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Palladium-catalyzed cross-coupling of organic halides, alkenes and nucleophiles

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Tu, Chi, Ph.D.

Iowa State University, 1993

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300 N. Zeeb Rd.
Ann Arbor, MI 48106

Palladium-catalyzed cross-coupling of organic halides, alkenes and nucleophiles

by

Chi Tu

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
1993

To my husband and parents

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
br	Broad
bp	Boiling point
Bu	Butyl
dba	Dibenzylideneacetone
DIBAL	Diisobutylaluminum hydride
DMA	*N,N*-Dimethylacetamide
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dt	Doublet of triplets
Et	Ethyl
g	Grams
GC	Gas chromatography
HRMS	High resolution mass spectrometry
IR	Infrared
M	Molar
m	Multiplet
Me	Methyl
mL	Milliliters
mmol	Millimoles

NMR	Nuclear magnetic resonance
Ph	Phenyl
Pr	Propyl
rt	Room temperature
q	Quartet
s	Singlet
t	Triplet
TBAC	Tetra-*n*-butylammonium chloride
Tf	Trifluoromethanesulfonyl
Ts	*p*-Toluenesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography

GENERAL INTRODUCTION

Organopalladium chemistry has become one of the most active areas of organometallic chemistry directed towards organic synthesis. This dissertation focuses on the development of useful synthetic methodologies for the palladium-promoted cross-coupling of organic halides, alkenes and nucleophiles. The transformations discovered in these studies are unique, involving the simultaneous formation of two new bonds under mild reaction conditions.

Format explanation

This dissertation is divided into two papers. Each paper is presented with its own introduction, results and discussion, experimental section, conclusion, and references.

The first paper of this dissertation focuses on the development of the palladium-promoted cross-coupling of vinylic halides with alkenes and nucleophiles. The reactions of vinylic halides with alkenes and carbon nucleophiles are the first observed examples of this type of coupling reaction. A wide variety of vinylic halides, alkenes and nucleophiles have been employed in this reaction to explore the scope and limitations of this synthetic transformation.

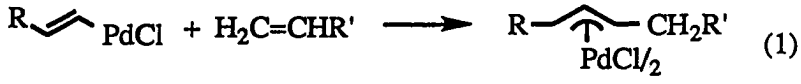
The focus of the second paper of this dissertation is on the palladium-catalyzed cross-coupling of nitrogen-substituted organic halides with allenes. These reactions provide a wide variety of nitrogen-containing heterocycles. A number of compounds of different ring size have been synthesized. The scope and limitations of this process have been determined and will be discussed.

Following the second paper is a general summary.

PAPER I. PALLADIUM(0)-PROMOTED CROSS-COUPLING OF VINYLIC HALIDES WITH ALKENES AND NUCLEOPHILES

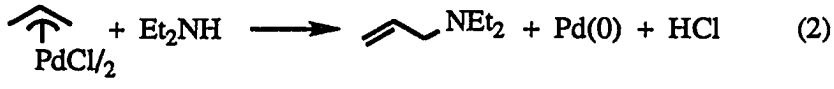
INTRODUCTION

Larock first demonstrated in 1976 that π-allylpalladium compounds are readily formed by the reaction of vinylpalladium compounds and alkenes (eq. 1).[1]



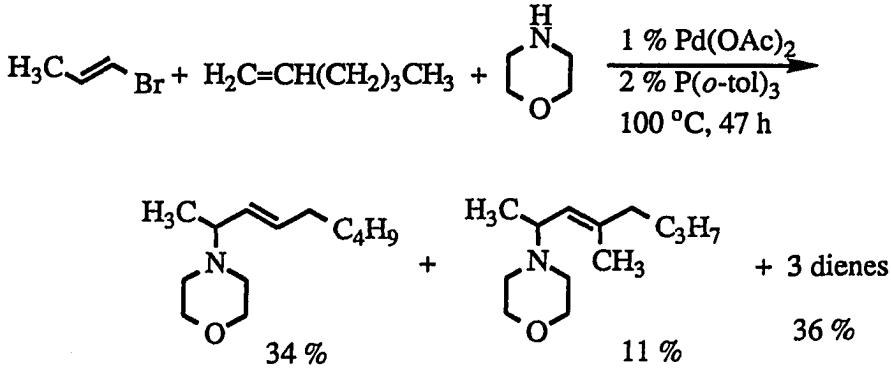
(1)

A wide variety of nucleophiles, such as 1° and 2° amines will displace palladium from π-allylpalladium compounds (eq. 2).[2]



(2)

Heck recognized the potential of combining these two processes and reported that the reaction of vinylic halides, alkenes and secondary amines as nucleophiles provided tertiary allylic amines (eq. 3).[3] Some diene products are also obtained under his reaction

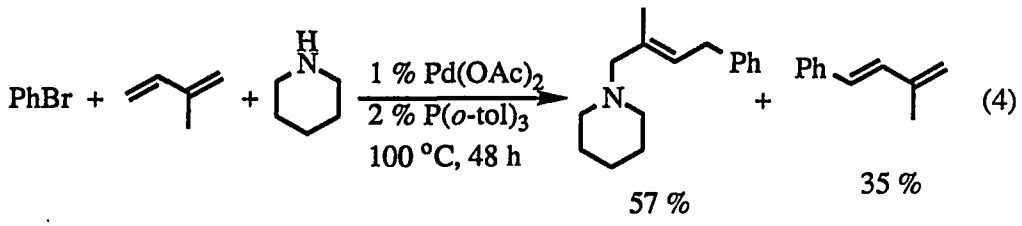


(3)

conditions. The disadvantage of this reaction is that an isomeric mixture of products was obtained in modest yield while substantial amounts of diene by-products were also formed.

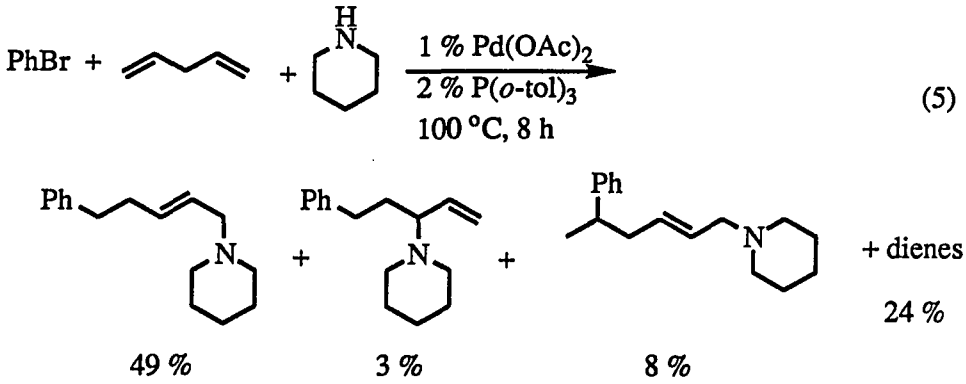
It is also known that the addition of organopalladium species to conjugated dienes leads directly to π-allylpalladium complexes.[4] Heck has used π-allylpalladium complexes

formed in this fashion from the reaction of 1,3-dienes with aryl[5] and vinylic[6] halides to prepare allylic amines (eq. 4).



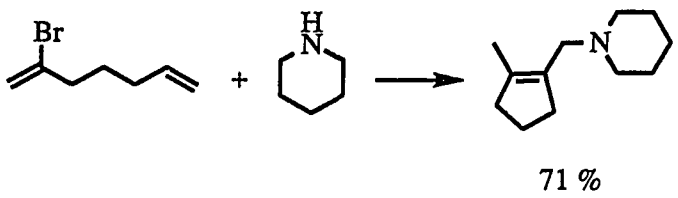
(4)

Another route to π-allylpalladium complexes is via organopalladium additions to non-conjugated dienes.[7] Palladium in the initially formed σ-alkylpalladium complex migrates down the alkyl chain by a series of β-hydride elimination-readdition steps until a π-allylpalladium complex is formed. Heck has obtained good yields of allylic amine products in reactions of aryl and vinylic halides with 1,4-dienes and 2° amines, although mixtures of allylic isomers are obtained, as well as some diene products (eq. 5).[8]



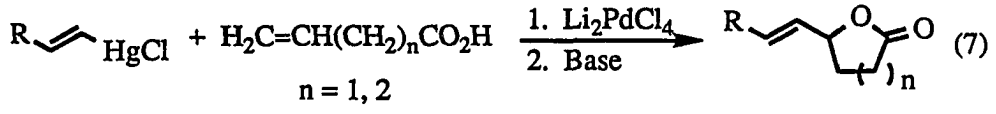
(5)

Subsequent intramolecular versions of this chemistry using bromodienes or bromodienyl ethers or amines also produce coupling products (eq. 6).[9]



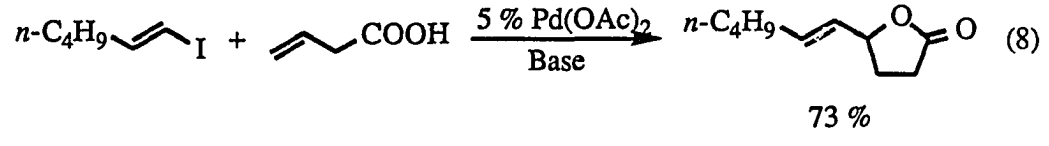
(6)

More recently, Larock found that vinylic mercurials couple cleanly in high yield with alkenoic acids to produce π-allylpalladium intermediates, which undergo intramolecular displacement to afford high yields of 5- and 6-membered ring lactones (eq. 7).[10]



(7)

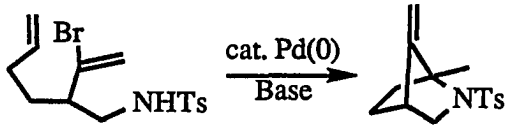
The same transformation can also be achieved using vinylic halides and catalytic amounts of palladium acetate in the presence of *n*-Bu4NCl (eq. 8).[11] This reaction is highly regioselective, affords high yields under mild reaction conditions and accommodates a wide variety of starting materials.



73 %

(8)

Recently, Weinreb and co-workers[12] reported that nitrogen-containing heterocyclic compounds can be synthesized by a sequential variation of the Heck reaction (eq. 9). They applied this methodology to the synthesis of several functionalized bicyclic nitrogen systems in good yields.



(9)

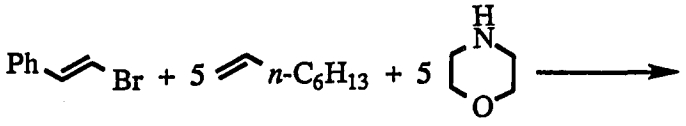
As indicated by Heck's results, the palladium-promoted cross-coupling of vinylic halides with alkenes and amines provides a mixture of regioisomers (eq. 3). We have elected to examine this same general process in the hope of finding reaction conditions which would provide higher yields of isomerically pure allylic amines and less diene side

products. We also wanted to examine the reactivity of non-conjugated dienes. Another area of interest was the use of nucleophiles other than amines, such as stabilized carbon nucleophiles, which can be formed in-situ by choosing an appropriate base. In this part of the dissertation, the palladium(0)-catalyzed cross-coupling of vinylic halides, alkenes and nucleophiles will be discussed. The palladium(0)-catalyzed reaction of vinylic halides with alkenes and nitrogen nucleophiles will first be covered, followed by the reaction of a wide variety of carbon nucleophiles with alkenes or dienes plus vinylic halides or triflates.

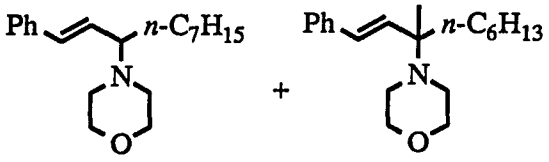
RESULTS AND DISCUSSION

Cross-Coupling with Nitrogen Nucleophiles

As a first step towards meeting the previously mentioned objectives and establishing the palladium-catalyzed cross-coupling of vinylic halides, alkenes and amines as a new and useful synthetic method, an extensive series of reactions was performed with various reaction conditions using the reaction of β-bromostyrene, 1-octene, and morpholine as a model system (eq. 10). The results are tabulated in Table 1.



(10)



1a **1b**

With regard to the yield and isomeric outcome of this reaction, the following observations can be made. In general, the reaction produced a mixture of two isomers, **1a** and **1b**, with compound **1a** as the major product. The isomer ratio was not significantly effected by altering the reaction conditions, although solvents had a great impact on the reaction yield.

Water played an important role in the reaction (entries 1-7). The reason for this is not clearly understood at this point. Water may act as a ligand to enhance the rate of the reaction by displacing the olefin product from the palladium metal after the product is formed; therefore, more palladium(0) is made available for the initial step of the reaction,

Table 1. The palladium(0)-catalyzed reaction of β-bromostyrene, 1-octene and morpholine[a]

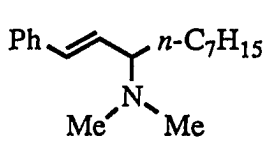
Entry	Solvent	Temp. (°C)	Time (day)	Water (equiv.)	% Yield[b] **1a+1b**	Ratio **1a:1b**
1	DMF	100	2	0	38	70:30
2	DMF	100	2	1	34	75:25
3	DMF	100	2	5	43	73:27
4	DMF	100	2	10	58	77:23
5	DMF	100	2	20	39	75:25
6	DMF	100	2	30	38	76:24
7	DMF	100	2	50	39	70:30
8	DMF	100	1	10	41	76:24
9	DMF	100	3	10	46	79:21
10	CH_3CN	100	2	10	61	70:30
11	9:1 DMF/HMPA	100	2	10	45	80:20
12	DMA	100	2	10	98	85:15
13	DMF	130	2	10	37	70:30
14	DMF	80	2	10	trace	-
15	DMF	60	2	10	0	-

[a] All reactions were carried out using 1 equiv. of vinylic halide (0.25 mmol), 5 equiv. of alkene (1.25 mmol), 5 mol % $Pd(dba)_2$, 1.1 equiv. of *n*-Bu_4NCl (0.27 mmol), and 5 equiv. of amine (1.25 mmol) in 2 mL of solvent.

[b] Isolated yield

oxidative addition of the vinylic halide to palladium(0). The use of ten equivalents of water gave the best result in terms of yield and regioselectivity (entry 4).

The model reaction was also run using four different solvent systems to determine what effect this would have on the yield and regioselectivity of the reaction (entries 4 and 10-12). When *N,N*-dimethylformamide was used, significant amounts (30 %) of dimethylamino-containing side products (**2** and **3**) were observed, which are obviously derived from the solvent. The use of *N,N*-dimethylacetamide or acetonitrile eliminates



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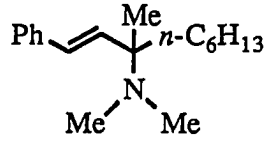


3

this problem, giving higher yields of the desired products (entries 10 and 12). *N,N*-Dimethylacetamide is the best solvent for the reaction, providing the desired products in near quantitative yield.

Addition of the vinylic group of the vinylic palladium species to the terminal carbon of the alkene is more favorable than coupling to the internal carbon. The ratio of the resulting allylic amine products is usually approximately 3-4 : 1. Although solvents do have an effect on the product yield, they generally do not have a significant effect on the isomer ratio. It is noted, however, that the reaction when run in DMA as the solvent, gives a higher ratio of **1a** to **1b**, 85 to 15.

The effects of temperature and time were also investigated. Reactions proceed very slowly at low temperatures, such as 60 and 80 °C (entries 14 and 15). The best yield was obtained when the reaction was carried out for two days at 100 °C (entries 4, 10 and 12). Prolonged reaction times or higher reaction temperatures tended to decompose the products.

Entry 12 represents the best reaction conditions. These are 1 equiv. of vinylic halide (0.25 mmol), 5 equiv. of alkene (1.25 mmol), 5 equiv. of amine (1.25 mmol), 1.1 equiv. of *n*-Bu_4NCl (0.27 mmol), 5 mol % of $Pd(dba)_2$ (0.0125 mmol), and DMA (2 mL) at 100 °C for 2 days (procedure A). Using these conditions, a quantitative yield of products **1a** and **1b** was obtained. The isomer ratio of **1a** to **1b** was 85 to 15.

A mechanism which explains the formation of these products is presented in Scheme 1. The first step of the reaction is oxidative addition of the vinylic bromide to the palladium metal to generate vinylpalladium species **4**. This intermediate then adds to the alkene to generate σ-homoallylpalladium intermediates **5** and **6**. β-Hydride elimination and subsequent readdition with the opposite regiochemistry lead to new σ-allylpalladium species **8** and **13** respectively, which collapse to π-allylpalladium species **9** and **14**. Heck-type products **7** and **12** can form during the β-hydride elimination. Nucleophilic displacement of palladium in the π-allylpalladium species **9** and **14** gives the four possible products, **10, 11, 15,** and **16**. The ratio of these possible products is dependent upon the regiochemistry of alkene insertion into the initial vinylpalladium intermediate, the nature of the nucleophile, and the electron density and steric effects present in the π-allylpalladium species **9** and **14**.

After the reaction conditions for this model system had been thoroughly investigated, a variety of vinylic halides, alkenes and nucleophiles were employed in a study to determine the scope and limitations of this palladium(0)-catalyzed process. Table 2 summarizes the results of the reaction of vinylic halides with alkenes and amines.

β-Bromostyrene reacted with 1-octene and piperidine smoothly to produce a mixture of two isomers (86:14) in 51 % yield (entry 2). By comparison, a near quantitative yield of the desired products having the same isomeric ratio was obtained (entry 1). The higher yield with morpholine is presumably due to the electron-withdrawing character of the oxygen in the morpholine.

Scheme 1

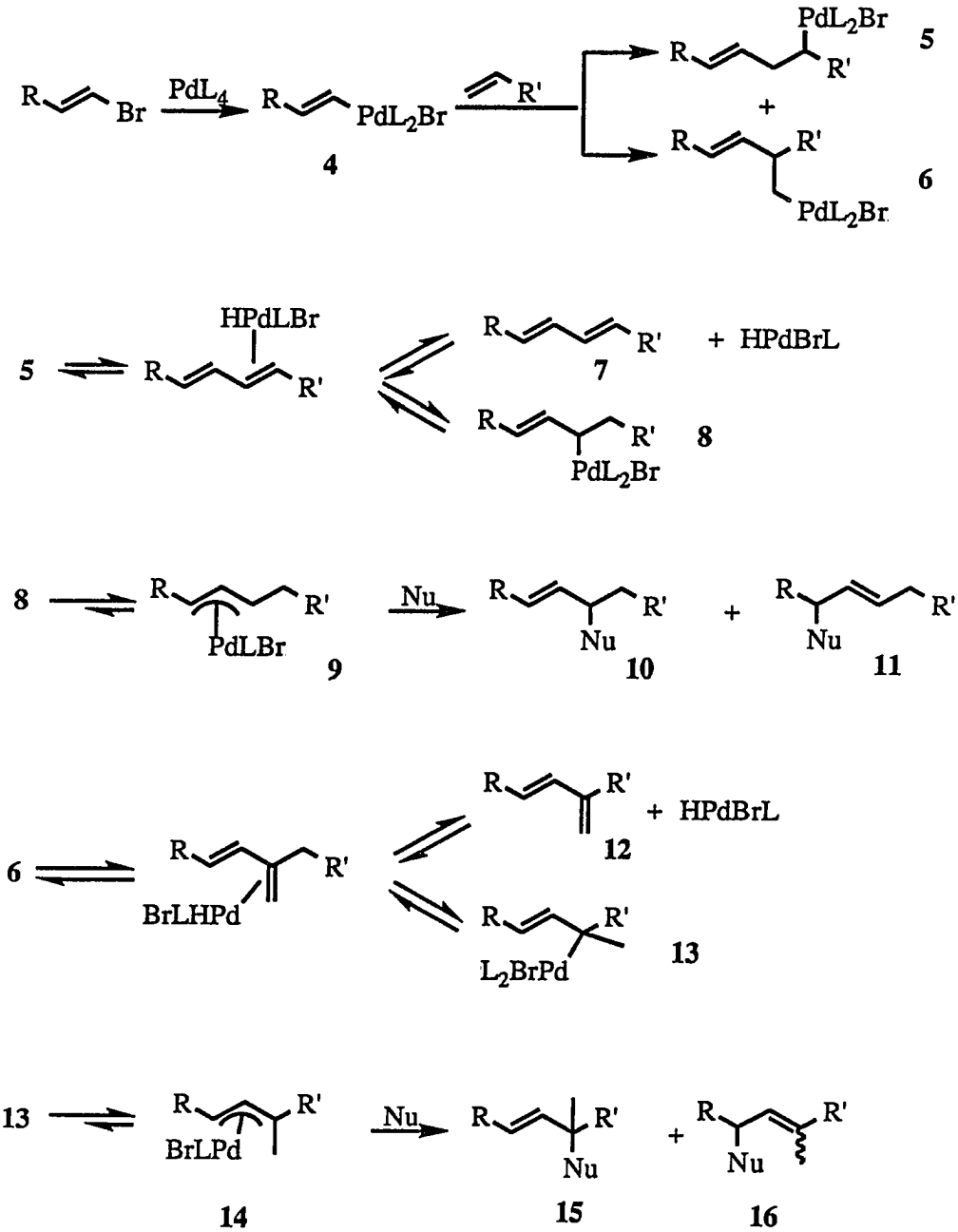
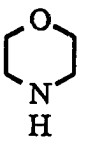
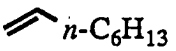
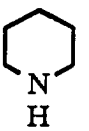
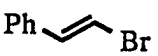
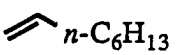
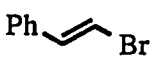
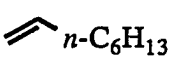

PdL4
PdL2Br
4
5
6
HPdLBr
7
8
+ HPdBrL
9
Nu
10
11
12
13
BrLHPd
L2BrPd
14
15
16

Table 2. Palladium-catalyzed cross coupling of vinylic halides, alkenes and amines

Entry	Vinylic Halide	Alkene	Amine
1			
2			
3			$(n\text{-Bu})_2NH$
4			$t\text{-BuNH}_2$

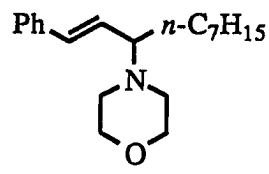
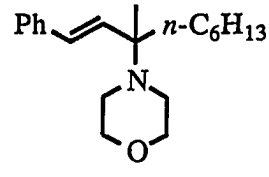
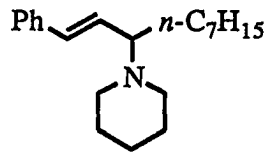
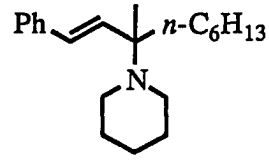
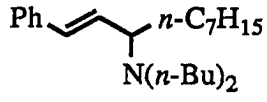
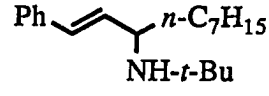
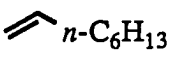
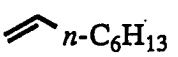
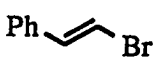
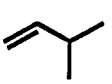
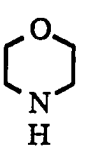
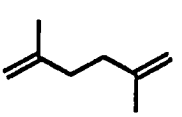
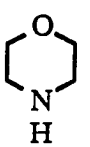
Product(s)	% Isolated Yield (Ratio)
 **1a**  **1b**	98 (85:15)
 **17a**  **17b**	51 (86:14)
 **18**	6
	0

Table 2. (Continued)

Entry	Vinylic Halide	Alkene	Amine
5			n-$BuNH_2$
6			$PhNH_2$
7			
8			

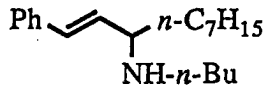
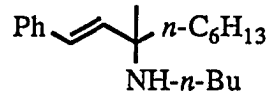
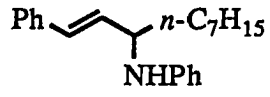
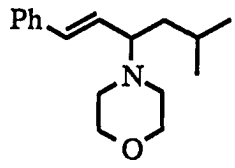
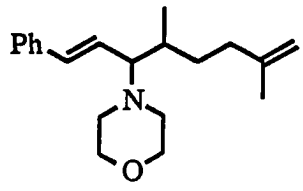
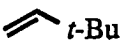
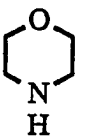
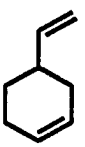
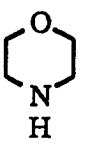
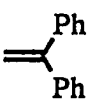
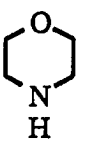
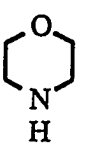
Product(s)	% Isolated Yield (Ratio)
 **19a**  **19b**	36 (67:33)
	0
 **20**	20
	0

Table 2. (Continued)

Entry	Vinylic Halide	Alkene	Amine
9			
10			
11			
12			

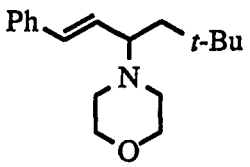
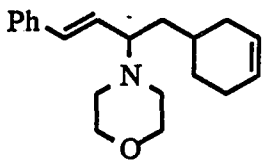
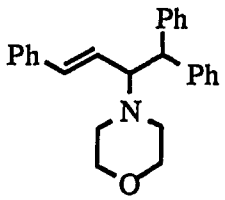
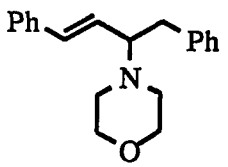
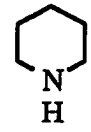
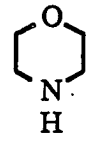
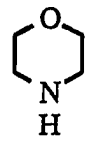
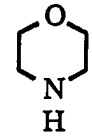
Product(s)	% Isolated Yield (Ratio)
	0
	0
	0
 **21**	29

Table 2. (Continued)

Entry	Vinylic Halide	Alkene	Amine
13			
14			
15			
16			

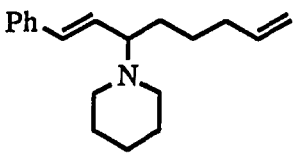
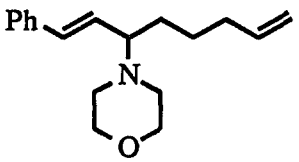
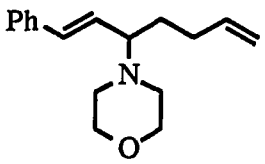
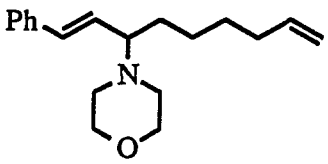
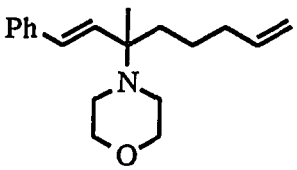
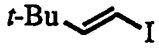
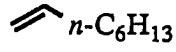
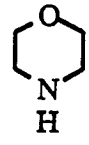
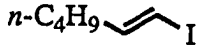
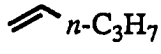
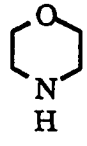
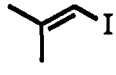
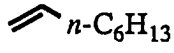
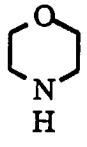
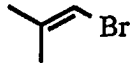
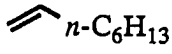
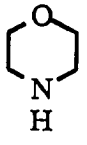
Product(s)	% Isolated Yield (Ratio)
 **22**	50
 **23**	95
 **24**	45
 **25a**  **25b**	68 (75:25)

Table 2. (Continued)

Entry	Vinylic Halide	Alkene	Amine
17			
18			
19			
20			

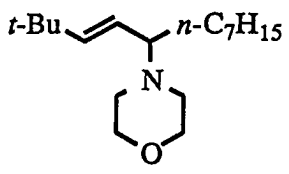
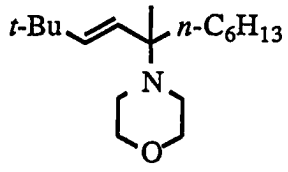
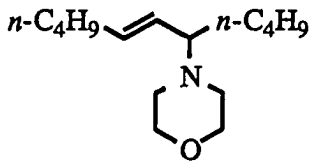
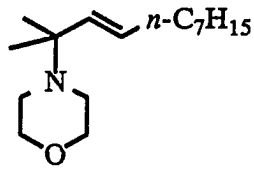
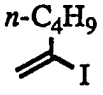
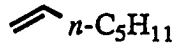
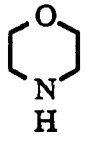
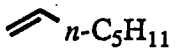
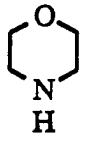
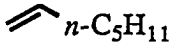
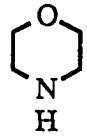
Product(s)	% Isolated Yield (Ratio)
 **26a**  **26b**	40 (80:20)
	0
 **27**	29
27	0

Table 2. (Continued)

Entry	Vinylic Halide	Alkene	Amine
21			
22			
23			

[a] *Z*/*E* isomer ratio

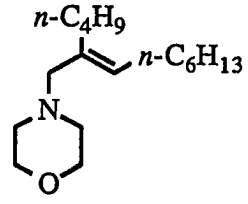
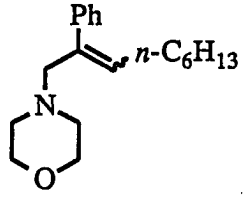
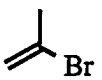
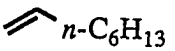
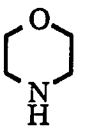
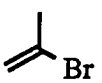
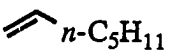
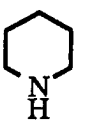
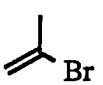
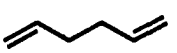
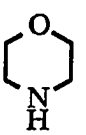
Product(s)	% Isolated Yield (Ratio)
	0
 **28**	24 (60:40)[a]
28	11 (60:40)[a]

Table 2. (Continued)

Entry	Vinylic Halide	Alkene	Amine
24			
25			
26			

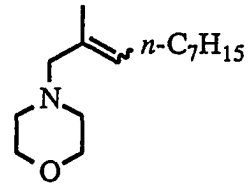
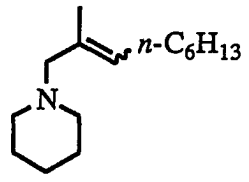
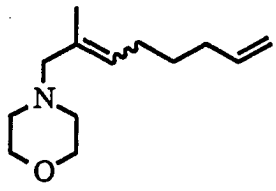
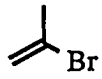
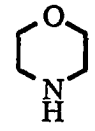
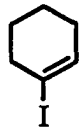
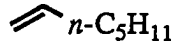
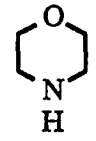
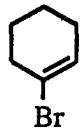
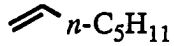
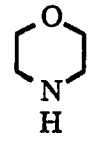
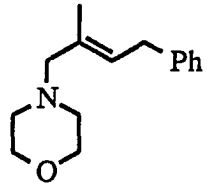
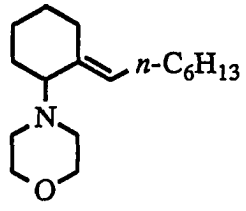
Product(s)	% Isolated Yield (Ratio)
 **29**	73 (80:20)[a]
 **30**	57 (89:11)[a]
 **31**	98 (83:17)[a]

Table 2. (Continued)

Entry	Vinylic Halide	Alkene	Amine
27			
28			
29			

Product(s)	% Isolated Yield (Ratio)
 **32**	35
 **33**	4
33	4

Several acyclic amines were employed under the same reaction conditions. *n*-Butylamine being less sterically hindered gave a 36 % yield of products, while more hindered *t*-butylamine produced none of the desired products (entries 4 and 5). Di-*n*-butylamine and aniline both gave little or none of the desired products in the reaction with β-bromostyrene and 1-octene (entries 3 and 6). The fact that less of the desired product was obtained with the 2° amine di-*n*-butylamine than the 1° amine *n*-$BuNH_2$ is probably due to steric hindrance again. The same explanation is probably applicable when comparing the difference in the amount of the products formed when using acyclic and cyclic amines. In general, acyclic amines are more sterically hindered than cyclic amines; therefore, acyclic amines provide significantly lower yields of products.

