s, 1 H).

General procedure for the preparation of 1,2-dihydroindoles and 1,2,3,4-tetrahydroquinolines

To a 1 dram vial were added the $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), a vinylic halide (0.25 mmol), Na_2CO_3 (0.88 mmol), *n*-Bu_4NCl (0.28 mmol), CH_3CN (1.2 mL), and the *o*-alkenylaniline derivative (0.38 mmol). The vial was capped with a screw-cap containing a teflon liner. After heating at 100 °C for an appropriate time interval, the reaction mixture was diluted with Et_2O and washed with saturated NH_4Cl, followed by water. The organic layer was then dried over $MgSO_4$, filtered, concentrated, and purified via flash column chromatography (silica gel, hexane/EtOAc as eluents).

_N_-Tosyl-2,3-dihydro-2-((_E_)-β-styryl)indole (Table 7, entry 3)

This compound was obtained in 60 % yield from the reaction of (_E_)-β-bromostyrene and _N_-tosyl-2-ethenylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 2.73 (dd, 1 H, J = 15.9, 2.7 Hz), 3.08 (dd, 1 H, J = 16.2, 12.6 Hz), 4.86-5.05 (m, 1 H), 6.15 (dd, 1 H, J = 15.6, 6.9 Hz), 6.68 (d, 1 H, J = 15.6 Hz), 6.99-7.09 (m, 2 H), 7.15 (d, 2 H, J = 8.1 Hz), 7.20-7.35 (m, 6 H), 7.61 (d, 2 H, J = 8.1 Hz), 7.67 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 35.5, 63.9, 116.6, 124.4, 125.2, 126.6, 127.2, 127.8, 127.9, 128.4, 128.7, 129.5, 131.2, 135.7, 136.3, 141.4, 143.8 (one peak is not seen due to overlap); IR ($CDCl_3$) 3063 (=CH)), 1599 (C=C), 1167 (SO_2) cm^{-1}; HRMS m/z 375.1301 (Calcd. 375.1293 for $C_{23}H_{21}NO_2$).

_N_-Tosyl-2-_n_-butyl-2,3-dihydro-5-methylbenzazepine (Table 9, entry 1)

This compound was obtained in 72 % yield from the reaction of (_E_)-1-iodo-1-hexene and _N_-tosyl-2-isopropenylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 6.6 Hz), 1.08-1.49 (m, 8 H), 1.57 (s, 3 H), 2.31 (s, 3 H), 4.63 (q, 1 H, J = 6.3 Hz), 5.36 (dd, 1 H, J = 5.7, 1.2 Hz), 7.0 (d, 2 H, J = 8.1 Hz), 7.10 (dd, 1 H, J = 7.5, 1.5 Hz), 7.19-7.24 (m, 3 H), 7.29 (td, 1 H, J = 7.2, 1.2 Hz), 7.70 (dd, 1 H, J = 7.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.8, 21.4, 22.6, 25.1, 31.4, 33.1, 54.9, 123.0, 125.6, 126.5, 127.3, 127.7, 128.3, 128.7, 129.1, 130.8, 132.9, 136.1, 142.9; IR ($CDCl_3$) 3065 (=CH), 1598 (C=C), 1167 (SO_2) cm^{-1}; HRMS m/z 369.1767 (Calcd. 369.1763 for $C_{22}H_{27}NO_2S$).

_N_-Tosyl-2,3-dihydro-5-methyl-2-phenylbenzazepine (Table 9, entry 4)

This compound was obtained in 39 % yield from the reaction of (_E_)-β-bromostyrene and _N_-tosyl-2-isopropenylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3 H), 2.30 (s, 3 H), 2.58-2.72 (m, 2 H), 4.15 (q, 1 H, J = 7.2 Hz), 5.33 (dd, 1 H, J = 5.7, 1.2

Hz), 7.0 (d, 2 H, J = 8.1 Hz), 7.12-7.35 (m, 10 H), 7.69 (dd, 1 H, J = 7.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 17.8, 21.5, 40.1, 55.9, 123.2, 124.8, 126.4, 126.6, 127.4, 128.0, 128.2, 128.8, 129.5, 129.8, 130.7, 131.2, 133.0, 136.1, 137.2, 143.0; IR ($CDCl_3$) 2954 (=CH), 1600 (C=C), 1166 (SO_2) cm^{-1}; HRMS m/z 389.1442 (Calcd. 389.1445 for $C_{24}H_{23}NO_2S$).

N-Tosyl-2-*t*-butyl-2,3-dihydro-5-methylbenzazepine (Table 9, entry 5)

This compound was obtained in 67 % yield from the reaction of (*E*)-1-iodo-3,3-dimethyl-1-butene and N-tosyl-2-isopropenylaniline at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 1.01 (s, 9 H), 1.07-1.36 (m, 2 H), 1.51 (s, 3 H), 2.31 (s, 3 H), 4.90 (m, 1 H), 5.30 (dd, 1 H, J = 6.0, 1.2 Hz), 7.01 (d, 2 H, J = 8.1 Hz), 7.07 (dd, 1 H, J = 7.8, 1.5 Hz), 7.16 (d, 2 H, J = 8.1 Hz), 7.23 (td, 1 H, J = 7.5, 1.5 Hz), 7.31 (td, 1 H, J = 7.5, 1.5 Hz), 7.68 (dd, 1 H, J = 7.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.7, 21.4, 29.9, 30.6, 45.3, 52.6, 122.9, 126.5, 126.7, 127.4, 127.6, 128.6, 128.8, 131.4, 132.9, 135.9, 142.9 (one peak is not seen due to overlap); IR ($CDCl_3$) 3064 (=CH), 1597 (C=C), 1161 (SO_2) cm^{-1}; HRMS m/z 369.1771 (Calcd. 369.1763 for $C_{22}H_{27}NO_2S$).

N-Tosyl-2,3-dihydro-2-methoxycarbonyl-5-methylbenzazepine (Table 9, entry 6)

This compound was obtained in 44 % yield from the reaction of methyl (*E*)-β-bromoacrylate and N-tosyl-2-isopropenylaniline at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 1.58 (d, 3 H, J = 0.6 Hz), 2.32 (s, 3 H), 2.34-2.51 (m, 2 H), 3.69 (s, 3 H), 5.20 (q, 1 H, J = 6.9 Hz), 5.46 (dd, 1 H, J = 6.0, 1.2 Hz), 7.04 (d, 2 H, J = 8.1 Hz), 7.11 (dd, 1 H, J = 7.5, 1.5 Hz), 7.22 (d, 2 H, J = 8.4 Hz), 7.24 (td, 1 H, J = 7.5, 1.2 Hz), 7.32 (td, 1 H, J = 7.5, 1.5 Hz), 7.70 (dd, 1 H, J = 7.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 17.8, 21.5, 38.9, 51.3, 51.9, 123.2, 123.5, 126.9, 127.4, 128.2, 128.4, 128.8, 130.3, 130.7, 132.6, 135.6, 143.3,

170.5; IR ($CDCl_3$) 2953 (=CH), 1734 (C=O), 1599 (C=C), 1167 (SO_2) cm^{-1}; HRMS m/z 371.1194 (Calcd. 371.1191 for $C_{20}H_{21}NO_4S$).

