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

Yao Wang
Iowa State University

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

by

Yao Wang

A Dissertation Submitted to the

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Department: Chemistry
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For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1995

To Lóngmèi

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LIST OF ABBREVIATIONS

Ac	acetyl
Ar	aryl
atm	atmosphere
br	broad
Bu	butyl
cat.	catalyst
d	doublet or days
dba	dibenzylideneacetone
DMA	*N*,*N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equation
equiv.	equivalents
Et	ethyl
g	grams
GC	gas chromatography
GC-MS	gas chromatography – mass spectrometry
h	hours
HRMS	high resolution mass spectrometry
IR	infrared
M	molar
m	multiplet

Me	methyl
mg	milligrams
min	minutes
ml	milliliters
mm Hg	millimeters of mercury
mmol	millimoles
mol	moles
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
Py	pyridine
r.t.	room temperature
q	quartet
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl

GENERAL INTRODUCTION

Organopalladium chemistry has become more and more important in the area of organic synthesis. The formation of carbon-carbon bonds and/or carbon-heteroatom bonds catalyzed by palladium proceeds quite smoothly under mild reaction conditions. Palladium-catalyzed three component coupling of aryl halides, nonconjugated dienes and nucleophiles has provided a very efficient method to rapidly increase molecular complexity. This dissertation focuses on the development and applications of this methodology.

This dissertation is divided into five papers. Each paper is presented with its own introduction, results and discussion, experimental section, conclusion, and references. Following the last paper is a general summary. The first name of the authors in each paper is the major professor, and the second name is the Ph.D. candidate who is primarily responsible for the research and writing of the papers.

The first paper deals with the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and phenylmetallics, which provides a very useful method to make long chain hydrocarbons with an aromatic group at each end.

The focus of the second paper is on the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and amines. Secondary amines have proven to be excellent nucleophiles in this coupling process, where both acyclic and cyclic nonconjugated dienes and a variety of aryl iodides have been examined. The regiochemistry of this reaction is also discussed.

The third paper presents some successful applications of our palladium-catalyzed coupling process to the synthesis of the naturally-occurring alkaloids

theonelladins C and D, niphatesine C and xestamine D. Only two to three steps are needed to accomplish the total synthesis of these natural products from readily available starting materials.

In the fourth paper, several different types of heteroatom nucleophiles other than amines have been investigated in order to explore the scope and limitations of the palladium-catalyzed coupling process.

The focus of the last paper is on the preparation of C-5 substituted pyrimidine nucleosides via palladium-catalyzed coupling. It has been proven that the coupling of 5-iodo-2'-deoxyuridine with nonconjugated dienes and amines is improved significantly by the use of a Lewis acid, such as $ZnCl_2$.

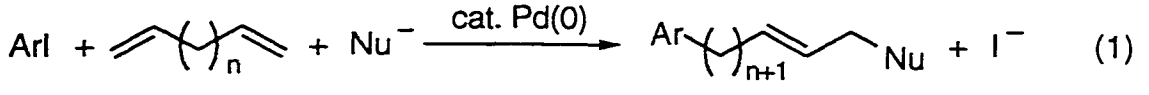
PALLADIUM–CATALYZED COUPLING OF ARYL IODIDES, NONCONJUGATED DIENES AND PHENYLMETALLICS

A paper to be submitted to the *Journal of Organic Chemistry*

Richard C. Larock and Yao Wang

Introduction

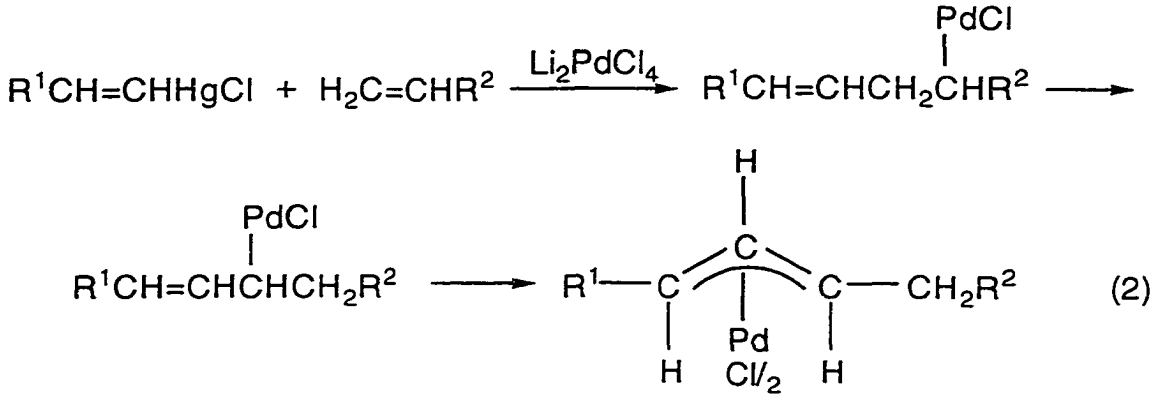
"Efficient synthetic methods required to assemble complex molecular arrays include reactions that are both selective (chemo-, regio-, diastereo-, and enantio-) and economical in atom count (maximum number of atoms of reactants appearing in the products)."[1] It has become more and more important to discover and develop synthetic methods which can rapidly increase molecular complexity, especially methodology that generates more than one carbon-carbon bond at a time. Some good examples include cyclization reactions, such as the Diels-Alder reaction[2] and metal-catalyzed [2+2+2]-cycloaddition reactions.[3] However, not much attention has been focused on developing such methods for the synthesis of long-chain complex molecules. Here, we report our efforts on just such methodology involving the palladium-catalyzed three-component coupling shown in equation 1.