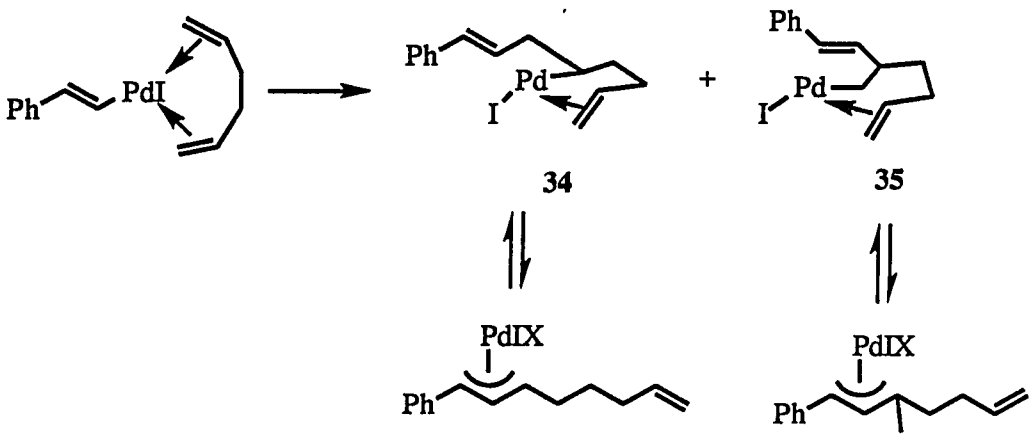
In order to investigate the steric effect of the coupling reactions, a variety of substituted alkenes and vinylic halides were employed in this reaction. It was found that substitutions on the carbon-carbon double bond of the alkene or in the allylic position of the alkene gave sharply lower yields of products (entries 7-11). Substitutions at the allylic position of the vinylic halides do not effect the regioselectivity (entry 17), while substitution at the β position of the vinylic halide gave a single isomer in low yield (entry 19).

The reaction of *E*-1-iodo-1-hexene with 1-pentene should provide a symmetrical π-allylpalladium intermediate which should be attacked by the nucleophile to produce a single product. Unfortunately, none of the desired product was observed when morpholine was used in this reaction (entry 18).

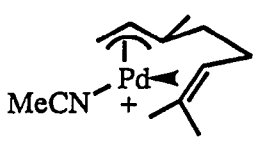
This palladium-catalyzed cross-coupling becomes much more attractive when 1,5-hexadiene is used in the reaction. As indicated in entries 13 - 15, only a single isomer was observed in good to excellent yields. The unexpected high regioselectivity of alkene insertion can be explained by a possible mechanism involving chelated intermediates. As shown in Scheme 2, both double bonds in 1,5-hexadiene may coordinate to the σ-vinylic

palladium species. Cross-coupling between the σ-vinylic palladium species and the diene affords two possible chelated intermediates (**34** and **35**). The ratio of these two intermediates may depend on the stability of the precursor diene complex or of these two cyclic species. For steric reasons, intermediate **34** may have a more stable chair conformation than **35** and thus predominates. Whatever the explanation, the isomer derived from intermediate **34** is obtained exclusively.

Scheme 2



This type of cyclic intermediate is similar to one reported by Ciajolo in 1985.[13] He synthesized and isolated a stable π-allylpalladium species **36** in which the double bond was intramolecularly coordinated to the palladium atom. The structure of **36** was identified by X-ray analysis.



36

The formation of this unique stabilized cyclic intermediate **34** required a specific chain length in the side chain of the olefin in order to produce the stable chair

conformation. Therefore, one more or one less carbon in the diene might interrupt the structure of the chelated intermediate making intramolecular chelation more difficult. To examine this hypothesis, reactions with 1,4-pentadiene and 1,6-heptadiene were investigated under exactly the same reactions conditions (entries 15 and 16). 1,4-Pentadiene produced a much lower yield of a single product. It seems that the cyclic chelating species may still exist, but the interaction between the palladium and the double bond is weakened. 1,6-Heptadiene provided a mixture of isomers in a moderate yield (entry 16). Similar results were obtained with 1-octene (entry 2). Apparently, the chelated intermediate is not present in this reaction. These results agree nicely with our expectations.

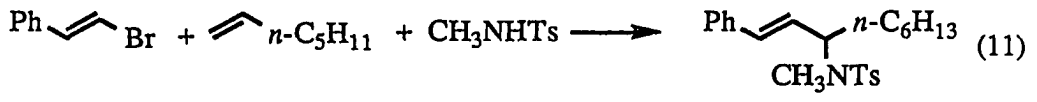
Vinylic halides substituted at the α-position provided mixed results. 2-Iodo-1-hexene or α-iodostyrene both gave little or none of the desired products in the reaction with 1-heptene and morpholine (entries 21 and 22), while 2-bromopropene produced the desired product in high yields (entries 24-27). However, in all of these cases with α-substituted halides, the nucleophile attacked exclusively at the less hindered end of the π-allylpalladium species. In some cases, *E*/*Z* isomers were obtained (entries 22 and 23, 25 and 26). The isomer ratio (*Z*/*E* = 83:17) was determined by integration of the allylic hydrogen adjacent to the nitrogen atom in the ^{1}H NMR spectrum. The stereochemistry of compound **31** was determined by the coupling pattern of the allylic hydrogen adjacent to the nitrogen in the ^{1}H NMR spectrum. The peak corresponding to the *Z*-isomer is a singlet, while the *E*-isomer possesses a doublet with J = 2.7 Hz. The splitting pattern of the *Z*-isomer is due to long-range coupling between the allylic and vinylic hydrogens. The chemical shift of the singlet CH_2 group adjacent to the nitrogen atom of the *E*-isomer of compound **31** is further downfield (1.70 ppm) than the *Z*-isomer (1.64 ppm). With this in mind, the stereochemistry of compounds **28** to **30** was determined by comparison of the corresponding methylene group chemical shifts with those observed in compound **31**.

The reaction of 2-bromopropene with 1-octene and morpholine produced a single product in high yield (entry 24). Unlike morpholine, piperidine gave products in a moderate yield as an isomeric mixture (entry 25). Again, morpholine is a better nucleophile than piperidine. The use of 1,5-hexadiene gave a quantitative yield of products (entry 26). The stereoselectivity favoring the *E* isomer can be explained by formation of the more stable *syn* π-allylpalladium intermediate. The use of styrene provided the desired product in low yield as a single stereoisomer (entry 27). A significant amount of Heck-type product was also observed.

A difference in reactivity between vinylic iodides and vinylic bromides was also observed. Vinylic iodides are more reactive than vinylic bromides and provided higher yields of products (entries 19 and 20, 22 and 23). The reaction of 1-iodo-2-methylpropene with 1-octene and morpholine produced a low yield (29 %) of a single product, while the bromo analogue gave none of the desired product (entries 19 and 20). The nucleophile attacked at the less substituted end of the π-allylpalladium species. The reaction of α-bromostyrene with 1-heptene and morpholine, produced a low yield (11 %) of a 60:40 *E/Z* isomeric mixture of allylic amines arising from attack of the amine at the less hindered end of the π-allylpalladium intermediate. The iodo analogue provided a slightly higher yield (24 %) of the same product with an identical *E/Z* isomer ratio (entry 23). Interestingly, the reactions of 1-bromo- or 1-iodocyclohexene both produced the same low yield of product (entries 29 and 30). The observed product was derived from attack of morpholine on the ring. The structure of the product was assigned based on the ^{1}H NMR spectral observation that the vinylic hydrogen in the ^{1}H NMR spectrum is a simple triplet, while a more complicated coupling pattern is expected if the vinylic hydrogen were on the cyclic ring.

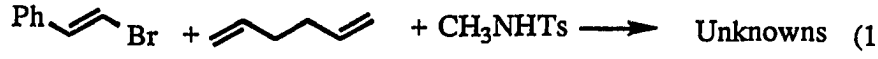
N-Methyltosyl amide was also examined as a nucleophile in these reactions using 1 equiv. of vinylic halide (0.25 mmol), 5 equiv. of alkene (1.25 mmol), 5 equiv. of *N*-methyltosyl amide (1.25 mmol), 2 equiv. of TBAC (0.50 mmol), 5 mol % of $Pd(OAc)_2$

(0.0125 mmol), 4 equiv. of Na_2CO_3 (1.0 mmol), DMA (2 mL) as the solvent at 100 °C for 2 days. These reaction conditions were developed by Yao Wang in the Larock group for the coupling of iodobenzene, nonconjugated dienes and N-methyltosyl amide. Moderate to good yields of products have been obtained in his system. In our reactions, the use of 1-heptene showed no evidence of the formation of products (eq. 11), while 1,5-hexadiene



(11)

under the same conditions produced a mixture of isomers (eq.12). The ^1H NMR spectrum of the products was very complicated, and the actual structures could not be identified. Several bases were used in the hope of improving the reaction's regio- and stereo-selectivity. These studies found that all three bases employed, Na_2CO_3, K_2CO_3, and



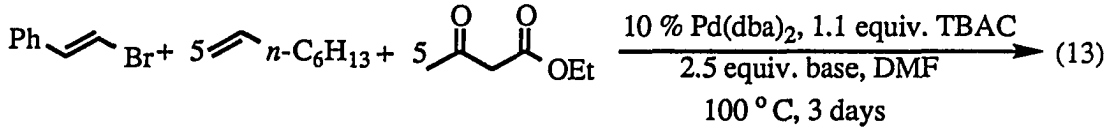
(12)

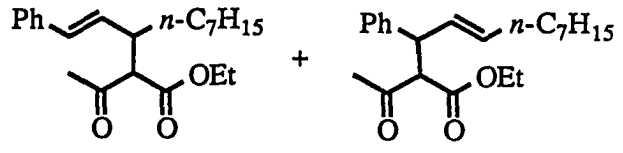
$NaHCO_3$, produced the same isomers. Two other bases, NaOAc and Li_2CO_3, showed no evidence for the formation of products. Unfortunately, the products decomposed during gas chromatography, so the isomer ratio could not be determined.

In summary, the cross-coupling of vinylic halides, alkenes and amines produces a mixture of regioisomers due to external and internal addition of the σ-palladium species to the carbon-carbon double bond of the alkenes. The ratio of external to internal addition is usually around 4 to 1. 1,5-Hexadiene provides the desired products in higher yields and better stereoselectivity than simple alkenes. β-Bromostyrene produces higher yields of the desired products than other vinylic halides. Cyclic amines are better nucleophiles than acyclic ones.

Cross-Coupling with Carbon Nucleophiles

Carbon nucleophiles were also investigated in this project. The model reaction chosen was the reaction of β-bromostyrene, 1-octene and ethyl acetoacetate (eq. 13). Various reaction conditions have been studied as shown in Table 3.





37a **37b**

The yield of the reaction can be significantly altered by changing the base. Sodium carbonate provided predominately the desired product, while triethylamine gave none of the desired product (entries 1, 5, and 6). The reaction is slightly regioselective, favoring formation of the conjugated product (**37a**). Varying reaction conditions, such as base and solvent, did not effect the ratio of the two regioisomers. Therefore, the best reaction conditions (procedure B) are 1 equiv. of vinylic halide (0.25 mmol), 5 equiv. of alkene (1.25 mmol), 5 equiv. of carbon nucleophile (1.25 mmol), 1.1 equiv. of TBAC (0.27 mmol), 10 mol % of $Pd(dba)_2$ (0.025 mmol), 2.5 equiv. of Na_2CO_3 in DMA (2 mL) at 100 °C for 3 days .

Once the reaction procedure for the model system had been established, a variety of vinylic halides or triflates, alkenes and carbon nucleophiles were employed in order to determine the scope and limitations of this palladium(0)-catalyzed process. The results of this investigation are summarized in Table 4.

Table 3. Palladium-catalyzed reaction of β-bromostyrene, 1-octene and ethyl acetoacetate

Entry	Base (2.5 equiv.)	Solvent	Heck product (%)	**37a+37b** (%)	**37a:37b**
1	Et_3N	DMF	58	0	-
2	NaOAc	DMF	60	7	58:42
3	KOAc	DMF	60	15	58:42
4	$NaHCO_3$	DMF	34	28	58:42
5	Na_2CO_3	DMF	0	45	58:42
6	Na_2CO_3	DMA	0	80	59:41

The use of β-bromostyrene, 1-octene and ethyl acetoacetate produced an isomeric mixture in good yield, while dimethyl malonate provided a mixture of isomers in low yield (entries 1 and 2). The same reaction with acetylacetone produced a 23 % yield of a single product (entry 3). Similar reactions with the diketones 5,5-dimethyl-1,3-cyclohexanedione and 2-methyl-1,3-cyclopentanedione gave none of the desired product (entries 4 and 5).

Analogous reactions using 1,5-hexadiene provided much higher yields of products (entries 6 and 8). The use of ethyl acetoacetate in this reaction gave the desired products in an 82 % isolated yield (37:63 ratio) (entry 6). In order to improve the ratio of products, different bases and solvents were employed. The isomer ratios were determined by gas chromatography. With DMF as the solvent and sodium carbonate as the base, the reaction provided a 78 % yield of a mixture in the ratio of 50:50, while sodium acetate along with DMF provided a 43 % yield of the products in the ratio of 56:44. The organic base, Et_3N, produced only a 7 % yield of the products. Although the exact mass spectral analysis indicated the expected molecular weight for the products, the ^1H NMR spectrum was very complicated; therefore the structures of the products could only be assigned tentatively.

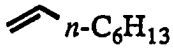
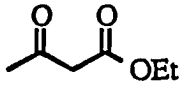
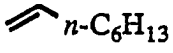
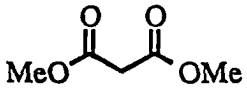
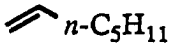
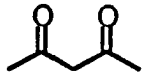
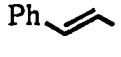
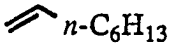
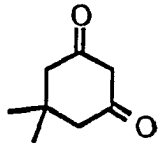
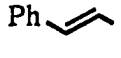
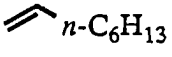
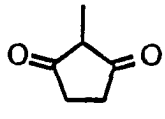
Different bases were also used in the reaction with ethyl acetoacetate. Sodium carbonate remained the best base for the reaction. Other bases gave products in lower yield with similar isomeric ratios. However, the reaction with acetylacetone provided an excellent yield (96%) of two isomers arising from addition of the carbon of the σ-vinyl-palladium intermediate to the external and internal carbons of the alkene with a selectivity of 63:37 respectively (entry 7). Surprisingly, dimethyl malonate produced only a single product in high yield (entry 8).

The use of malononitrile as the nucleophile provided none of the desired products, while ethyl cyanoacetate gave a mixture of products in 40 % yield (entries 9 and 10). Since the ^{1}H NMR spectrum of the products was very complicated, the appropriate structure for the products could not be assigned. When employing ethyl phenyl-sulphonylacetate, unknown products were isolated in a 56 % yield. The mass spectrum of the products did not indicate the molecular weight expected for the desired products (entry 11). The use of 2-acetylbutyrolactone produced the desired products in moderate yield (57 %) (entry 13). In contrast, 5,5-dimethyl-1,3-cyclohexanedione produced none of the desired product (entry 12). This is probably due to steric hindrance.

A variety of internal vinylic halides and triflates were also used in the reaction. These results were not encouraging. The use of α-bromostyrene, 2-iodo-1-hexene and 1-hexenyl-2-triflate in the coupling reactions failed to give any of the desired products (entries 15-17).

In order to investigate steric effects in these coupling reactions, a variety of substituted alkenes and vinylic halides were employed in this reaction. The hindered alkenes, 3,3-dimethyl-1-butene and 4-vinylcyclohexene, also produced none of the desired product (entries 14 and 25). Trisubstituted vinylic halides were also used in the reaction. The reaction of 1-bromo-2-methylpropene with 1-octene and ethyl acetoacetate afforded

Table 4. Palladium-catalyzed cross-coupling of vinylic halides, alkenes and carbon nucleophiles

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
1			
2			
3			
4			
5			

[a] DMF was used as the solvent.

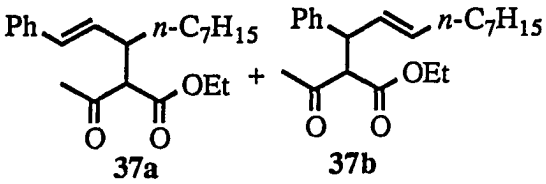
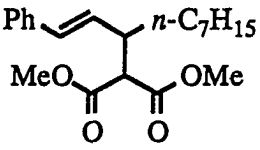
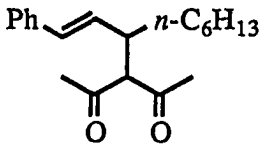
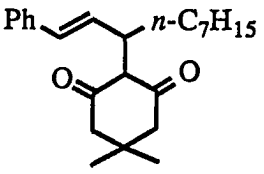
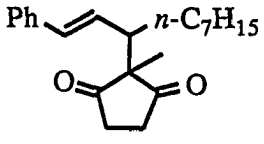
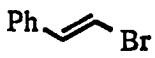
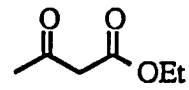
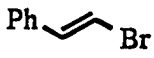
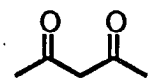
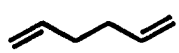
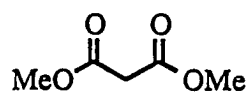
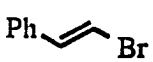
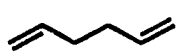
Product(s)	% Isolated Yield (Ratio)
 **37a** + **37b**	80 (59:41)
 + Isomer **38a** **38b**	20 (50:50)[a]
 **39**	23
	0
	0

Table 4. (Continued)

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
6			
7			
8			
9			$NCCH_2CO_2Et$

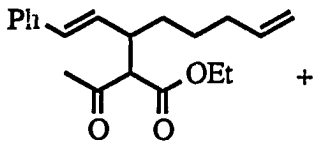
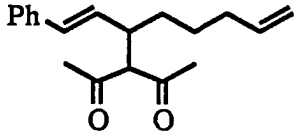
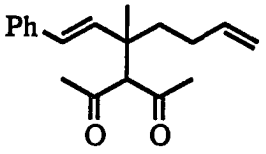
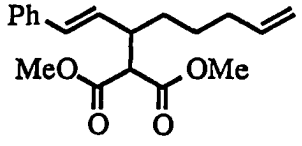
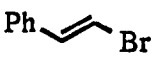
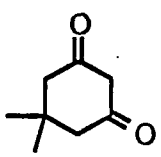
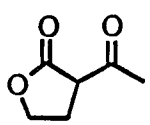
Product(s)	% Isolated Yield (Ratio)
 + Isomer **40a** **40b**	82 (37:63)
 +  **41a** **41b**	96 (63:37)[a]
 **42**	77[a]
Unknown mixture	40

Table 4. (Continued)

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
10			$NCCH_2CN$
11			$PhSO_2CH_2CO_2Et$
12			
13			

[b] The major stereoisomer is uncertain.

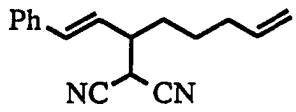
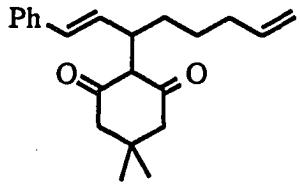
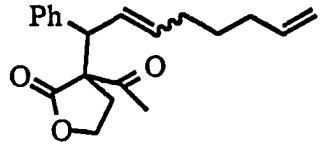
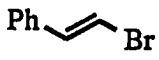
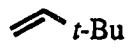
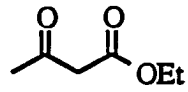
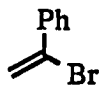
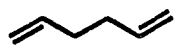
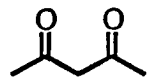
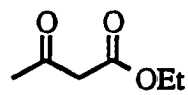
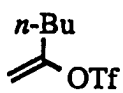
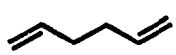
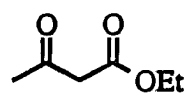
Product(s)	% Isolated Yield (Ratio)
	0
Unknowns	56
	0
 43	57 (78:22)[b]

Table 4. (Continued)

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
14			
15			
16			
17			

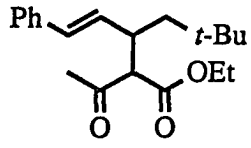
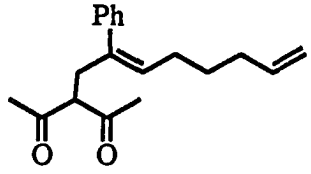
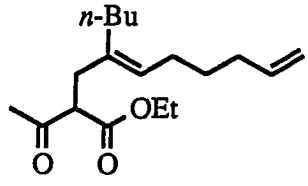
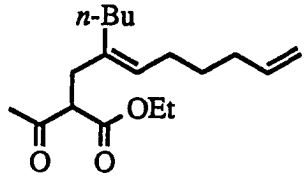
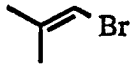
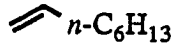
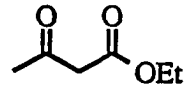
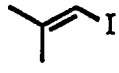
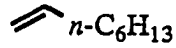
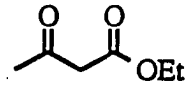
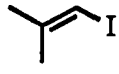
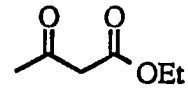
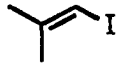
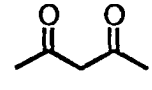
Product(s)	% Isolated Yield (Ratio)
	0
	0
	0
	0

Table 4. (Continued)

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
18			
19			
20			
21			

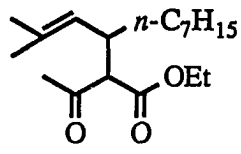
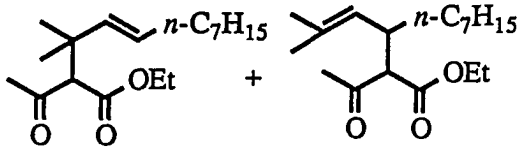
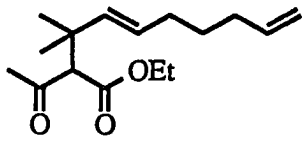
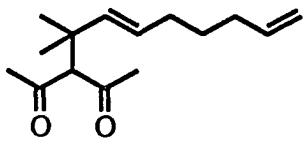
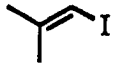
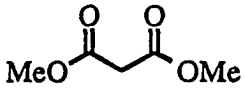
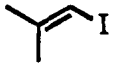
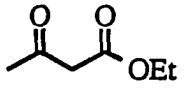
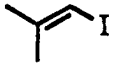
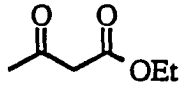
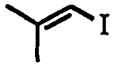
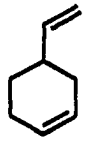
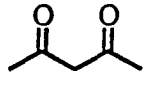
Product(s)	% Isolated Yield (Ratio)
	0
 **44a** **44b**	12 (80:20)
 **45**	84
 **46**	36

Table 4. (Continued)

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
22			
23			
24			
25			

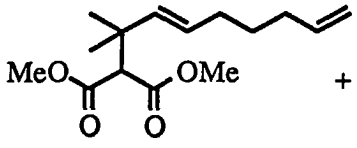
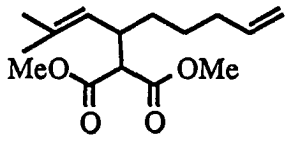
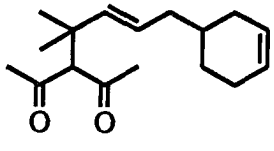
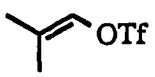
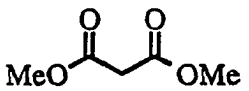
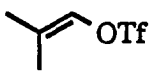
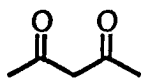
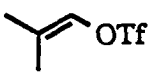
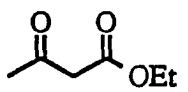
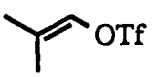
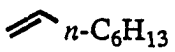
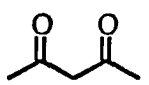
Product(s)	% Isolated Yield (Ratio)
 **47a** +  **47b**	44 (82:18)
Unknowns	52
Unknowns	57
	0

Table 4. (Continued)

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
26			
27			
28			
29			

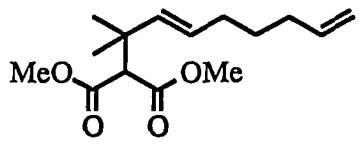
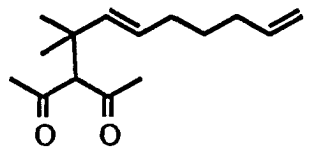
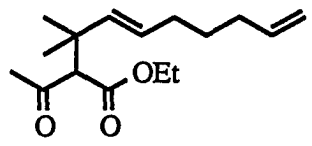
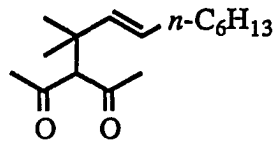
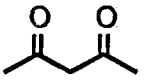
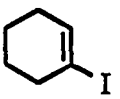
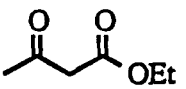
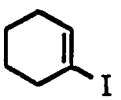
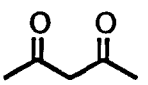
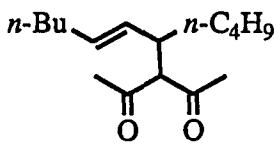
Product(s)	% Isolated Yield (Ratio)
 **47**	31
 **46**	34
 **45**	32
	0

Table 4. (Continued)

Entry	Vinylic Halide or Triflate	Alkene	Carbon Nucleophile
30			
31			
32			

Product(s)	% Isolated Yield (Ratio)
	0
Unknowns	66
Unknowns	60

none of the desired product (entry 18). Since vinylic iodides are usually more reactive than vinylic bromides, 1-iodo-2-methylpropene was prepared and used in various reactions with different alkenes and carbon nucleophiles. The reaction of 1-iodo-2-methylpropene, 1-octene and ethyl acetoacetate produced a low yield of an isomeric mixture (entry 19), while the same substrates reacted with 1,5-hexadiene to produce a single product in high yield (entry 20). The analogous reaction with acetylacetone produced a moderate yield of a single product (entry 21). In these two cases, as discussed previously, a cyclic chelated intermediate may be involved. An effort to establish the existence of the cyclic chelated intermediate was made by running reactions with 1,4-pentadiene and 1,6-heptadiene (entries 23 and 24). Moderate yields of isomeric mixtures were obtained from these reactions. After purification, GC and ^{1}H NMR spectroscopy both indicated that more than 3 compounds were present as a single spot on TLC analysis. Due to the difficulties in separation and the complexity of the spectral data obtained, no structures have been assigned. However, the results of these comparison studies with different chain length dienes indicated that the cyclic chelating species may also play an important role in the reaction of 1,5-hexadiene with carbon nucleophiles as shown in entries 20 and 21 where higher yields of a single product were obtained. In general, substituents on the alkenes reduced the yields significantly, while substituents on the vinylic halides still provided good yields of products.

William Gong, while working in the Larock group, studied the reaction of vinylic triflates with cyclic olefins in the presence of a palladium catalyst to produce diene products.[14] His results indicated that in some cases vinylic triflates give better yields than vinylic iodides. With this in mind, 2-methyl-1-propenyl triflate was allowed to react with 1,5-hexadiene and several carbon nucleophiles (entries 26-28). In all cases, the reactions

led to a single product in moderate yield. However, none of the desired product was observed in the reaction with 1-octene and acetylacetone (entry 29).

The reaction of *E*-1-iodo-1-hexene with 1-pentene would provide a symmetrical π-allylpalladium intermediate which could be attacked by a nucleophile to produce a single product. Unfortunately, none of the desired product was observed when acetylacetone was used in this reaction (entry 30).

The reactions of 1-iodocyclohexene with 1,5-hexadiene and acetylacetone or ethyl acetoacetate were run (entries 31 and 32). After purification, GC and ^{1}H NMR spectroscopy both indicated that more than 3 compounds were present as a single spot on TLC analysis. Due to the difficulties in separation and the complexity of the spectral data obtained, no structures have been assigned.

In summary, the palladium(0)-catalyzed cross-coupling of vinylic halides with alkenes and carbon nucleophiles produces a mixture of products due to non-regioselective displacement of palladium from the unsymmetrical π-allylpalladium species by the carbon nucleophiles or external and internal addition of the σ-palladium species to the carbon-carbon double bond of the alkenes. 1,5-Hexadiene provides better results than simple alkenes in terms of overall yield and regioselectivity. β-Bromostyrene generally gives better results than other vinylic halides. Vinylic triflates also produced regioselective products in moderate yields.

CONCLUSION

The palladium(0)-promoted cross-coupling of vinylic halides or triflates with alkenes and nucleophiles has been investigated. Both carbanion and amine nucleophiles are readily accommodated in the reaction. In most cases, amine nucleophiles reacted with 1-octene to give a mixture of isomers in approximately a 4:1 ratio in moderate to low yields. Addition of the carbon of the vinylic palladium species to the alkene was predominately to the terminal carbon of the double bond, but internal addition was commonly observed. 1,5-Hexadiene produced higher yields and better regioselectively compared with 1-octene, which is probably the result of a cyclic chelating intermediate. Cyclic amines are better nucleophiles than acyclic amines for steric reasons. β-Bromostyrene provided higher yields than other simple vinylic halides. Vinylic iodides are more reactive than the corresponding bromides, leading to higher yields of products, while vinylic triflates produce regiospecific products in moderate yield.

The results from the palladium(0)-catalyzed cross-coupling of vinylic halides, alkenes and carbon nucleophiles presented in this part of the thesis are the first observed examples of this type of three component coupling. The reaction often produces a mixture of isomers and the isomer ratio is not significantly effected by altering reaction conditions. Again, better results are observed with 1,5-hexadiene than with simple alkenes in terms of yield and regioselectivity, although the regioselectivity is usually not as good as that for nitrogen nucleophiles. Vinylic triflates also produce regioselective products in moderate yields.

In conclusion, the palladium(0)-catalyzed cross-coupling of vinylic halides or triflates with alkenes and nucleophiles proceeds under mild conditions. This reaction

provides a very efficient route for the formation of two new carbon-carbon and/or carbon-nitrogen bonds simultaneously, but mixtures of products are common.

EXPERIMENTAL SECTION

Spectral Data and Analysis

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 an IBM IR/98 FT-IR spectrometer or on a Beckmann 4250 spectrometer. High resolution mass spectral analyses were performed on a Kratos or an MS-50 high resolution mass 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 $KMnO_4$ solution (3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL 5% NaOH + 300 mL H_2O).

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. *N, N*-Dimethylformamide (DMF) and *N, N*-dimethylacetamide were dried over 4 Å molecular sieves. TBAC was purchased from Lancaster Synthesis Inc. $Pd(OAc)_2$ was generously provided by Johnson Matthey Inc. and Kawaken Fine Chemical Co., Inc. β-Bromostyrene, 1-bromo-2-methylpropene, 2-bromopropene, *E*-1-bromopropene, 1-octene, 1,5-hexadiene, styrene, cyclopentene, 3-methyl-1-butene, 2,5-dimethyl-1,5-hexadiene, 3,3-dimethyl-1-butene, morpholine, piperidine, *n*-butylamine, di-*n*-butylamine, *t*-butylamine, aniline, dimethyl malonate, ethyl acetoacetate, 5,5-dimethyl-1,3-cyclohexanedione, acetylacetone, and 4-vinyl-1-cyclohexene were obtained from Aldrich Chemical Company, Inc. 1-Iodo-2-methyl-1-propene was prepared according to a literature procedure.[15] $Pd(dba)_2$ was prepared according to a literature procedure.[16]

General Procedure for the Palladium-Catalyzed Cross-Coupling Reactions

Procedure A

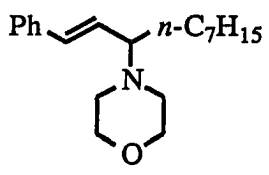
Into a one or two-dram screw-capped vial, equipped with a Teflon-lined cap and a magnetic stirrer, was placed the $Pd(dba)_2$ (5 mol %), tetra-*n*-butylammonium chloride (1.1 equiv), *N,N*-dimethylacetamide (2 mL), vinylic halide (0.25 mmol), alkene (5 equiv) and amine (5 equiv). The vial was then capped and suspended in an oil bath at the desired reaction temperature for an appropriate period of time. The reaction was monitored by TLC. When the reaction was considered complete, it was allowed to cool to room temperature and diluted with ethyl ether (10 mL). The mixture was washed with brine, and dried over magnesium sulfate. After removal of the solvent, the residue was chromatographed on a silica gel column (230-400 mesh silica gel) with an appropriate eluent, unless otherwise specified. The desired products were collected and the solvents were removed by rotary evaporation. The products were further purified by chromatography on a silica gel column when necessary.

Procedure B

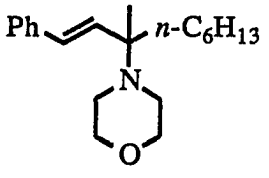
Into a one or two-dram screw-capped vial, equipped with a Teflon-lined cap and a magnetic stirrer, was placed the $Pd(dba)_2$ (10 mol %), tetra-*n*-butylammonium chloride (1.1 equiv), sodium carbonate (2.5 equiv), *N,N*-dimethylacetamide (2 mL), vinylic halide (0.25 mmol), alkene (5 equiv), and carbon nucleophile (5 equiv). The vial was then capped and suspended in an oil bath at the desired reaction temperature for a certain period of time. At the desired time, the reaction was monitored by TLC. When the reaction was considered complete, it was allowed to cool to room temperature and diluted with ethyl ether (10 mL). The mixture was washed with brine, and dried over magnesium sulfate. After removal of the solvent, the residue was chromatographed on a silica gel column (230-400 mesh silica gel) with an appropriate eluent, unless otherwise specified. The

desired products were collected and the solvents were removed by rotary evaporation. The products were further purified by chromatography on a silica gel column when necessary.