_N_-Tosyl-2,3-dihydro-2-methyl-2-((_E_)-β-styryl)indole (Table 10, entry 8)

This compound was obtained in 54 % yield from the reaction of (_E_)-β-bromostyrene and _N_-tosyl-2-((_E_)-1-propenyl)aniline at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 1.92 (s, 3 H), 2.31 (s, 3 H), 3.06 (d, 1 H, J = 16.2 Hz), 3.20 (d, 1 H, J = 15.9 Hz), 6.20 (d, 1 H, J = 16.8 Hz), 6.57 (d, 1 H, J = 16.2 Hz), 6.80-7.40 (m, 10 H), 7.65-7.71 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.2, 45.3, 71.5, 114.3, 122.9, 125.0, 126.7, 127.2, 127.7, 127.8, 128.1, 128.5, 129.1, 129.4, 132.2, 136.3, 138.7, 142.0, 143.3; IR ($CDCl_3$) 2960 (=CH), 1599 (C=C), 1168 (SO_2) cm^{-1}; HRMS m/z 389.1456 (Calcd. 389.1450 for $C_{24}H_{25}NO_2S$)

_N_-Tosyl-2-((_E_)-1-hexenyl)-1,2,3,4-tetrahydroquinoline (Table 12, entry 2)

This compound was obtained in 85 % yield along with a small amout of a diene (88:12 ratio) from the reaction of (_E_)-1-iodo-1-hexene and _N_-tosyl-2-allylaniline at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 6.9 Hz), 1.15-1.30 (m, 4 H), 1.50-1.61 (m, 1 H), 1.70-1.85 (m, 1 H), 1.90-2.10 (m, 3 H), 2.37 (s, 3 H), 2.40-2.55 (m, 1 H), 4.85 (q, 1 H, J = 5.7 Hz), 5.34 (ddt, 1 H, J = 15.3, 5.4, 1.2 Hz), 5.66 (dtd, 1 H, J = 15.6, 6.6, 1.2 Hz), 6.96 (d, 1 H, J = 7.5 Hz), 7.06 (td, 1 H, J = 7.5, 1.2 Hz), 7.15-7.25 (m, 3 H), 7.44 (d, 2 H, J = 8.4 Hz), 7.73 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.6, 22.1, 24.3, 28.0, 31.2, 31.9, 56.9, 125.0, 126.3, 126.6, 127.1, 128.4, 128.5, 129.4, 132.1, 132.7, 135.7, 136.9, 143.3; IR ($CDCl_3$) 2927 (=CH), 1599 (C=C), 1165 (SO_2) cm^{-1}; HRMS m/z 369.1773 (Calcd. 369.1763 for $C_{22}H_{27}NO_2S$).

_N_-Tosyl-2-((_E_)-β-styryl)-1,2,3,4-tetrahydroquinoline (Table 12, entry 3)

This compound was obtained in 80 % yield from the reaction of (_E_)-β-bromostyrene and _N_-tosyl-2-allylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 1.60-1.73 (m, 1 H), 1.83-1.94 (m, 1 H), 1.97-2.08 (m, 1 H), 2.37 (s, 3 H), 2.45-2.56 (m, 1 H), 5.07 (qd, 1 H, J = 5.7, 1.5 Hz), 6.11 (dd, 1 H, J = 15.9, 5.7 Hz), 6.59 (dd, 1 H, J = 15.9, 1.5 Hz), 6.97 (dd, 1 H, J = 7.8, 0.9 Hz), 7.08 (td, 1 H, J = 7.2, 1.2 Hz), 7.15-7.31 (m, 8 H), 7.45 (d, 2 H, J = 8.4 Hz), 7.81 (dd, 1 H, J = 8.4, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 24.5, 28.2, 57.2, 125.3, 125.5, 126.4, 126.5, 126.7, 127.1, 127.5, 128.4, 128.6, 129.5, 131.2, 132.2, 135.5, 136.5, 136.6, 143.5; IR ($CDCl_3$) 2995 (=CH), 1599 (C=C), 1166 (SO_2) cm^{-1}; HRMS m/z 389.1460 (Calcd. 389.1450 for $C_{24}H_{23}NO_2S$).

_N_-Tosyl-2-((_E_)-3,3-dimethyl-1-butenyl)-1,2,3,4-tetrahydroquinoline (Table 12, entry 4)

This compound was obtained in 72 % yield along with a small amout of a diene (95:5 ratio) from the reaction of (_E_)-1-bromo-3,3-dimethyl-1-butene and _N_-tosyl-2-allylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 9 H), 1.50-1.61 (m, 1 H), 1.74-1.86 (m, 1 H), 1.97-2.07 (m, 1 H), 2.37 (s, 3 H), 2.41-2.52 (m, 1 H), 4.86 (qd, 1 H, J = 6.0, 1.2 Hz), 5.24 (dd, 1 H, J = 15.6, 5.7 Hz), 5.66 (dd, 1 H, J = 15.9, 1.5 Hz), 6.96 (d, 1 H, J = 7.5 Hz), 7.06 (td, 1 H, J = 7.2, 0.9 Hz), 7.15-7.20 (m, 3 H), 7.45 (d, 2 H, J = 8.1 Hz), 7.71 (d, 1 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 24.4, 28.4, 29.5, 32.8, 57.1, 123.4, 125.0, 126.2, 126.5, 127.1, 128.3, 129.4, 132.1, 135.7, 137.0, 143.3, 143.4; IR ($CDCl_3$) 2959 (=CH), 1599 (C=C), 1164 (SO_2) cm^{-1}; HRMS m/z 369.1771 (Calcd. 369.1763 for $C_{22}H_{27}NO_2S$).

_N_-Tosyl-2-(2-methyl-1-propenyl)-1,2,3,4-tetrahydroquinoline and _N_-tosyl-2,3-dihydro-2-((_E_)-3-methyl-1-butenyl)indole (Table 12, entry 5)

_N_-Tosyl-2-(2-methyl-1-propenyl)-1,2,3,4-tetrahydroquinoline was obtained in 66 % yield along with a small amount of _N_-tosyl-2,3-dihydro-2-((_E_)-3-methyl-1-butenyl)indole (77:23 ratio) from the reaction of 1-iodo-2-methylpropene and _N_-tosyl-2-allylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 1.40- 1.47 (m, 1 H), 1.66 (s, 3 H), 1.78 (s, 3 H), 1.70-1.85 (m, 1 H), 2.00-2.15 (m, 1 H), 2.37 (s, 3 H), 2.45-2.51 (m, 1 H), 5.05-5.10 (m, 2 H), 6.99 (d, 1 H, J = 7.8 Hz), 7.08 (td, 1 H, J = 7.5, 0.9 Hz), 7.15-7.22 (m, 3 H), 7.44 (d, 2 H, J = 8.1 Hz), 7.69 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.2, 21.5, 24.4, 25.7, 28.4, 54.0, 123.6, 125.1, 126.5, 127.0, 127.6, 128.4, 129.4, 132.2, 134.0, 135.6, 137.0, 143.2; IR ($CDCl_3$) 2960 (=CH), 1599 (C=C), 1165 (SO_2) cm^{-1}; HRMS m/z 341.1458 (Calcd. 341.1450 for $C_{20}H_{23}NO_2S$).

_N_-Tosyl-2,3-dihydro-2-((_E_)-3-methyl-1-butenyl)indole: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3 H, J = 6.9 Hz), 0.96 (d, 3 H, J = 6.9 Hz), 2.90-3.10 (m, 1 H), 4.70-4.77 (m, 1 H), 5.41 (ddd, 1 H, J = 15.6, 6.9, 1.2 Hz), 5.75 (ddd, 1 H, J = 16.2, 6.0, 0.98 Hz). Other peaks can't be assigned.