(1)

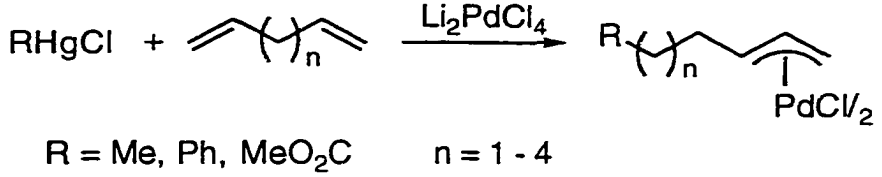
Applications of palladium chemistry in organic synthesis have rapidly developed.[4] One of the most interesting areas is π-allylpalladium chemistry. Since first reported in 1957,[5] π-allylpalladium compounds have received much attention. The most important procedures for preparing π-allylpalladium compounds are the insertion of palladium(0) reagents into allylic substrates[6] and the direct allylic hydrogen substitution of alkenes by palladium salts.[7] It is also common to prepare π-allylpalladium compounds from dienes,[8] cyclopropanes[9] and alkynes,[10] as well as via organomercurials.[11]

Larock and Mitchell have found that vinylmercurials react with Li_2PdCl_4 and simple alkenes to afford π-allylpalladium compounds through a palladium hydride rearrangement (eq. 2).[11b]



(2)

Later on, Larock and coworkers further investigated the remote palladium migration in the preparation of π-allylpalladium compounds. The reactions of organomercurials with Li_2PdCl_4 and non-conjugated dienes generated good to excellent yields of π-allylpalladium compounds (eq. 3)[12]



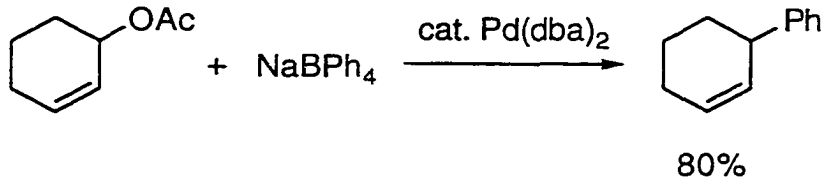
(3)

R = Me, Ph, MeO_2C n = 1 - 4

through a process which apparently involved initial organopalladium addition to the less hindered double bond of the diene, followed by a series of palladium hydride elimination-readdition reactions until a π-allylpalladium compound is formed.

It is well known that π-allylpalladium compounds, as reactive intermediates, are involved in many reactions, the most important of which is nucleophilic displacement by carbon[13] or heteroatom[14] nucleophiles. Organometallics, such as organoboron[15] and organotin[16] reagents, have also been widely used as nucleophiles in many types of reactions, including cross-coupling with π-allylpalladium compounds.[17]

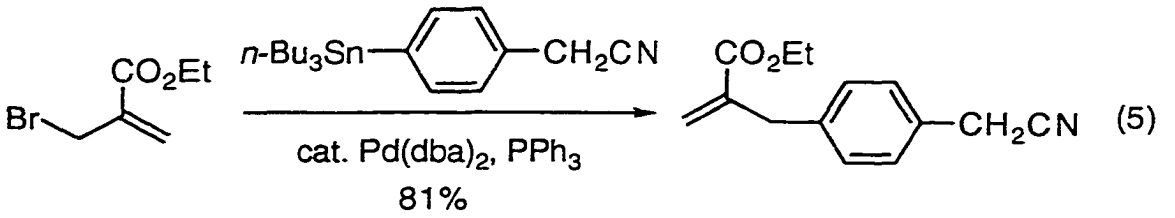
Legros and Fiaud have reported sodium tetraphenylborate as a convenient carbonucleophile in the palladium-catalyzed phenylation of allylic acetates (eq. 4).[17a]



(4)

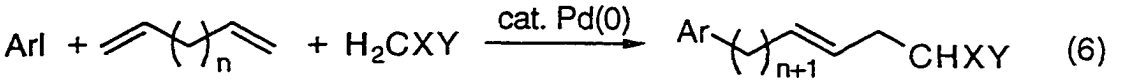
80%

The palladium-catalyzed cross-coupling of allylic halides with organotin compounds has been reported by Sheffy and Stille.[17d] Generally, aryl or vinylic tin reagents in this coupling process give high yields of the products (eq. 5).



(5)

Larock and coworkers have recently reported a unique palladium-catalyzed coupling of aryl iodides, non-conjugated dienes and stabilized carbanion nucleophiles (eq. 6).[18] This process allows three major components to combine together to form two carbon-carbon bonds. Apparently, the reaction involves (1) palladium(0) oxidative addition to an aryl iodide, (2) arylpalladium addition to one of the carbon-carbon double bonds of a diene, (3) palladium migration through a series of reversible palladium hydride elimination-readditions, (4) formation of a π-allylpalladium intermediate, and (5) carbanion displacement of the palladium moiety.