Compounds **1a** and **1b**



1a



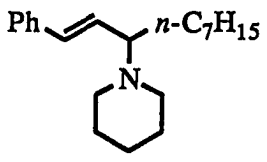
1b

Obtained in 98 % yield as a separable mixture (**1a**:**1b** = 85:15) from the reaction of β-bromostyrene, morpholine and 1-octene using procedure A.

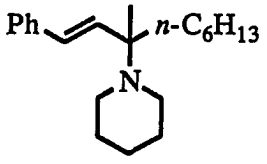
Isomer **1a**: TLC (4:1 hexanes/EtOAc) R_f = 0.24; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.9 Hz, CH_3), 1.30-1.75 (m, 12 H, 6 CH_2), 2.53-2.60 (m, 4 H, $(CH_2)_2N$), 2.83 (m, 1 H, CHN), 3.72 (m, 4 H, $(CH_2)_2O$), 6.08 (dd, 1 H, J = 15.9, 9.0 Hz, PhCH=C<u>H</u>), 6.43 (d, 1 H, J = 15.9 Hz, PhCH=), 7.35 (m, 5 H, aryl); IR (neat) 2955, 2926, 1450 (C=C), 1267, 1119, 970, 748, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 26.2, 29.1, 29.6, 31.7, 31.8, 50.5, 67.1, 68.3, 126.2, 127.3, 128.4, 129.7, 132.7, 136.8; HRMS m/z 200.1439 (Calcd. 200.1439 for $C_{21}H_{33}N$ - C_7H_{15}).

Isomer **1b**: TLC (4:1 hexanes/EtOAc) Rf = 0.44; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 6.7 Hz, CH_3), 1.18 (s, 3 H, CH_3), 1.25-1.55 (m, 10 H, 5 CH_2), 2.60 (t, 4 H, J = 4.5 Hz, $(CH_2)_2N$), 3.71 (t, 4 H, J = 4.5 Hz, $(CH_2)_2O$), 6.19 (d, 1 H, J = 16.5 Hz, PhCH=C<u>H</u>), 6.36 (d, 1 H, J = 16.5 Hz, PhCH=), 7.30 (m, 5 H, aryl); IR (neat) 2954, 1733, 1452 (C=C), 1118, 963, 747, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.1, 16.8, 22.7, 23.8, 30.0, 31.8, 39.2, 46.6, 60.5, 67.9, 126.2, 127.2, 128.5, 128.9, 136.5, 137.3; HRMS m/z 200.1439 (Calcd. 200.1439 for $C_{21}H_{33}N$ - C_7H_{15}).

Compounds **17a** and **17b**



17a



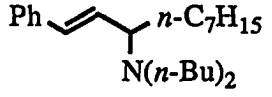
17b

Obtained in 51 % yield as separable isomers (**17a:17b** = 86:14) from the reaction of β-bromostyrene, piperidine and 1-octene using procedure A.

Isomer **17a**: TLC (11:1 hexanes/EtOAc) $R_f = 0.21$; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, $J = 5.8$ Hz, CH_3), 1.30-1.72 (m, 18 H, 9 CH_2), 2.47-2.60 (m, 4 H, $(CH_2)_2N$), 2.86 (m, 1 H, CHN), 6.14 (dd, 1 H, $J = 15.9$, 9.0 Hz, PhCH=C<u>H</u>), 6.39 (d, 1 H, $J = 15.9$ Hz, PhCH=), 7.35 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.8, 26.4, 26.7, 29.2, 29.7, 31.8, 32.4, 50.9, 68.5, 126.2, 127.1, 128.4, 130.3, 132.0, 137.2; IR (neat) 2926, 2853, 1451 (C=C), 1099, 968, 747, 692 cm^{-1}; HRMS m/z 200.1439 (Calcd. 200.1439 for $C_{21}H_{33}N$ - C_7H_{15}).

Isomer **17b**: TLC (11:1 hexanes/EtOAc) $R_f = 0.32$; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, $J = 5.8$ Hz, CH_3), 1.18 (s, 3 H, CH_3), 1.28-1.57 (m, 16 H, 8 CH_2), 2.52 (m, 4 H, $(CH_2)_2N$), 6.25 (d, 1 H, $J = 16.5$ Hz, PhCH=C<u>H</u>), 6.33 (d, 1 H, $J = 16.5$ Hz, PhCH=), 7.35 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.7, 22.7, 24.0, 25.2, 27.0, 27.0, 30.1, 31.8, 39.8, 47.3, 126.2, 126.9, 128.0, 128.5, 128.5, 138.1; IR (neat) 2927, 1622, 1449 (C=C), 1338, 1185, 1097, 981, 748, 694 cm^{-1}; HRMS m/z 299.2609 (Calcd. 299.2613 for $C_{21}H_{33}N$).

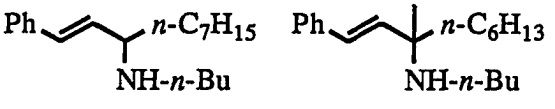
Compound **18**



18

Obtained in 6 % yield from the reaction of β-bromostyrene, di-*n*-butylamine and 1-octene using procedure A. TLC (15:1 hexanes/EtOAc) $R_f = 0.61$; ^1H NMR ($CDCl_3$) δ 0.90 (m, 9 H, 3 CH_3), 1.30-1.62 (m, 20 H, 10 CH_2), 2.38-2.54 (m, 4 H, $(CH_2)_2N$), 3.15 (m, 1 H, CHN), 6.12 (dd, 1 H, J = 15.9, 8.7 Hz, PhCH=C<u>H</u>), 6.38 (d, 1 H, J = 15.9 Hz, PhCH=), 7.30 (m, 5 H, aryl). There was not enough material for IR, ^{13}C NMR and HRMS analysis.

Compounds **19a** and **19b**



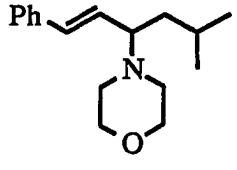
19a **19b**

Obtained in 36 % yield as an inseparable mixture (**19a**:**19b** = 67:33) from the reaction of β-bromostyrene, *n*-butylamine and 1-octene using procedure A. The isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers: TLC (2:1 hexanes/EtOAc) $R_f = 0.06$; ^{13}C NMR ($CDCl_3$) δ 14.1, 20.6, 20.6, 22.6, 23.7, 23.8, 26.1, 29.2, 29.7, 29.9, 31.8, 32.5, 33.2, 36.2, 41.1, 42.2, 47.3, 61.6, 126.2, 126.3, 127.0, 127.2, 127.8, 128.5, 130.8, 133.7, 137.9; IR (neat) 2956, 1466 (C=C), 1449 (C=C), 980, 692 cm^{-1}; HRMS m/z 287.2610 (Calcd. 287.2613 for $C_{20}H_{33}N$).

Isomer **19a**: ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6 H, 2 CH_3), 1.30-1.42 (m, 16 H, 8 CH_2), 2.51 (m, 2 H, NCH_2), 2.83 (m, 1 H, CHN), 5.99 (dd, 1 H, J = 15.8, 8.4 Hz, PhCH=C<u>H</u>), 6.43 (d, 1 H, J = 15.8 Hz, PhCH=), 7.35 (m, 5 H, aryl).

Isomer **19b**: ^{1}H NMR ($CDCl_3$) same as **19a** or not seen, except δ 2.18 (s, 3 H, CH_3), 3.14 (m, 2 H, NCH_2), 6.11 (d, 1 H, J = 16.3 Hz, PhCH=C<u>H</u>), 6.36 (d, 1 H, J = 16.3 Hz, PhCH=).

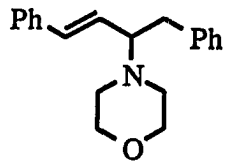
Compound **20**



20

Obtained in 20 % yield from the reaction of β-bromostyrene, morpholine and 3-methyl-1-butene using procedure A. TLC (2:1 hexanes/EtOAc) R_f = 0.22; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 6 H, J = 5.7 Hz, 2 CH_3), 1.55 (m, 3 H, CH_2, CH), 2.55 (m, 2 H, NCH_2), 2.65 (m, 2 H, NCH_2), 2.95 (m, 1 H, CHN), 3.70 (m, 4 H, $(CH_2)_2O$), 6.37 (dd, 1 H, J = 15.9, 9.1 Hz, PhCH=C<u>H</u>), 6.60 (d, 1 H, J = 15.9 Hz, PhCH=), 7.33 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.7, 24.8, 40.9, 50.4, 66.2, 67.3, 126.2, 127.4, 128.6, 129.4, 132.6, 136.0; IR (neat) 2954, 1451 (C=C), 1285, 1118, 971, 749, 694 cm^{-1}; HRMS m/z 202.1233 (Calcd. 202.1232 for $C_{17}H_{25}NO$ - C_4H_9).

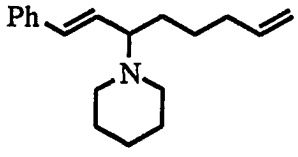
Compound **21**



21

Obtained in 29 % yield from the reaction of β-bromostyrene, morpholine and styrene using procedure A. ^{1}H NMR ($CDCl_3$) δ 2.68 (m, 6 H, $(CH_2)_2N$, CH_2Ph), 3.15 (m, 1 H, CHN), 3.74 (m, 4 H, $(CH_2)_2O$), 6.08 (dd, 1 H, J = 15.9, 8.1 Hz, PhCH=C<u>H</u>), 6.20 (d, 1 H, J = 15.9 Hz, PhC<u>H</u>=), 7.20 (m, 10 H, aryl); ^{13}C NMR ($CDCl_3$) δ 38.4, 50.5, 67.2, 69.8, 126.0, 126.2, 127.4, 128.1, 128.4, 129.5, 129.5, 133.2, 136.8, 139.1; IR (neat) 2954, 1600, 1494, 1452 (C=C), 1117, 1030, 921, 746, 695 cm^{-1}; HRMS m/z 293.1780 (Calcd. 293.1773 for $C_{20}H_{23}NO$).

Compound **22**

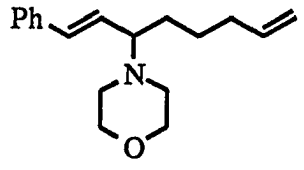


22

Obtained in 50 % yield from the reaction of β-bromostyrene, piperidine and 1,5-hexadiene using procedure A. TLC (2:1 hexanes/EtOAc) R_f = 0.14; ^{1}H NMR ($CDCl_3$) δ 1.41-1.73 (m, 10 H, 5 CH_2), 2.70 (m, 2 H, CH_2C=), 2.45-2.58 (m, 4 H, $N(CH_2)_2$), 2.88 (m, 1 H, CHN), 4.93 (d, 1 H, J = 11.1 Hz, =C<u>H</u>H), 5.48 (d, 1 H, J = 20.4 Hz, =CH<u>H</u>), 5.80 (m, 1 H, C<u>H</u>=CH_2), 6.15 (dd, 1 H, J = 17.4, 9.0 Hz, PhCH=C<u>H</u>), 6.42 (d, 1 H, J = 17.4 Hz,

PhCH=), 7.31 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.1, 25.4, 31.9, 33.8, 50.9, 68.4, 114.4, 126.2, 127.2, 128.5, 130.1, 132.2, 137.1, 139.8; IR (neat) 2919, 1641, 1494 (C=C), 1443 (C=C), 992, 969, 910, 748, 693 cm^{-1}; HRMS m/z 200.1445 (Calcd. 200.1439 for $C_{19}H_{25}N$ - C_5H_9).

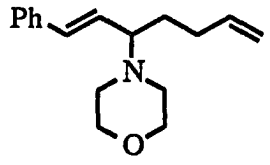
Compound **23**



23

Obtained in 95 % yield from the reaction of β-bromostyrene, morpholine and 1,5-hexadiene using procedure A. TLC (6:1 hexanes/EtOAc) $R_f = 0.23$; ^1H NMR ($CDCl_3$) δ 1.47-1.82 (m, 4 H, 2 CH_2), 2.08 (m, 2 H, CH_2C=), 2.55 (m, 2 H, CH_2N), 2.60 (m, 2 H, CH_2N), 2.85 (m, 1 H, CHN), 3.71 (m, 4 H, $(CH_2)_2O$), 4.96 (d, 1 H, J = 10.2 Hz, =CHH), 4.99 (d, 1 H, J = 18.6 Hz, =CHH), 5.77 (m, 1 H, CH=CH_2), 6.10 (dd, 1 H, J = 15.9, 9.0 Hz, PhCH=CH), 6.44 (d, 1 H, J = 15.9 Hz, PhCH=), 7.32 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 25.5, 31.2, 33.7, 50.5, 67.2, 68.1, 114.5, 126.2, 127.3, 128.4, 129.6, 132.7, 136.8, 138.5; IR (neat) 2953, 2854, 1500 (C=C), 1450 (C=C), 1190, 970, 912, 750, 694 cm^{-1}; HRMS m/z 271.19385 (Calcd. 271.1936 for $C_{18}H_{25}NO$).

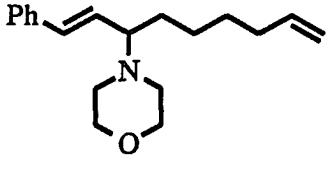
Compound **24**



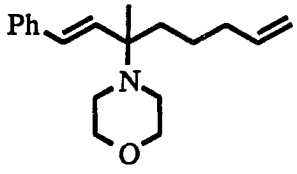
24

Obtained in 45 % yield from the reaction of β-bromostyrene, morpholine and 1,4-pentadiene using procedure A. TLC (1:1 hexanes/EtOAc) $R_f = 0.31$; ^1H NMR ($CDCl_3$) 1.70 (m, 2 H, CH_2), 2.10 (m, 2 H, CH_2C=), 2.60 (m, 4 H, $(CH_2)_2N$), 2.90 (m, 1H, CHN), 3.78 (m, 4 H, $(CH_2)_2O$), 4.96 (d, 1 H, J = 18.9 Hz, =C<u>H</u>H), 5.01 (d, 1 H, J = 9.9 Hz, C=CH<u>H</u>), 5.80 (m, 1 H, C<u>H</u>=CH_2), 6.09 (dd, 1 H, J = 15.9, 9.0 Hz, PhCH=C<u>H</u>), 6.45 (d, 1 H, J =15.9 Hz, PhCH=), 7.33 (m, 5 H, aryl); IR (neat) 2954, 1643, 1494 (C=C), 1452 (C=C), 1118, 970 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 30.4, 30.9, 50.5, 67.2, 67.6, 114.7, 126.3, 127.5, 128.6, 129.2, 133.1, 136.8, 138.4; HRMS m/z 257.0780 (Calcd. 257.1779 for $C_{17}H_{23}NO$).

Compounds **25a** and **25b**



25a



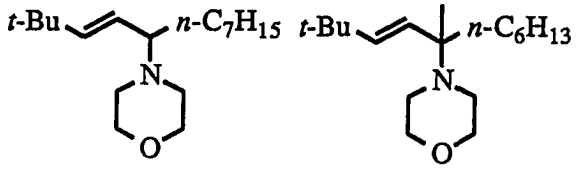
25b

Obtained in 68 % yield as a separable mixture (**25a**:**25b** = 75:25) from the reaction of β-bromostyrene, morpholine and 1,6-heptadiene using procedure A.

Isomer **25a**: TLC (2:1 hexanes/EtOAc) $R_f = 0.35$; ^1H NMR ($CDCl_3$) δ 0.95 (m, 2 H, CH_2), 1.38 (m, 4 H, 2 CH_2), 1.72 (m, 2 H, CH_2C=), 2.58 (m, 4 H, $(CH_2)_2N$), 2.85 (m, 1 H, CHN), 3.62 (m, 4 H, $(CH_2)_2O$), 4.92 (d, 1 H, J = 10.8 Hz, =C<u>H</u>H), 4.97 (d, 1 H, J = 20.1 Hz, =CH<u>H</u>), 5.78 (m, 1 H, <u>H</u>C=CH_2), 6.09 (dd, 1 H, J = 15.9, 9.0 Hz, PhCH=C<u>H</u>), 6.44 (d, 1 H, J = 15.9 Hz, PhCH=), 7.38 (m, 5 H, aryl); IR (neat) 2932, 1495 (C=C), 1450 (C=C), 1267, 1119, 993, 970, 750, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 25.5, 29.0, 31.2, 33.7, 50.5, 67.2, 68.1, 114.5, 126.2, 127.3, 128.4, 129.6, 132.7, 136.8, 138.5; HRMS m/z 285.2091 (Calcd. 285.2093 for $C_{19}H_{27}NO$).

Isomer **25b**: TLC (2:1 hexanes/EtOAc) $R_f = 0.51$; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H, CH_3), 1.40 (m, 2 H, CH_2), 1.59 (m, 2 H, CH_2), 2.01 (m, 2 H, CH_2C=), 2.57 (m, 4 H, $(CH_2)_2N$), 3.70 (m, 4 H, $(CH_2)_2O$), 4.94 (d, 1 H, J = 10.8 Hz, =C<u>H</u>H), 4.99 (d, 1 H, J = 17.7 Hz, =CH<u>H</u>), 5.78 (m, 1 H, C<u>H</u>=CH_2), 6.19 (d, 1 H, J = 16.2 Hz, PhCH=), 6.37 (d, 1 H, J = 16.2 Hz, PhCH=C<u>H</u>), 7.35 (m, 5 H, aryl); IR (neat) 2921, 1640, 1494 (C=C), 1446 (C=C), 1118, 911, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 16.9, 23.2, 34.3, 38.5, 46.6, 52.0, 67.8, 114.7, 126.2, 126.9, 128.0, 128.6, 129.1, 136.3, 138.7; HRMS m/z 285.2093 (Calcd. 285.2093 for $C_{19}H_{27}NO$).

Compounds **26a** and **26b**



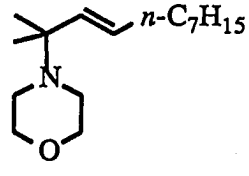
26a **26b**

Obtained in 40 % yield as separable isomers (**26a**:**26b** = 80:20) from the reaction of *E*-1-iodo-3,3-dimethyl-1-butene, morpholine and 1-octene using procedure A.

Isomer **26a**: TLC (11:1 hexanes/EtOAc) R_f = 0.40; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 4.7 Hz, CH_3), 1.02 (s, 9 H, $(CH_3)_3C$), 1.28 (m, 10 H, 5 CH_2), 1.60 (m, 2 H, CH_2), 2.42 (m, 2 H, CH_2N), 2.75 (m, 3 H, CH_2N, CHN), 3.72 (m, 4 H, $(CH_2)_2O$), 5.15 (dd, 1 H, *J* = 15.6, 9.1 Hz, CH=C<u>H</u>), 5.58 (d, 1 H, *J* = 15.6 Hz, C<u>H</u>=CH); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 26.3, 29.2, 29.6, 29.7, 31.8, 31.9, 33.1, 50.9, 67.3, 68.2, 128.6, 146.8; IR (neat) 2955, 2927, 1452 (C=C), 1362, 1119, 977 cm^{-1}; HRMS m/z 182.1548 (Calcd. 182.1545 for $C_{18}H_{25}NO$ - C_8H_{17}).

Isomer **26b**: TLC (11:1 hexanes/EtOAc) Rf = 0.45; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 4.7 Hz, CH_3), 1.02 (s, 9 H, $(CH_3)_3C$), 1.28 (m, 9 H, 3 CH_2, CH_3), 1.42 (m, 2 H, CH_2), 1.62 (m, 2 H, CH_2), 2.51 (m, 4 H, $(CH_2)_2N$), 3.69 (m, 4 H, $(CH_2)_2O$), 5.24 (d, 1 H, *J* = 16.3 Hz, CH=C<u>H</u>), 5.48 (d, 1 H, *J* = 16.3 Hz, C<u>H</u>=CH); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.0, 22.6, 23.8, 29.3, 29.9, 30.0, 31.8, 33.1, 39.0, 46.4, 67.8, 140.9, 143.3; IR (neat) 2955, 1672, 1614, 1454 (C=C), 1120, 985, 963, 697 cm^{-1}; HRMS m/z 281.2717 (Calcd. 281.2719 for $C_{18}H_{35}NO$).

Compound **27**

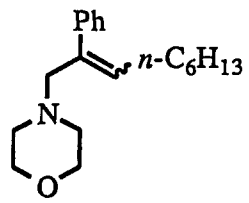


27

Obtained in 29 % yield from the reaction of 1-iodo-2-methylpropene, morpholine and 1-octene using procedure A. TLC (2:1 hexanes/EtOAc) R_f = 0.31; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 6.7 Hz, CH_3), 1.12 (s, 6 H, $(CH_3)_2C$), 1.28 (m, 10 H, 5 CH_2), 2.03 (m, 2 H, CH_2C=), 2.53 (t, 4 H, *J* = 4.8 Hz, $(CH_2)_2N$), 3.72(t, 4 H, *J* = 4.8 Hz, $(CH_2)_2O$), 5.42

(m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 18.0, 23.6, 25.9, 28.5, 32.9, 34.1, 44.4, 51.8, 52.2, 52.3, 52.4, 64.7, 124.2, 133.6; IR (neat) 2957, 2814, 1466 (C=C), 1452, 1381, 1275, 1177, 1130, 978, 959, 862 cm^{-1}; HRMS m/z 253.4320 (Calcd. 253.4316 for $C_{16}H_{31}NO$).

Compound **28**



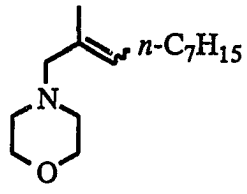
28

Obtained in 24 % yield as an inseparable mixture (*Z*/*E* = 60:40) from the reaction of α-iodostyrene, morpholine and 1-heptene using procedure A. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers: TLC (4:1 hexanes/EtOAc) R_f = 0.63; ^{13}C NMR ($CDCl_3$) δ 16.1, 16.8, 24.5, 28.2, 31.7, 31.7, 31.9, 33.0, 44.6, 51.7, 52.1, 114.5, 127.0, 127.2, 127.8, 128.5, 128.7, 128.9, 129.8, 132.9, 133.8, 134.4; HRMS m/z 287.2249 (Calcd. 287.2247 for $C_{19}H_{29}NO$). There was not enough material for IR.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 6.0 Hz, CH_3), 1.33 (m, 8 H, 4 CH_2), 2.25 (m, 2 H, CH_2C=), 2.52 (m, 4 H, $(CH_2)_2N$), 3.36 (s, 2 H, NCH_2C=), 3.64 (m, 4 H, $(CH_2)_2O$), 5.92 (t, 1 H, *J* = 7.5 Hz, =CH), 7.24 (m, 5 H, aryl)

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as that of the *E* isomer or not seen, except δ 3.20 (s, 2 H, NCH_2C=), 5.61 (t, 1 H, *J* = 6.9 Hz, =CH).

Compound **29**



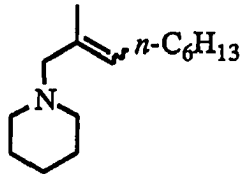
29

Obtained in 73 % yield from the reaction of 2-bromopropene, morpholine and 1-octene as an inseparable mixture of isomers (*Z*/*E* = 89:11) using procedure A. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens adjacent to the nitrogen atom. The following data were taken from a mixture of the isomers: TLC (4:1 hexanes/EtOAc) R_f = 0.29; ^{13}C NMR ($CDCl_3$) δ 14.1, 15.3, 22.7, 27.8, 29.2, 29.8, 31.9, 53.6, 66.9, 67.1, 67.9, 128.8, 131.7; IR (neat) 2922, 1453 (C=C), 1289, 1119, 1007, 908, 869 cm $^{-1}$; HRMS m/z 239.2249 (Calcd. 239.2245 for $C_{18}H_{25}NO$).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 8.5 Hz, CH_3), 1.26 (m, 10 H, 5 CH_2), 1.66 (s, 3 H, CH_3), 2.03 (m, 2 H, $=CCH_2$), 2.35 (m, 4 H, $(CH_2)_2N$), 2.83 (s, 2 H, CH_2N), 3.70 (m, 4 H, $(CH_2)_2O$), 5.32 (t, 1 H, *J* = 8.6 Hz, =CH).

The *E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *Z*-isomer or not seen, except δ 2.91 (s, 2 H, CH_2N).

Compound **30**



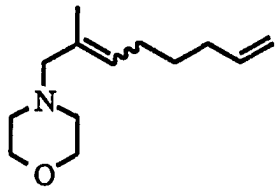
30

Obtained in 57 % yield from the reaction of 2-bromopropene, piperidine and 1-heptene as an inseparable mixture of isomers (*Z*/*E* = 89:11) using procedure A. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens adjacent to the nitrogen atom. The following data were taken from a mixture of the isomers: ^{13}C NMR ($CDCl_3$) δ 14.1, 15.2, 22.6, 24.4, 25.8, 27.8, 29.0, 29.6, 31.7, 54.4, 68.2, 118.5, 128.6; IR (neat) 2930, 1466 (C=C), 1338, 1119, 1104, 863, 808 cm^{-1}; HRMS m/z 223.2296 (Calcd. 223.2300 for $C_{15}H_{29}N$).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.27-1.57 (m, 14 H, 7 CH_2), 1.64 (s, 3 H, CH_3), 2.01 (m, 2 H, CH_2C=C), 2.30 (4 H, $(CH_2)_2N$), 2.83 (s, 2 H, CH_2N), 5.29 (t, 1 H, *J* = 7.2 Hz, HC=C).

The *E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *Z*-isomer or not seen, except δ 2.94 (s, 2 H, CH_2N).

Compound **31**



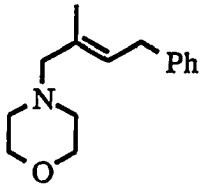
31

Obtained in 98 % yield from the reaction of 2-bromopropene, morpholine and 1,5-hexadiene as an inseparable mixture of isomers (*Z*/*E* = 83:17) using procedure A. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens adjacent to the nitrogen atom. The following data were taken from a mixture of the isomers: IR (neat) 2927, 1453 (C=C), 1290, 1119, 1640 cm $^{-1}$; HRMS m/z 209.1785 (Calcd. 209.1780 for $C_{13}H_{23}NO$).

The *Z*-isomer: TLC (2:1 hexanes/EtOAc) R_f = 0.34; ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 2 H, CH_2), 1.64 (s, 3 H, CH_3), 2.05 (m, 4 H, 2 CH_2C=), 2.35 (m, 4 H, $(CH_2)_2N$), 2.83 (s, 2 H, NCH_2C=), 3.70 (m, 4 H, $(CH_2)_2O$), 4.94 (d, 1 H, *J* = 9.0 Hz, =C<u>H</u>H), 4.99 (d, 1 H, *J* = 18.0 Hz, =CH<u>H</u>), 5.30 (t, 1 H, *J* = 6.0 Hz, =CH), 5.81 (m, 1 H, <u>H</u>C=CH_2); ^{13}C NMR ($CDCl_3$) δ 15.0, 27.2, 28.8, 33.4, 53.5, 67.0, 67.8, 114.4, 128.5, 131.8, 138.8.

The *E*-isomer: TLC (2:1 hexanes/EtOAc) R_f = 0.42; ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.70 (s, 3 H, CH_3), 2.90 (d, 2 H, *J* = 2.7 Hz, NCH_2C=); ^{13}C NMR ($CDCl_3$) same as the *Z*-isomer or not seen, except δ 22.3, 29.2, 33.3, 34.4, 59.0, 61.4, 128.3, 129.3, 132.0.

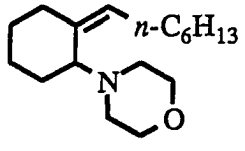
Compound **32**



32

Obtained in 35 % yield from the reaction of 2-bromopropene, morpholine and styrene using procedure A. TLC (2:1 hexanes/EtOAc) $R_f = 0.27$; ^1H NMR ($CDCl_3$) δ 1.77 (s, 3 H, CH_3), 2.36 (t, 4 H, $J = 4.5$ Hz, $(CH_2)_2N$), 2.88 (s, 2 H, CH_2N), 3.39 (d, 2 H, $J = 7.2$ Hz, CH_2Ph), 3.70 (t, 4 H, $J = 4.5$ Hz, $(CH_2)_2O$), 5.52 (t, 1 H, $J = 7.2$ Hz, =CH), 7.22 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.1, 34.1, 53.6, 67.1, 67.7, 125.8, 126.8, 128.3, 128.4, 133.0, 141.2; IR (neat) 2957, 2805, 1602 (C=C), 1452, 1117, 1005, 866, 743 cm^{-1}; HRMS m/z 231.1622 (Calcd. 231.1623 for $C_{15}H_{21}NO$).

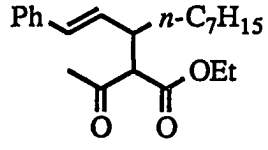
Compound **33**



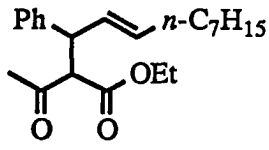
33

Obtained in 4 % yield from the reaction of 1-iodocyclohexene, morpholine and 1-heptene using procedure A. TLC (4:1 hexanes/EtOAc) $R_f = 0.46$; ^1H NMR ($CDCl_3$) δ 0.81 (t, 3 H, $J = 6.9$ Hz, CH_3), 1.20 (m, 16 H, 8 CH_2), 1.69 (m, 2 H, CH_2C=), 2.28 (m, 5 H, $(CH_2)_2N$, CHN), 3.62 (t, 4 H, $J = 4.8$ Hz, $(CH_2)_2O$), 5.15 (t, 1 H, $J = 6.9$ Hz, =CH). There was not enough material for ^{13}C NMR, IR and HRMS analysis.

Compounds **37a** and **37b**



37a



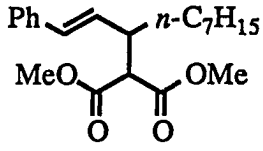
37b

Obtained in 80 % yield as an inseparable mixture (**37a:37b** = 59:41) from the reaction of β-bromostyrene, ethyl acetoacetate and 1-octene using procedure B. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectra peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers: TLC (11:1 hexanes/EtOAc) R_f = 0.41; ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 22.6, 27.0, 27.2, 29.1, 29.3, 31.8, 32.9, 33.0, 43.4, 43.5, 61.2, 61.3, 65.3, 65.4, 126.2, 126.3, 127.3, 127.4, 128.4, 128.5, 129.7, 129.8, 132.4, 132.5, 168.6, 168.7, 168.7; IR (neat) 2921, 1747 (C=O), 1740 (C=O), 1455 (C=C) cm^{-1}; HRMS m/z 344.2342 (Calcd. 344.2352 for $C_{22}H_{32}O_3$).

Isomer **37a**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, *J* = 5.7 Hz, CH_3), 1.25 (m, 15 H, 6 CH_2, CH_3), 1.95 (m, 1 H, =CCH), 2.48 (s, 3 H, CH_3CO), 3.60 (d, 1 H, *J* = 3.0 Hz, COCHCO), 4.22 (q, 2 H, *J* = 6.6 Hz, OCH_2), 6.10 (dd, 1 H, *J* = 15.6, 9.6 Hz, PhCH=C<u>H</u>), 6.53 (d, 1 H, *J* = 15.6 Hz, PhCH=), 7.4 (m, 5 H, aryl).

Isomer **37b**: ^{1}H NMR ($CDCl_3$) same as **37a** or not seen, except δ 2.28 (s, 3 H, CH_3CO), 3.07 (m, 1 H, PhCHC=), 3.62 (d, 1 H, *J* = 3.5 Hz, COCHCO), 4.30 (m, 2 H, OCH_2), 5.62 (m, 1 H, PhCC=CH), 6.02 (dd, 1 H, *J* = 15.6, 10.2 Hz, PhCCH=).

Compounds **38a** and **38b**



+ Isomer

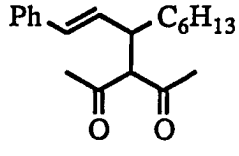
38a **38b**

Obtained in 20 % yield as an inseparable mixture (**38a**:**38b** = 50:50) from the reaction of β-bromostyrene, dimethyl malonate and 1-octene using procedure B. The isomer ratio was determined by gas chromotography. The following data were taken from a mixture of the isomers: TLC (6:1 hexanes/EtOAc) $R_f = 0.43$. There was not enough material for IR, ^{13}C NMR and HRMS analysis.

Isomer **38a**: ^1H NMR ($CDCl_3$) δ 0.89 (m, 3 H, CH_3), 1.22 (m, 10 H, 5 CH_2), 1.63 (m, 2 H, CH_2), 3.64 (m, 1 H, =CCH), 3.65 (s, 3 H, CH_3O), 3.74 (m, 4 H, OCCHCO, CH_3O), 6.01 (dd, 1 H, J = 15.8, 9.7 Hz, PhC=CH), 6.45 (d, 1 H, J = 15.8 Hz, PhCH=), 7.30 (m, 5 H, aryl).