_N_-Tosyl-2-(2-hexenyl)-1,2,3,4-tetrahydroquinoline (Table 12, entry 6)

This compound was obtained in 52 % yield along with a small amout of a diene (91:9 ratio) from the reaction of 2-iodo-1-hexene and _N_-tosyl-2-allylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.2 Hz), 1.20-2.40 (m, 10 H), 2.37 (s, 3 H), 4.74 (t, 1 H, J = 6.9 Hz), 4.84 (s, 1 H), 5.02 (s, 1 H), 6.93 (d, 1 H, J = 7.5 Hz), 7.07 (t, 1 H, J = 7.5 Hz), 7.16 (d, 2 H, J = 8.1 Hz), 7.22 (t, 1 H, J = 7.8 Hz), 7.40 (d, 2 H, J = 8.1 Hz), 7.77 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.6, 25.1, 28.2, 29.9, 30.4, 32.2, 60.2, 110.4, 125.4, 126.6, 126.8, 127.1, 127.9, 129.4, 129.9, 133.5, 136.2, 143.4, 148.6;

IR ($CDCl_3$) 2957 (=CH), 1599 (C=C), 1165 (SO_2) cm^{-1}; HRMS m/z 369.1764 (Calcd. 369.1763 for $C_{22}H_{27}NO_2S$).

_N_-Tosyl-2-((_E_)-1-ethyl-1-butenyl)-1,2,3,4-tetrahydroquinoline (Table 12, entry 7)

This compound was obtained in 31 % yield along with a small amount of a diene (91:9 ratio) from the reaction of (*E*)-3-iodo-3-hexene and *N*-tosyl-2-allylaniline at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7.5 Hz), 1.06 (t, 3 H, J = 7.5 Hz), 1.50-1.74 (m, 2 H), 1.87-2.05 (m, 1 H), 1.99 (q, 4 H, J = 7.5 Hz), 2.25-2.35 (m, 1 H), 2.37 (s, 3 H), 4.66 (t, 1 H, J = 7.8 Hz), 5.35 (t, 1 H, J = 7.2 Hz), 6.93 (d, 1 H, J = 6.9 Hz), 7.08 (dd, 1 H, J = 7.2, 1.2 Hz), 7.15 (d, 2 H, J = 8.1 Hz), 7.23 (td, 1 H, J = 6.6, 1.2 Hz), 7.38 (d, 2 H, J = 8.4 Hz), 7.74 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 14.5, 20.9, 21.6, 25.6, 29.6, 61.8, 125.4, 126.7, 126.9, 127.1, 127.6, 128.2, 129.3, 134.7, 136.4, 136.5, 139.6, 143.2; IR ($CDCl_3$) 2964 (=CH), 1599 (C=C), 1165 (SO_2) cm^{-1}; HRMS m/z 369.1761 (Calcd. 369.1763 for $C_{22}H_{27}NO_2S$).

_N_-Tosyl-2-((_E_)-1-hexenyl)-3-methyl-1,2,3,4-tetrahydroquinoline and _N_-tosyl-2,3-dihydro-2-((_E_)-1-heptenyl)-2-methylindole (Table 13, entry 1)

N-Tosyl-2-((*E*)-1-hexenyl)-3-methyl-1,2,3,4-tetrahydroquinoline was obtained as an inseparable mixture of stereoisomers (*cis* / *trans* = 66 / 34) along with *N*-tosyl-2,3-dihydro-2-((*E*)-1-heptenyl)-2-methylindole, which was obtained cleanly from the reaction of (*E*)-1-iodo-1-hexene (see entry 2 of Table 13), in a 19:81 ratio from the reaction of (*E*)-1-bromo-1-hexene and *N*-tosyl-2-methallylaniline at 100 °C for 24 hours: *cis* -Isomer: ^1H NMR ($CDCl_3$) δ 4.80 (dd, 1 H, J = 7.5, 4.2 Hz), 5.18 (ddt, 1 H, J = 15.0, 7.5, 0.9 Hz). Other peaks can't be assigned. *trans* -Isomer: ^1H NMR ($CDCl_3$) δ 4.22 (t, 1 H, J = 5.7 Hz), 5.36 (ddt, 1 H, J = 15.3, 6.9, 1.5 Hz). Other peaks can't be assigned.

_N_-Tosyl-2,3-dihydro-2-((_E_)-1-heptenyl)-2-methylindole (Table 13, entry 2)

_N_-Tosyl-2,3-dihydro-2-((_E_)-1-heptenyl)-2-methylindole was obtained in 31 % yield from the reaction of (_E_)-1-iodo-1-hexene and _N_-tosyl-2-methallylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.3 Hz), 1.20-1.40 (m, 6 H), 1.77 (s, 3 H), 1.90-2.10 (m, 2 H), 2.37 (s, 3 H), 2.95 (d, 1 H, J = 15.9 Hz), 3.10 (d, 1 H, J = 15.9 Hz), 5.58 (d, 1 H, J = 15.6 Hz), 5.70 (dt, 1 H, J = 15.9, 6.3 Hz), 6.94 (t, 1 H, J = 7.5 Hz), 7.07 (d, 1 H, J = 6.9 Hz), 7.15 (t, 1 H, J = 8.1 Hz), 7.20 (d, 2 H, J = 8.1 Hz), 7.55 (d, 1 H, J = 8.4 Hz), 7.74 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.6, 22.6, 26.3, 28.8, 31.5, 32.3, 45.2, 71.7, 114.1, 122.6, 124.9, 127.1, 127.7, 128.4, 129.3, 130.4, 132.8, 139.0, 142.0, 143.2; IR ($CDCl_3$) 2958 (=CH), 1600 (C=C), 1167 (SO_2) cm^{-1}; HRMS m/z 383.1925 (Calcd. 383.1919 for $C_{23}H_{29}NO_2S$).

_N_-Tosyl-2,3-dihydro-2-methyl-2-((_E_)-3-phenyl-1-propenyl)indole and _N_-tosyl-3-methyl-2-((_E_)-β-styryl)-1,2,3,4-tetrahydroquinoline (Table 13, entry 3)

_N_-Tosyl-2,3-dihydro-2-methyl-2-((_E_)-3-phenyl-1-propenyl)indole was obtained in 48 % yield from the reaction of (_E_)-β-bromostyrene and _N_-tosyl-2-methallylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 2.37 (s, 3 H), 2.95 (d, 1 H, J = 16.2 Hz), 3.14 (d, 1 H, J = 15.9 Hz), 3.27-3.44 (m, 2 H), 5.76 (d, 1 H, J = 15.6 Hz), 5.87 (dt, 1 H, J = 15.6, 6.3 Hz), 6.94 (t, 1 H, J = 7.5 Hz), 7.07 (d, 1 H, J = 6.9 Hz), 7.15-7.35 (m, 8 H), 7.42 (d, 1 H, J = 8.1 Hz), 7.74 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.1, 38.6, 45.1, 71.7, 114.1, 122.7, 124.9, 126.1, 127.0, 127.7, 128.3, 128.5, 128.6, 129.4, 134.8, 138.9, 139.9, 141.8, 143.3 (one peak is not seen due to overlap); IR ($CDCl_3$) 2959 (=CH), 1600 (C=C), 1165 (SO_2) cm^{-1}; HRMS m/z 403.1610 (Calcd. 403.1606 for $C_{25}H_{25}NO_2S$).