(6)

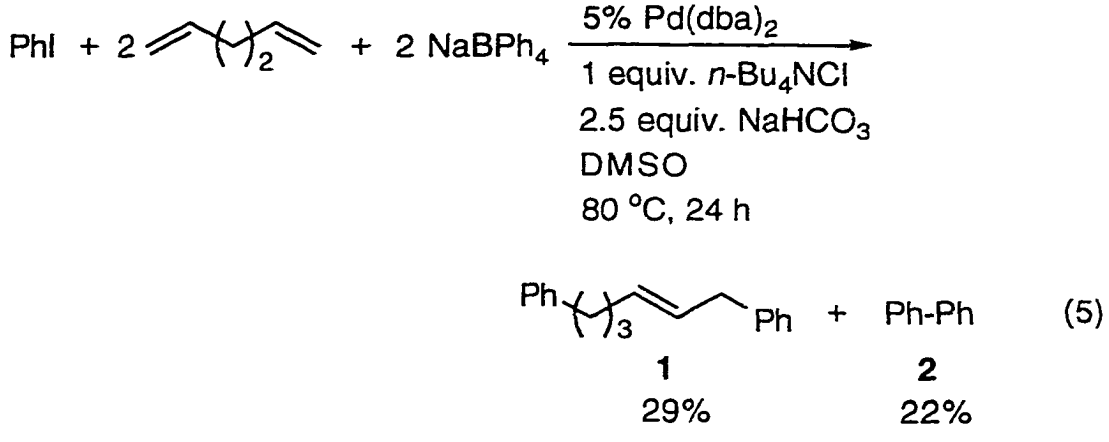
X, Y = COR, CO_2R, CN
n = 2 - 10

52 - 82%

The purpose of this dissertation is to extend this type of palladium-catalyzed coupling to other nucleophiles and apply this methodology to the synthesis of some biologically active compounds. In this paper, phenyl-metallics, used as nucleophiles in the palladium-catalyzed three-component coupling, will be discussed.

Results and Discussion

The coupling of iodobenzene, 1,5-hexadiene and sodium tetraphenylborate ($NaBPh_4$) was chosen as a model system for our exploratory investigations. First of all, this coupling reaction was examined under the best conditions of reaction 4 as shown below. The desired product **1** was obtained in only 29%



yield, alongside a cross-coupling product biphenyl (**2**) in 22% yield. Apparently, the reaction conditions need to be optimized before further testing the scope and limitation of this type of coupling. Catalysts, bases and solvents were therefore examined. The results are summarized in Table 1.

From the results in Table 1, one can see that $Pd(dba)_2$ as a catalyst is better than $Pd(OAc)_2$, and $NaHCO_3$ is the right choice of a base. Although DMSO is a good solvent for reaction 4, in our system, however, DMF appears to be better than DMSO. We also tested the effect of PPh_3 on the coupling reaction, and found that PPh_3 made the reaction worse (entries 6 and 11).

GC analysis indicated that the reaction had not gone to completion after running for 24 hours at 80 °C. So we decided to raise the temperature and

Table 1. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Sodium Tetraphenylborate[a]

entry	catalyst (5%)	base (2.5 equiv)	solvent	% yield[b]	
				1	**2**
1	$Pd(dba)_2$	$NaHCO_3$	DMSO	29	22
2		Na_2CO_3	DMSO	18	14
3		KOAc	DMSO	0	trace
4		KOAc	DMF	17	17
5		$NaHCO_3$	DMF	34	20
6[c]		$NaHCO_3$	DMF	3	24
7	$Pd(OAc)_2$	$NaHCO_3$	DMSO	12	28
8		Na_2CO_3	DMSO	15	15
9		KOAc	DMSO	0	trace
10		$NaHCO_3$	DMF	21	19
11[c]		$NaHCO_3$	DMF	12	18

[a] Reactions were run in the presence of 1 equiv. of *n*-Bu_4NCl using 2 equiv. of diene and 2 equiv. of $NaBPh_4$ at 80 °C for 24 hours.

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

[c] 5 Mol % of PPh_3 added.

extend the reaction time in an attempt to complete the reaction and obtain a higher yield of the desired product. The results are summarized in Table 2. $NaHCO_3$ was chosen as the base, and both DMF and DMSO were tested again as the solvent in this reaction. One can see that the reactions run at 100 °C

Table 2. Effect of Reaction Temperature and Time on the Palladium-catalyzed Coupling[a]

entry	solvent	temp. (°C)	time (d)	% yield[b]	
				1	**2**
1	DMSO	80	0.5	16	11
2		80	1	29	22
3		80	3	32	22
4		80	5	35	13
5		100	1	38	26
6		100	3	33	22
7		100	5	38	26
8		100	7	43	22
9	DMF	80	1	31	19
10		80	3	43	17
11		80	5	48	17
12		100	1	39	33
13		100	3	51	29
14		100	5	53	32
15		100	7	46	36

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$, 1 equiv. of *n*-Bu_4NCl and 2.5 equiv. of $NaHCO_3$ using 2 equiv. of diene and 2 equiv. of $NaBPh_4$.

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

gave higher yields of both **1** and **2** than those run at 80 °C, and longer reaction times were also better for the reaction, but not longer than 5 days when DMF was used as the solvent (entries 14 and 15). DMF again proved to be a better solvent than DMSO.

We also examined the reaction at a still higher temperature. For example, a reaction was run at 120 °C to give 43% and 44% yields of **1** and **2** respectively. Other reaction conditions except temperature were the same as those of entries 10 and 13. The effect of the temperature on the reaction is clearly shown in Figure 1. The yield of compound **2** increased gradually with the rise of temperature, while the desired compound **1** reached the highest yield at 100 °C.