Isomer **38b**: ^1H NMR ($CDCl_3$) same as the **38a** or not seen, except δ 5.53 (m, 2 H, HC=CH), 6.34 (d, 1 H, J = 2.4 Hz, CH=).

Compound **39**

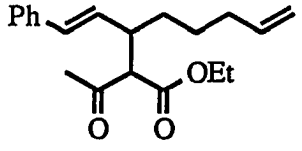


39

Obtained in 23 % yield from the reaction of β-bromostyrene, acetylacetone and 1-heptene using procedure B: TLC (10:1 hexanes/EtOAc) $R_f = 0.20$; ^1H NMR ($CDCl_3$) δ

0.90 (m, 3 H, CH_3), 1.10 (m, 10 H, 5 CH_2), 2.04 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 2.21 (m, 1 H, HCC=), 3.69 (d, 1 H, J = 10.8 Hz, COCHCO), 5.77 (dd, 1 H, J = 15.6, 9.6 Hz, PhCH=C<u>H</u>), 6.35 (d, 1 H, J = 15.6 Hz, PhCH=C), 7.30 (m, 5 H, aryl). There was not enough material for IR, ^{13}C NMR and HRMS analysis.

Compounds **40a** and **40b**



+ Isomer

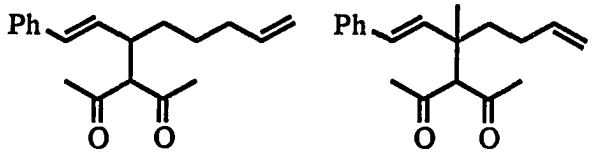
40a **40b**

Obtained in 82 % yield as an inseparable mixture (**40a**:**40b** = 37:63) from the reaction of β-bromostyrene, ethyl acetoacetate and 1,5-hexadiene using procedure B. The isomer ratio was determined by gas chromatography. The following data were taken from a mixture of the isomers: ^{13}C NMR ($CDCl_3$) δ 13.7, 14.1, 28.3, 28.4, 29.6, 29.9, 29.6, 29.9, 31.7, 31.9, 33.0, 48.7, 49.7, 61.0, 61.2, 61.4, 65.5, 65.8, 114.5, 126.2, 126.8, 127.3, 127.8, 128.5, 129.7, 130.0, 132.2, 132.6, 138.4, 140.7, 140.9 167.7, 167.9, 201.8, 202.0; IR (neat) 2940, 1700 (C=O), 1630 (C=O), 1450 (C=C), 1360 (C-O) cm^{-1}; HRMS m/z 314.1873 (Calcd. 314.1882 for $C_{20}H_{26}O_3$).

Isomer **40a**: ^1H NMR ($CDCl_3$) δ 1.24 (m, 7 H, 2 CH_2, CH_3), 2.16 (m, 2 H, CH_2C=), 2.22 (s, 3 H, CH_3CO), 2.50 (m, 1H, HCC=), 4.15 (m, 3 H, OCH_2, OCCHCO), 4.92 (d, 1 H, J = 6.9 Hz, =C<u>H</u>H), 4.95 (d, 1 H, J = 15.2 Hz, =CH<u>H</u>), 5.50 (m, 1 H, PhC=CH), 5.76 (m, 1 H, <u>H</u>C=CH_2), 6.32 (d, 1 H J = 15.3 Hz, PhCH=C), 7.30 (m, 5 H, aryl).

Isomer **40b**: ^1H NMR ($CDCl_3$) same as isomer **40a** or not seen, except δ 3.90 (m, 3 H, OCH_2, COCHCO), 5.54 (m, 1 H, PhCH=C<u>H</u>), 6.41 (m, 1 H, PhC<u>H</u>=CH).

Compounds **41a** and **41b**



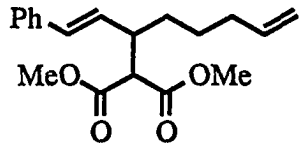
41a **41b**

Obtained in 96 % yield as an inseparable isomers (**41a**:**41b** = 63:37) from the reaction of β-bromostyrene, acetylacetone and 1,5-hexadiene using procedure B. The isomer ratio was determined by gas chromatography. The following data were taken from a mixture of isomers: TLC (11:1 hexanes/EtOAc) $R_f = 0.37$; ^{13}C NMR ($CDCl_3$) δ 14.1, 20.2, 20.8, 26.2, 28.4, 28.9, 29.7, 30.1, 31.6, 32.4, 33.4, 38.9, 43.6, 53.8, 114.7, 114.8, 126.2, 126.3, 127.4, 127.6, 128.5, 128.6, 129.1, 129.4, 132.8, 134.7, 136.6, 138.2, 138.3, 203.4, 204.4; IR (neat) 2970, 1720 (C=O), 1690 (C=O), 1435 (C=C), 1356, 910 cm^{-1}; HRMS m/z 314.1873 (Calcd. 314.1882 for $C_{22}H_{32}O_3$).

Isomer **41a**: ^1H NMR ($CDCl_3$) δ 1.26 (m, 2 H, CH_2), 1.40 (m, 2 H, CH_2), 2.02 (m, 2 H, CH_2C=), 2.20 (s, 3 H, CH_3CO), 2.22 (s, 3 H, CH_3CO), 2.42 (m, 1 H, =CCH), 3.76 (d, 1 H, J = 10.5 Hz, COCHCO), 4.93 (d, 1 H, J = 10.5 Hz, =C<u>H</u>H), 4.98 (d, 1 H, J = 17.4 Hz, =CH<u>H</u>), 5.75 (m, 1 H, C<u>H</u>=CH_2), 6.31 (d, 1 H, J = 16.2 Hz, =CHPh), 6.45 (dd, 1 H, J = 16.2, 9.6 Hz, =CH), 7.30 (m, 5 H, aryl).

Isomer **41b**: ^1H NMR (CDCl3) same as isomer **41a** or not seen, except δ 3.87 (s, 1 H, COCHCO), 5.87 (d, 1 H, J = 9.6 Hz, CH=C<u>H</u>), 6.41 (d, 1 H, J = 9.6 Hz, C<u>H</u>=CH).

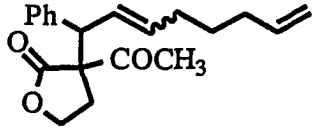
Compound **42**



42

Obtained in 77 % yield from the reaction of β-bromostyrene, dimethyl malonate and 1,5-hexadiene using procedure B. TLC (6:1 hexanes/EtOAc) $R_f = 0.40$; ^1H NMR ($CDCl_3$) δ 1.40 (m, 4 H, 2 CH_2), 2.00 (m, 2 H, CH_2C=), 3.47 (s, 3 H, CH_3O), 3.71 (s, 3 H, CH_3O), 3.66 (d, 1 H, J = 14.7 Hz, COCHCO), 4.06 (m, 1 H, CHC=), 4.92 (d, 1 H, J = 7.6 Hz, =CHH), 4.96 (d, 1 H, J = 18.1 Hz, =CHH), 5.47 (m, 1 H, PhC=CH), 5.77 (m, 1 H, CH=CH_2), 6.38 (s, 1 H, PhCH=), 7.27 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 28.2, 31.5, 32.7, 48.8, 51.9, 57.6, 126.0, 126.6, 127.5, 128.2, 129.5, 132.4, 138.2, 140.6, 167.5, 167.8; IR (neat) 2954, 1760 (C=O), 1742 (C=O), 1430 (C=C), 1253, 1151, 1032, 915 cm^{-1}; HRMS m/z 316.3983 (Calcd. 316.3982 for $C_{19}H_{24}O_4$).

Compounds **43**



43

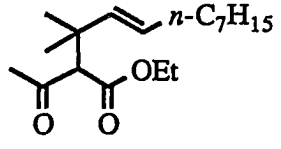
Obtained in 57 % yield as a separable mixture (ratio = 78:22) from the reaction of β-bromostyrene, 1,5-hexadiene and 2-acetylbutyrolactone using procedure B.

The major isomer: TLC (4:1 hexanes/EtOAc) $R_f = 0.49$; ^1H NMR ($CDCl_3$) δ 1.42 (m, 2 H, CH_2), 2.05 (m, 5 H, 2 CH_2C=, OCH_2CHH), 2.41 (s, 3 H, CH_3), 3.00 (m, 1 H,

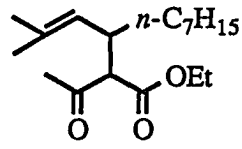
OCH_2CHH), 3.49 (m, 1 H, $OCHH$), 3.94 (m, 1 H, $OCHH$), 4.43 (d, 1 H, J = 8.4 Hz, PhCHC=), 4.45 (d, 1 H, J = 6.6 Hz, =CHH), 4.99 (d, 1 H, J = 15.3 Hz, =CHH), 5.60 (m, 2 H, CH=CH), 5.68 (m, 1 H, CH=CH_2), 7.26 (m, 5 H, aryl); IR (neat) 2924, 2855, 1761(C=O), 1714 (C=O), 1453 (C=C), 1374, 1357, 1160, 1029, 975, 913, 703 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.2, 25.7, 28.2, 31.9, 33.1, 50.9, 66.2, 66.8, 114.8, 126.2, 127.6, 128.6, 129.0, 135.1, 138.3, 138.8, 174.6, 201.3; HRMS m/z 312.4117 (Calcd. 312.4118 for $C_{20}H_{24}O_3$).

The minor isomer: TLC (4:1 hexanes/EtOAc) R_f = 0.43; ^1H NMR ($CDCl_3$) δ 1.42 (m, 2 H, CH_2), 2.00 (m, 4 H, 2 =CCH_2), 2.21 (s, 3 H, CH_3), 2.53 (m, 1 H, OCH_2CHH), 3.02 (m, 1 H, OCH_2CHH), 4.11 (m, 2 H, OCH_2), 4.36 (d, 1 H, J = 7.2 Hz, =CHH), 4.93 (d, 1 H, J = 6.0 Hz, =CHH), 5.46 (m, 1 H, CH=CH), 5.61 (dd, 1 H, J = 15.3, 6.0 Hz, CH=CH), 5.75 (m, 1 H, CH=CH_2), 7.20 (m, 5 H, aryl); IR (neat) 2922, 2855, 1777(C=O), 1710(C=O), 1356, 1162, 978 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.2, 26.3, 28.2, 31.9, 33.1, 52.3, 66.4, 66.5, 114.6, 127.5, 127.9, 128.3, 128.9, 135.4, 138.4, 138.5, 174.8, 201.5; HRMS m/z 312.4118 (Calcd. 312.4118 for $C_{20}H_{24}O_3$).

Compounds **44a** and **44b**



44a



44b

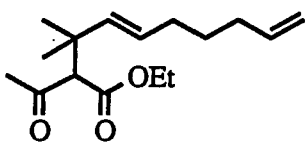
Obtained in 12 % yield as an inseparable mixture (**44a**:**44b** = 80:20) from the reaction of 1-iodo-2-methylpropene, 1-octene and ethyl acetoacetate using procedure B. The isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the single hydrogen between the carbonyl groups. The following data

were taken from a mixture of the isomers: TLC (15:1 hexanes/EtOAc) $R_f = 0.25$; HRMS m/z 296.2352 (Calcd. 296.2351 for $C_{18}H_{32}O_3$). There was not enough material for ^{13}C NMR and IR analysis.

Isomer **44a**: ^1H NMR ($CDCl_3$) δ 0.90 (m, 3 H, CH_3), 1.30 (m, 19 H, 3 CH_3, 5 CH_2), 2.00 (m, 2 H, $=CCH_2$), 2.20 (s, 3 H, CH_3CO), 3.40 (s, 1 H, COCHCO), 4.20 (m, 2 H, OCH_2, overlapped by OCH_2 of isomer **44b**), 5.40 (m, 1 H, $=C\underline{H}CH_2$), 5.60 (d, 1 H, J = 16.2 Hz, CH=).

Isomer **44b**: ^1H NMR ($CDCl_3$) same as that of compound **44a** or not seen, except δ 1.65 (s 3 H, $CH_3C=C$), 1.70 (s 3 H, $CH_3C=C$), 2.22 (s, 3 H, CH_3CO), 3.05 (m, 1 H, =CCH), 3.32 (d, 1 H, J = 10.6 Hz, COCHCO), 4.85 (d, 1 H, J = 10.6 Hz, =CH).

Compound **45**

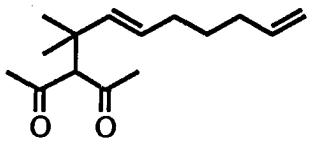


45

Obtained in 84 % yield from the reaction of 1-iodo-2-methylpropene, 1,5-hexadiene and ethyl acetoacetate using procedure B. TLC (15:1 hexanes/EtOAc) R_f = 0.33; ^1H NMR ($CDCl_3$) δ 1.20 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.25 (t, 3 H, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.43 (m, 2 H, CH_2), 2.03 (m, 4 H, 2 $=CCH_2$), 2.20 (s, 3 H, CH_3CO), 3.40 (s, 1 H, COCHCO), 4.15 (q, 2 H, J = 7.1 Hz, OCH_2), 4.94 (d, 1 H, J = 10.7 Hz, $=C\underline{H}H$), 5.02 (d, 1 H, J = 16.1 Hz, $=C\underline{H}H$), 5.40 (dt, 1 H, J = 15.7, 6.8 Hz, $HC=C\underline{H}$), 5.63 (d, 1 H, J = 15.7 Hz, $C\underline{H}$=CH), 5.78 (m, 1 H, $C\underline{H}=CH_2$); ^{13}C NMR ($CDCl_3$) δ 14.1, 25.7, 25.8, 28.6, 31.3, 32.0, 33.1, 38.6, 60.7, 68.4, 114.4, 127.9, 136.9, 138.6, 168.6, 202.8; IR(neat) 2976,

2930, 1736 (C=O), 1718 (C=O), 1177, 1144 cm^{-1}; HRMS m/z 251.1650 (Calcd. 251.1647 for $C_{15}H_{23}O_3$).

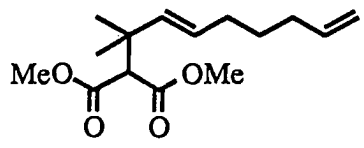
Compound **46**



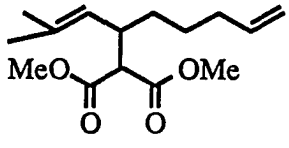
46

Obtained in 36 % yield from the reaction of 1-iodo-2-methylpropene, 1,5-hexadiene and acetylacetone using procedure B. TLC (15:1 hexanes/EtOAc) $R_f = 0.16$; ^1H NMR ($CDCl_3$) δ 1.18 (s, 6 H, 2 CH_3), 1.46 (m, 2 H, CH_2), 2.06 (m, 4 H, 2 CH_2C=), 2.19 (s, 6 H, 2 CH_3CO), 3.71 (s, 1 H, COCHCO), 5.00 (d, 1 H, J = 17.9 Hz, =CHH), 5.40 (m, 1 H, =C<u>H</u>CH_2), 5.63 (d, 1 H, J = 15.7 Hz, C<u>H</u>=CH), 5.78 (m, 1 H, C<u>H</u>=CH_2); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.0, 28.7, 32.0, 32.4, 33.2, 39.6, 114.5, 128.2, 136.6, 138.6, 204.1; IR (neat) 2968, 2928, 1724 (C=O), 1695 (C=O), 1421 (C=C), 1356, 1146, 980, 910 cm^{-1}; HRMS m/z 225.1542 (Calcd. 225.1542 for $C_{15}H_{24}O_2$).

Compounds **47a** and **47b**



47a



47b

Obtained in 44 % yield as an inseparable mixture (**47a**:**47b** = 82:18) from the reaction of 1-iodo-2-methylpropene, 1,5-hexadiene and dimethyl malonate using procedure

B. The isomer ratio was determined by gas chromatography. The following data were taken from a mixture of the isomers: TLC (15:1 hexanes/EtOAc) $R_f = 0.33$; ^{13}C NMR ($CDCl_3$) δ 25.6, 28.7, 31.9, 33.0, 38.3, 42.1, 51.9, 52.0, 56.8, 60.9, 114.4, 117.1, 127.9, 131.0, 136.8, 138.7, 168.3; IR (neat) 2955, 1759 (C=O), 1735 (C=O), 1435 (C=C), 1243, 1146, 1034, 913 cm^{-1}; HRMS m/z 268.1675 (Calcd. 268.1673 for $C_{15}H_{24}O_4$).

Isomer **47a**: ^1H NMR ($CDCl_3$) δ 1.22 (s, 6 H, 2 CH_3), 1.42 (m, 2 H, CH_2), 2.04 (m, 4 H, 2 CH_2C=), 3.37 (s, 1 H, COCHCO), 3.68 (s, 6 H, 2 CH_3O), 4.94 (d, 1 H, J = 15.7 Hz, =CHH), 5.00 (d, 1 H, J = 17.9 Hz, =CHH), 5.42 (dt, 1 H, J = 15.7, 6.8 Hz, HC=CHCH$_2$), 5.60 (d, 1 H, J = 15.7 Hz, CH=CH), 5.80 (m, 1 H, CH=CH$_2$);

Isomer **47b**: ^1H NMR ($CDCl_3$) same as that of compound **47a** or not seen, except δ 1.59 (s, 3 H, CH_3C=), 1.65 (s, 3 H, CH_3C=), 3.72 (s, 6 H, 2 CH_3O), 5.10 (d, 1 H, J = 9.6 Hz, =CHCH).

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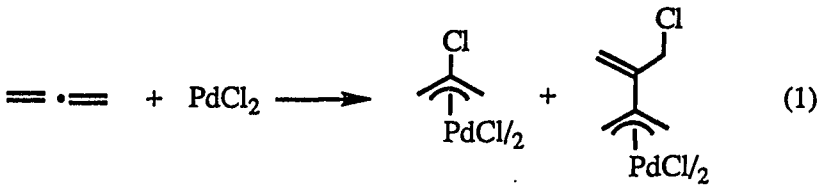
PAPER II. LARGE RING FORMATION VIA PALLADIUM(0)-CATALYZED ANNULATION OF 1,2-DIENES

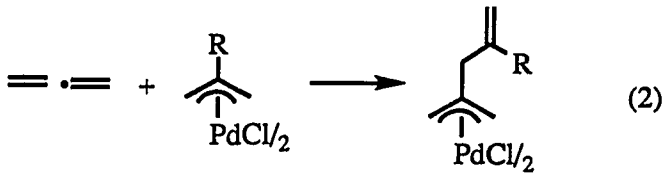
INTRODUCTION

The substitution of palladium in π-allylpalladium species by a nucleophile constitutes a highly versatile approach to bond formation. Allylation of nucleophiles using π-allylpalladium species derived from allenes was first reported in 1964 by two independent groups.[1,2] Lupin reported that the reaction of 1,2-propadiene with palladium chloride provided two dimeric complexes selectively and in good yields (eq. 1).[1] The ratio of these complexes depended on the nature of the solvent employed and the mode of addition.



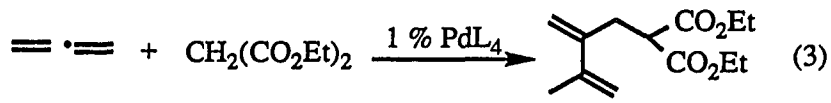
(1)

At the same time, Schultz also observed the insertion of allenes into π-allylpalladium complexes (eq. 2).[2]



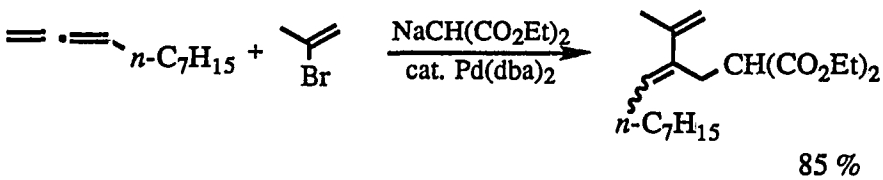
(2)

The pioneering work using catalytic amounts of palladium and allenes for organic synthesis was carried out by Coulson.[3] He was able to use a catalytic amount of palladium with a malonate ester as a nucleophile to trap the π-allylpalladium intermediate. Eventually, he obtained malonate derivatives, presumably via the palladium complex formed by the dimerization of allene (eq. 3).



(3)

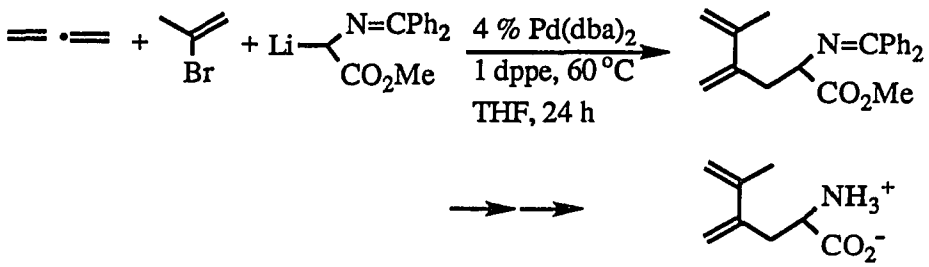
However, few synthetic efforts using this facile addition of organopalladium species to an allene were reported until 1984.[4] Using $Pd(dba)_2$ as a catalyst and dppe as a ligand, Gore and associates were able to carry out the carbopalladation of allenes with vinylic halides and sodium diethyl malonate (eq. 4).



(4)

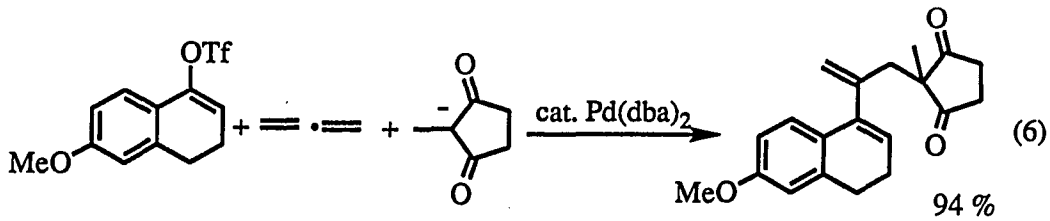
85 %

Starting from 1,2-propadiene, vinylic bromides and Schiff bases derived from methyl glycinate, Gore and associates successfully applied this palladium-catalyzed procedure to the synthesis of a new class of unsaturated amino acids with a 1,3-dienic functionality, which might have potentially modified biological properties (eq. 5).[5]



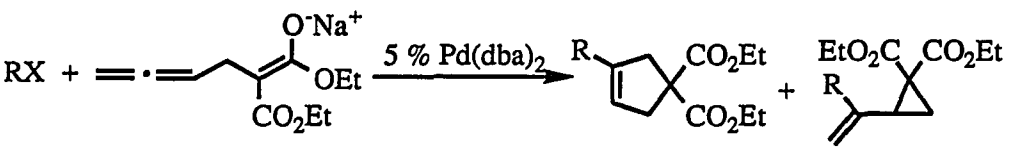
(5)

Using the same methodology, Gore and associates coupled 1,2-propadiene, the enol triflate derived from 6-methoxy-1-tetralone and 2-methyl-1,3-cyclopentanedione into the corresponding dienone (eq. 6).[6]



(6)

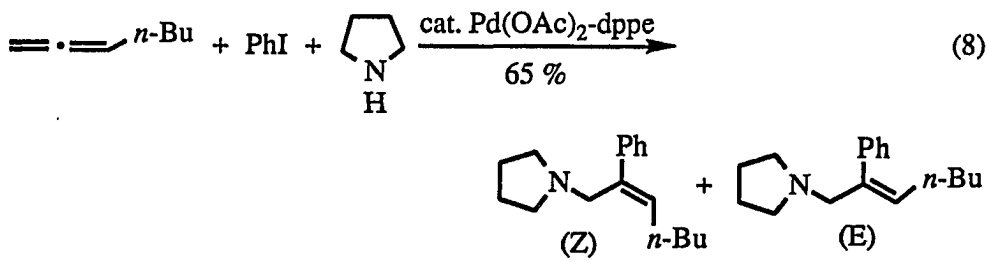
An intramolecular version of this reaction has been examined. Palladium-catalyzed addition of vinylic or aryl halides to the enolate of β-allenyl malonates produced the corresponding cyclopentenes and/or cyclopropanes (eq. 7).[7] Apparently, the more bulky the organic halide was, the more selective the reaction became. A change in solvent was also found to affect the regioselectivity of the reaction.



(7)

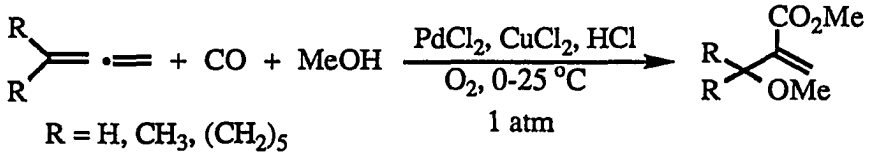
RX = vinyl bromide	80 %	0	:	100
iodobenzene	65 %	100	:	0
1-bromocyclohexene	50 %	96	:	4

In 1984, Tsuji and Shimizu carried out the palladium-catalyzed reaction of allenes with aryl or vinylic halides using secondary amines as nucleophiles.[8] They were able to obtain allylic amines in moderate to good yields by using $Pd(OAc)_2$ as the catalyst, dppe as the ligand, and MeCN as the solvent. They also found that the (Z)-isomers among the products were usually predominant (eq. 8).



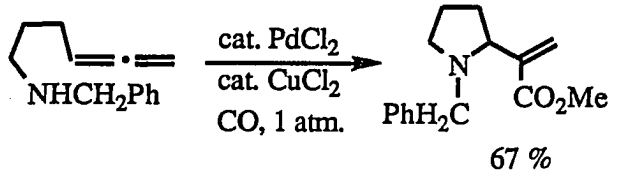
(8)

The use of allenes in organopalladium chemistry is not just limited to the synthesis of π-allylpalladium complexes. Allenes have also been used to prepare alkenylpalladium intermediates. This can be seen in the work of Alper et al.[9] They have reported the alkoxycarbonylation of allene and several substituted allenes, under mild reaction conditions, to afford the corresponding acrylates (eq. 9).



(9)

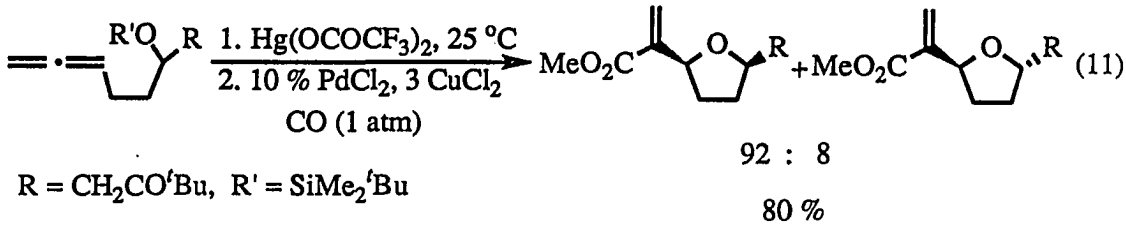
Gallagher and associates extended this procedure to intramolecular cyclizations using functionalized allenes as starting materials.[10] Thus, functionalized five- and six-membered N-containing heterocycles were synthesized using the same procedure (eq. 10).



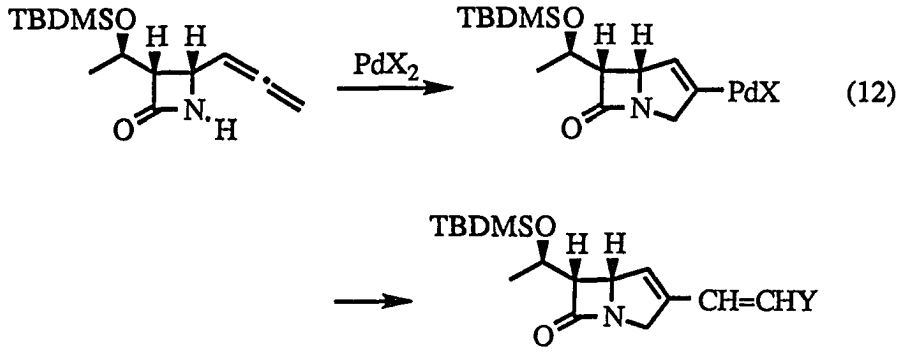
(10)

Using functionalized allenes, Walkup and Park synthesized 2-(2-tetrahydrofuranyl)acrylates *in situ* via alkoxycarbonylation of vinylpalladium intermediates obtained

from the nucleomercuration/transpalladation or direct nucleopalladation of allenic alcohols or their *t*-butyldimethylsilyl derivatives (eq. 11).[11]

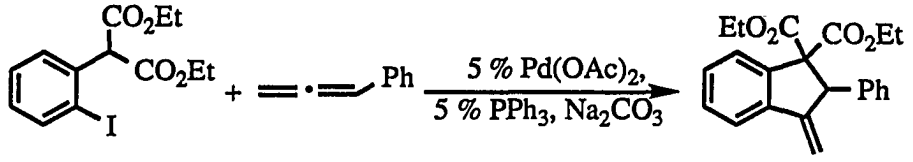


In a similar way, Liebeskind and Prasad carried out the transformation of 4-allenylazetidinones to Δ^1-carbapenems.[12] In these reactions, the palladium(II) catalyst induces nucleophilic closure of the azetidinone nitrogen on a pendant allene, and the resulting vinylic palladium intermediate reacts in a subsequent step with allylic halides or activated alkenes (CH_2=CHY, Y = COOEt, COMe, CHO, CN) to provide 2-functionalized carbapenems. The allylation requires only a catalytic amount of palladium, while the reaction with CH_2=CHY proceeds in the presence of a stoichiometric amount of palladium (eq. 12).



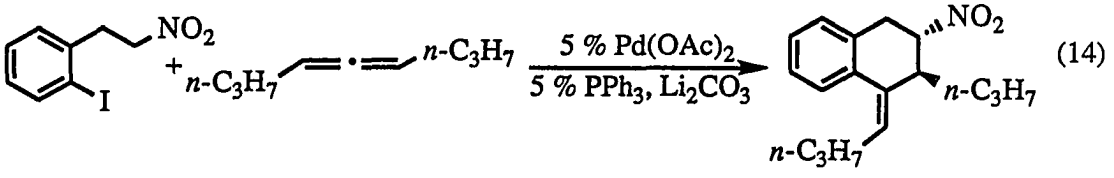
Larock and associates succeeded in the palladium-catalyzed hetero- and carboannulation of allenes using functionalized aryl iodides.[13] Thus, functionalized five-

and six-membered rings were obtained in good yields, as well as good regio- and stereo-selectivity (eqs. 13 and 14).



(13)

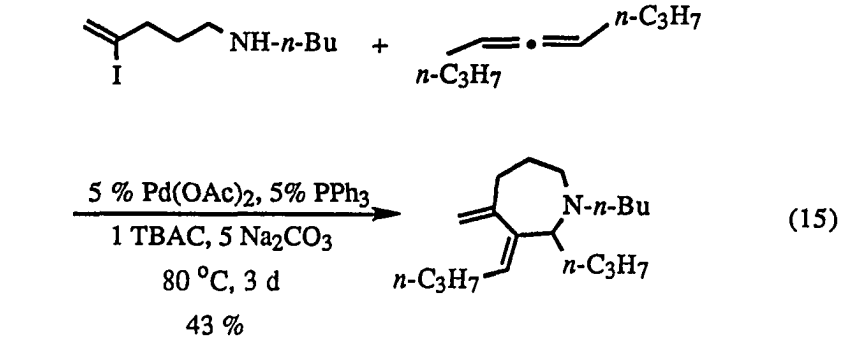
95 %



(14)

86 %

Recently, Yun He in the Larock group also studied the palladium-catalyzed hetero-annulation using vinylic halides and allenes to form five- and six-membered ring compounds and even one seven-membered ring amine (eq. 15).[14] He found that palladium acetate was the best catalyst and sodium carbonate was the best base. As a natural extension of this work, it was thought that if a seven-membered ring could be synthesized, eight- or even



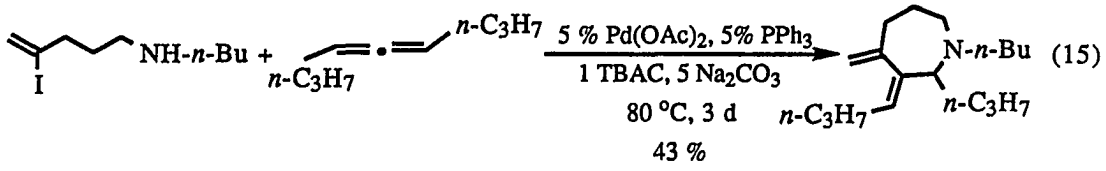
(15)

larger-membered rings could probably be synthesized in a similar manner. Therefore, a variety of vinylic or aryl halides and allenes were explored to examine the scope and limitations of this heteroannulation process.