N-Tosyl-3-methyl-2-((*E*)-β-styryl)-1,2,3,4-tetrahydroquinoline was obtained in 24 % yield as an inseparable mixture of stereoisomers (*cis* / *trans* = 67 / 33). *cis* -Isomer: ^{1}H NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 6.9 Hz), 5.04 (dd, 1 H, J = 7.2, 3.9 Hz), 5.95 (dd, 1 H, J = 15.9, 7.5 Hz), 6.61 (dd, 1 H, J = 15.6, 1.2 Hz). Other peaks can't be assigned. *trans* -Isomer: ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3 H, J = 6.6 Hz), 4.43 (t, 1 H, J = 7.8 Hz), 6.00 (dd,1 H, J = 15.9, 6.9 Hz). Other peaks can't be assigned.

_N_-Tosyl-2,3-dihydro-2-((*E*)-4,4-dimethyl-1-pentenyl)-2-methylindole and _N_-tosyl-2-((*E*)-3,3-dimethyl-1-butenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (Table 13, entry 4)

N-Tosyl-2,3-dihydro-2-((*E*)-4,4-dimethyl-1-pentenyl)-2-methylindole was obtained in 27 % yield from the reaction of (*E*)-1-bromo-3,3-dimethyl-1-butene and *N*-tosyl-2-methallylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 9 H), 1.79 (s, 3 H), 1.75-2.00 (m, 2 H), 2.38 (s, 3 H), 2.97 (d, 1 H, J = 15.6 Hz), 3.11 (d, 1 H, J = 15.6 Hz), 5.63 (d, 1 H, J = 15.3 Hz), 5.74 (dt, 1 H, J = 15.3, 6.9 Hz), 6.93 (t, 1 H, J = 7.5 Hz), 7.07 (d, 1 H, J = 7.2 Hz), 7.14 (t, 1 H, J = 7.2 Hz), 7.21 (d, 2 H, J = 8.1 Hz), 7.51 (d, 1 H, J = 6.6 Hz), 7.76 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 26.1, 29.4, 31.2, 45.4, 46.8, 72.0, 114.1, 122.6, 124.9, 127.0, 127.2, 127.9, 128.3, 129.4, 135.3, 139.0, 142.0, 143.2; IR ($CDCl_3$) 2957 (=CH), 1164 (SO_2) cm^{-1}; HRMS m/z 383.1910 (Calcd. 383.1919 for $C_{23}H_{29}NO_2S$).

N-Tosyl-2-((*E*)-3,3-dimethyl-1-butenyl)-3-methyl-1,2,3,4-tetrahydroquinoline was obtained in 25 % yield as an inseparable mixture of stereoisomers (*cis* / *trans* = 67 / 33) along with a small amount of unknowns. *cis* -Isomer: ^{1}H NMR ($CDCl_3$) δ 4.84 (dd,1 H, J = 7.5, 3.9 Hz), 5.07 (dd, 1 H, J = 15.6, 7.8 Hz). Other peaks can't be assigned. *trans* -Isomer: ^{1}H

NMR ($CDCl_3$) δ 4.24 (t, 1 H, J = 7.5 Hz), 5.22 (dd, 1 H, J = 15.6, 7.2 Hz). Other peaks can't be assigned.

N-Tosyl-2,3-dihydro-2-methyl-2-((*E*)-3-methyl-1-butenyl)indole (Table 13, entry 5)

This compound was obtained in 61 % yield from the reaction of 1-iodo-2-methylpropene and N-tosyl-2-methallylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3 H, J = 6.6 Hz), 0.98 (d, 3 H, J = 6.6 Hz), 1.76 (s, 3 H), 2.15-2.30 (m, 1 H), 2.37 (s, 3 H), 2.95 (d, 1 H, J = 15.9 Hz), 3.01 (d, 1 H, J = 15.9 Hz), 5.57 (d, 1 H, J = 15.9 Hz), 5.66 (dd, 1 H, J = 15.9, 6.0 Hz), 6.94 (t, 1 H, J = 7.2 Hz), 7.08 (d, 1 H, J = 7.2 Hz), 7.14 (t, 1 H, J = 8.1 Hz), 7.20 (d, 2 H, J = 8.1 Hz), 7.54 (d, 1 H, J = 8.1 Hz), 7.75 (d, 2 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.0, 22.1, 26.4, 30.8, 45.3, 71.7, 114.1, 122.6, 124.9, 127.0, 127.7, 128.4, 129.3, 130.2, 136.9, 139.2, 142.0, 143.3; IR ($CDCl_3$) 2961 (=CH), 1599 (C=C), 1166 (SO_2) cm^{-1}; HRMS m/z 355.1612 (Calcd. 355.1606 for $C_{21}H_{25}NO_2S$).

N-Tosyl-2-methyl-2-((*E*)-β-styryl)-1,2,3,4-tetrahydroquinoline (Table 14, entry 1)

This compound was obtained in 32 % yield from the reaction of (*E*)-β-bromostyrene and N-tosyl-2-crotylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.70-1.82 (m, 1 H), 1.88-2.00 (m, 1 H), 2.37 (s, 3 H), 2.55-2.70 (m, 2 H), 6.31 (d, 1 H, J = 16.2 Hz), 6.40 (d, 1 H, J = 16.2 Hz), 7.04 (d, 1 H, J = 7.5 Hz), 7.10-7.35 (m, 9 H), 7.38 (d, 2 H, J = 8.4 Hz), 7.69 (dd, 1 H, J = 8.1, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 24.2, 28.1, 29.8, 32.8, 62.2, 125.9, 126.0, 126.5, 127.5, 127.6, 128.1, 128.5, 129.2, 129.3, 133.0, 134.7, 136.9, 137.6, 139.4, 143.0 (one peak is not seen due to overlap); IR ($CDCl_3$) 2959 (=CH), 1165 (SO_2) cm^{-1}; HRMS m/z 403.1617 (Calcd. 403.1606 for $C_{25}H_{25}NO_2S$).

_N_-Tosyl-2-((_E_)-3,3-dimethyl-1-butenyl)-2-methyl-1,2,3,4-tetrahydroquinoline (Table 14, entry 2)

This compound was obtained in 22 % yield from the reaction of (_E_)-1-bromo-3,3-dimethyl-1-butene and _N_-tosyl-2-crotylaniline at 100 °C for 24 hours: ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9 H), 1.44 (s, 3 H), 1.60-1.80 (m, 2 H), 2.39 (s, 3 H), 2.45-2.60 (m, 2 H), 5.35 (d, 1 H, J = 16.2 Hz), 5.47 (d, 1 H, J = 16.2 Hz), 6.90 (d, 1 H, J = 6.0 Hz), 7.10 (td, 1 H, J = 7.2, 1.2 Hz), 7.12-7.20 (m, 3 H), 7.44 (d, 2 H, J = 8.4 Hz), 7.57 (dd, 1 H, J = 8.1, 1.2 Hz): ^{13}C NMR ($CDCl_3$) δ 21.6, 24.1, 28.6, 29.3, 32.0, 32.7, 62.3, 125.6, 125.8, 127.5, 128.0, 129.3, 129.5, 130.0, 138.3, 139.2, 139.5, 143.0 (one peak is not seen due to overlap); IR ($CDCl_3$) 2958 (=CH), 1167 (SO_2) cm^{-1}; HRMS m/z 383.1909 (Calcd. 383.1919 for $C_{23}H_{29}NO_2S$).