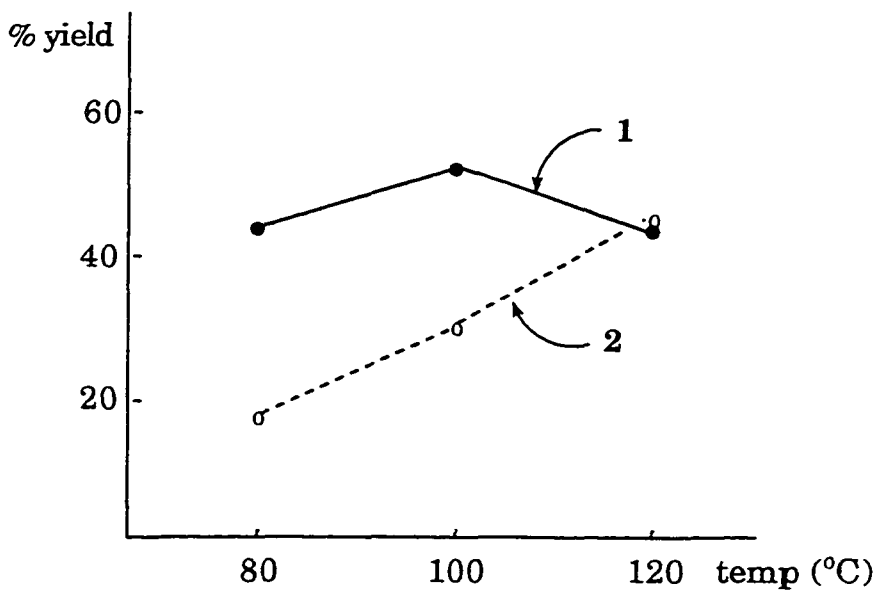


Figure 1. Effect of the temperature on the palladium-catalyzed coupling.

The effect of the amounts of *n*-Bu_4NCl and $NaHCO_3$ used in the reaction was next examined. From the results shown in Table 3, one can see that there is no significant change in the yields of **1** and **2** with the variation of *n*-Bu_4NCl and $NaHCO_3$ (entries 1–5). The reaction still afforded a modest yield of the

Table 3. Effect of the Amounts of *n*-Bu_4NCl and $NaHCO_3$ and the Stoichiometry on the Palladium-catalyzed Coupling[a]

entry	PhI/diene/$NaBPh_4$	*n*-Bu_4NCl (equiv)	$NaHCO_3$ (equiv)	% yield[b] **1**	**2**
1	1/2/2	1.0	2.5	51	29
2		1.5	2.5	48	28
3		0	2.5	48	37
4		1.0	1.5	50	28
5		1.0	0	45	29
6	1/2/5	1.0	2.5	40	68
7	1/5/5	1.0	2.5	57	57
8	1/5/2	1.0	2.5	71	28
9	1/5/1	1.0	2.5	61	10
10	1/5/1	2.0	2.5	54	8
11	1/5/2	2.0	2.5	66	18
12	1/5/2	--[c]	2.5	62	26

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$ at 100 °C for 3 days.

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

[c] 2.0 Equiv of LiCl were used instead of *n*-Bu_4NCl.

desired product (**1**) even without *n*-Bu_4NCl or $NaHCO_3$. However, it appears to be desirable to have *n*-Bu_4NCl and $NaHCO_3$ present.

In an attempt to further improve the reaction, especially the selectivity of the products, the stoichiometry of the reactants was investigated. The results are given in Table 3. In general, increasing the amount of 1,5-hexadiene to 5.0 equiv gave higher yields of **1**. However, when 5.0 equiv of $NaBPh_4$ was used in the reaction, the yield of **2** was dramatically increased (entries 6 and 7). In these cases, the total yields of **1** and **2** were actually over 100%. Apparently, some of the biphenyl (**2**) is formed directly from $NaBPh_4$. Comparing entries 9 and 10 with entries 8 and 11, one can see that decreasing the amount of $NaBPh_4$ not only limited the formation of **2**, but also reduced the yield of **1**. LiCl was tried in the reaction instead of *n*-Bu_4NCl, but it did not improve the yield of **1** (entry 12).

With the optimized conditions in hand, we started to examine other systems, e.g., a variety of aromatic iodides, non-conjugated dienes and phenyl nucleophiles. Triphenylboron (Ph_3B) and phenylboronic acid ($PhB(OH)_2$) as nucleophiles were first employed in the coupling reaction under the best conditions (entry 8, Table 3). $PhB(OH)_2$ provided a much better selectivity than Ph_3B, and even better than $NaBPh_4$. The results are shown in Table 4. We expected to improve the reaction (with $PhB(OH)_2$ as the nucleophile) by changing the stoichiometry of reactants. However, no better results were obtained, even when the reaction time was extended to 5 days.

With careful investigation, we have found that the desired coupling product (**1**) was actually a mixture of several isomers. For example, the GC-MS analysis for the reaction described in entry 2 of Table 4 indicated that

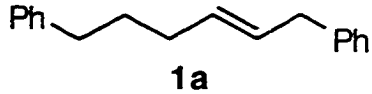
Table 4. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Phenyl Nucleophiles[a]

entry	PhI/diene/Nu	Nu	time (d)	% yield[b]	
				1	**2**
1	1 / 5 / 2	Ph_3B	3	53	55
2	1 / 5 / 2	$PhB(OH)_2$	3	62	trace
3	1 / 5 / 3	$PhB(OH)_2$	3	59	18
4	1 / 5 / 3	$PhB(OH)_2$	5	55	trace
5	1 / 2 / 2	$PhB(OH)_2$	3	42	5
6	1 / 2 / 2	$PhB(OH)_2$	5	52	trace

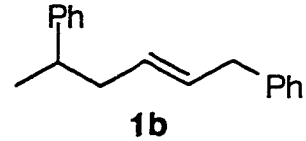
[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$, 1 equiv of *n*-Bu_4NCl and 2.5 equiv of $NaHCO_3$ at 100 °C.