RESULTS AND DISCUSSION

Formation of Cyclic Amines

Previous studies by Yun He in the Larock group showed that *E*-*N*-*n*-butyl-2-*n*-propyl-3-*n*-butylidene-4-methylidene cyclohexamine (**1**) can be synthesized by the reaction of *n*-butyl(4-iodo-4-pentenyl)amine with 4,5-nonadiene in the presence of a palladium catalyst and a base (eq. 15). The annulation conditions developed by Yun He



(15)

1

utilized 1 equiv. of vinylic iodoamine (0.25 mmol), 2 equiv. of allene (0.5 mmol), 5 mol % $Pd(dba)_2$ (0.0125 mmol), 5 mol % PPh_3 (0.0125 mmol), 1 equiv. of TBAC (0.25 mmol), 5 equiv. of Na_2CO_3 (1.25 mmol), and 1.0 mL of DMF at 80 °C for 3 days.

This reaction was selected as a model system and was further investigated using various reaction conditions in an attempt to increase the yield of this process. The results are tabulated in Table 1.

Our first effort was devoted to choosing the best catalyst for the reaction (entries 1-4). Our results indicated that $Pd(dba)_2$ was the best choice in terms of yield, although $Pd(OAc)_2$ gave a comparable yield.

A study of a variety of solvents and reaction times indicated that the best solvent and reaction time were either DMA/1 day or DMSO/3 days (entries 5-11).

Table 1. Palladium(0)-catalyzed reaction of *n*-butyl(4-iodo-4-pentenyl)amine with 4,5-nonadiene[a]

Entry	Pd Catalyst	Solvent	Time (d)	Base	Comments	% Isolated Yield of **1**
1	$Pd(OAc)_2$	DMA	3	5 Na_2CO_3	-	41
2	$PdCl_2$	DMA	3	5 Na_2CO_3	-	18
3	$Pd(dba)_2$	DMA	3	5 Na_2CO_3	-	49
4	$Pd(PPh_3)_4$	DMA	3	5 Na_2CO_3	-	32
5	$Pd(dba)_2$	DMA	0.75	5 Na_2CO_3	-	47
6	$Pd(dba)_2$	DMA	1	5 Na_2CO_3	-	61
7	$Pd(dba)_2$	DMA	2	5 Na_2CO_3	-	46
8	$Pd(dba)_2$	DMA	3	5 Na_2CO_3	-	42
9	$Pd(dba)_2$	DMSO	3	5 Na_2CO_3	-	57
10	$Pd(dba)_2$	DMSO	1	5 Na_2CO_3	-	31
11	$Pd(dba)_2$	DMF	1	5 Na_2CO_3	-	35
12	$Pd(dba)_2$	DMA	1	5 K_2CO_3	-	34
13	$Pd(dba)_2$	DMA	1	5 $NaHCO_3$	-	43
14	$Pd(dba)_2$	DMA	1	5 Li_2CO_3	-	0
15	$Pd(dba)_2$	DMA	1	5 NaOAc	-	42
16	$Pd(dba)_2$	DMA	1	5 KOAc	-	35
17	$Pd(dba)_2$	DMA	1	2 Na_2CO_3	-	37
18	$Pd(dba)_2$	DMA	1	5 Na_2CO_3	No PPh_3	35
19	$Pd(dba)_2$	DMA	1	5 Na_2CO_3	110 °C	55
20	$Pd(dba)_2$	DMA	1	5 Na_2CO_3	LiCl[b]	48
21	$Pd(dba)_2$	DMA	2	5 Na_2CO_3	LiCl	48

[a] All reactions were carried out using 1 equiv. of vinylic iodoamine (0.25 mmol), 2 equiv. of allene (0.5 mmol), 5 mol % Pd catalyst (0.0125 mmol), 5 mol % PPh_3 (0.0125 mmol), 1 equiv. of TBAC (0.25 mmol), 2 or 5 equivs. of base (0.5 or 1.25 mmol), and 1.0 mL of solvent at 80 °C; [b] TBAC was not used.

The reaction yield was also base dependent (entries 12-17). Five equiv. of sodium carbonate provided 61 % of the desired product while lithium carbonate in the same

stoichiometry afforded none of the desired product, and $NaHCO_3$, K_2CO_3, NaOAc and KOAc gave results in between these two bases.

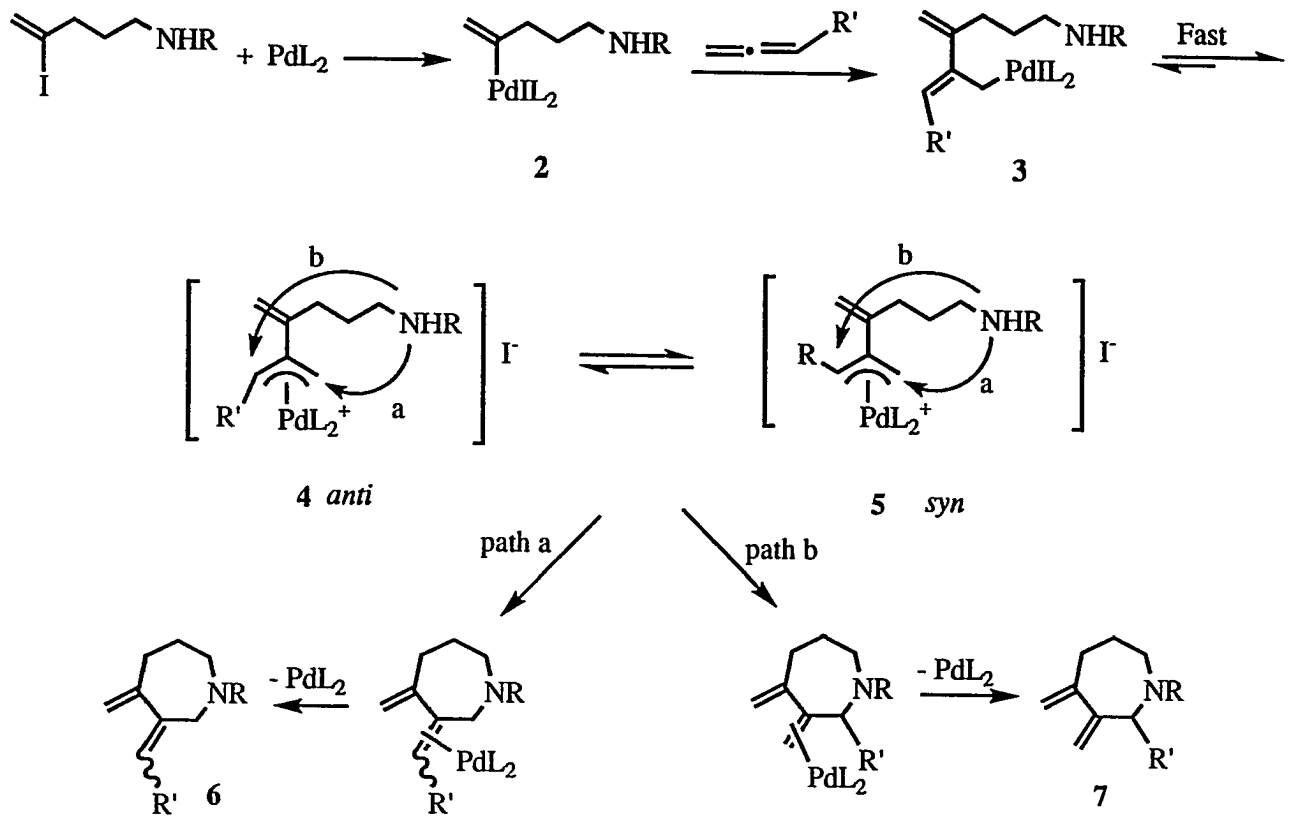
In the absence of 5 mol % PPh_3, the reaction yield was sharply reduced (entry 18). PPh_3 may act as a ligand and coordinate with palladium which may improve the dissociation of the palladium(0) from the newly formed olefin after formation of the product. Therefore, more palladium(0) species is available for the initial oxidative addition step.

Chloride ion is also necessary in the reaction. The chloride anions may exchange with iodide anions to form an organopalladium chloride. This creates a more electropositive organopalladium species, which promotes the insertion of the allene into the organopalladium species. Two different sources of chloride ion were used in the model reaction. Tetra-*n*-butylammonium chloride (TBAC) has been used extensively in palladium-catalyzed reactions with good results, but it is an expensive and moisture sensitive compound. Therefore, an effort has been made to replace it with a suitable reagent. LiCl was tested, (entries 20 and 21); however, TBAC continued to provide better results than LiCl.

Based on the model system, the best procedure for this annulation reaction is as follows: 1 equiv. of vinylic iodoamine (0.25 mmol), 2 equiv. of allene (0.5 mmol), 5 mol % $Pd(dba)_2$ (0.0125 mmol), 5 mol % PPh_3 (0.0125 mmol), 1 equiv. of *n*-Bu_4NCl (0.25 mmol), 5 equiv. of Na_2CO_3 (1.25 mmol), and 1.0 mL of DMA at 80 °C for 1 day.

A possible mechanism for the above heterocyclization process is depicted in Scheme 1. The first step of the reaction is oxidative addition of the vinylic halide to palladium(0) to generate an intermediate vinylpalladium species (**2**). This intermediate then adds to the allene (placing the vinylic group on the center carbon of the allene) generating a σ-allylpalladium intermediate (**3**) which collapses to a π-allylpalladium complex. The *anti* conformation (**4**) is more stable than the *syn* conformation (**5**) due to steric effects.

Scheme 1

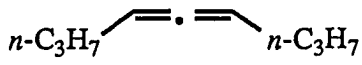
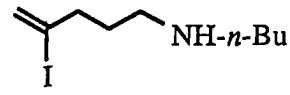
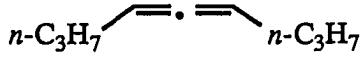
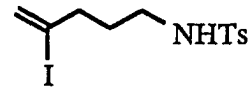
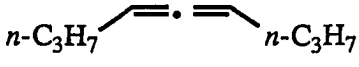
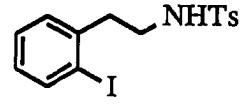

NHR
I
+ PdL2
PdIIL2
R'
2
3
Fast
b
a
R'
PdL2+
I-
4 anti
5 syn
path a
path b
- PdL2
6
7

Intramolecular nucleophilic displacement of palladium in the unsymmetrical π-allylpalladium species can generate two regioisomers (**6** and **7**).

Once the reaction conditions were thoroughly investigated, a variety of organic halides and allenes were employed in a study to determine the scope and limitations of these palladium-catalyzed annulation reactions. The results of this investigation into the formation of seven-membered ring compounds are summarized in Table 2.

The reactions of an internal allene, 4,5-nonadiene, with *n*-butyl(4-iodo-4-pentenyl)-amine, *n*-butyl(Z-4-iodo-3-butenyl)amine and N-tosyl-2-(2-iodophenyl)ethylamine produced a single isomer in good yields (entries 1, 3 and 4). The stereoselectivity of the reactions can be explained by intermediate **5** in the proposed mechanism (Scheme 1). In order to minimize steric hindrance in the intermediate, the alkyl groups should stay away from each other, thus forming a *syn*-π-allylpalladium species which eventually leads to the products observed. The stereochemistry of compound **10** was assigned based on a 2-D NOESY experiment. The aryl proton and vinylic proton exhibited no NOE interaction, while the exo-vinyl proton interacted strongly with the CH proton between the vinylic carbon and nitrogen. The ^{1}H NMR and NOE spectra of compound **10** are presented in Figure 1. A similar NOE experiment was also conducted with compound **19b**. The same result was obtained with the interaction between the exo-vinyl proton and with the CH proton between vinylic carbon and nitrogen of compound **19b**. In comparing the ^{1}H NMR spectra of compounds **19a** and **19b**, one notices that the chemical shift of the exo-vinyl proton in the nonylidene group in the *syn* product **19a** is further downfield (5.71 ppm) than the corresponding exo-vinyl proton of the *anti* product **19b** (5.36 ppm). With this in mind, the *syn* and *anti* isomers encountered during the course of the research were determined by comparison of the corresponding vinylic hydrogen chemical shifts with those observed in compounds **10**, **19a** and **19b**.

Table 2. Palladium-catalyzed seven-membered ring formation

Entry	Allene	Organic Iodide
1		
2		
3		
4[a]		

[a] 100 °C, 3 days

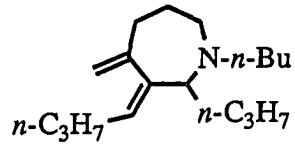
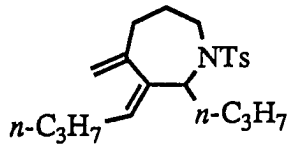
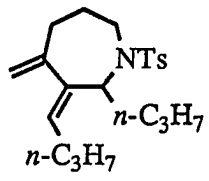
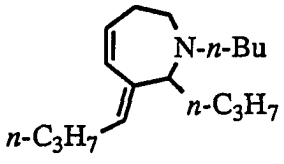
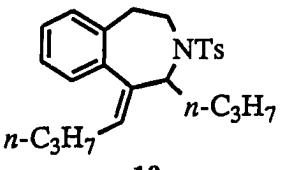
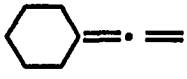
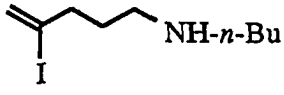
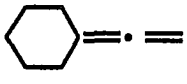
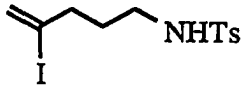
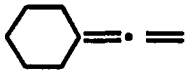
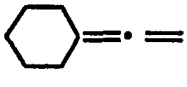
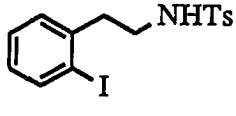
Product(s)	% Isolated Yield (Ratio)
 **1**	61
 **8a** +  **8b**	25 (60:40)
 **9**	81
 **10**	94

Table 2. (Continued)

Entry	Allene	Organic Iodide
5		
6		
7		
8 9[b] 10[c] 11[a]		

[b] 80 °C, 3 days; [c] without PPh_3, 80 °C, 3 days.

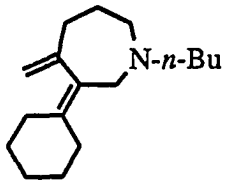
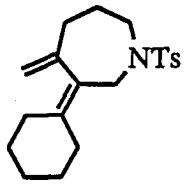
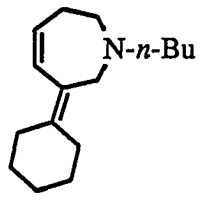
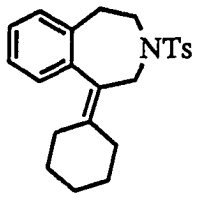
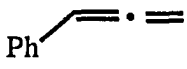
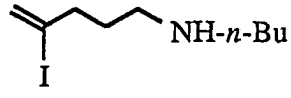
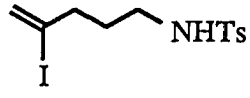
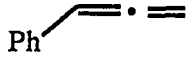
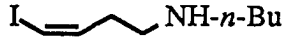
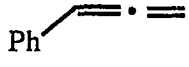
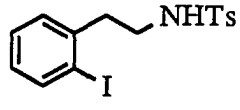
Product(s)	% Isolated Yield (Ratio)
 **11**	43
 **12**	71
 **13**	23
 **14**	31 51 30 95

Table 2. (Continued)

Entry	Allene	Organic Iodide
12		
13		
14		
15[a]		

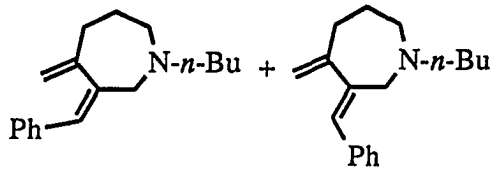
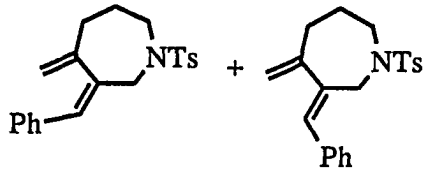
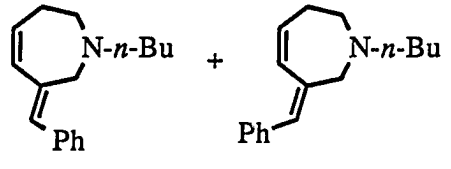
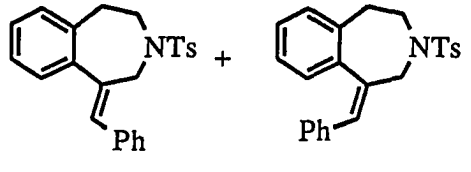
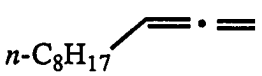
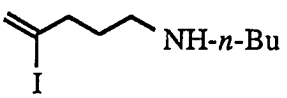
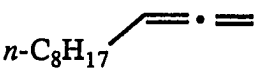
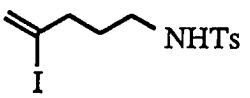
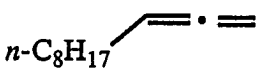
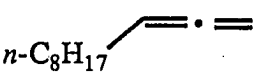
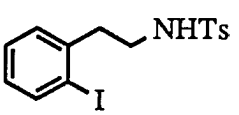
Product(s)	% Isolated Yield (Ratio)
 **15a** **15b**	80 (55:45)
 **16a** **16b**	91 (60:40)
 **17a** **17b**	83 (64:36)
 **18a** **18b**	54 (79:21)

Table 2. (Continued)

Entry	Allene	Organic Iodide
16		
17		
18		
19[a]		

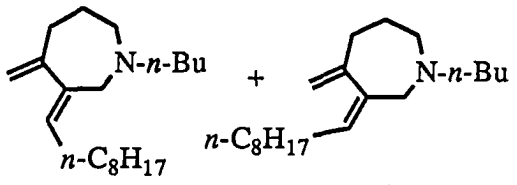
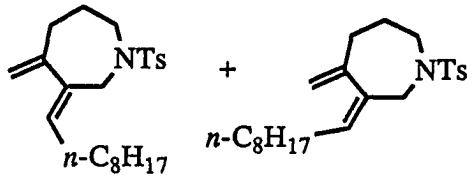
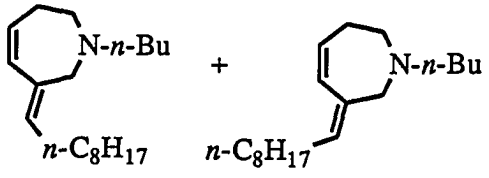
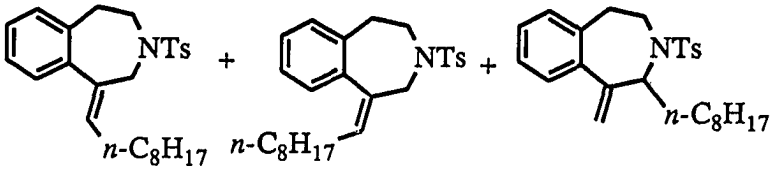
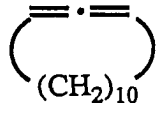
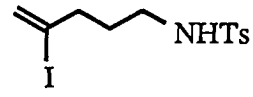
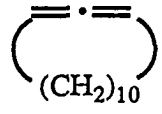
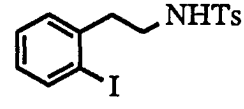
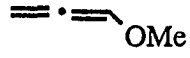
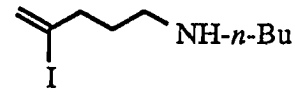
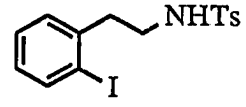
Product(s)	% Isolated Yield (Ratio)
 **19a** **19b**	80 (55:45)
 **20a** **20b**	51 (61:39)
 **21a** **21b**	85 (70:30)
 **22a** **22b** **22c**	86 (72:20:8)

Table 2. (Continued)

Entry	Allene	Organic Iodide
20		
21[a]		
22		
23[a] 24[b]		

[b] Reaction was run in the absence of methoxyallene.

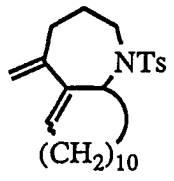
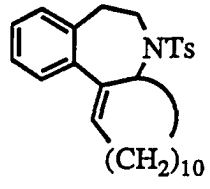
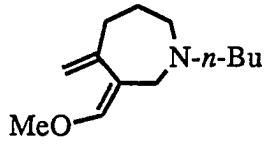
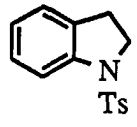
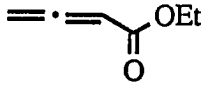
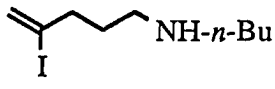
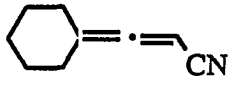
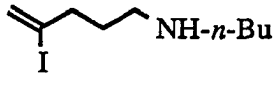
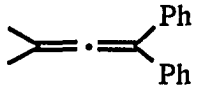
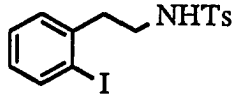
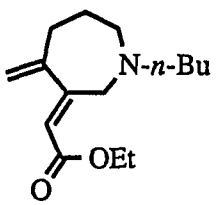
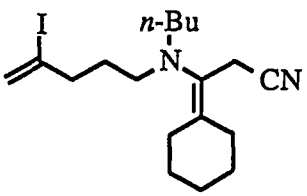
Product(s)	% Isolated Yield (Ratio)
	0
	0
	0
 **23**	65 97

Table 2. (Continued)

Entry	Allene	Organic Iodide
25		
26		
27		

Product(s)	% Isolated Yield (Ratio)
	0
	50
Heck Products	30

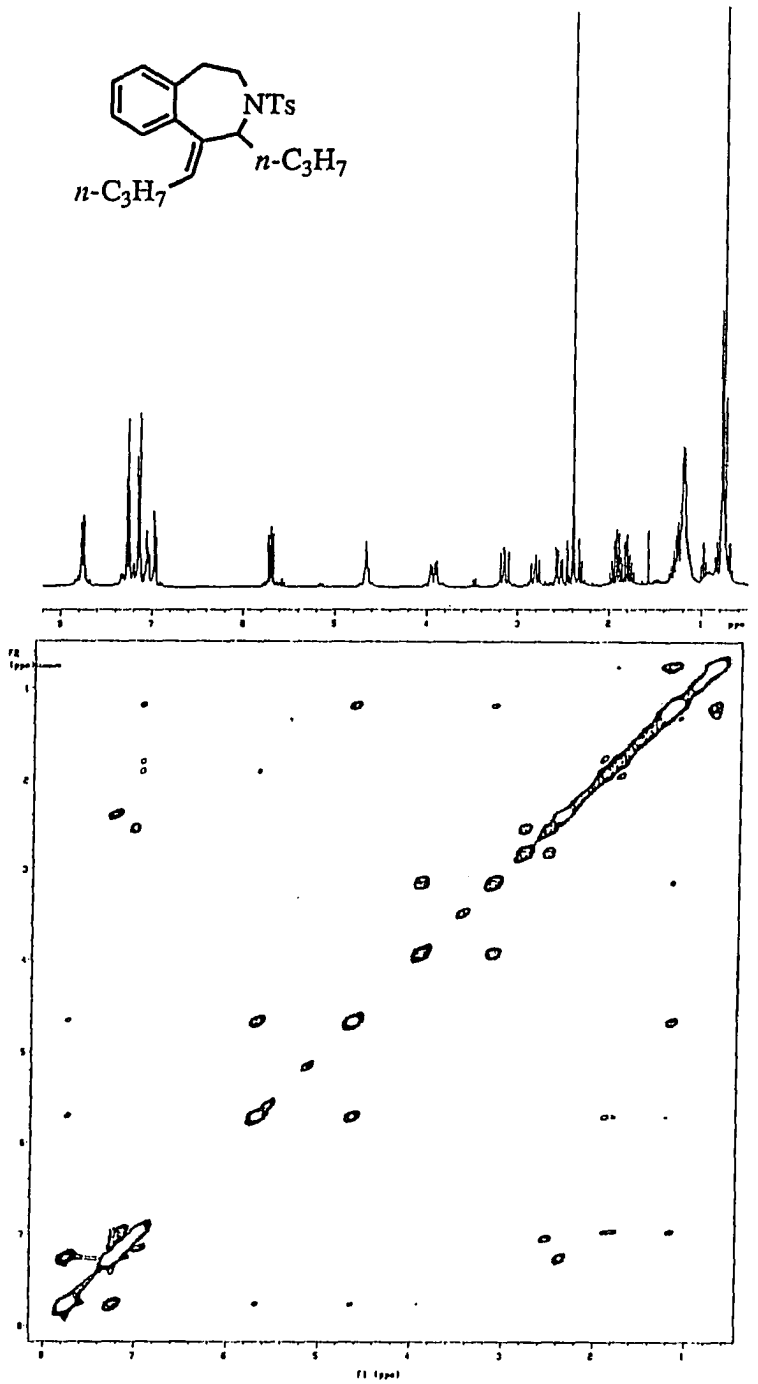


Figure 1. ^{1}H NMR and NOESY Spectra of Compound **10**

The use of *N*-tosyl(4-iodo-4-pentenyl)amine and 4,5-nonadiene gave the desired product as a mixture of stereoisomers in low yield (entry 2). The isomeric ratio of compounds **8a** and **8b** was determined by integration of the exo-vinyl protons in the ^1H NMR spectrum of the mixture. The stereochemistry of compounds **1, 8** and **9** was determined by comparison of the exocyclic vinylic hydrogen chemical shifts with those observed in compounds **10** and **19b.**

The reactions of vinylidene cyclohexane with organic halides always provided one single isomer (entries 5-11). The nitrogen nucleophiles attacked the less hindered end of the π-allylpalladium intermediates for steric reasons. Higher yields were obtained when aryl halides were used in the cyclization process, although a higher reaction temperature was required (entries 8-11).

Terminal allenes, such as phenyl allene and 1,2-undecadiene, produced a mixture of isomers in good yields (entries 12-19). Moderate stereoselectivity was observed, usually favoring the *anti* conformation of the π-allylpalladium intermediate. Again, the stereochemistry of products **15** to **22** was determined by comparison of the vinylic hydrogen chemical shifts with those observed in compounds **10** and **19b.**

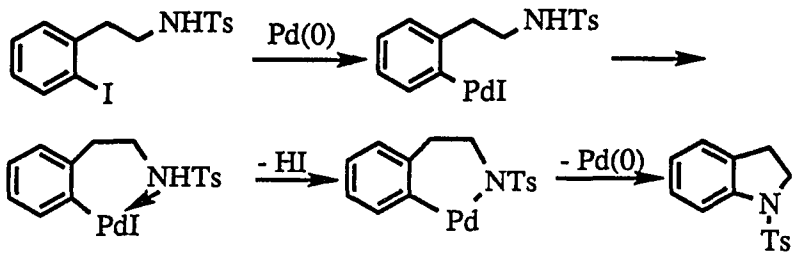
The reaction of the aryl halide with 1,2-undecadiene produced three isomers (entry 19). A small amount of annulation product arising from nitrogen attack at the more hindered end of the π-allylpalladium species was observed.

The reaction of a vinylic or aryl halide with 1,2-cyclotridecadiene produced none of the desired product (entries 20 and 21).

The use of an electron-rich allene, methoxy allene, in the cyclization was studied (entries 22-24). None of the desired product was observed. An intramolecular cyclization product (**23**) was isolated in high yield from the reaction involving an aryl halide. This is the first example of such a palladium-catalyzed nucleophilic aromatic substitution process

involving a heteroatom-containing nucleophile. A possible mechanistic explanation for this unexpected intramolecular cyclization is depicted in Scheme 3. After the oxidative addition of the aryl iodide onto the palladium(0) to generate a σ-arylpalladium intermediate, the nitrogen of the same molecule coordinates with palladium by donating a pair of electrons to form a chelated species. Halide displacement and reductive elimination of palladium(0) generate the observed product.

Scheme 3



The difficulty observed in the cyclization of the electron-rich allene led us to work with an electron-deficient allene, which might react with organo iodoamines. Therefore, the reaction of ethyl 2,3-butadienoate with *n*-butyl(4-iodo-4-pentenyl)amine was examined under the standard conditions (entry 25), with no evidence of the formation of the desired products. According to the literature,[15] this ester allene is not stable under basic conditions. It may be isomerized to an internal acetylene under our reaction conditions. Therefore, another electron-deficient allene, cyanovinylidene cyclohexane, was synthesized and used in the annulation process (entry 26). None of the desired product was isolated. Instead, a product of nucleophilic addition to the allene was obtained in 50 % yield.

The reaction of the sterically hindered allene, 1,1-diphenyl-3-methyl-1,2-butadiene, with the aryl halide produced none of the desired products (entry 27). Heck-type products were isolated.

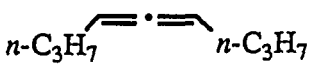
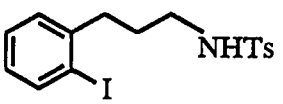
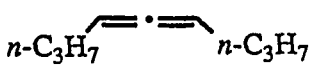
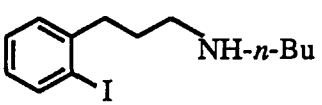
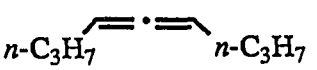
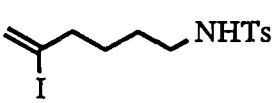
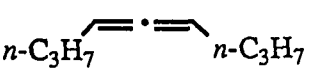
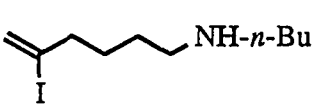
In summary, it is observed that *E* and *Z* isomers are obtained in the formation of seven-membered ring nitrogen-containing compounds derived from the *syn* and *anti* π-allylpalladium intermediates. The *Z*-isomers are favored apparently due to formation of the more stable *anti* π-allylpalladium intermediate. Aryl iodides usually produce higher yields than the vinylic iodides, although higher reaction temperatures and longer reaction times are required. The analogous tosyl derivatives are more reactive than the *n*-butyl derivatives toward the π-allylpalladium species, thus higher yields of the desired products were obtained.

The formation of eight-membered heterocyclic ring compounds was also studied and the results are tabulated in Table 3. The previous best reaction conditions were adopted. A lower reaction temperature and shorter reaction time was used with the vinylic halides (80 °C, 1 day), while a higher reaction temperature and longer reaction time was employed with the aryl halides (100 °C, 3 days). The stereochemistry of the newly formed double bond was assigned by comparison of the chemical shifts of the vinylic hydrogen to the corresponding seven-membered ring compounds.

The internal allene, 4,5-nonadiene, reacted only with *N*-tosyl-3-(2-iodophenyl)-propylamine to produce a good yield of a stereoisomeric mixture (entry 1). The other organic iodides examined gave none of the desired products (entries 2-4).

The reaction of *N*-tosyl-3-(2-iodophenyl)propylamine with vinylidene cyclohexane afforded a single product in good yield (entry 5). The nitrogen nucleophile attacks the less hindered end of the π-allylpalladium intermediate for steric reasons. The N-alkyl analogue, as well as the two vinylic halides, produced none of the desired products (entries 6-8). Instead, Heck-type product was isolated in the use of *N*-tosyl-5-iodohexenylamine (entry 7).