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SYNTHESIS OF CARBOCYCLES VIA PALLADIUM-CATALYZED COUPLING OF VINYLIC HALIDES WITH FUNCTIONALLY-SUBSTITUTED ALKENES

A paper to be submitted to *Tetrahedron*

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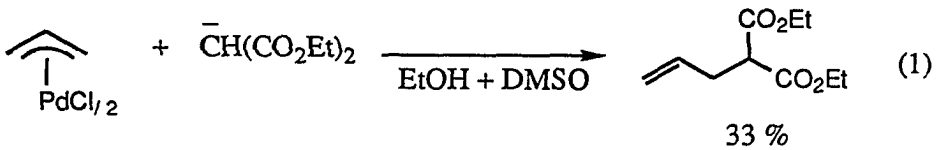
Introduction

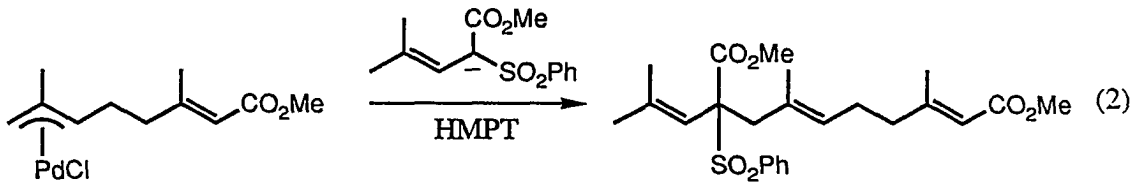
The formation of new carbon-carbon bonds is very important in organic synthesis. The displacement of π-allylpalladium compounds by carbon nucleophiles has become one of the most useful and convenient methods for achieving this objective due to the high reactivity of π-allylpalladium compounds towards carbon nucleophiles.[1] Of carbon nucleophiles reported, enolates,[2] organotin compounds,[3] organozinc compounds,[4] organoaluminum and zirconium compounds,[5] organomagnesium and lithium compounds,[6] organoboron compounds[7] and soft carbon nucleophiles are the most widely used. In this paper, the palladium-catalyzed coupling of vinylic halides with alkenes containing a soft carbon nucleophile will be discussed.

The first example of π-allylpalladium displacement using a soft carbon nucleophile was reported by Tsuji in 1965 (eq. 1).[8] Since Tsuji's work, many palladium-catalyzed allylic alkylations have been reported.[9]



33 % (1)

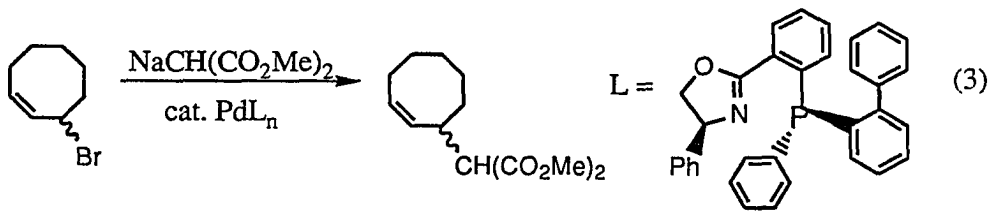
In 1978, Trost reported the alkylation of π-allylpalladium complexes with carbon nucleophiles, such as malonates, β-keto sulfones, β-keto sulfoxides, and β-keto sulfides.[9] This methodology was successfully used in converting lower terpenes into higher terpenes (eq. 2).



(2)

63 %

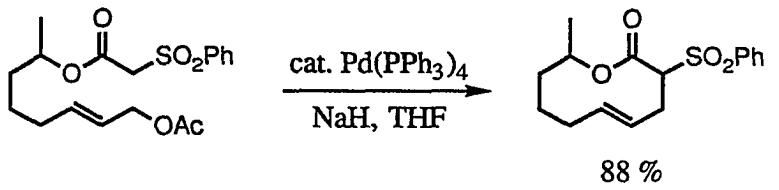
Palladium-catalyzed, asymmetric, allylic alkylations have also been reported. For example, 85 % ee was obtained from the reaction of 3-bromocyclooctene with dimethyl malonate in the presence of a chiral oxazoline ligand (eq. 3).[10]



(3)

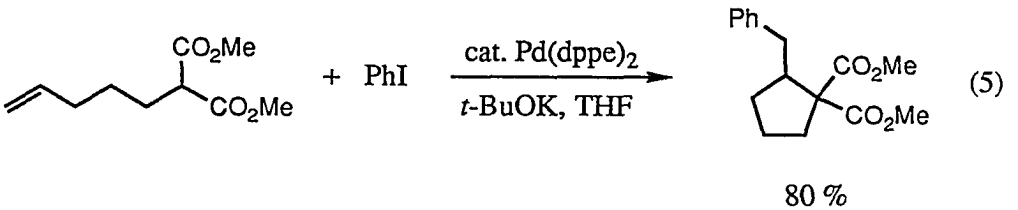
85 % ee

Intramolecular displacement of π-allylpalladium species by carbon nucleophiles has also been reported. Trost[11] and Tsuji[12] used this approach successfully in the synthesis of medium-sized ring compounds (eq. 4).

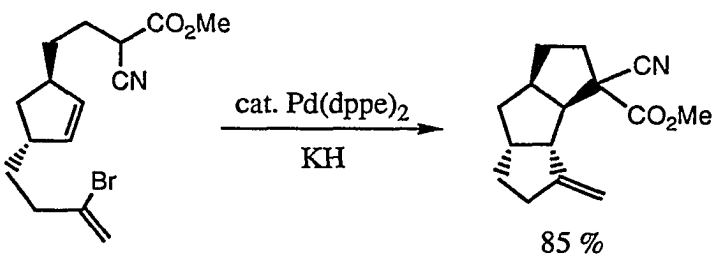


88 % (4)

The palladium-catalyzed coupling of vinylic or aryl halides with functionally-substituted alkenes or alkynes has been studied extensively by Gore.[13] Interestingly, all these reactions were found to proceed without the involvement of π-allylpalladium species (eq. 5). In his studies, he proposed that the reactions proceed by nucleophilic attack on the double bond activated by a σ-alkylpalladium species, rather than on a π-allylpalladium species. Later, his methodology was employed in the synthesis of triquinanes (eq. 6).[14]



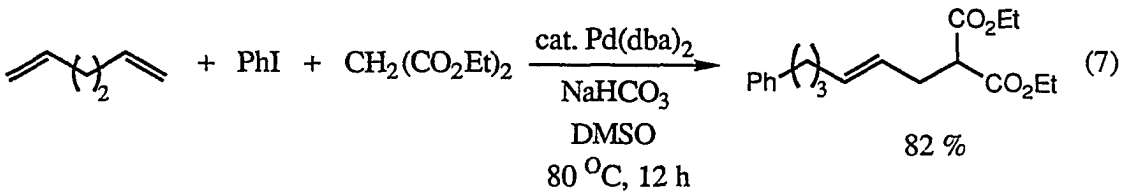
80 % (5)

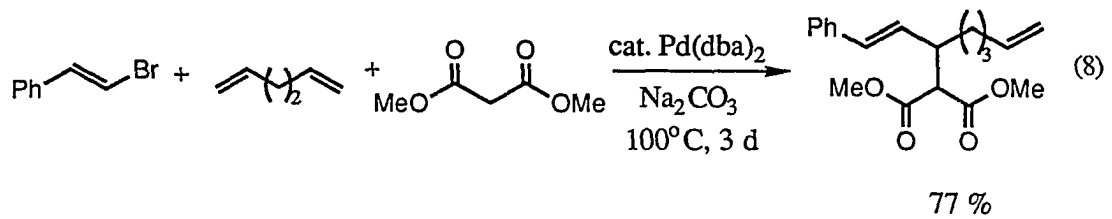


85 % (6)