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

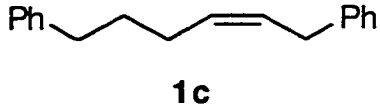
there were 7 isomers present in the product. According to the GC-MS and ^1H NMR spectrum, two major isomers were identified as **1a** and **1b**. We also could identify two minor isomers **1c** and **1d** with structures shown below. The structures of the other isomers were not identified since they are present in only trace amounts.



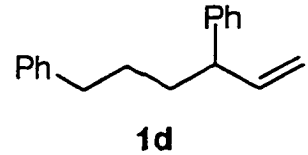
1a



1b



1c



1d

The formation of the identified isomers can be rationalized by the mechanism shown in Scheme 1. The oxidative addition of palladium(0) to iodobenzene is followed by arylpalladium addition to one of the carbon-carbon double bonds of the diene. There are two possibilities here; the phenyl group can add to the less hindered carbon of the double bond to give intermediate **3**, which predominates, or the phenyl group can add to the more hindered carbon of the double bond to form intermediate **4**. Intermediate **3** undergoes palladium migration through a series of palladium hydride β-eliminations and readditions to form a π-allylpalladium complex which exists in two comformations, *syn* and *anti*. The transmetallation of a phenyl group from boron to palladium then gives intermediates **5** and **6** respectively. The major, desired product **1a** is generated by the reductive elimination of **6** by coupling of the phenyl group to the less hindered carbon of the π-allyl system. Similar reductive elimination of **5** will generate **1c**. Both **5** and **6** can form **1d** when the phenyl group couples to the more hindered carbon of the π-allyl system. In a similar way, the three other isomers **1b**, **1e** and **1f** can be formed from intermediate **4**.

The ratio of the isomers of the desired coupling product was examined when we tested a variety of aryl iodides and non-conjugated dienes in this palladium-catalyzed coupling. We chose $PhB(OH)_2$ as the nucleophile, because it provided good selectivity (Table 4) and gave somewhat better yields of the products than $NaBPh_4$ in our later investigations (entries 1 and 2, Table 5).

From the results shown in Table 5, one can see that substituted aromatic iodides generally work as well as iodobenzene. The functional group can be either an electron-donating or electron-withdrawing group. Aromatic iodides bearing electron-withdrawing groups appear to give higher overall yields of the

Scheme 1

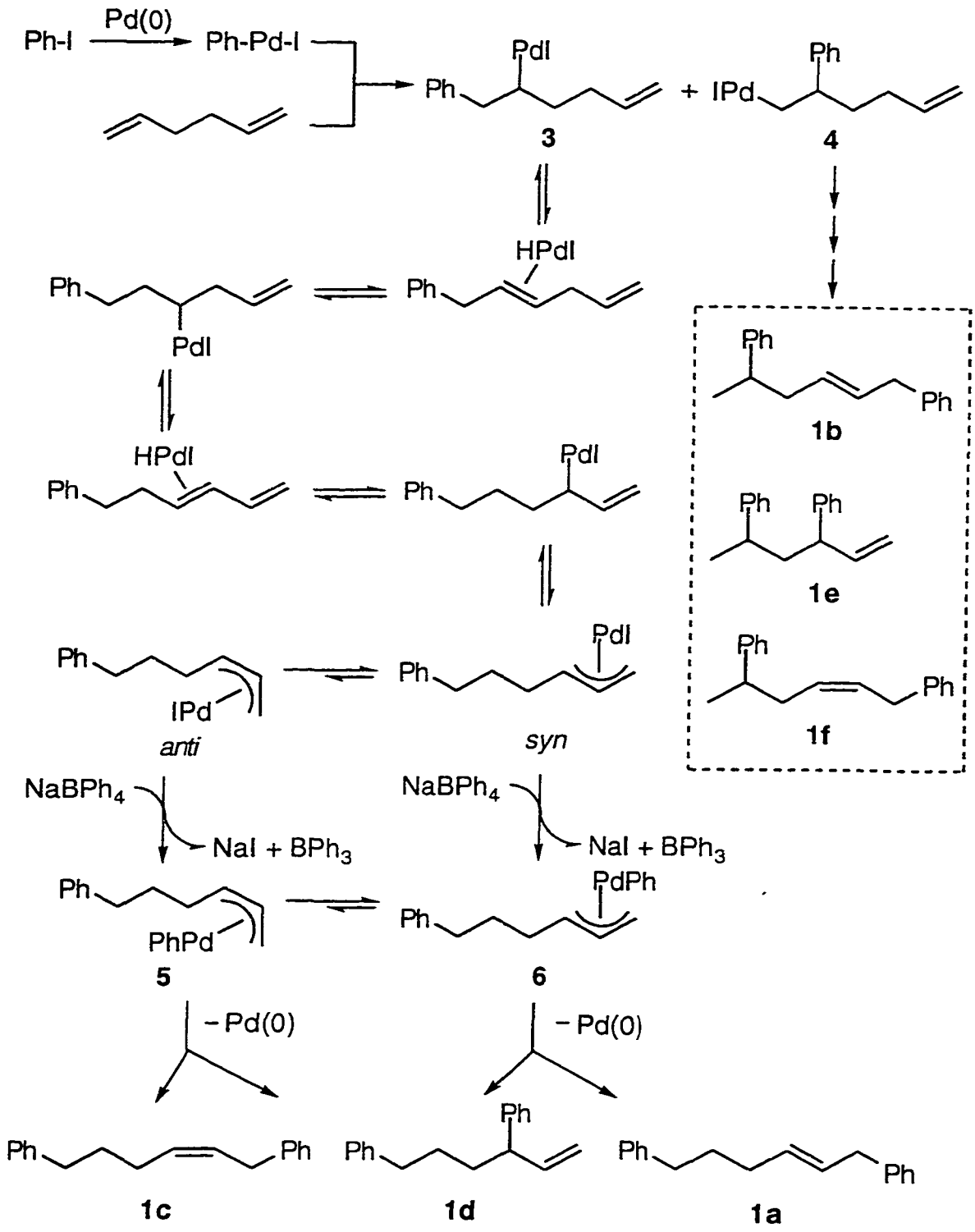
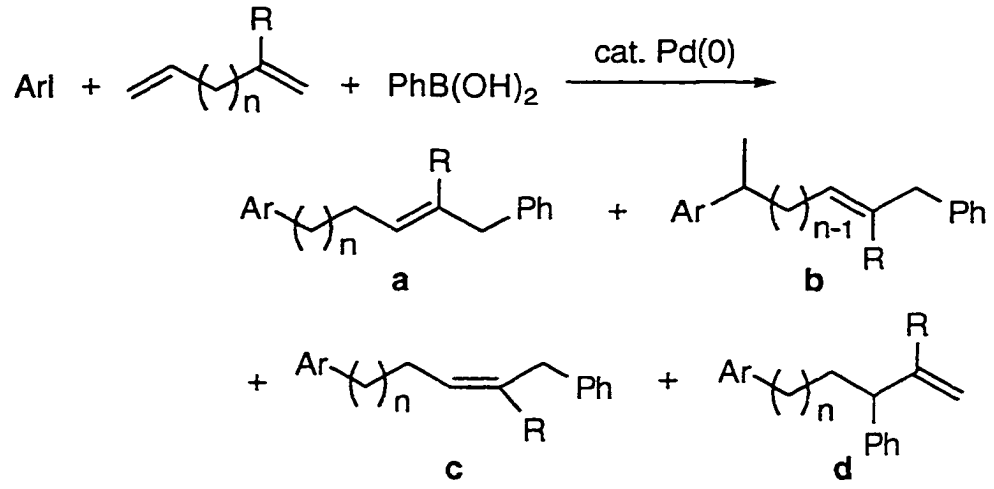