Table 3. Palladium(0)-catalyzed formation of eight-membered rings

Entry	Allene	Organic Halide
1		
2		
3		
4		

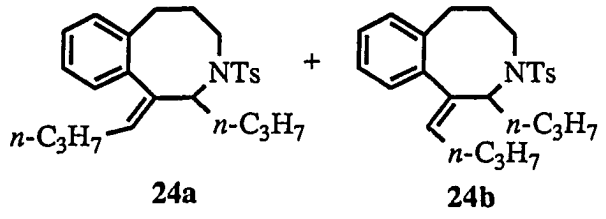
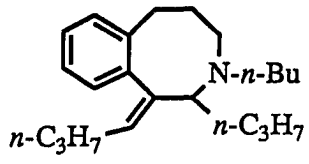
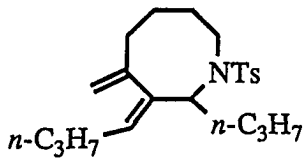
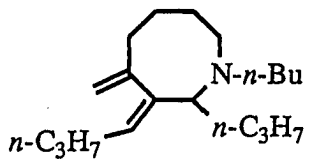
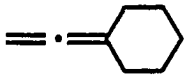
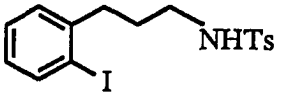
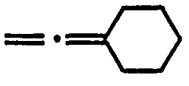
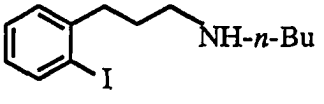
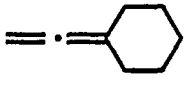
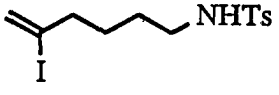
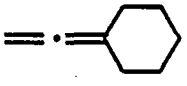
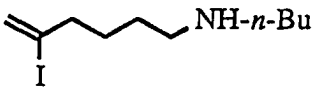
Product(s)	% Isolated Yield (Ratio)
 **24a** + **24b**	68 (84:16)
	0
	0
	0

Table 3. (Continued)

Entry	Allene	Organic Halide
5		
6		
7		
8		

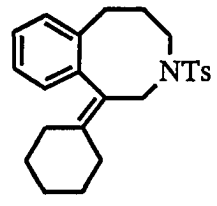
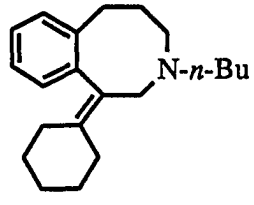
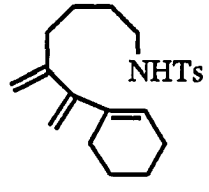
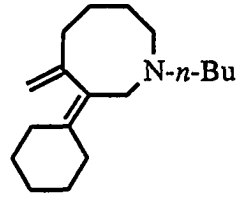
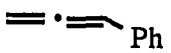
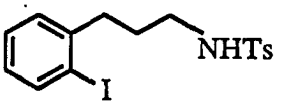
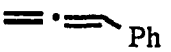
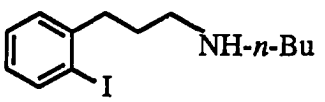
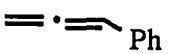
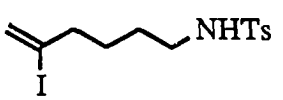
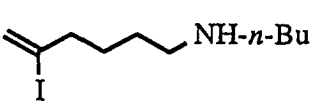
Product(s)	% Isolated Yield (Ratio)
 **25**	62
	0
	21
	0

Table 3. (Continued)

Entry	Allene	Organic Halide
9		
10		
11		
12		

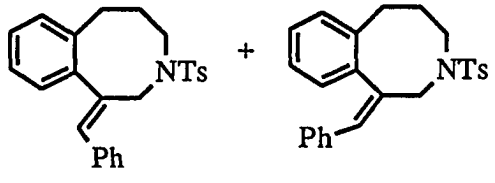
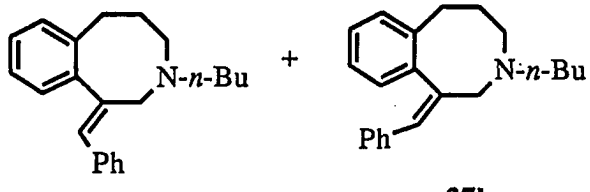
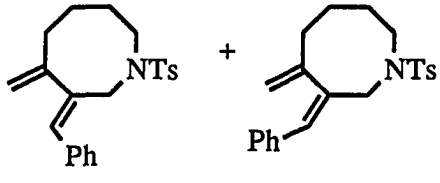
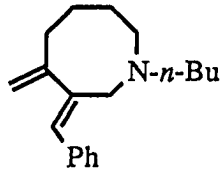
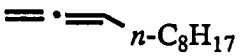
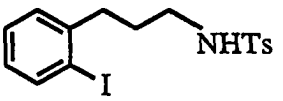
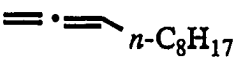
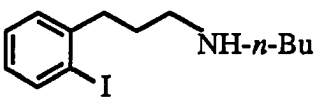
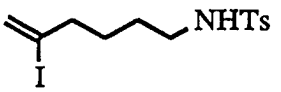
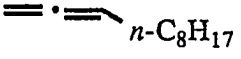
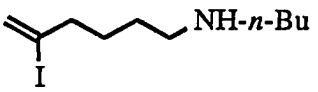
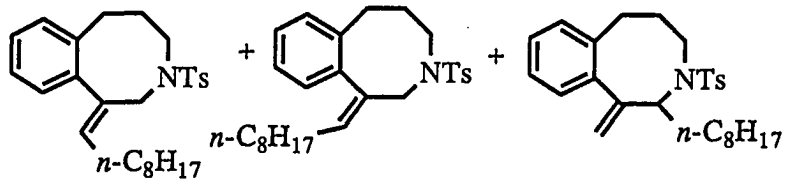
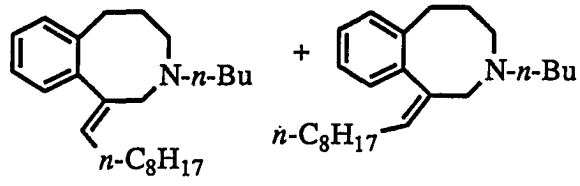
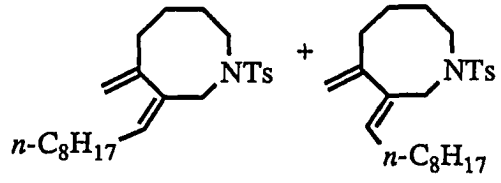
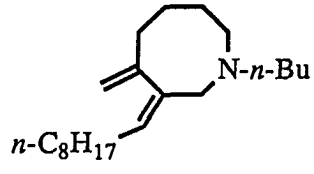
Product(s)	% Isolated Yield (Ratio)
 **26a** **26b**	94 (91:9)
 **27a** **27b**	98 (78:22)
 **28a** **28b**	16 (74:26)
	0

Table 3. (Continued)

Entry	Allene	Organic Halide
13		
14		
15		
16		

Product(s)	% Isolated Yield (Ratio)
 **29a** **29b** **29c**	88 (39:44:17)
 **30a** **30b**	84 (78:22)
	0
	0

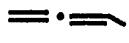
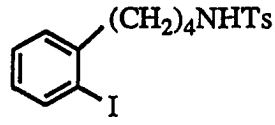
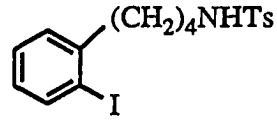
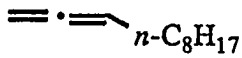
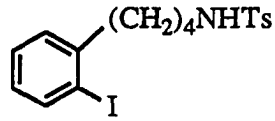
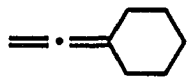
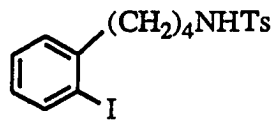
The reaction of phenyl allene with the aryl iodides gave excellent yields of products with high stereoselectivities (entries 9 and 10). A higher isomeric ratio was observed with the N-tosyl derivative. Use of the vinylic iodide tosyl derivative produced only 16 % of the desired products and the corresponding *n*-butylamine gave no cyclized product (entries 11 and 12).

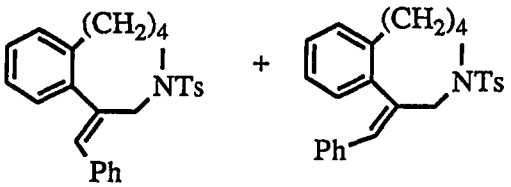
The reactions of the sterically unhindered terminal allene, 1,2-undecadiene, with the aryl iodides provided high yields of isomeric products (entries 13 and 14). A regioisomeric product (**29c**) was also observed in the reaction with *N*-tosyl-3-(2-iodophenyl)propylamine. None of the desired products were obtained in the reactions with vinylic halides (entries 15 and 16).

In summary, it was observed that more than one isomer was obtained in the formation of eight-membered ring nitrogen-containing compounds apparently due to the formation of both *syn* and *anti* π-allylpalladium intermediates. The use of aryl iodides and allenes produced eight-membered heterocyclic ring compounds in much higher yields than vinylic iodides. The analogous N-tosyl amine derivatives were more reactive toward the π-allylpalladium species and higher yields of products were obtained. Compared to the corresponding seven-membered heterocylic rings, eight-membered rings are more difficult to form.

Nine-membered ring nitrogen-containing compounds were also synthesized using the same methodology. The results are summarized in Table 4. The reaction of phenyl allene and N-tosyl-4-(2-iodophenyl)butylamine produced a mixture of isomers in good yield (entry 1). Again, the stereochemistry of the newly formed double bond was assigned by the comparison of the chemical shifts of the vinylic hydrogens to those of the corresponding seven-membered ring compounds.

Table 4. Palladium(0)-catalyzed formation of nine-membered rings

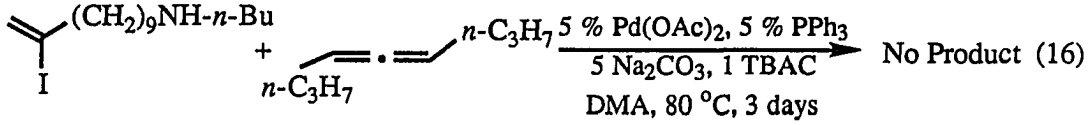
Entry	Allene	Organic Iodide
1		
2		
3		
4		

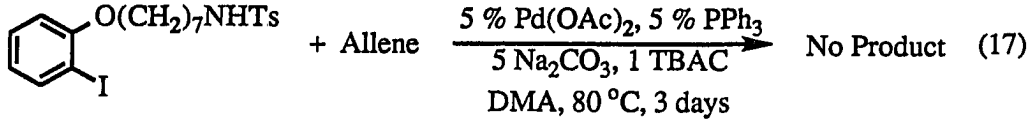
Product(s)	% Isolated Yield (Ratio)
 **31a** + **31b**	83 (86:14)
Heck Products	22
Heck Products	50
Heck Products	85

The use of three other allenes and N-tosyl-4-(2-iodophenyl)butylamine gave exclusively Heck-type products (entries 2-4). In general, formation of large-ring compounds required longer reaction times. Apparently, β-hydride elimination takes place before the nitrogen nucleophile has a chance to attack the π-allylpalladium center, which leads to the formation of Heck-type products. In the case of the π-allylpalladium intermediates derived from phenyl allene, there are no β-hydrogens present. Thus, it is impossible for β-hydride elimination to occur, and the reaction proceeded smoothly forming the desired products in good yield.

Formation of nine-membered ring compounds was much more difficult than formation of eight- or seven-membered ring compounds, because the β-hydride elimination proceeds in preference to the cyclization.

Formation of thirteen-membered nitrogen-containing ring compounds has also been studied. The reaction of *n*-butyl(10-iodo-10-undecenyl)amine with 4,5-nonadiene was carried out under the standard reaction conditions (eq. 16). None of the desired product was isolated. Other allenes, such as 4,5-nonadiene, phenyl allene, vinylidene cyclohexane, and



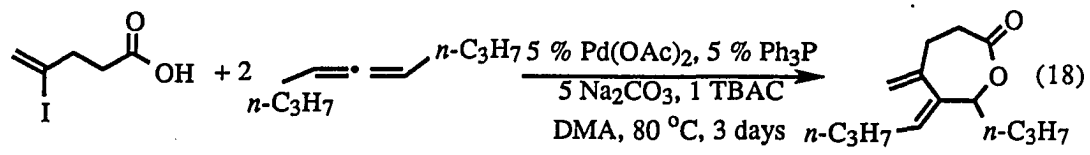


1,2-undecadiene, were also used in the reaction. Again, none of the desired product was observed. Similar studies were conducted with aryl analogues and 1,2-undecadiene, vinylidene cyclohexane, phenyl allene and 4,5-nonadiene (eq. 17). The results were not encouraging either. None of the desired product was detected.

From the studies conducted above, we can conclude that the ease of formation of the nitrogen-containing heterocyclic compounds with this methodology is seven > eight > nine > thirteen. Thirteen-membered ring compounds could not be synthesized with our methodology.

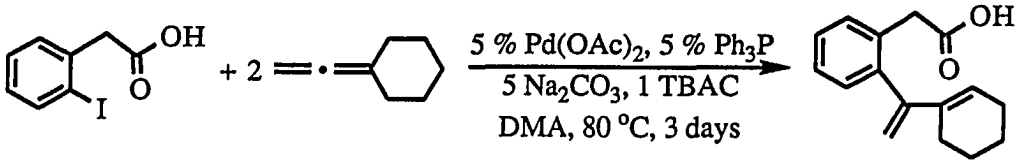
Attempted Formation of Cyclic Lactones

Since oxygen heterocycles commonly exist in natural products, the formation of oxygen heterocycles using palladium-catalyzed annulation would be very attractive. With this in mind, the annulation of organic acids and allenes by our methodology have been studied. The model reaction chosen was that of 4-iodo-4-pentenoic acid and 4,5-nonadiene (eq. 18). The reactions were run with the standard reaction conditions developed earlier and with varying reaction temperatures, reaction times and bases as well. There was no evidence



(18)

to indicate the formation of the desired product. Similar studies were carried out with 2-iodophenylacetic acid and vinylidene cyclohexane (eq. 19). Again, none of the desired product was formed. Instead, a high yield of Heck-type product (74 %) was isolated.



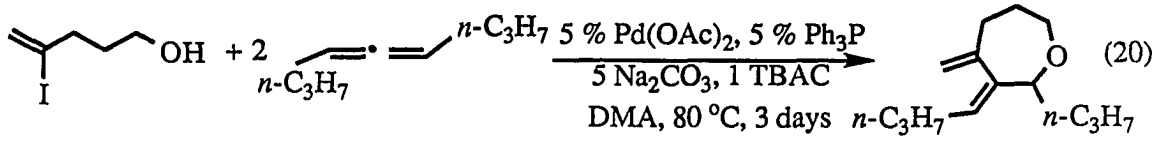
(19)

74 %

The cross-coupling between the σ-palladium species and the allene occurred smoothly, but the oxygen nucleophile failed to cyclize to form the desired product.

Attempted Formation of Cyclic Ethers

The annulation of iodo alcohols and allenes has been studied. The model reaction was chosen to be the reaction of 4-iodo-4-penten-1-ol and 4,5-nonadiene under the standard

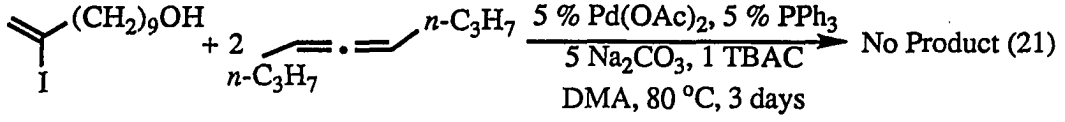


(20)

reaction conditions used earlier (eq. 20). A large portion of the starting vinylic halide remained unreacted, and none of the desired product was detected. Various reaction conditions were then studied with the results tabulated in Table 5.

The use of sodium or lithium carbonate and sodium or lithium acetate gave most of the starting material back (entries 1-7, 9 and 10). When potassium acetate was used as the base, the starting material was completely consumed (entries 8, 11-14). However, the desired product was still not observed. Again, base, solvent and reaction temperature were varied, but the desired product was not observed.

Other alcohols were also used in analogous reactions under the standard conditions. None of the desired products were observed (eqs. 21 and 22).



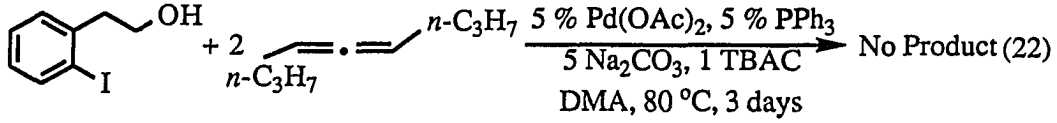


Table 5. Attempted optimization of reaction conditions for the formation of cyclic ethers[a]

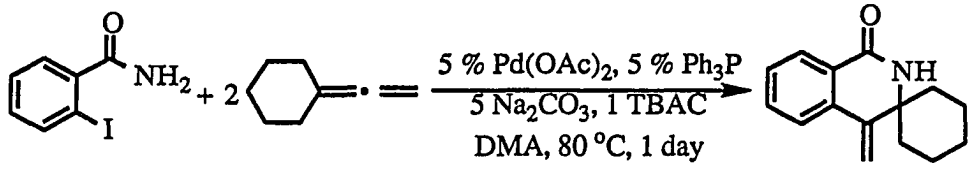
Entry	Base	Time (d)	Temp. (°C)	Solvent	% Yield
1	Li_2CO_3	2	80	DMA	0 (SM)
2	Li_2CO_3	2	100	DMA	0 (SM)
3	Li_2CO_3	2	130	DMA	0 (SM)
4[b]	Li_2CO_3	2	100	DMA	0 (SM)
5[c]	Li_2CO_3	2	100	DMA	0 (SM)
6	Na_2CO_3	2	100	DMA	0 (SM)
7	K_2CO_3	2	100	DMA	0 (SM)
8	KOAc	1	100	DMA	0
9	LiOAc	2	100	DMA	0 (SM)
10	NaOAc	2	100	DMA	0 (SM)
11	KOAc	2	100	DMSO	0
12	KOAc	1	100	DMF	0
13	KOAc	1	100	CH_3CN	0
14	KOAc	1	100	THF	0

[a] All reactions were carried out using 1 equiv. of vinylic iodo alcohol (0.25 mmol), 2 equiv. of allene (0.5 mmol), 5 mol % $Pd(OAc)_2$ (0.0125 mmol), 5 mol % PPh_3 (0.0125 mmol), 1 equiv. of TBAC (0.25 mmol), 5 equiv. of base (1.25 mmol), and 1.0 mL of DMA; [b] No PPh_3 was used; [c] 1 equiv. of LiCl was used in the absence of TBAC.

Formation of Cyclic Lactams

Since Yun He of the Larock group synthesized cyclic lactams from vinylic iodo amides in good yield,[14] the analogous reaction of 2-iodobenzamide with allenes has been examined. The model reaction was chosen to be that of 2-iodobenzamide and vinylidene

cyclohexane using the standard conditions developed earlier, which are 1 equiv. of 2-iodobenzamide (0.25 mmol), 2 equiv. of allene (0.5 mmol), 5 mol % $Pd(dba)_2$ (0.0125 mmol), 5 mol % PPh_3 (0.0125 mmol), 1 equiv. of TBAC (0.25 mmol), 5 equiv. of Na_2CO_3 (1.25 mmol) and 1.0 mL of DMA at 80 °C for 1 day (eq. 23). This model system was extensively investigated using these reaction conditions, plus many others. The results of these studies are tabulated in Table 6.



(23)

33

Temperature effects on the reaction have been evaluated. These studies indicated that higher reaction temperatures afford the product in better yield (entries 1-4). DMSO or DMA as the solvent produced a better yield than DMF (entries 2, 5 and 6). Base effects were also studied for the model reaction. Sodium carbonate was a better choice than sodium acetate or potassium carbonate (entries 4, 7 and 8). It was observed that the product decomposed during the course of the reaction. Therefore, efforts have been devoted to increasing the reaction rate in order to shorten the reaction time. From previous experience, the ligand, PPh_3, sometimes retards the reaction rate, therefore a shorter reaction time may be achieved in the absence of PPh_3. Experimental results showed that a higher yield of product was obtained at higher temperatures in the absence of PPh_3 (entries 9-11). The yield was optimized when the reaction was run for approximately 18 hours at 100 °C. Therefore, the best reaction conditions are 1 equiv. of 2-iodobenzamide, 2 equiv. of allene, 5 mol %

Table 6. Optimization of reaction conditions for the formation of lactam 33[a]

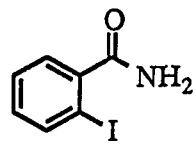
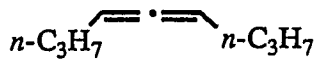
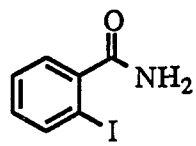
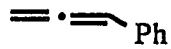
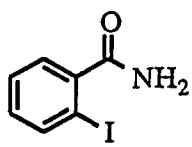
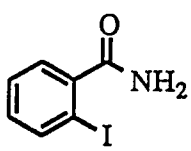
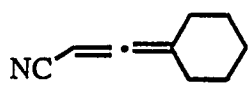
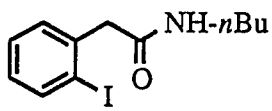
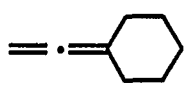
Entry	Temp. (°C)	Time	Solvent	Base	Ligand	Yield (%)
1	RT	1 d	DMF	Na_2CO_3	PPh_3	0
2	80	1 d	DMF	Na_2CO_3	PPh_3	24
3	90	12 h	DMA	Na_2CO_3	PPh_3	31
4	100	20 h	DMA	Na_2CO_3	PPh_3	54
5	80	1 d	DMA	Na_2CO_3	PPh_3	28
6	100	1 d	DMSO	Na_2CO_3	PPh_3	54
7	100	1 d	DMA	K_2CO_3	PPh_3	0
8	100	1 d	DMA	NaOAc	PPh_3	30
9	80	1 d	DMA	Na_2CO_3	-	25
10	100	1 d	DMA	Na_2CO_3	-	64
11	100	18 h	DMA	Na_2CO_3	-	89
12	100	12 h	DMA	Na_2CO_3	-	58
13[b]	100	1 d	DMA	Na_2CO_3	PPh_3	15

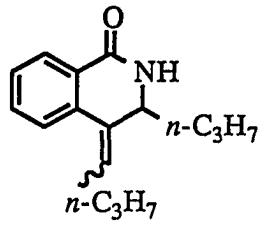
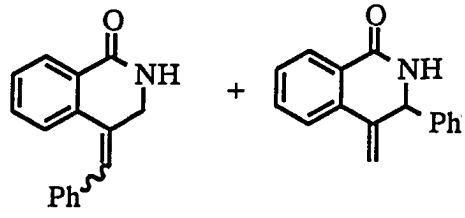
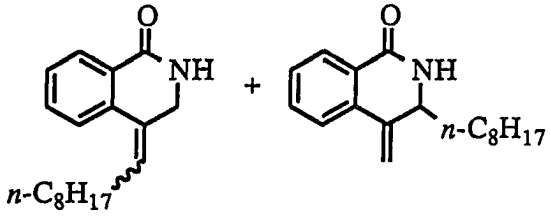
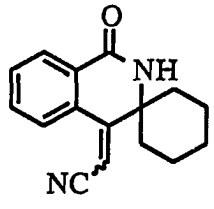
[a] All reactions were carried out using 1 equiv. of aryl halide (0.25 mmol), 2 equiv. of allene (0.5 mmol), 5 mol % $Pd(OAc)_2$ (0.0125 mmol), 5 mol % PPh_3 (0.0125 mmol), 1 equiv. of TBAC (0.25 mmol), 5 equiv. of base (1.25 mmol), and 1.0 mL of DMA unless otherwise indicated; [b] 1 Equiv. LiCl was used instead of TBAC.

$Pd(dba)_2$, 1 equiv. of TBAC, 5 equiv. of Na_2CO_3, and 1 mL of DMA at 100 °C for 18 hours.

After optimizing the reaction conditions for the model system, the analogous reactions with various other allenes were conducted. The results are tabulated in Table 7. 4,5-Nonadiene, phenyl allene, 1,2-undecadiene and cyanovinylidene cyclohexane were employed in the reaction with 2-iodobenzamide. Unfortunately, none of the desired

Table 7. Attempted palladium(0)-catalyzed formation of lactams

Entry	Aryl Halide	Allene
1		
2		
3		
4		
5		

Product	% Isolated Yield (Ratio)
	0
	0
	0
	0
Heck Product	21

products were observed (entries 1-4). The reaction of N-*n*-butyl-2-iodophenylacetamide with vinylidene cyclohexane also provided none of the desired product (entry 5). Instead, a low yield of Heck-type product was isolated.

CONCLUSION

The palladium(0)-catalyzed annulation of allenes by nitrogen-containing organic iodides has been investigated. The reactions are promoted by catalytic amounts of palladium under mild conditions. Five different types of nucleophiles, amines, sulfonamides, amides, alcohols and acids, were employed in the annulations. The best results were obtained with amine and tosylamide nucleophiles. Alcohols and acids both failed to give the desired products, while one lactam product was obtained with an amide nucleophile.

The annulation with vinylic iodides often produced a mixture of isomeric compounds with only moderate stereoselectivity. N-Alkyl aryl iodo amines and the analogous N-tosyl derivatives produced higher yields than the vinylic halide analogues. Seven-membered nitrogen-containing heterocycles are more readily formed than eight- or larger-membered ring nitrogen-containing compounds.

In conclusion, the palladium(0)-catalyzed annulation of allenes by aryl or vinylic iodo amines or sulfonamides provides an efficient route to the formation of seven- or eight-membered ring nitrogen-containing heterocycles.

EXPERIMENTAL SECTION

Spectral Data and Analysis

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 an IBM IR/98 FT-IR spectrometer or on a Beckmann 4250 spectrometer. High resolution mass spectral analyses were performed on a Kratos or an MS-50 high resolution mass 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 $KMnO_4$ solution (3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL 5% NaOH + 300 mL H_2O).

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. *N, N*-Dimethylformamide (DMF) and *N, N*-dimethylacetamide (DMA) were dried over 4 Å molecular sieves. 5-Chloro-1-pentyne, and tetra-*n*-butylammonium chloride were purchased from Lancaster Synthesis, Inc. $Pd(OAc)_2$ was generously provided by Johnson Matthey, Inc., and Kawaken Fine Chemical Co., Inc. 2-Iodobenzyl chloride was purchased from Aldrich Chemical Company.

Preparation of Starting Materials

n-Butyl(4-iodo-4-pentenyl)amine was prepared following the procedure reported by He.[14] The ^1H NMR spectrum was identical with that previously reported by He.

n-Butyl(5-iodo-5-hexenyl)amine was prepared in 90 % yield from the reaction of 5-iodo-5-hexenyl mesylate and *n*-butylamine following the procedure reported by He.[14] ^1H

NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7.2 Hz, CH_3), 1.38-1.52 (m, 9 H, NH, 4 CH_2), 2.90 (t, 2 H, J = 6.9 Hz, $=CCH_2$), 2.62 (m, 4 H, $N(CH_2)_2$), 5.69 (s, 1 H, $=C\underline{H}H$), 6.03 (s, 1 H, $=CH\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.3, 26.7, 28.5, 19.2, 32.1, 44.9, 43.9, 112.1, 125.2; IR (neat) 3305 (N-H), 2928, 1616 (C=C), 1456, 1131, 891, 744 cm^{-1}.

10-Iodo-10-undecen-1-ol was prepared in 48 % yield following the procedure reported by He.[14] TLC (4:1 hexanes/EtOAc) R_f = 0.38; ^1H NMR ($CDCl_3$) δ 1.91 (m, 12 H, 6 CH_2), 1.52 (m, 3 H, OH, CH_2), 2.97 (t, 2 H, J = 6.9 Hz, $=CCH_2$), 3.64 (t, 2 H, J = 6.6 Hz, CH_2O), 5.68 (s, 1 H, $=C\underline{H}H$), 6.00 (s, 1 H, $=CH\underline{H}$); IR (neat) 3338 (OH), 2924, 2825, 1616, 1463 (C=C), 1055, 891 cm^{-1}.

4-Iodo-4-penten-1-ol was prepared in 50 % yield following the procedure reported by He.[14] TLC (1:1 hexanes/EtOAc) R_f = 0.41; ^1H NMR ($CDCl_3$) δ 1.35 (s, 1 H, OH), 1.79 (m, 2 H, CH_2), 2.51 (t, 2 H, J = 7.0 Hz, $=CCH_2$), 3.68 (t, 2 H, J = 6.2 Hz, OCH_2), 5.72 (d, 1 H, J = 1.3 Hz, $=C\underline{H}H$), 6.07 (d, 1 H, J = 1.3 Hz, $=CH\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 31.8, 41.6, 60.8, 111.5, 125.8; IR (neat) 3333 (OH), 2940, 1617, 1428 (C=C), 1058, 1038, 895 cm^{-1}.

5-Iodo-5-hexen-1-ol was prepared in 21 % yield following the procedure reported by He.[14] ^1H NMR($CDCl_3$) δ 1.60 (m, 5 H, 2 CH_2, OH), 2.42 (t, 2 H, J = 6.2 Hz, $=CCH_2$), 3.69 (t, 2 H, J = 6.2 Hz, OCH_2), 5.72 (d, 1 H, $=C\underline{H}H$), 6.07 (d, 1 H, $=CH\underline{H}$).

5-Iodo-5-hexenyl mesylate was prepared in 87 % yield following the procedure reported by Hightower.[16] ^1H NMR ($CDCl_3$) δ 1.72 (m, 4 H, 2 CH_2), 2.47 (t, 2 H, J = 7.2 Hz, $=CCH_2$), 3.02 (s, 3 H, CH_3), 4.28 (t, 2 H, J = 7.2 Hz, OCH_2), 5.76 (d, 1 H, $=C\underline{H}H$), 6.07 (d, 1 H, $=CH\underline{H}$).

5-Iodo-5-hexenenitrile was prepared in 88 % yield following the procedure reported by He.[14] ^1H NMR ($CDCl_3$) δ 2.00 (m, 2 H, CH_2), 2.37 (m, 2 H, $=CCH_2$), 2.51 (m, 2 H, $NCCH_2$), 5.80 (s, 1 H, $=C\underline{H}H$), 6.15 (s, 1 H, $=CH\underline{H}$).

3-Iodo-3-buten-1-ol was prepared in 68 % yield following the procedure reported by He.[14] ^{1}H NMR ($CDCl_3$) δ 2.00 (br s, 1 H, OH), 2.65 (t, 2 H, J = 6.2 Hz, CH_2), 3.78 (t, 2 H, J = 6.2 Hz, OCH_2), 5.88 (s, 1 H, =CHH), 6.20 (s, 1 H, =CHH).

2,4-Diiodo-1-butene was prepared in 50 % yield via halogenation of 3-iodo-3-buten-1-ol following a procedure reported by Hightower.[16] ^{1}H NMR($CDCl_3$) δ 2.90 (t, 2 H, J = 7.2 Hz, ICH_2), 3.28 (t, 2 H, J = 7.2 Hz, CH_2), 5.85 (s, 1 H, =CHH), 6.13 (s, 1 H, =CHH).

4-Iodo-4-pentenenitrile was synthesized in 50 % yield via 2,4-diiodo-1-butene and sodium cyanide according to the procedure reported by Hightower.[16] ^{1}H NMR($CDCl_3$) δ 2.52 (m, 2 H, J = 8.2 Hz, $NCCH_2$), 2.60 (m, 2 H, J = 8.2 Hz, CH_2), 5.88 (s, 1 H, =CHH), 6.23 (s, 1 H, =CHH).

4-Iodo-4-pentenylamine was prepared in 80 % yield via reduction of 4-iodo-4-pentenenitrile with aluminum hydride following the procedure reported by Yoon and Brown.[17]

5-Iodo-5-hexenylamine was prepared via reduction of 5-iodo-5-hexenenitrile with aluminum hydride in 60 % yield following the procedure reported by Yoon and Brown.[17]

N-Tosyl(4-iodo-4-pentenyl)amine was prepared in 90 % yield from 4-iodo-4-pentenylamine following the procedure reported by Hendrickson.[18] TLC (2:1 hexanes/EtOAc) R_f = 0.4; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2 H, CH_2), 2.36 (t, 2 H, J = 6.9 Hz, $=CCH_2$), 2.43 (s, 3 H, $ArCH_3$), 2.94 (t, 2 H, J = 6.3 Hz, CH_2N), 5.16 (br s, 1 H, NH), 5.66 (s, 1 H, =CHH), 5.99 (s, 1 H, =CHH), 7.32 (d, 2 H, J = 9.3 Hz, aryl), 7.77 (d, 2 H, J = 9.3 Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 21.2, 29.3, 41.1, 41.6, 110.1, 126.0, 126.6, 129.3, 136.4, 142.8.

N-Tosyl(5-iodo-5-hexenyl)amine was prepared in 92 % yield from 5-iodo-5-hexenylamine following the procedure reported by Hendrickson.[18] TLC (1:1 hexanes/

EtOAc) R_f = 0.67; ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 4 H, 2 CH_2), 2.31 (t, 2 H, J = 9.7 Hz, =CCH_2), 2.43 (s, 3 H, $ArCH_3$), 2.94 (dt, 2 H, J = 6.6, 6.6 Hz, NCH_2), 4.63 (t, 1 H, J = 6.6 Hz, NH), 5.66 (d, 1 H, J = 1.2 Hz, =C<u>H</u>H), 5.97 (d, 1 H, J = 1.2 Hz, =CH<u>H</u>), 7.31 (d, 2 H, J = 8.1 Hz, aryl), 7.75 (d, 2 H, J = 8.1 Hz, aryl); IR (neat) 3520 (NH), 2926, 2862, 1917, 1616, 1598, 1427 (C=C), 1324 (RSO_2N), 1159 (RSO_2N), 1093, 894, 814, 663 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 21.3, 25.6, 27.6, 42.5, 44.2, 112.0, 125.4, 126.7, 129.4, 136.5, 143.0.