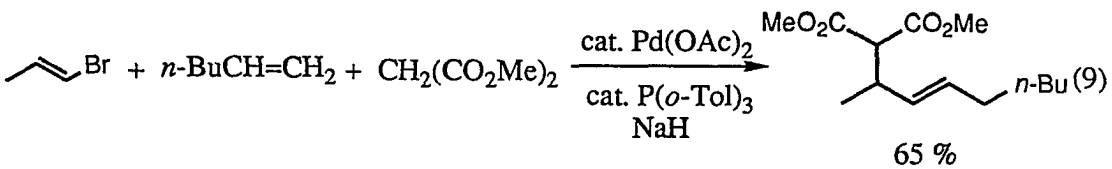
The palladium-catalyzed coupling of three components, such as vinylic or aryl halides, alkenes, and carbon nucleophiles, has been used in the formation of new carbon-carbon bonds.[15] Larock reported that aryl iodides, nonconjugated dienes, and carbon nucleophiles react to give good yields of coupled products apparently formed by arylpalladium generation

and addition to the less substituted end of the diene, palladium migration down the carbon chain to form the π-allylpalladium intermediate, followed by the carbanion displacement of the palladium moiety (eq. 7).[16] A similar process has been examined using vinylic halides. The products were obtained via the π-allylpalladium intermediate as anticipated, rather than that obtained through palladium migration to the other terminal double bond (eq. 8).[17]

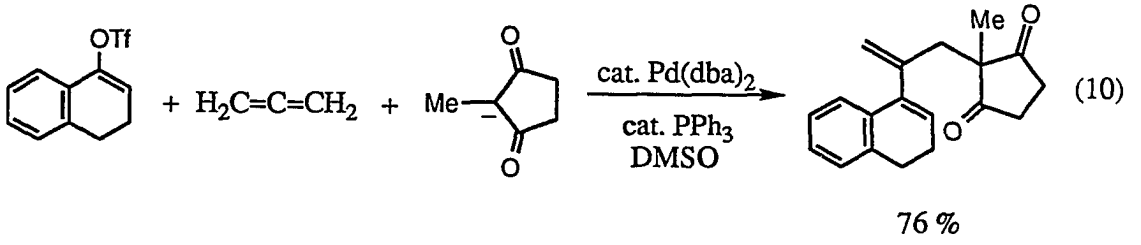




Weinreb has also performed similar reactions using vinylic bromides and unactivated olefins (eq. 9).[18] He also showed that the intramolecular version of this reaction produced functionalized carbobicyclic compounds.

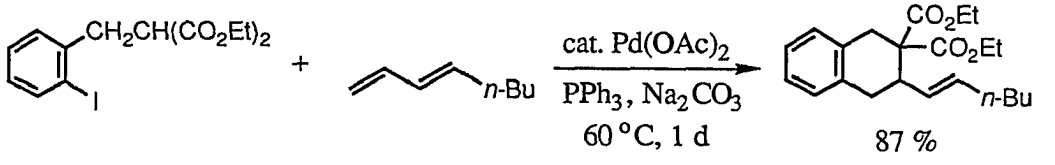


Similarly, Gore has prepared compounds which were transformed into steroidal trienones by using 1,2-dienes (eq. 10).[19]

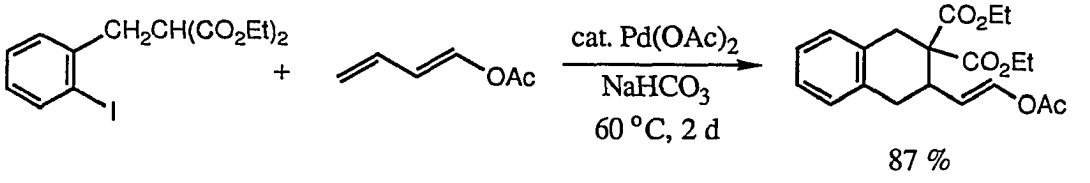


(10)

Finally, Larock has demonstrated the palladium-catalzyed carboannulation of 1,3-dienes,[20] and oxygen-substituted 1,3-dienes[21] by functionalized aryl halides, a process which has proven to be very useful in preparing a variety of carbocycles (eqs. 11 and 12).



(11)



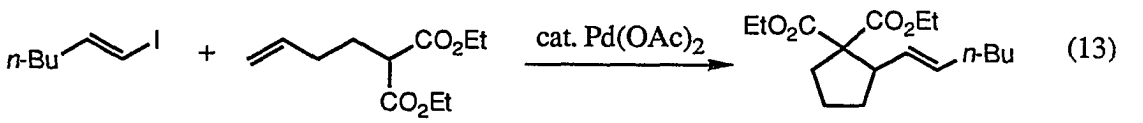
(12)

This literature survey indicates that much work has been done in the area of palladium-catalyzed reactions with carbon nucleophiles. However, relatively little attention has been paid to the palladium-catalyzed coupling of vinylic halides with functionalized alkenes despite its usefulness in preparing heterocycles. Even though Gore studied this approach, the reactions

were found to proceed without the involvement of a π-allylpalladium species. Hence, our prior success in carboannulation and Weinreb's results encouraged us to examine the palladium-catalyzed coupling of vinylic halides with functionalized alkenes bearing potential sites of carbanion formation. In this part of the dissertation, our results are discussed.

Results and Discussion

Initial studies were aimed at the establishment of optimum reaction conditions for the reaction of (*E*)-1-iodo-1-hexene with diethyl (3-butenyl)malonate (eq. 13).



1 **2** **3** (13)

First, reactions were run using five different bases at 80 °C in the presence of TBAC as the chloride source (entries 1 - 5 in Table 1). Of the bases examined, none gave satisfactory results. In addition, TLC analysis indicated that a small amount of compound **1** still remained unreacted after 2 days. Therefore, these reactions were run again at 100 °C and improvements in yield were indeed observed (entries 6 - 10). Na_2CO_3 was the best base, producing the product in 45 % yield. Acetate bases, such as NaOAc and KOAc, provided lower yields and organic amines were found to be ineffective. The use of PPh_3 provided almost identical results regardless of the amounts used (entries 12 and 13). Virtually the same yield, 46 %, was obtained when 10 mol % $Pd(OAc)_2$ was used instead of 5 mol % $Pd(OAc)_2$ (entry 14). Nonetheless, more reactions were run using 10 mol % $Pd(OAc)_2$. Once again, the use of triphenylphosphine and 1,2-bis(diphenylphosphino)ethane didn't effect the reactions positively

Table 1. Effect of Base, Temperature, Solvent, Ligand, Palladium Source, and Amount of Palladium Catalyst on the Reaction of (*E*)-1-Iodo-1-hexene with Diethyl (3-butenyl)malonate using TBAC as the Chloride Source.[a]

entry	$Pd(OAc)_2$ (mol %)	PPh_3 (mol %)	base (4.5 equivs.)	solvent, time (d)	% isolated yield **3**
1[b]	5	-	Na_2CO_3	DMF, 2	23
2[b]	5	-	NaOAc	DMF, 2	28
3[b]	5	-	KOAc	DMF, 2	22
4[b]	5	-	Et_3N	DMF, 2	5
5[b]	5	-	*i*-Pr_2NEt	DMF, 2	5
6	5	-	Na_2CO_3	DMF, 2	45
7	5	-	NaOAc	DMF, 2	26
8	5	-	KOAc	DMF, 2	29
9	5	-	Et_3N	DMF, 2	7
10	5	-	*i*-Pr_2NEt	DMF, 2	5
11	5	-	Na_2CO_3	DMSO, 2	29
12	5	5	Na_2CO_3	DMF, 2	43
13	5	10	Na_2CO_3	DMF, 2	43
14	10	-	Na_2CO_3	DMF, 2	46

[a]Reactions were run using 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.50 mmol), 2.0 equivs. of diethyl (3-butenyl)malonate, 1.0 equiv. of TBAC, 4.5 equivs. of a base, and 2 mL of DMF for 2 days at 100 °C. The reactions described in entries 15 - 27 were run on a 0.25 mmol scale. [b]Reactions were run at 80 °C.