Ph-I
Pd(0)
Ph-Pd-I
PdI
Ph
+ IPd
3
4
HPdI
1b
1e
1f
IPd
anti
syn
NaBPh4
NaI + BPh3
PhPd
PdPh
5
6
- Pd(0)
1c
1d
1a

Table 5. Palladium-catalyzed Coupling of Aryl Iodides, Non-conjugated Dienes and Phenyl Nucleophiles[a]



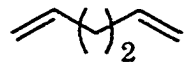
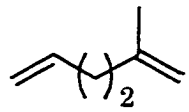
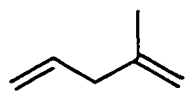
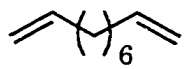
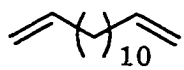
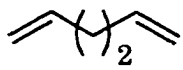
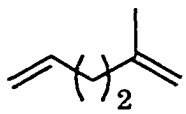
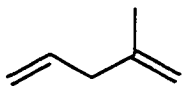
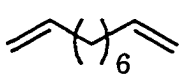
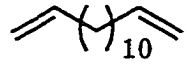
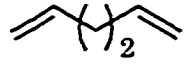
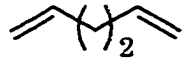
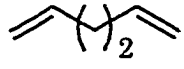
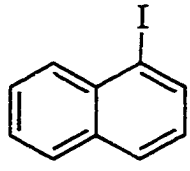
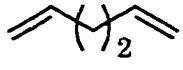
entry	aryl iodide	diene	% isolated yield[b]	ratio (**a**:**b**:**c**:**d**)[c]
1	PhI		65 (63)	66 : 14 : 12 : 8
2			57 (51)	62 : 16 : 13 : 9
3			56	66 : 13 : 12 : 9
4			46	78 : 15 : 0 : 7
5			43	81 : 10 : 0 : 9
6	*p*-$MeOC_6H_4I$		57	60 : 13 : 17 : 10
7			63	62 : 14 : 15 : 9
8			53	65 : 15 : 11 : 9
9			42	81 : 11 : 0 : 8

Table 5. (continued)

entry	aryl iodide	diene	% isolated yield	ratio (**a**:**b**:**c**:**d**)
10	*p*-$MeOC_6H_4I$		42	80 : 9 : 0 : 11
11	*o*-$MeOC_6H_4I$		53	72 : 6 : 11 : 11
12	*p*-$EtO_2CC_6H_4I$		72	67 : 11 : 12 : 10
13	*p*-$MeCOC_6H_4I$		70	68 : 11 : 12 : 9
14			56	75 : 6 : 11 : 8

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$, 1 equiv of *n*-Bu_4NCl and 2.5 equiv of $NaHCO_3$ using 5 equiv of diene and 2 equiv of nucleophile in DMF at 100 °C for 3 days.

[b] Numbers in parentheses are yields from the reactions with $NaBPh_4$ as a nucleophile.