N-Tosyl-2-(2-iodophenyl)ethylamine was prepared in 91 % yield from 2-(2-iodophenyl)ethylamine following the procedure reported by Hendrickson.[18] TLC (2:1 hexanes/ EtOAc) R_f = 0.4; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3 H, $ArCH_3$), 2.90 (t, 2 H, J = 7.2 Hz, $ArCH_2$), 3.20 (dt, 2 H, J = 7.2, 7.2 Hz, CH_2N), 4.5 (br s, 1 H, NH), 6.9-7.8 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.3, 40.4, 42.6, 100.2, 126.9, 128.2, 129.5, 129.9, 139.5, 139.5, 139.2, 140.0, 143.0; IR (neat) 3280 (NH), 3060, 2926, 1598, 1435, 1324 (RSO_2N), 1159 (RSO_2N), 753, 665 cm^{-1}.

N-Tosyl-3-(2-iodophenyl)propylamine was prepared in 91 % yield from 3-(2-iodophenyl)propylamine following the procedure reported by Hendrickson.[18] TLC (2:1 hexanes/EtOAc) R_f = 0.45; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 2 H, CH_2), 2.43 (s, 3 H, $ArCH_3$), 2.69 (t, 2 H, J = 7.5 Hz, CH_2Ar), 3.02 (m, 2 H, CH_2N), 4.82 (br s, NH), 6.86-7.78 (m, 8 H, aryl); IR (neat) 3283 (NH), 2928, 1465, 1326 (RSO_2N), 1158 (RSO_2N), 1094 cm^{-1}.

N-Tosyl-4-(2-iodophenyl)butylamine was prepared in 94 % yield from 4-(2-iodophenyl)butylamine following the procedure reported by Hendrickson.[18] ^{1}H NMR ($CDCl_3$) δ 1.54 (m 4 H, 2 CH_2), 2.41 (s, 3 H, $ArCH_3$), 2.62 (m, 2 H, $ArCH_2$), 2.96 (m, 2 H, CH_2N), 4.79 (m, 1 H, NH), 6.8-7.7 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.0, 29.0, 40.0, 42.9, 100.4, 127.0, 127.3, 1273, 129.3, 129.6, 136.4, 139.4, 143.3, 144.3; IR (neat) 3281 (NH), 2935, 1434, 1325 (RSO_2N), 1157 (RSO_2N), 1093, 751, 648 cm^{-1}.

n-Butyl(10-iodo-10-undecenyl)amine was prepared in 98 % yield from 10-iodo-10-undecen-1-ol following the procedure reported by He.[14] TLC (1:2 hexanes/acetone) R_f = 0.17; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.22 (m, 12 H, 6 CH_2), 1.40 (m, 6 H, 3 CH_2), 2.30 (t, 2 H, *J* = 7.5 Hz, $=CCH_2$), 2.52 (m, 4 H, $N(CH_2)_2$), 5.60 (s, 1 H, =C<u>H</u>H), 5.93 (s, 1 H, =CH<u>H</u>); IR (neat) 3278 (NH), 2925, 2808 (NR), 1616, 1597, 1463 (C=C), 1324, 1129, 1093, 890, 773 cm^{-1}.

2-Iodophenylacetonitrile was prepared in 81 % yield from 2-iodobenzyl alcohol following the procedure reported by Hightower.[16] ^{1}H NMR ($CDCl_3$) δ 4.55 (s, 2 H, CH_2), 7.00-8.00 (m, 4 H, aryl).

2-(2-Iodophenyl)ethylamine was prepared 50 % yield by reduction of the corresponding nitrile following the procedure reported by Yoon and Brown.[17] ^{1}H NMR ($CDCl_3$) δ 2.83 (m, 4 H, CH_2CH_2), 6.92-7.92 (m, 4 H, aryl).

3-(2-Iodophenyl)propylamine was prepared in 84 % yield by reduction of the corresponding nitrile following the procedure reported by Yoon and Brown.[17]

4-(2-Iodophenyl)butylamine were prepared in 78 % yield by reduction of the corresponding nitrile following the procedure reported by Yoon and Brown.[17]

4-Iodo-4-pentenoic acid was prepared in 85 % yield from the oxidation of 4-iodo-4-penten-1-ol following the procedure reported by Millar, Oehlschlager and Wong.[19] TLC (1:1 hexanes/ EtOAc) R_f = 0.43; ^{1}H NMR ($CDCl_3$) δ 2.53 (t, 2 H, *J* = 6.8 Hz, $=CCH_2$), 2.67 (t, 2 H, *J* = 6.8 Hz, CH_2CO), 5.68 (s, 1 H, =C<u>H</u>H), 6.04 (s, 1 H, =CH<u>H</u>), 10.67 (br s, 1 H, COOH); IR (neat) 3086 (OH), 2915, 1709, 1430 (C=C), 1293, 1110, 899 cm^{-1}.

n-Butyl-3-(2-iodophenyl)propylamine was prepared in 98 % yield by the alkylation of the corresponding chloride following a procedure reported by He.[14] ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.40-1.80 (m, 6 H, 3 CH_2), 1.59 (br s, 1 H, NH), 2.72 (m, 6 H, $N(CH_2)_2$, $ArCH_2$), 6.80-7.80 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.5, 30.4,

32.2, 38.5, 49.3, 49.5, 100.5, 127.5, 128.2, 129.2, 139.2, 147.7; IR (neat) 3300 (NH), 3058, 2926, 2811 (NR), 1464, 1129, 1010, 749 cm^{-1}.

2-Iodobenzaldehyde was prepared in 94 % yield from PCC oxidation of the corresponding alcohol following the literature procedure.[20] ^1H NMR ($CDCl_3$) δ 7.28–8.00 (m, 4 H, aryl), 10.06 (s, 1 H, OCH).

Ethyl 2-cyano-3-(2-iodophenyl)acrylate was prepared in 96 % yield from the condensation of 2-iodobenzaldehyde and ethyl cyanoacetate following the procedure reported by Kasturi.[21] ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H, J = 8.7 Hz, CH_3), 4.35 (q, 2 H, J = 8.7 Hz, OCH_2), 7.10–8.00 (m, 4 H, aryl), 8.40 (s, 1 H, =CH).

Ethyl 2-cyano-3-(2-iodophenyl)propanoate was prepared in 90 % yield from the reduction of ethyl 2-cyano-3-(2-iodophenyl)acrylate following the procedure reported by Nanjo.[22] ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.2 Hz, CH_3), 3.15 (dd, 1 H, J = 9.9, 13.8 Hz, ArC<u>H</u>H), 3.40 (m, 1 H, CH), 3.85 (dd, 1 H, J = 9.9, 13.8 Hz, ArCH<u>H</u>), 4.21 (q, 2 H, J = 7.2 Hz, OCH_2), 6.93–7.82 (m, 4 H, aryl).

3-(2-Iodophenyl)propanenitrile was prepared in 94 % yield from decarboxylation of ethyl 2-cyano-3-(2-iodophenyl)propanoate following a procedure reported by Krapcho.[23] ^1H NMR ($CDCl_3$) δ 2.56 (t, 2 H, J = 7.2 Hz, CH_2), 2.97 (t, 2 H, J = 7.2 Hz, CH_2), 6.93–7.92 (m, 4 H, aryl).

Diethyl 2-iodobenzyl malonate was prepared from 2-iodobenzyl chloride and diethyl malonate following the procedure reported by Fried.[24] The ^1H NMR spectrum was identical with that previously reported by Fried.

3-(2-Iodophenyl)propanoic acid was prepared in 90 % yield from diethyl 2-iodobenzyl malonate following the procedure reported by Cooke and Widene.[25] ^1H NMR ($CDCl_3$) δ 2.74 (t, 2 H, J = 7.9 Hz, CH_2), 3.15 (t, 2 H, J = 7.9 Hz, CH_2), 6.93–7.92 (m, 4 H, aryl), 10.00 (br s, COOH).

3-(2-Iodophenyl)propanol was prepared in 90 % yield from reduction of 3-(2-iodophenyl)propanoic acid with borane following the literature procedure.[26] ^{1}H NMR ($CDCl_3$) δ 1.62 (br s, 1 H, OH), 1.90 (m, 2 H, CH_2), 2.85 (t, 2 H, J = 9.8 Hz, $ArCH_2$), 3.78 (t, 2 H, J = 9.8 Hz, CH_2O), 6.93–7.92 (m, 4 H, aryl).

3-(2-Iodophenyl)propyl iodide was prepared in 68 % yield from 3-(2-iodophenyl)-propanol following the procedure reported by Hightower.[16] ^{1}H NMR ($CDCl_3$) δ 2.07 (m, 2 H, CH_2), 2.88 (t, 2 H, J = 10.1 Hz, CH_2), 3.22 (t, 2 H, J = 10.1 Hz, CH_2), 6.93–7.92 (m, 4 H, aryl).

4-(2-Iodophenyl)butanenitrile was prepared in 65 % yield from 3-(2-iodophenyl)-propyl iodide following the procedure reported by Hightower.[16]

n-Butyl-3-(2-iodophenyl)propylamine was prepared in 98 % yield from 3-(2-iodophenyl)propyl chloride following the procedure reported by He.[14] ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.2 Hz, CH_3), 1.39 (m, 2 H, CH_2), 1.50 (m, 2 H, CH_2), 1.60 (s, 1 H, NH), 1.80 (m, 2 H, CH_2), 2.72 (m, 6 H, $N(CH_2)_2$, $ArCH_2$), 6.80-7.80 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.5, 30.4, 32.2, 38.5, 49.3, 49.5, 100.5, 127.5, 128.2, 129.2, 139.2, 147.7; IR (neat) 3300 (NH), 3058, 2926, 2811, 1464, 1129, 1010, 749 cm^{-1}.

6-Bromohexyl 2-iodophenyl ether was prepared in 100 % yield from 2-iodophenol and 1,6-dibromohexane according to the literature procedure.[27] ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 4 H, 2 CH_2), 1.90 (m, 4 H, 2 CH_2), 3.42 (t, 2 H, J = 8.8 Hz, CH_2), 4.02 (t, 2 H, J = 8.8 Hz, CH_2), 6.30-8.50 (m, 4 H, aryl).

N-Tosyl-7-(2-iodophenoxy)heptylamine was prepared in 50 % yield following the procedure reported by Hendrickson.[18] TLC (2:1 hexanes/ EtOAc) R_f = 0.4; ^{1}H NMR ($CDCl_3$) δ 1.20-1.90 (m, 10 H, 5 CH_2), 2.43 (s, 3 H, $ArCH_3$), 2.94 (m, 2 H, CH_2N), 4.00 (t, 2 H, J = 6.3 Hz, OCH_2), 4.50 (br s, 1 H, NH), 6.70-7.70 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.2, 25.6, 26.1, 28.0, 28.3, 28.5, 42.8, 68.6, 88.9, 111.8, 121.9, 126.7, 129.1,

129.3, 136.6, 138.9, 142.8, 157.1; IR (neat) 3284 (NH), 2930, 1733, 1598, 1469, 1326, 1245, 1160, 750.

N-*n*-Butyl-2-iodophenylacetamide was prepared in 33 % yield following the literature procedure.[28] TLC (1:1 hexanes/ EtOAc) R_f = 0.4; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.27-1.44 (m, 6 H, 3 CH_2), 3.22 (m, 2 H, NCH_2), 3.70 (s, 2 H, $ArCH_2$), 5.40 (br s, 1 H, NH), 6.99-7.87 (m, 4 H, aryl).

Ethyl 2,3-butadienoate was prepared in 66 % yield according to the literature procedure.[15] TLC (14:1 hexanes/EtOAc) Rf = 0.33; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, *J* = 7.2 Hz, CH_3), 4.21 (q, 2 H, *J* = 7.2 Hz, CH_2), 5.22 (d, 2 H, *J* = 6.6 Hz, H_2C=), 5.64 (t, 1 H, *J* = 6.6 Hz, =CHCO); IR (neat) 2939, 2115, 1970, 1942, 1710 (C=O), 1368 (C=C), 1335 (C=C), 1256, 1164, 1036, 857 cm^{-1}.

Cyanovinylidene cyclohexane was prepared in 49 % yield according to the literature procedure.[29] TLC (4:1 hexanes/EtOAc) R_f = 0.67; ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 2 H, CH_2), 1.64 (m, 4 H, 2 CH_2), 2.21 (m, 4 H, =C(CH_2)$_2$), 5.07 (m, 1 H, =CHCN); IR (neat) 3009, 2934, 2855, 2221 (CN), 1958, 1446 (C=C), 767 cm^{-1}.

Z-4-Iodo-3-buten-1-ol was prepared in 56 % yield from 4-iodo-3-butyn-1-ol according to the procedure reported by Gong.[30] The ^{1}H NMR spectrum was identical with that previously reported by Gong.

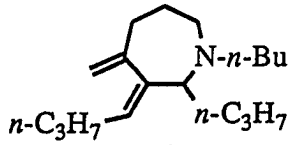
n-Butyl(*Z*-4-iodo-3-butenyl)amine was prepared in 80 % yield from *Z*-4-iodo-3-buten-1-ol according to the procedure reported by Berrios-Peña.[31] ^{1}H NMR ($CDCl_3$) δ 0.922 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.36 (m, 2 H, CH_2), 1.50 (m, 2 H, CH_2), 0.88 (br s, 1 H, NH), 2.37 (m, 2 H, CH_2), 2.65 (t, 2 H, *J* = 7.5 Hz, CH_2), 2.76 (t, 2 H, *J* = 7.2 Hz, CH_2), 6.27 (m, 2 H, HC=CH); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.4, 32.0, 35.1, 47.8, 49.4, 83.9, 139.0.

General Procedure for the Palladium-Catalyzed Heteroannulation Reactions

Into a one or two-dram screw-capped vial, equipped with a Teflon-lined cap and a magnetic stirrer, was placed the $Pd(dba)_2$ (5 mol %), triphenylphosphine (5 mol %), tetra-*n*-butylammonium chloride (1 equiv.), sodium carbonate (5 equiv.), the organic halide (0.25 mmol), and the allene (2 equiv.). The vial was then capped and suspended in an oil bath at the desired reaction temperature for a certain period of time. At the desired time, the reaction was monitored by TLC. When the reaction was considered complete as measured by disappearance of the organic iodide, it was allowed to cool to room temperature and was directly chromatographed on a silica gel column (230-400 mesh silica gel) with an appropriate eluent, unless otherwise specified. The desired products were collected and the solvents were removed by rotary evaporation. The products were further purified by flash column chromatography if necessary.

Spectral Data for Annulation Products

Compound **1**

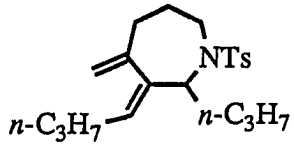


1

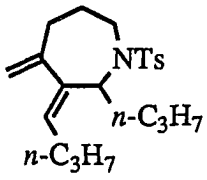
Obtained in 61% yield from the reaction of *n*-butyl(4-iodo-4-pentenyl)amine and 4,5-nonadiene. TLC (1:1 hexanes/EtOAc) $R_f = 0.48$; ^1H NMR ($CDCl_3$) δ 0.85-0.95 (m, 9 H, 3 CH_3), 1.20-1.66 (m, 20 H, 10 CH_2), 2.95 (t, 1 H, $J = 7.5$ Hz, =CCHN), 4.85 (s, 1 H, =C<u>H</u>H), 5.00 (s, 1 H, =CH<u>H</u>), 5.18 (t, $J = 7.2$ Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 14.1, 19.9, 20.7, 23.5, 24.2, 30.0, 30.8, 34.0, 35.1, 49.6, 52.3, 68.1, 113.7, 130.0,

141.0, 146.5; IR ($CHCl_3$) 3076, 2959, 2932 (NR_3), 1622 (C=C), 1464 (C=C), 1377, 1111, 897, 760 cm^{-1}; HRMS m/z 263.2608 (Calcd. 263.2613 for $C_{18}H_{33}N$).

Compounds **8a** and **8b**



8a



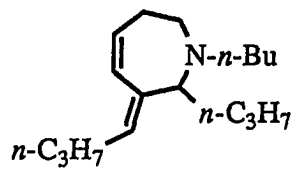
8b

Obtained in 25% yield as an inseparable mixture (**8a/8b** = 60:40) from the reaction of N-tosyl-(4-iodo-4-pentenyl)amine and 4,5-nonadiene. The isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers. TLC (4:1 hexanes/EtOAc) $R_f = 0.51$; IR (neat) 2955, 1627 (C=C), 1456 (C=C), 1333 (RSO_2N), 1157, 1092, 900 cm^{-1}; HRMS m/z 361.2069 (Calcd. 361.2076 for $C_{21}H_{31}NSO_2$). There was not enough material for ^{13}C NMR analysis.

Isomer **8a**: ^1H NMR ($CDCl_3$) δ 0.87 (m, 6 H, 2 CH_3), 1.25 (m, 4 H, 2 CH_2), 1.52 (m, 4 H, 2 CH_2), 1.98 (m, 2 H, $=CCH_2$), 2.08 (m, 2 H, $=CCH_2$), 2.25 (m, 2 H, CH_2), 2.40 (s, 3 H, $ArCH_3$), 3.10 (m, 1 H, CHN), 4.41 (t, 1 H, J = 7.8 Hz, =CH), 4.62 (s, 1 H, =CHH), 4.98 (s, 1 H, =CHH), 7.24 (d, 2 H, J = 11.1 Hz, aryl), 7.69 (d, 2 H, J = 11.1 Hz, aryl).

Isomer **8b**: ^1H NMR ($CDCl_3$) same as that for **8a** or not seen, except δ 3.64 (m, 1 H, CHN), 4.52 (m, 1 H, =CH), 5.26 (t, 1 H, J = 7.5 Hz, =CH).

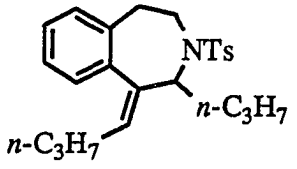
Compound **9**



9

Obtained in 81 % yield from the reaction of *n*-butyl(*Z*-4-iodo-3-butenyl)amine and 4,5-nonadiene. TLC (1:2 hexanes/acetone) $R_f = 0.05$; ^1H NMR ($CDCl_3$) δ 0.94 (m, 9 H, 3 CH_3), 1.40 (m, 10 H, 5 CH_2), 2.06 (m, 4 H, 2 CH_2, $=CH_2$), 2.50 (m, 3 H, $=CCH_2$, NCHH), 2.76 (m, 1 H, NCHH), 3.02 (m, 2 H, CH_2N), 3.12 (m, 1 H, =CCHN), 5.30 (t, 1 H, $J = 7.2$ Hz, HC=CH), 5.66 (m, 1 H, HC=CH), 6.09 (t, 1 H, $J = 11.7$ Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.0, 14.1, 20.4, 20.8, 22.8, 28.5, 29.7, 29.9, 36.3, 47.8, 52.9, 69.6, 125.9, 129.9, 131.7, 137.1; IR (neat) 2957, 1463 (C=C), 1376, 1092 cm^{-1}; HRMS m/z 249.2457 (Calcd. 249.2460 for $C_{17}H_{31}N$)

Compound **10**

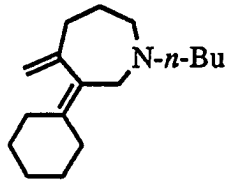


10

Obtained in 94 % yield from the reaction of N-tosyl-2-(2-iodophenyl)ethylamine and 4,5-nonadiene. TLC (4:1 hexanes/EtOAc) $R_f = 0.47$; ^1H NMR ($CDCl_3$) δ 0.76 (m, 6 H, 2 CH_3), 1.20 (m, 6 H, 3 CH_2), 1.80 (m, 1 H, =CCHH), 1.90 (m, 1 H, =CCHH), 2.40 (s, 3 H, $ArCH_3$), 2.56 (dd, 1 H, $J = 15.0$, 7.5 Hz, NCHH), 2.80 (t, 1 H, $J = 15.0$ Hz, ArCHH),

3.15 (t, 1 H, J = 15.0 Hz, ArCH<u>H</u>), 3.93 (dd, 1 H, J = 15.0, 7.5 Hz, NC<u>H</u>H), 4.66 (m, 1 H, CHN), 5.69 (t, 1 H, J = 6.6 Hz, HC=C), 6.97-7.80 (4 m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.8, 19.1, 21.4, 22.6, 30.7, 32.8, 36.7, 41.2, 62.1, 126.0, 127.1, 127.3, 128.9, 129.4, 130.6, 133.4, 137.3, 138.6, 138.9, 140.0, 142.7; IR (neat) 3024, 2956, 2871, 2363, 1738, 1454 (C=C), 1309 (RSO_2N), 1161 (RSO_2N), 1048, 910, 754, 673 cm^{-1}; HRMS m/z 397.5855 (Calcd. 397.5852 for $C_{24}H_{31}SO_2N$).

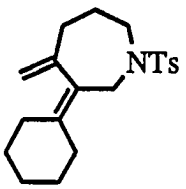
Compound **11**



11

Obtained in 43% yield from the reaction of *n*-butyl(4-iodo-4-pentenyl)amine and vinylidene cyclohexane. TLC (1:2 hexanes/EtOAc) R_f = 0.25; ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 3 H, CH_3), 1.29 (m, 4 H, 2 CH_2), 1.55 (m, 8 H, 4 CH_2), 2.21 (m, 4 H, =C(CH_2)$_2$), 2.32 (t, 2 H, =CCH_2), 2.43 (dd, 2 H, J = 9.5, 7.4 Hz, NCH_2), 2.63 (dd, 2 H, J = 7.4, 5.3 Hz, NCH_2), 3.20 (s, 2 H, =CCH_2N), 4.62 (t, 1 H, J = 1.6 Hz, =C<u>H</u>H), 4.90 (d, 1 H, J = 2.3 Hz, =CH<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 26.9, 28.2, 28.8, 30.3, 32.1, 35.3, 56.0, 56.3, 56.8, 111.3, 111.3, 111.3, 150.4; IR(neat) 2924, 2800 (NR_3), 1656 (C=C), 1630 (C=C), 1446, 890 cm^{-1}; HRMS m/z 247.2300 (Calcd. 247.2302 for $C_{17}H_{29}N$).

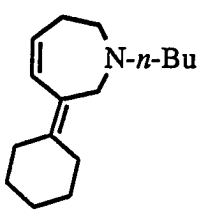
Compound **12**



12

Obtained in 71% yield from the reaction of N-tosyl-(4-iodo-4-pentenyl)amine and vinylidene cyclohexane. TLC (4:1 hexanes/EtOAc) $R_f = 0.48$; ^1H NMR($CDCl_3$) δ 1.53 (m, 6 H, 3 CH_2), 1.69 (m, 2 H, CH_2), 2.17 (m, 6 H, 3 $=CCH_2$), 2.42 (s, 3 H, $ArCH_3$), 3.26 (m, 2 H, NCH_2), 3.91 (s, 2 H, $=CCH_2N$), 4.61 (s, 1 H, $=C\underline{H}H$), 4.91 (s, 1 H, $=CH\underline{H}$), 7.27 (d, 2 H, $J = 8.1$ Hz, aryl), 7.36 (d, 2 H, $J = 8.1$ Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.7, 28.0, 28.5, 28.6, 30.1, 32.1, 36.1, 48.4, 49.5, 113.2, 127.2, 127.2, 128.2, 129.5, 138.1, 142.8, 148.0; IR (neat) 3070, 2920, 1651 (C=C), 1597 (C=C), 1447 (C=C), 1331 (RSO_2N), 1162, 1091, 893 cm^{-1}; HRMS m/z 345.1756 (Calcd. 345.1763 for $C_{20}H_{27}NSO_2$).

Compound **13**

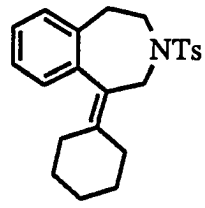


13

Obtained in 23 % yield from the reaction of *n*-butyl(*Z*-4-iodo-3-butenyl)amine and vinylidene cyclohexane. TLC (1:2 hexanes/acetone) $R_f = 0.06$; ^1H NMR ($CDCl_3$) δ 1.00

(m, 3 H, CH_3), 1.22 (m, 2 H, CH_2), 1.55 (m, 8 H, 4 CH_2), 2.30 (m, 4 H, 2 $=CCH_2$), 2.40 (m, 4 H, NCH_2, $=CCH_2$), 2.77 (dd, 2 H, J = 5.4, 5.1 Hz, NCH_2), 3.53 (s, 2 H, $=CCH_2N$), 5.69 (m, 1 H, HC=CH), 6.42 (d, 1 H, J = 11.4 Hz, HC=CH). There was not enough material for ^{13}C NMR, IR and HRMS analysis.

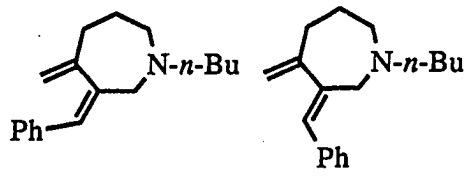
Compound **14**



14

Obtained in 95 % yield from the reaction of N-tosyl-2-(2-iodophenyl)ethylamine and vinylidene cyclohexane. TLC (4:1 hexanes/EtOAc) R_f = 0.48; ^1H NMR ($CDCl_3$) δ 1.60 (m, 2 H, CH_2), 1.75 (m, 2 H, CH_2), 2.06 (m, 2 H, CH_2), 2.37 (s, 3 H, $ArCH_3$), 2.55 (m, 2 H, $=CCH_2$), 2.8 (m, 2 H, $=CCH_2$), 3.04 (t, 2 H, J = 12 Hz, $ArCH_2$), 3.4 (m, 2 H, CH_2N), 4.75 (s, 1 H, NCHH), 4.79 (s, 1 H, NCHH), 6.9-7.6 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.6, 28.3, 28.6, 30.4, 32.4, 35.5, 48.1, 49.2, 126.2, 126.3, 126.6, 127.3, 128.8, 128.9, 129.5, 134.4, 138.2, 142.5, 142.8, 143.2; IR (neat) 3090, 3017, 2923, 2851, 2257, 1598 (C=C), 1448 (C=C), 1377 (RSO_2N), 1164 (RSO_2N), 914, 714 cm^{-1}; HRMS m/z 381.1762 (Calcd. 381.1763 for $C_{23}H_{27}SO_2N$).

Compounds **15a** and **15b**



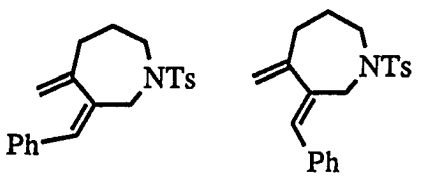
15a **15b**

Obtained in 80% yield as a separable mixture (**15a/15b** = 55:45) from the reaction of *n*-butyl(4-iodo-4-pentenyl)amine and phenylallene.

Isomer **15a**: TLC (1:2 hexanes/acetone) $R_f = 0.63$; ^1H NMR ($CDCl_3$) δ 0.83 (m, 3 H, CH_3), 1.26 (m, 4 H, 2 CH_2), 1.72 (m, 2 H, CH_2), 2.44 (m, 4 H, $=CCH_2$, NCH_2), 2.79 (t, 2 H, J = 5.5 Hz, NCH_2), 3.52 (s, 2 H, $=CCH_2N$), 4.80 (s, 1 H, $=C\underline{H}H$), 5.24 (d, 1 H, J = 1.8 Hz, $=CH\underline{H}$), 6.79 (s, 1 H, =CHPh), 7.30 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 28.8, 29.5, 35.6, 54.7, 55.3, 57.9, 109.8, 126.5, 126.5, 126.5, 126.5, 128.1, 129.1, 153.2; IR (neat) 3077, 3021, 2927, 2858 (NR_3), 1657 (C=C), 1630 (C=C), 1463, 1459, 890, 699 cm^{-1}; HRMS m/z 255.1987 (Calcd 255.1991 for $C_{18}H_{25}N$).

Isomer **15b**: TLC (1:2 hexanes/acetone) $R_f = 0.28$; ^1H NMR ($CDCl_3$) δ 0.92 (m, 3 H, CH_3), 1.28 (m, 2 H, CH_2), 1.42 (m, 2 H, CH_2), 1.71 (m, 2 H, CH_2), 2.55 (m, 4 H, NCH_2, $=CCH_2$), 2.80 (t, 2 H, J = 5.5 Hz, NCH_2), 3.44 (s, 2 H, $=CCH_2N$), 4.86 (d, 1 H, J = 1.7 Hz, $=C\underline{H}H$), 4.90 (s, 1 H, $=CH\underline{H}$), 6.27 (s, 1 H, =CHPh), 7.25 (m, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 26.9, 29.7, 34.9, 54.4, 55.7, 62.8, 114.8, 126.3, 127.1, 127.5, 128.0, 128.0, 128.1, 128.8; IR(neat) 3078, 2954, 1715 (NR_3), 1582 (C=C), 1451 (C=C), 751, 698 cm^{-1}; HRMS m/z 255.1998 (Calcd 255.1991 for $C_{18}H_{25}N$).

Compounds **16a** and **16b**



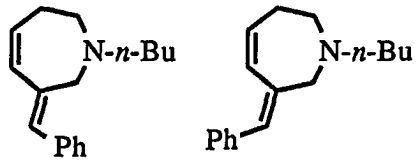
16a **16b**

Obtained in 91% yield as an inseparable mixture (**16a/16b** = 60:40) from the reaction of N-tosyl-(4-iodo-4-pentenyl)amine and phenyl allene. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of isomers. ^{13}C NMR ($CDCl_3$) δ 21.4, 29.8, 31.0, 34.6, 34.8, 47.8, 49.2, 51.3, 56.6, 113.0, 126.2, 127.0, 127.1, 127.1, 127.5, 128.1, 128.6, 128.8, 129.3, 129.5, 142.8, 145.8, 150.3; IR(neat) 2939, 1623 (C=C), 1598 (C=C), 1447 (C=C), 1337 (RSO_2N), 1163 (RSO_2N), 1111, 909, 734 cm^{-1}; HRMS m/z 353.1431 (Calcd. 353.1450 for $C_{20}H_{23}NSO_2$).

Isomer **16a**: ^{1}H NMR($CDCl_3$) δ 1.75 (m, 2 H, CH_2), 2.30 (t, 2 H, J = 6.3 Hz, CH_2C=), 2.40 (s, 3 H, CH_3), 3.34 (m, 2 H, CH_2N), 4.05 (d, 2 H, J = 1.5 Hz, =CCH_2N), 4.85 (d, 1 H, J = 1.5 Hz, =C<u>H</u>H), 4.99 (t, 1 H, J = 0.6 Hz, =CH<u>H</u>), 6.28 (s, 1 H, =CHPh), 7.22-7.77 (m, 9 H, aryl).

Isomer **16b**: ^{1}H NMR ($CDCl_3$) same as the isomer **16a** or not seen, except δ 2.39 (s, 3 H, CH_3), 3.41 (t, 2 H, J = 5.7 Hz, CH_2N), 4.24 (d, 2 H, J = 1.5 Hz, =CCH_2N), 4.77 (t, 1 H, J = 0.6 Hz, =C<u>H</u>H), 5.07 (d, 1 H, J = 1.5 Hz, =CH<u>H</u>), 6.68 (s, 1 H, =CHPh).

Compounds **17a** and **17b**



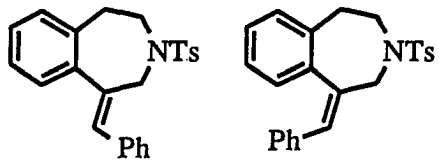
17a **17b**

Obtained in 83 % yield as a separable mixture (**17a/17b** = 64:36) from the reaction of *n*-butyl(*Z*-4-iodo-3-butenyl)amine and phenyl allene.

Isomer **17a**: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H, J = 7.2 Hz, CH_3), 1.30 (m, 4 H , 2 CH_2), 2.41 (m, 4 H, $=CCH_2$, CH_2N), 3.01 (t, 2 H, J = 5.4 Hz, CH_2N), 3.64 (s, 2 H, $=CCH_2N$), 5.73 (m, 1 H, HC=CH), 6.23 (d, 1 H, J = 11.1 Hz, HC=CH), 6.56 (s, 1 H, =CHPh), 7.30 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.6, 27.7, 29.9, 54.4, 54.6, 54.7, 126.7, 128.1, 128.1, 128.1, 129.2, 130.9, 132.2, 134.2; IR (neat) 2929, 1673, 1463 (C=C), 1437 (C=C), 1119, 695 cm^{-1}; HRMS m/z 241.1828 (Calcd. 241.1831 for $C_{17}H_{23}N$).

Isomer **17b**: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.2 Hz, CH_3), 1.34 (m, 2 H, CH_2), 1.54 (m, 2 H, CH_2), 2.46 (m, 2 H, NCH_2), 2.54 (m, 2 H, $=CCH_2$), 2.93 (t, 2 H, J = 5.4 Hz, NCH_2), 3.58 (s, 2 H, $=CCH_2N$), 5.92 (m, 1 H, HC=CH), 6.37 (s, 1 H, =CHPh), 6.43 (d, 1 H, J = 8.4 Hz, HC=CH), 7.2-7.7 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 27.9, 30.1, 54.0, 54.2, 61.3, 126.8, 128.0, 128.6, 129.4, 129.7, 130.1, 132.0, 133.4; IR (neat) 2927, 1674 (C=C), 1598 (C=C), 1464 (C=C), 1102, 699 cm^{-1}; HRMS m/z 241.1831 (Calcd. 241.1831 for $C_{17}H_{23}N$).