Table 1. (Continued)

entry	$Pd(OAc)_2$ (mol %)	PPh_3 (mol %)	base (4.5 equivs.)	solvent, time (d)	% isolated yield **3**
15	10	10	Na_2CO_3	DMF, 2	39
16[c]	10	10	Na_2CO_3	DMF, 2	38
17[d]	10	-	Na_2CO_3	DMF, 2	32
18	10	-	Na_2CO_3	THF, 7	18
19	10	-	Na_2CO_3	HMPA, 7	45
20	10	-	NaH	DMF, 7	13
21[e]	10	-	Na_2CO_3	DMF, 7	46
22[f]	10	-	Na_2CO_3	DMF, 2	39
23[g]	5	-	Na_2CO_3	DMF, 2	41
24[g]	5	5	Na_2CO_3	DMF, 2	37
25[g]	5	10	Na_2CO_3	DMF, 2	40
26[g]	5	-	Na_2CO_3	CH_3CN, 2	27
27[g]	10	-	Na_2CO_3	DMF, 2	45

[c]1,2-Bis(diphenylphosphino)ethane, instead of PPh_3, was used. [d]The reaction was run at 120 °C. [e]$MgSO_4$ (4.5 equivs.) was also added. [f]The reaction was run without the use of TBAC. [g]$Pd(dba)_2$ was used.

(entries 15 and 16). The use of a higher temperature, 120 °C, or a stronger base, NaH, dropped the yield significantly (entries 17 and 20). Two reactions were run based on the idea that the formation of enolates might be prevented due to the presence of water in the TBAC,

resulting in lower yields. Therefore, one reaction was run using $MgSO_4$ as a drying agent. (entry 21) and another reaction was run in the absence of the TBAC (entry 22). However, no significant changes were observed with regard to the yield. In a survey of solvents, DMF was found to be better than THF, CH_3CN, DMSO, and HMPA (entries 11, 18, 19 and 26). Reactions were also run using $Pd(dba)_2$. However, the results were very similar to those obtained from the reactions using $Pd(OAc)_2$ (entries 23 - 27).

Next, reactions were run in the presence of LiCl as the chloride source and the results are shown in Table 2. As shown in entries 1 and 2, the reaction run at 120 °C gave the product in much higher yield than that run at 100 °C. However, both yields were much lower than those obtained from the reactions using TBAC. As a result, more reactions were run using different bases in order to improve the yield, but the results were not satisfactory. Na_2CO_3, K_2CO_3, and NaOAc gave the product in almost equal amounts (entries 2, 4, and 6). For KOAc, the product was contaminated with unknowns (entry 7). The use of 2 equivs. of LiCl or 10 mol % $Pd(OAc)_2$ was also found to be ineffective (entries 9 and 10). The addition of 5 mol % PPh_3 increased the yield by only 6 % (entry 11), but this yield was still lower than the 46 % yield obtained from the reactions using TBAC. Reactions using different stoichiometries of starting materials in the presence of PPh_3 didn't afford any improvements in the yield. Considering the fact that the reaction of (*E*)-1-iodo-1-hexene with diethyl (3-butenyl)malonate in the presence of LiCl proceeded better at a higher temperature, a reaction was run using 5 mol % $Pd(OAc)_2$ and TBAC at 120 °C and a 51 % yield was obtained, which is the highest ever obtained (entry 15). Given the fact that a similar reaction run at 120 °C using 10 mol % $Pd(OAc)_2$ and TBAC gave only a 32 % yield of the product (entry 17 in Table 1), it is not clear what caused the significant increase in the yield.

Finally, functionalized alkenes, such as dicyano and cyanoester compounds, were used instead of malonate. Unfortunately, the reactions using these functionalized alkenes produced

Table 2. Effect of Base, Temperature, and Amount of Palladium Catalyst on the Reaction of (*E*)-1-Iodo-1-hexene with Diethyl (3-butenyl)malonate using LiCl as the Chloride Source.[a]

entry	$Pd(OAc)_2$ (mol %)	PPh_3 (mol %)	base (4.5 equivs.)	solvent (1 mL), time (d)	% isolated yield **3**
1[b]	5	-	Na_2CO_3	DMF, 2	8
2	5	-	Na_2CO_3	DMF, 2	32
3	5	-	Li_2CO_3	DMF, 1	14
4	5	-	K_2CO_3	DMF, 1	30
5	5	-	Cs_2CO_3	DMF, 1	27
6[c]	5	-	NaOAc	DMF, 1	32
7[c]	5	-	KOAc	DMF, 1	39
8	5	-	*i*-Pr_2NEt	DMF, 1	28
9[d]	5	-	Na_2CO_3	DMF, 2	28
10	10	-	Na_2CO_3	DMF, 2	31
11	5	5	Na_2CO_3	DMF, 2	38
12	5	10	Na_2CO_3	DMF, 2	34

[a]Reactions were run using 1.0 equiv. of (*E*)-1-iodo-1-hexene (0.25 mmol), 2.0 equivs. of diethyl (3-butenyl)malonate, 1.0 equiv. of LiCl, 4.5 equivs. of a base, and 1 mL of DMF at 120 °C. [b]The reaction was run at 100 °C. [c]The purity of the products is 90 % based on G. C. analysis. [d]2.0 Equivs. of LiCl were used.

Table 2. (Continued)

entry	$Pd(OAc)_2$ (mol %)	PPh_3 (mol %)	base (4.5 equivs.)	solvent (1 mL), time (d)	% isolated yield **3**
13[e]	5	5	Na_2CO_3	DMF, 1	26
14[c,f]	5	5	Na_2CO_3	DMF, 1	36
15[g]	5	-	Na_2CO_3	DMF, 1	51

[e]A 1:1 ratio of (*E*)-1-iodo-1-hexene to diethyl (3-butenyl)malonate was used. [f]A 2:1 ratio of (*E*)-1-iodo-1-hexene to diethyl (3-butenyl)malonate was used. [g]TBAC was used instead of LiCl.

the products with a significant amount of unknowns. For example, the reaction of (*E*)-1-iodo-1-hexene and 2-cyano-3-butenenitrile gave a 73 % overall yield of an inseparable 53:47 mixture of the desired 5-membered ring product along with an unknown using Na_2CO_3, TBAC, and DMF at 100 °C for 1 day. An inseparable 66:34 mixture of the desired product along with an unknown was also obtained in 44 % overall yield from the reaction of methyl 2-cyano-5-hexenoate and (*E*)-1-iodo-1-hexene under the same conditions.

In summary, attempts to establish optimum reaction conditions for the reaction of (*E*)-1-iodo-1-hexene with diethyl (3-butenyl)malonate and other functionally-substituted alkenes were not very successful and further investigations will be necessary to determine the scope and limitations of this methodology.