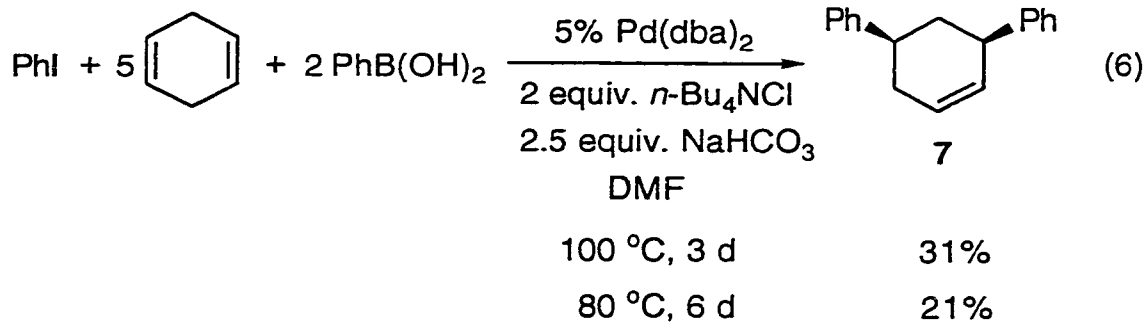
[c] Ratios were determined by ^1H NMR spectroscopy.

products and slightly better regioselectivity (compares entries 6, 12 and 13). From the mechanism described earlier, we believed that a bulkier aryl iodide would provide higher regioselectivity, because of more selective addition to the double bond of the diene. This proved to be true when we changed the position of the methoxy group in the aryl iodide. The ratio of **a** and **b** significantly increased from 60:13 to 72:6 when the CH_3O group was moved from the *para* to the *ortho* position (entries 6 and 11). For similar reasons, 1-iodonaphthalene also provided higher regioselectivity (entry 14).

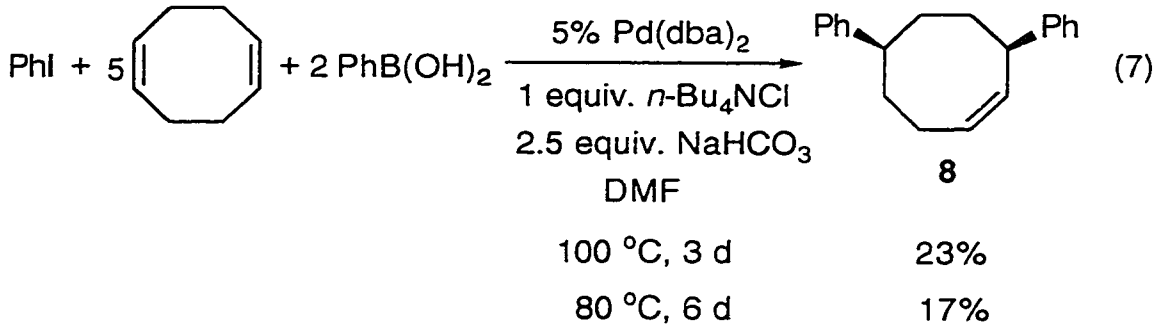
A variety of non-conjugated dienes were employed in this coupling process. As we expected, palladium can migrate a long distance along the C-C chain to form a relatively stable π-allylpalladium species. Acyclic dienes containing 1 to 10 carbons between the two double bonds all worked well and afforded modest to good yields of the products. When dienes with a methyl group on one of the double bonds were used in the reaction, the initial arylpalladium species added to the less substituted double bond exclusively. However, the ratio of **a**, **b**, **c** and **d** isomers changed little.

There is one thing unusual about the ratio of isomers. In the product from a long chain diene, only three isomers were detected by ^{1}H NMR spectroscopy. It seems that no *Z*-isomer (**c**) is formed; in the meanwhile, only the amount of the *E*-isomer (**a**) increased while the amounts of the other isomers remained about the same. This is hard to explain by our proposed mechanism. In the products of reactions involving short chain dienes, the chemical shifts of the protons of $=CCH_2Ph$ are different for the *Z*- and *E*-isomers. They are probably the same when the carbon chain is quite long. So we suggest that there are perhaps still four isomers in the product in the reactions of long chain dienes, and the first number of the ratio is the sum of **a** and **c**. For example, in entry 4, the ratio might be (**a**+**c**):**b**:**d** = 78:15:7.

Generally, acyclic dienes employed in the coupling reaction give good yields of the desired products. We also tried a couple of reactions with cyclic non-conjugated dienes, such as 1,4-cyclohexadiene (eq. 6) and 1,5-cyclooctadiene (eq. 7). Unfortunately, the desired products were only obtained in low yields. Unlike acyclic dienes, both 1,4-cyclohexadiene and 1,5-cyclooctadiene afforded isomerically pure products (**7** and **8** respectively) with both phenyl groups on



(6)