Compounds **18a** and **18b**



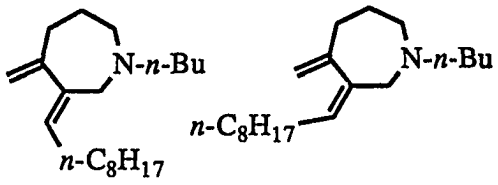
18a **18b**

Obtained in 54 % yield as an inseparable mixture (**18a/18b** = 79:21) from the reaction of N-tosyl-2-(2-iodophenyl)ethylamine and phenyl allene. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of isomers: TLC (4:1 hexanes/EtOAc) R_f = 0.31; ^{13}C NMR ($CDCl_3$) δ 21.41, 36.1, 47.4, 55.8, 62.8, 127.2, 127.3, 127.7, 127.9, 128.5, 129.3, 129.4, 129.5, 129.6, 131.8, 132.0, 138.3, 143.2; IR (neat) 3062, 3025, 2933, 2256, 1598 (C=C), 1447, 1353 (RSO_2N), 1163 (RSO_2N), 920 cm^{-1}; HRMS m/z 389.1449 (Calcd. 389.1450 for $C_{24}H_{23}SO_2N$).

Isomer **18a**: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3 H, $ArCH_3$), 2.98 (t, 2 H, J = 6.4 Hz, $ArCH_2$), 3.42 (m, 2 H, CH_2N), 3.98 (s, 2 H, $=CCH_2N$), 6.79 (s, 1 H, =CH), 6.8-7.7 (m, 13 H, aryl).

Isomer **18b**: ^{1}H NMR ($CDCl_3$) same as compound **18a** or not seen, except δ 2.37 (s, 3 H, $ArCH_3$), 2.90 (t, 2 H, J = 6.0 Hz, $ArCH_2$), 3.51 (t, 2 H, J = 12.0 Hz, CH_2N), 4.29 (s, 2 H, $=CCH_2N$), 6.72 (s, 1 H, =CH).

Compounds **19a** and **19b**



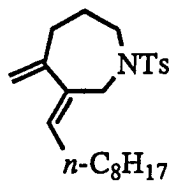
19a **19b**

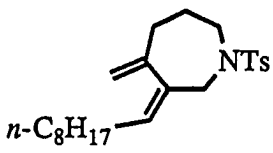
Obtained in 65% yield as a separable mixture (**19a/19b** = 79:21) from the reaction of *n*-butyl(4-iodo-4-pentenyl)amine and 1,2-undecadiene.

Isomer **19a**: TLC (1:2 hexanes/acetone) R_f = 0.34; ^{1}H NMR($CDCl_3$) δ 0.89 (m, 6 H, 2 CH_3), 1.28 (m, 16 H, 8 CH_2), 1.66 (m, 2 H, CH_2), 2.07 (dt, 2 H, *J* = 14.4, 7.2 Hz, =CCH_2), 2.35 (t, 2 H, *J* = 5.1 Hz, =CCH_2), 2.45 (t, 2 H, *J* = 7.5 Hz, NCH_2), 2.78 (t, 2 H, *J* = 5.4 Hz, NCH_2), 3.36 (s, 2 H, NCH_2C=), 4.63 (s, 1 H, =C<u>H</u>H), 5.02 (d, 1 H, *J* = 2.1 Hz, =CH<u>H</u>), 5.72 (t, 1 H, *J* = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.8, 22.7, 28.0, 28.7, 29.4, 29.48, 29.6, 29.7, 29.7, 29.9, 31.9, 35.7, 53.0, 55.0, 58.5, 108.3, 127.9, 140.2, 153.0; IR (neat) 2924, 1463 (C=C), 1463 (C=C), 884 cm^{-1}; HRMS m/z 291.2921 (Calcd. 291.2921 for $C_{20}H_{37}N$).

Isomer **19b**: TLC (1:2 hexanes/acetone) R_f = 0.32; ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6 H, 2 CH_3), 1.26 (m, 16 H, 8 CH_2), 1.77 (m, 2 H, CH_2), 2.17 (m 2 H, =CCH_2), 2.33 (t, 2 H, *J* = 5.9 Hz, =CCH_2), 2.47 (t, 2 H, *J* = 7.7 Hz, NCH_2), 2.79 (t, 2 H, *J* = 5.8 Hz, NCH_2), 3.33 (s, 2 H, NCH_2C=), 4.82 (d, 1 H, *J* = 2.2 Hz, =C<u>H</u>H), 5.02 (t, 1 H, *J* = 2.2 Hz, =CH<u>H</u>), 5.74 (t, 1 H, *J* = 6.7 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 22.7, 27.6, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 30.3, 31.9, 36.0, 53.9, 56.9, 61.3, 105.2, 113.6, 130.3, 148.1; NOE ($CDCl_3$) showed a strong interaction between C=C<u>H</u>C_8H_{17} and C=CCH_2N; IR (neat) 2924, 1688 (C=C), 1604 (C=C), 1275, 895 cm^{-1}; HRMS m/z 291.2921 (Calcd. 291.2921 for $C_{20}H_{37}N$).

Compounds **20a** and **20b**





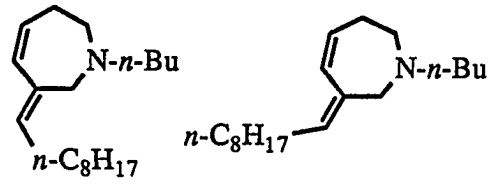
20a **20b**

Obtained in 51% yield as an inseparable mixture (**20a/20b** = 61:39) from the reaction of N-tosyl-(4-iodo-4-pentenyl)amine and 1,2-undecadiene. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of isomers. ^{13}C NMR ($CDCl_3$) δ 14.2, 21.4, 22.7 27.9, 29.1, 29.2, 29.3, 29.3, 29.4, 29.5, 29.8, 30.1, 30.3, 31.9, 34.7, 35.7, 47.9, 48.9, 51.1, 55.4, 110.9, 114.9, 127.0, 127.2, 127.3, 127.3, 128.6, 129.4, 129.4, 130.2, 136.8, 137.4, 137.7, 142.8, 145.8, 150.1; IR (neat) 2925, 2254, 1600 (C=C), 1598 (C=C), 1455 (C=C), 1338 (SO_2N), 1160 (SO_2N), 1111, 909, 734 cm^{-1}; HRMS m/z 389.2386 (Calcd. 389.2389 for $C_{23}H_{35}NSO_2$).

Isomer **20a**: ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 3 H, CH_3), 1.25 (m, 12 H, 6 CH_2), 1.68 (m, 2 H, CH_2), 2.10 (m, 4 H, 2 =CCH_2), 2.41 (s, 3 H, $ArCH_3$), 3.34 (m, 2 H, NCH_2), 4.00 (s, 2 H, =CCH_2N), 4.59 (s, 1 H, =CHH), 4.87 (s, 1 H, =CHH), 5.69 (t, 1 H, J = 7.2 Hz, =CH), 7.26 (d, 2 H, J = 7.8 Hz, aryl), 7.65 (d, 2 H, J = 7.8 Hz, aryl).

Isomer **20b**: ^{1}H NMR ($CDCl_3$) same as the isomer **20a** or not seen, except δ 3.90 (s, 2 H, =CCH_2N), 4.68 (s, 1 H, =CHH), 4.97 (s, 1 H, =CHH), 5.39 (t, 1 H, J = 7.5 Hz, =CH).

Compounds **21a** and **21b**



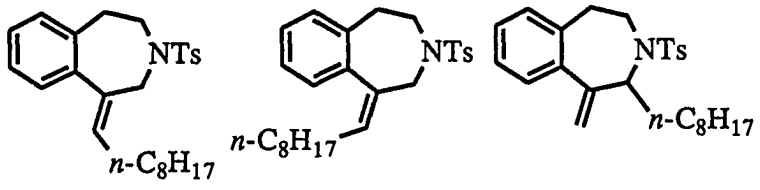
21a **21b**

Obtained in 85 % yield as a separable mixture (**21a/21b** = 70:30) from the reaction of *n*-butyl(Z-4-iodo-3-butenyl)amine and 1,2-undecadiene.

Isomer **21a**: ^{1}H NMR($CDCl_3$) δ 0.90 (m, 6 H, 2 CH_3), 1.27 (m, 14 H, 7 CH_2), 1.46 (m, 2 H, CH_2), 2.10 (m, 2 H, =CCH_2), 2.35 (m, 2 H, =CCH_2), 2.45 (m, 2 H, NCH_2), 2.87 (t, 2 H, J = 5.4 Hz, NCH_2), 3.41 (s, 2 H, =CCH_2N), 5.33 (t, 1 H, J = 7.2 Hz, =CH), 5.75 (m, 1 H, HC=C<u>H</u>), 6.32 (d, 1 H, J = 11.7 Hz, HC=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.8, 22.7, 27.8, 27.9, 29.3, 29.3, 29.3, 29.5, 29.6, 29.9, 31.9, 53.3, 54.3, 61.1, 127.8, 127.8, 130.9, 132.5; IR (neat) 2924, 1465 (C=C), 1458 (C=C), 1376, 1130, 721; HRMS m/z 277.2770 (Calcd. 277.2770 for $C_{19}H_{35}N$).

Isomer **21b**: ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6 H, 2 CH_3), 1.27 (m, 14 H, 7 CH_2), 1.48 (m, 2 H, CH_2), 2.09 (m, 2 H, =CCH_2), 2.35 (m, 2 H, =CCH_2), 2.45 (m, 2 H, NCH_2), 2.89 (t, 2 H, J = 5.7 Hz, NCH_2), 3.54 (s, 2 H, =CCH_2N), 5.54 (m, 2 H, 2 =CH), 6.02 (d, 1 H, J = 12 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 22.7, 28.2, 28.4, 29.3, 29.3, 29.4, 29.5, 29.8, 30.2, 31.9, 53.2, 54.2, 54.7, 128.0, 134.1, 134.2, 135.7; IR (neat) 2925, 1465 (C=C), 1426 (C=C), 1376, 1134, 722 cm^{-1}; HRMS m/z 277.2771 (Calcd. 277.2770 for $C_{19}H_{35}N$).

Compounds **22a**, **22b** and **22c**



22a **22b** **22c**

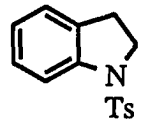
Obtained in 86 % yield as an inseparable (**22a/22b/22c** = 72:20:8) from the reaction of N-tosyl-2-(2-iodophenyl)ethylamine and 1,2-undecadiene. The isomer ratios were determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of all three isomers. TLC (4:1 hexanes/EtOAc) R_f = 0.50; ^{13}C NMR ($CDCl_3$) δ 14.1, 21.4, 22.7, 28.1, 29.1, 29.2, 29.2, 31.8, 34.4, 36.1, 47.0, 47.2, 47.7, 54.9, 126.2, 127.0, 127.1, 127.2, 127.3, 128.5, 129.2, 129.2, 129.5, 129.5, 133.4, 134.6, 135.8, 138.5, 139.5, 143.1; IR (neat) 2923, 2852, 1453 (C=C), 1336 (RSO_2N), 1163 (RSO_2N), 1094 cm^{-1}; HRMS m/z 425.2394 (Calcd. 425.2389 for $C_{26}H_{35}NSO_2$).

Isomer **22a**: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.6 Hz, CH_3), 1.20 (m, 12 H, 6 CH_2), 1.98 (dt, 2 H, J = 14.7, 7.5 Hz, $=CCH_2$), 2.38 (s, 3 H, $ArCH_3$), 2.87 (m, 2 H, $ArCH_2$), 3.33 (m, 2 H, CH_2N), 3.78 (s, 2 H, $=CCH_2N$), 5.87 (t, 1 H, J = 7.8 Hz, =CH), 7.00-7.70 (m, 8 H, aryl).

Isomer **22b**: ^{1}H NMR ($CDCl_3$) same as the isomer **22a** or not seen, except δ 3.43 (m, 2 H, NCH_2), 4.03 (s, 2 H, $ArCH_2$), 5.65 (t, 2 H, J = 7.8 Hz, =CH).

Isomer **22c**: ^{1}H NMR ($CDCl_3$) same as the isomer **22a** or not seen, except δ 5.08 (s, 1 H, =CH<u>H</u>), 5.12 (s, 1 H, =C<u>H</u>H).

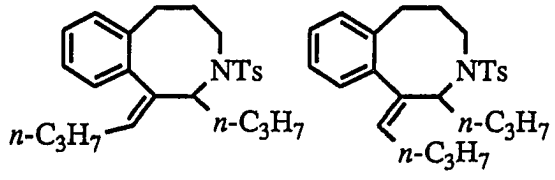
Compound **23**



23

Obtained in 97 % yield from the reaction of N-tosyl-2-(2-iodophenyl)ethylamine. TLC (4:1 hexanes/EtOAc) $R_f = 0.27$; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3 H, $ArCH_3$), 2.88 (t, 2 H, $J = 8.4$ Hz, $ArCH_2$), 3.91(t, 2 H, $J = 8.4$ Hz, CH_2N), 6.9-7.7 (4 m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.9, 49.9, 115.0, 123.7, 125.1, 127.1, 127.3, 127.5, 127.7, 129.6, 131.7, 144.0; IR (neat) 3067, 2923, 1599, 1479, 1354 (RSO_2N), 1167 (RSO_2N), 1103 cm^{-1}; HRMS m/z 273.0824 (Calcd. 273.0824 for $C_{15}H_{15}SO_2N$).

Compounds **24a** and **24b**



24a **24b**

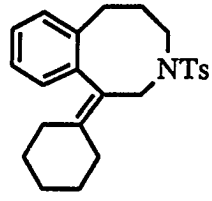
Obtained in 68 % yield as an inseparable mixture (**24a/24b** = 84:16) from the reaction of N-tosyl-3-(2-iodophenyl)propylamine and 4,5-nonadiene. The isomer ratio of **24a** and **24b** was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers. TLC (4:1 hexanes/EtOAc) $R_f = 0.50$; ^{13}C NMR ($CDCl_3$) δ 13.8, 19.8, 21.4, 22.2, 29.1, 30.5, 32.6, 32.7, 33.0, 39.7, 64.8, 125.6, 127.1, 127.6, 128.8, 129.3, 130.0, 133.3, 134.2, 137.4, 139.3, 139.7, 142.7; IR (neat) 2955, 1598 (C=C), 1453, 1351

(RSO_2N), 1157 (RSO_2N), 938, 676 cm^{-1}; HRMS m/z 411.225 (Calcd. 411.2232 for $C_{25}H_{33}SO_2N$).

Isomer **24a**: ^1H NMR ($CDCl_3$) δ 0.70-1.80 (m, 14 H, 4 CH_2, 2 CH_3), 2.20-2.60 (m, 4 H, $ArCH_2$, $=CCH_2$), 2.40 (s, 3 H, $ArCH_3$), 3.41 (m, 2 H, CH_2N), 4.54 (t, 1 H, J = 5.7 Hz, CHN), 5.67 (t, 1 H, J = 7.2 Hz, =CH), 6.81-7.80 (m, 8 H, aryl).

Isomer **24b**: ^1H NMR ($CDCl_3$) same as **24a** or not seen, except δ 5.34 (t, 1 H, J = 6.9 Hz, =CH).

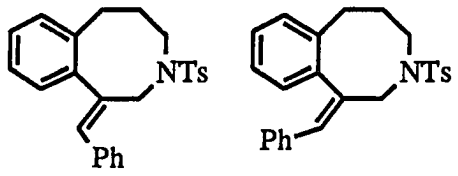
Compound **25**



25

Obtained in 62 % yield from the reaction of N-tosyl-3-(2-iodophenyl)propylamine and vinylidene cyclohexane. TLC (4:1 hexanes/EtOAc) R_f = 0.37; ^1H NMR ($CDCl_3$) δ 1.14 (m, 2 H, CH_2), 1.56 (m, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 1.82 (m, 2 H, CH_2), 1.88 (m, 1 H, CHH), 1.89 (m, 2 H, CH_2), 2.37 (s, 3 H, $ArCH_3$), 2.46 (m, 1 H, CHH), 2.57 (m, 1 H, ArCHH), 2.79 (m, 1 H, ArCHH), 3.02 (m, 2 H, CH_2N), 3.34 (d, 1 H, J = 13.2 Hz, =CCHHN), 4.47 (d, 1 H, J = 13.2 Hz, =CCHHN), 6.83-7.49 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.6, 27.8, 28.1, 29.9, 31.5, 32.3, 32.5, 48.5, 52.5, 126.3, 127.0, 127.0, 127.9, 128.7, 129.4, 136.4, 140.3, 141.0, 141.6, 142.6, 142.6; IR (neat) 2924, 2254, 1598 (C=C), 1447, 1333 (RSO_2N), 1159 (RSO_2N), 911, 748 cm^{-1}; HRMS m/z 395.1917 (Calcd. 395.1919 for $C_{24}H_{29}SO_2N$).

Compounds **26a** and **26b**



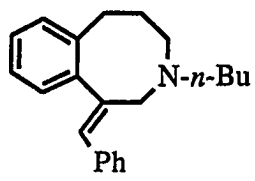
26a **26b**

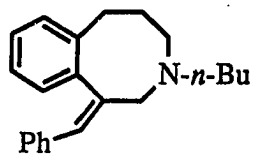
Obtained in 94 % yield (**26a**/**26b** = 91:9) from the reaction of N-tosyl-3-(2-iodophenyl)propylamine and phenyl allene as pure **26a** and a mixture of **26a** and **26b**. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens.

Isomer **26a**: TLC (4:1 hexanes/EtOAc) R_f = 0.31; ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 1 H, CHH), 1.92 (m, 1 H, CHH), 2.39 (s, 3 H, CH_3Ar), 2.62 (m, 2 H, $ArCH_2$), 3.12 (m, 1 H, NCHH), 3.36 (m, 1 H, NCHH), 3.92 (m, 1 H, =CCHHN), 4.12 (m, 1 H, =CCHHN), 6.62 (s, 1 H, =CHPh), 6.88-7.51 (m, 13 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.5, 32.1, 32.2, 48.7, 60.9, 127.1, 127.1, 127.2, 127.4, 127.9, 128.2, 128.7, 129.5, 129.6, 130.2, 135.5, 135.8, 137.9, 139.1, 140.1, 142.8; IR (neat) 3085, 2926, 2256, 1598 (C=C), 1494 (C=C), 1446, 1335 (RSO_2N), 1162 (RSO_2N), 933, 754 cm^{-1}; HRMS m/z 403.1604 (Calcd. 403.1606 for $C_{25}H_{25}SO_2N$).

Isomer **26b**: TLC (4:1 hexanes/EtOAc) Rf = 0.34. The following data were taken from a mixture of **26a** and **26b**. ^{1}H NMR ($CDCl_3$) same as the isomer **26a** or not seen, except δ 6.59 (s 1 H, =CHPh), 2.36 (s, 3 H, CH_3Ar); IR (neat) 3057, 2925, 1597 (C=C), 1445, 1335 (RSO_2N), 1158 (RSO_2N), 752 cm^{-1}; ^{13}C NMR ($CDCl_3$) same as the isomer **26a** or not seen, except δ 15.3, 31.5, 32.4, 49.7, 52.2, 65.8, 126.1, 127.3, 127.8, 128.3, 128.3, 128.4, 128.9, 129.1, 129.6; HRMS m/z 403.1601 (Calcd. 403.1606 for $C_{25}H_{25}SO_2N$).

Compounds **27a** and **27b**





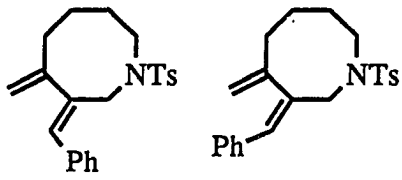
27a **27b**

Obtained in 98 % yield as a separable mixture (**27a/27b** = 78:22) from the reaction of N-tosyl-3-(2-iodophenyl)propylamine and phenyl allene.

Isomer **27a**: TLC (4:1 hexanes/EtOAc) $R_f = 0.41$; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3 H, $J = 7.2$ Hz, CH_3), 1.08 (m, 2 H, CH_2), 1.33 (m, 2 H, CH_2), 1.70 (m, 2 H, CH_2), 2.47 (t, 2 H, $J = 7.2$ Hz, $ArCH_2$), 2.68 (m, 4 H, $N(CH_2)_2$), 3.46 (s, 2 H, $=CCH_2N$), 6.51 (s, 1 H, =CHPh), 6.9-7.4 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.2, 30.0, 32.2, 33.0, 53.3, 55.8, 68.1, 126.5, 126.6, 126.7, 127.1, 127.4, 128.0, 128.6, 128.9, 140.6, 141.5, 136.8, 142.5; IR (neat) 3059, 2957, 2925, 1599 (C=C), 1447, 751, 693 cm^{-1}; HRMS m/z 305.2139 (Calcd. 305.2144 for $C_{22}H_{27}N$).

Isomer **27b**: TLC (4:1 hexanes/EtOAc) $R_f = 0.51$; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3 H, $J = 7.2$ Hz, CH_3), 1.1-1.7 (m, 6 H, 3 CH_2), 2.51 (m, 4 H, $ArCH_2$, NCH_2), 2.63 (t, 2 H, $J = 9.9$ Hz, NCH_2), 3.46 (s, 2 H, $=CCH_2N$), 6.46 (s, 1 H, =CH), 7.0-7.5 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.2, 30.2, 31.8, 32.4, 54.8, 58.0, 59.9, 125.6, 126.6, 127.0, 127.5, 127.9, 128.0, 128.0, 128.1, 128.4, 128.6, 129.2, 129.3, 129.5; HRMS m/z 305.2139 (Calcd. 305.2144 for $C_{22}H_{27}N$). There was not enough material for IR analysis.

Compounds **28a** and **28b**



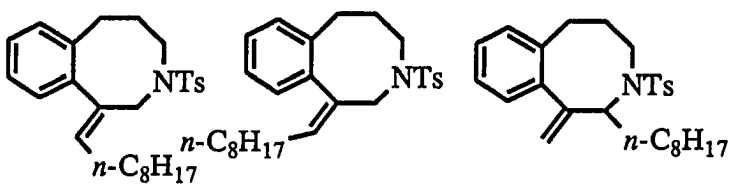
28a **28b**

Obtained in 16% yield as an inseparable mixture (**28a/28b** = 74:26) from the reaction of N-tosyl-5-iodo-5-hexenylamine and phenyl allene. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of isomers. TLC (4:1 hexanes/EtOAc) R_f = 0.51. There was not enough material for ^{13}C NMR, IR and HRMS analysis.

Isomer **28a**: ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 4 H, 2 CH_2), 2.42 (s, 3 H, $ArCH_3$), 3.20 (m, 2 H, $=CCH_2$), 2.60 (m, 2 H, CH_2N), 4.00 (s, 2 H, $=CCH_2N$), 5.05 (s, 1 H, $=C\underline{H}H$), 5.32 (s, 1 H, $=CH\underline{H}$), 6.41 (s, 1 H, PhCH=), 7.2-7.9 (m, 9 H, aryl).

Isomer **28b**: ^{1}H NMR ($CDCl_3$) same as isomer **28a** or not seen, except δ 4.31 (s, 2 H, $=CCH_2N$), 6.64 (s, 1 H, PhHC=).

Compounds **29a**, **29b**, and **29c**



29a **29b** **29c**

Obtained in 88 % yield (**29a**/**29b**/**29c** = 39:44:17) from the reaction of N-tosyl-3-(2-iodophenyl)propylamine and 1,2-undecadiene as pure **29a** and a mixture of **29b** and **29c**. The isomeric ratio of **29b** and **29c** was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens.

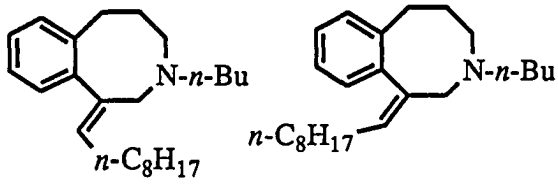
Isomer **29a**: TLC (4:1 hexanes/EtOAc) R_f = 0.41; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, *J* = 6.6 Hz, CH_3), 1.2 (4 m, 14 H, 7 CH_2), 1.72 (m, 2 H, CH_2), 2.40 (s, 3 H, $ArCH_3$), 2.62 (m, 2 H, $ArCH_2$), 3.10 (m, 2 H, CH_2N), 3.8 (m, 2 H, $=CCH_2N$), 5.73 (t, 1 H, *J* = 6.9 Hz, =CH), 6.82-7.50 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.3, 22.5, 28.7, 28.9, 29.0, 29.1, 29.2, 31.6, 31.7, 32.2, 48.1, 59.0, 126.2, 126.9, 127.0, 127.4, 127.7, 128.6, 128.8, 129.3, 132.7, 139.0, 139.9, 142.6; IR (neat) 2954, 2257, 1588 (C=C), 1454 (C=C), 1338 (RSO_2N), 1162 (RSO_2N) cm^{-1}; HRMS m/z 439.2545 (Calcd. 439.2545 for $C_{27}H_{37}SO_2N$).

The following data were taken from the mixture of isomers **29b** and **29c**. TLC (4:1 hexanes/EtOAc) R_f = 0.46; ^{13}C NMR ($CDCl_3$) δ 14.1, 21.4, 22.6, 26.4, 29.1, 29.3, 29.4, 29.5, 30.5, 31.2, 31.8, 32.0, 64.1, 125.6, 126.1, 127.1, 127.5, 127.8, 128.4, 128.6, 128.8, 129.4, 133.7, 136.3, 136.5, 138.6, 139.4, 140.0, 142.8, 142.9, 148.6; IR (neat) 3063, 2954, 1598 (C=C), 1454, 1338 (RSO_2N), 1159 (RSO_2N) cm^{-1}; HRMS m/z 439.2550 (Calcd. 439.2545 for $C_{27}H_{37}SO_2N$).

Isomer **29b**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.6 Hz, CH_3), 1.28 (m, 12 H, 6 CH_2), 1.81 (m, 2 H, CH_2), 2.26 (m, 2 H, =CCH_2), 2.39 (s, 3 H, $ArCH_3$), 2.76 (t, 2 H, J = 6 Hz, $ArCH_2$), 3.05 (t, 2 H, J = 5.4 Hz, NCH_2), 3.92 (s, 2 H, =CCH_2N), 5.47 (t, 1 H, J = 7.5 Hz, =CH), 6.9-7.82 (4 m, 8 H, aryl).

Isomer **29c**: ^{1}H NMR ($CDCl_3$) same as the isomer **29b** or not seen, except δ 4.58 (m, 1 H, =CCHN), 4.92 (s, 1 H, =C<u>H</u>H), 5.36 (s, 1 H, =CH<u>H</u>).

Compounds **30a** and **30b**



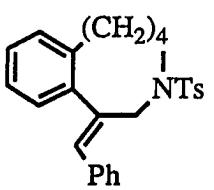
30a **30b**

Obtained in 84% yield as an inseparable mixture (**30a/30b** = 78:22) from the reaction of N-tosyl-3-(2-iodophenyl)propylamine and 1,2-undecadiene. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers. TLC (4:1 hexanes/EtOAc) R_f = 0.44; ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 20.3, 22.7, 28.8, 29.2, 29.3, 29.3, 29.4, 29.9, 31.9, 32.4, 32.7, 52.7, 52.1, 66.3, 125.7, 126.7, 127.5, 128.4, 129.5, 129.5, 129.6, 140.5; IR (neat) 2924, 2853, 1457 (C=C), 1376, 748 cm^{-1}; HRMS m/z 341.3073 (Calcd. 341.3083 for $C_{23}H_{39}N$).

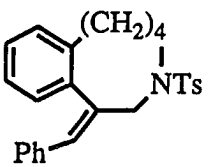
Isomer **30a**: ^{1}H NMR ($CDCl_3$) δ 0.86 (m, 6 H, 2 CH_3), 1.1 (m, 16 H, 8 CH_2), 1.80 (m, 4 H, 2 CH_2), 2.44 (m, 2 H, $ArCH_2$), 2.56 (m, 2 H, NCH_2), 2.63 (m, 2 H, NCH_2), 3.26 (s, 2 H, =CCH_2N), 5.57 (t, 1 H, J = 6.9 Hz, =CH), 6.9-7.2 (m, 4 H, aryl).

Isomer **30b**: ^{1}H NMR ($CDCl_3$) same as the isomer **30a** or not seen, except δ 2.20 (m, 2 H, CH_2), 2.72 (m, 2 H, $ArCH_2$), 3.35 (s, 2 H, $=CCH_2N$), 5.33 (t, 1 H, J = 6.9 Hz, =CH).

Compounds **31a** and **31b**



31a



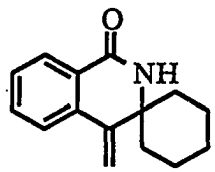
31b

Obtained in 83% yield as an inseparable mixture (**31a/31b** = 86:14) from the reaction of N-tosyl-4-(2-iodophenyl)butylamine and phenylallene. The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers. TLC (4:1 hexanes/EtOAc) R_f = 0.40; ^{13}C NMR ($CDCl_3$) δ 21.4, 25.6, 27.7, 31.0, 48.2, 58.3, 126.7, 127.1, 127.4, 127.8, 127.9, 128.3, 128.8, 129.3, 129.4, 129.5, 132.6, 136.2, 137.7, 139.4, 140.7, 143.1; IR(neat) 3062, 2921, 2256, 1730, 1598 (C=C), 1446 cm^{-1}; HRMS m/z 418.1802 (Calcd. for $C_{26}H_{28}SO_2N$ 418.1841).

Isomer **31a**: ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 1 H, C<u>H</u>H), 1.30 (m, 1 H, CH<u>H</u>), 1.57 (m, 1 H, C<u>H</u>H), 1.84 (m, 1 H, CH<u>H</u>), 2.40 (s, 3 H, $ArCH_3$), 2.51 (m, 1 H, ArC<u>H</u>H), 2.89 (m, 1 H, ArCH<u>H</u>), 2.98 (m, 1 H, NCH<u>H</u>), 3.4 (m, 1 H, NC<u>H</u>H), 3.96 (s, 1 H, C<u>H</u>HN), 4.01 (s, 1 H, CH<u>H</u>N), 6.80 (s, 1 H, =CHPh), 6.80-7.63 (6 m, 13 H, aryl).

Isomer **31b**: ^{1}H NMR ($CDCl_3$) same as the isomer **31a** or not seen, except δ 2.36 (s, 3 H, $ArCH_3$), 3.91 (s, 1 H, C<u>H</u>HN), 4.06 (s, 1 H, CH<u>H</u>N), 6.58 (s, 1 H, =CHPh).

Compound **33**



33

Obtained in 89 % yield from the reaction of 2-iodobenzamide and vinylidene cyclohexane. TLC (1:1 hexanes/EtOAc) $R_f = 0.41$; ^1H NMR ($CDCl_3$) δ 1.58 (m, 6 H, 3 CH_2), 1.76 (m, 2 H, CH_2), 2.0 (m, 2 H, CH_2), 5.30 (s, 1 H, C=C<u>H</u>H), 5.61 (s, 1 H, C=CH<u>H</u>), 7.46 (m, 3 H, aryl), 8.20 (d, 1 H, J = 16.0 Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 21.5, 25.5, 35.1, 79.8, 110.0, 124.6, 127.6, 128.5, 131.9, 145.4, three peaks were not observed due to overlap with others; IR (Neat) 3025, 2930, 2853, 1712 (C=O), 1650 (C=O), 1619, 1575 (C=C), 1330, 1187, 1097, 980 cm^{-1}; HRMS m/z 227.3085 (Calcd. 227.3088 for $C_{15}H_{17}NO$).

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GENERAL SUMMARY

In this dissertation, the palladium-promoted cross-coupling of organic halides, alkenes and nucleophiles has been demonstrated. The importance of these methodologies is that they allow one to form two new bonds in a single step under mild conditions using only catalytic amounts of palladium. In addition, organopalladium chemistry can accommodate a wide variety of important organic functional groups.

In the first part of this thesis, the development of the palladium(0)-catalyzed cross-coupling of vinylic halides with alkenes and nucleophiles was discussed. A variety of amine nucleophiles, as well as carbon nucleophiles, have been applied to this system. Functionalized alkenes were isolated in yields ranging from poor to good.

In the second part of this thesis, the palladium(0)-catalyzed annulation using functionalized organic halides and allenes was explored. A number of nitrogen-containing heterocyclic compounds with ring-sizes ranging from six to nine were synthesized. The difference in reactivity between aryl halides and vinylic halides in this reaction has been discussed.

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