Conclusion

The establishment of optimal reaction conditions for the reactions of (*E*)-1-iodo-1-hexene with diethyl (3-butenyl)malonate was attempted. During the study, significant improvements were not observed when different solvents and bases were used. In addition, the reactions of (*E*)-1-iodo-1-hexene with diethyl (3-butenyl)malonate were not affected substantially by using ligands or increasing the amount of catalyst. As a chloride source, TBAC was better than LiCl. At present this methodology appears to be rather limited. Further work will be needed to make this a synthetically useful process.

Experimental Section

Equipment

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz, respectively. All infrared spectra were recorded on a Beckman 4250 spectrometer and high resolution mass spectral analyses were performed on a Kratos MS-50 spectrometer. Thin-layer chromatography (TLC) was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic potassium permanganate solution.

Reagents

All reagents were used directly as obtained commercially unless otherwise noted. Palladium acetate was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride was purchased from Lancaster Synthesis Co. 4-Bromo-1-butene was purchased from Aldrich Chemical Co. Diethyl malonate was purchased

from Eastman Kodak Co. Other inorganic compounds were purchased from Fisher Scientific Co.

Diethyl 3-butenylmalonate

In a dry round bottom flask containing a stirring bar were added NaH (33 mmol) and 24 mL of DMF, followed by diethyl malonate (33 mmol) under a nitrogen atmosphere at room temperature. The mixture was stirred for 45 minutes until it became clear. After the addition of 4-bromo-1-butene (30 mmol) in 12 mL of THF, the mixture was stirred overnight. The mixture was diluted with ether (100 mL), washed with saturated NH_4Cl and water, dried over $MgSO_4$, concentrated in vacuo, and column chromatographed over silica gel using 8:1 hexane/EtOAc to afford the product in 79-85 % yield: ^1H NMR ($CDCl_3$) δ 1.27 (t, 6 H, J = 7.2 Hz), 1.99 (q, 2 H, J = 7.5 Hz), 2.74 (q, 2 H, J = 6.9 Hz), 2.35 (t, 1 H, J = 7.5 Hz), 4.20 (q, 4 H, J = 7.2 Hz), 5.00-5.07 (m, 2 H), 5.77 (ddt, 1 H, J = 17.1, 10.2, 6.3 Hz); IR ($CDCl_3$) 2984 (=CH), 1728 (C=O), 1641 (C=C) cm^{-1}.

General procedure for the reaction of (*E*)-1-iodo-1-hexene and diethyl 3-butenylmalonate

To a 1 dram vial were added $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), (*E*)-1-iodo-1-hexene (0.25 mmol), diethyl 3-butenylmalonate (0.5 mmol), Na_2CO_3 (1.125 mmol), *n*-Bu_4NCl (0.25 mmol), and 1 mL of DMF. The vial was capped with a screw-cap containing a teflon liner. After heating at 120 °C for 1 day, the reaction mixture was diluted with ether (Et_2O) and washed with saturated NH_4Cl, followed by water. The organic layer was then dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica gel, hexane/EtOAc as eluents).

1,1-Di(ethoxycarbonyl)-2-((*E*)-1-hexenyl)cyclopentane

This compound was obtained in 51 % yield from the reaction of (*E*)-1-iodo-1-hexene and diethyl 3-butenylmalonate after 1 day at 120 °C: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, *J* = 6.6 Hz), 1.19-1.30 (m, 10 H), 1.52-1.65 (m, 2 H), 1.77-2.10 (m, 5 H), 2.44 (dt, 1 H, *J* = 13.8, 8.4 Hz), 3.20 (q, 1 H, *J* = 7.5 Hz), 4.01-4.27 (m, 4 H), 5.36 (dd, 1 H, *J* = 15.3, 8.1 Hz), 5.50 (dt, 1 H, *J* = 15.6, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 23.1, 23.2, 31.8, 32.3, 33.9, 48.9, 60.8, 61.1, 64.4, 129.1, 132.1, 170.8, 172.4 (two peaks are not seen due to overlap); IR ($CDCl_3$) 2691 (=CH), 1772 (C=O) cm^{-1}; HRMS 296.1991 (Calcd. 296.1989 for $C_{17}H_{28}O_4$).

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GENERAL SUMMARY

In this dissertation, our successful development of the palladium-catalyzed coupling of vinylic halides with functionally-substituted alkenes for the synthesis of heterocycles has been discussed.

In the first paper, the synthesis of oxygen heterocycles using our newly developed methodology is discussed. The palladium-catalyzed coupling of vinylic halides or triflates with *o*-vinylbenzoic acid provides a convenient route to 3,4-dihydroisocoumarins in high yields. However, the use of more substituted *o*-vinylic benzoic acids was found to give inseparable mixtures of products. The synthesis of 3,4-dihydrobenzopyrans and 2,3-dihydrobenzofurans is also discussed. Three procedures A, B, and C have been established. Procedure B has been found to be effective in providing the desired products in most reactions. Generally, *o*-allylic phenols are more reactive than *o*-vinylic phenols, providing higher yields. The reactions of *o*-allylic phenols produce inseparable mixtures of 6- and 5-membered ring products in moderate to good yields with high isomeric ratios. In contrast, a single isomer was obtained in most cases from the reactions of *o*-vinylic phenols.

In the second paper, the synthesis of nitrogen heterocycles is discussed. For the synthesis of pyrrolidines, the *p*-toluenesulfonyl group on the nitrogen atom is more effective than the trifluoromethanesulfonyl group. In contrast, the trifluoromethanesulfonyl group is better than the *p*-toluenesulfonyl group for the synthesis of piperidines. Both pyrrolidines and piperidines are prepared in good yields using our methodology. This approach has also been utilized for the synthesis of 2,3-dihydroindoles, 2,3-dihydrobenzazepines, and 1,2,3,4-tetrahydroquinolines. Generally, the reactions of *N*-tosyl-2-allylic anilines proceed better than those of *N*-tosyl-2-vinylic anilines. Surprisingly, benzazepines, which generally require lengthy reaction processes to prepare, are obtained in good yields from the reactions of vinylic halides with *N*-tosyl-2-isopropenylanilines.

In the third paper, an attempted carbocyclization is discussed. Attempts to establish optimum reaction conditions for the synthesis of carbocycles using vinylic halides and functionally-substituted alkenes have not been very successful and further investigation is needed.

In conclusion, our newly developed palladium-catalyzed coupling procedure produces various heterocycles in moderate to good yields from easily available starting materials, such as vinylic halides and functionally-substituted alkenes, under mild reaction conditions. Our methodology provides a convenient new alternative to oxygen and nitrogen heterocycles.

ACKNOWLEDGMENTS

First of all, I would like to express my sincere gratitude to my advisor, Dr. Richard C. Larock. Without his encouragement, invaluable guidance, and understanding, it would have been more difficult for me to get where I am.

My thanks also go to the people who were and are around me. They made my stay at Iowa State University more comfortable and enjoyable. Especially, I wish to express my deep appreciation to Lisa Hasvold. It was fortunate for me to have been able to spend the last four years together with such a wonderful lady. I also would like to thank my friends, Liangqin Guo, Yao Wang, and Kelvin Sham for giving me wonderful memories which I cherish.

Finally, my deepest gratitude and appreciation go to the people who always pray for me, give me strength whenever I feel helpless, and whom I love most. To my mom, dad, and two sisters, I would like to dedicate this personal honor.