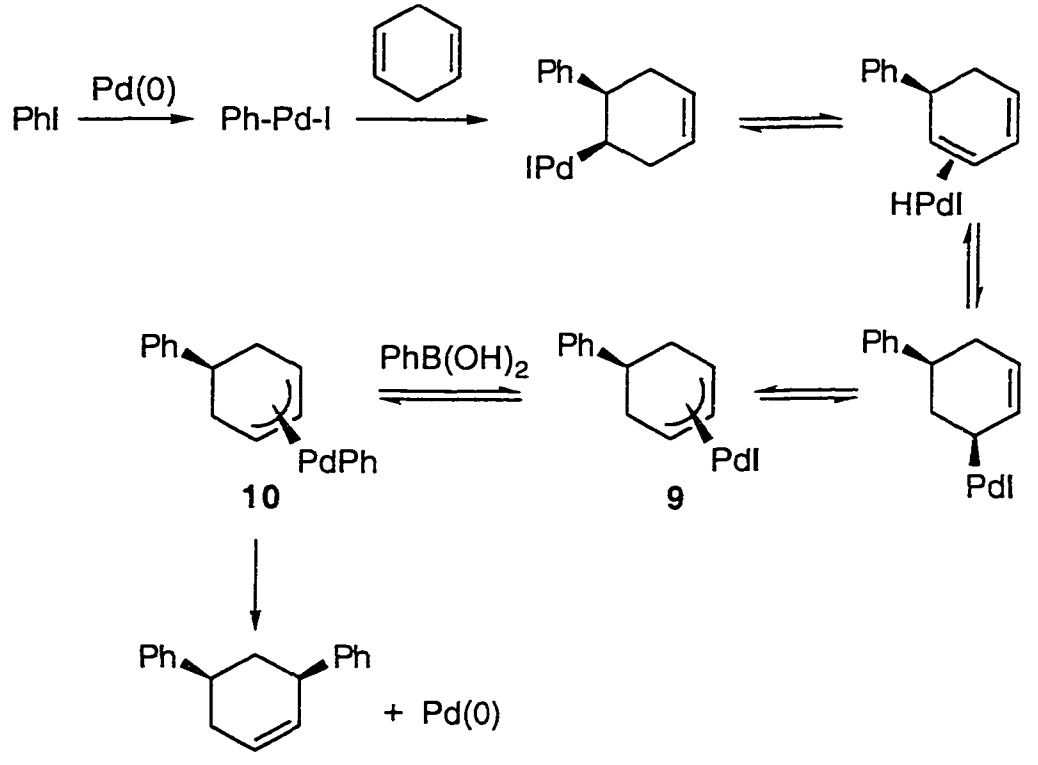
(7)

the same side of the ring.

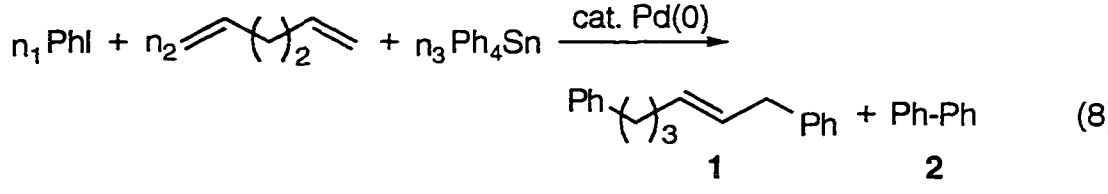
The stereochemistry can be rationalized by the mechanism shown in Scheme 2. Apparently, the π-allylpalladium intermediate (**9**) is formed via (1) formation of phenylpalladium iodide, (2) addition to the carbon-carbon double bond of the diene, and (3) palladium migration by a series of palladium hydride *β*-eliminations and readditions which occur in a *syn* fashion. In the presence of $PhB(OH)_2$, the ligand exchange of **9** with the organoboron compound forms a phenylpalladium π-allyl complex (**10**), followed by reduction elimination to give the coupling product **7** and palladium(0).

Finally, we tested some other organometallics as nucleophiles in this type of coupling. Aryltin compounds have often been used as nucleophiles in organic

Scheme 2



synthesis. Tetraphenyltin (Ph_4Sn) was then chosen as the nucleophile to react with iodobenzene and 1,5-hexadiene. We expected Ph_4Sn to give about the same results as the phenylboron compounds did. However, under the best conditions for $NaBPh_4$, Ph_4Sn only gave a very low yield of the desired product. To improve the yield, the reaction conditions were optimized. The results are summarized in equation 8 and Table 6.



(8)

Table 6. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Tetraphenyltin (Eq. 8)[a]

entry	$n_1/n_2/n_3$	*n*-Bu_4NCl (equiv)	$NaHCO_3$ (equiv)	temp (°C)	% yield[b] **1**	**2**
1	1 / 5 / 2	1.0	2.0	100	--[c]	--[c]
2	1 / 5 / 2	1.0	2.0	100	--[c]	--[c]
3	1 / 5 / 1	2.0	2.0	100	36	72
4	1 / 5 / 0.5	2.0	2.0	100	35	26
5	1 / 5 / 0.5	2.0	2.0	80	18	23
6[d]	1 / 5 / 0.5	2.0	1.0	100	20	27
7[d]	1 / 5 / 0.5	2.0	1.0	80	17	16
8	1 / 5 / 0.5	3.0	1.0	100	29	17
9	1 / 5 / 0.5	--[e]	2.0	100	--[c]	--[c]

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$ for 24 hours.

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

[c] **1** was found in only a small amount, and **2** was the major product.

[d] 2.5 Mol % $Pd(dba)_2$ was used.

[e] 2.0 Equiv of LiCl were used instead of *n*-Bu_4NCl.

From the results in Table 6, one can see that Ph_4Sn is not a suitable nucleophile for this coupling reaction. When 2 or 1 equiv of Ph_4Sn was used, biphenyl (**2**) was formed as the major product. Decreasing the amount of Ph_4Sn to 0.5 equiv gave **1** and **2** in about equal amounts, but the yields of the products were still very low. Changing the temperature and the amounts of

$Pd(dba)_2$, *n*-Bu_4NCl and base afforded no improvement at all. LiCl even made the reaction worse (entry 9).

We tried to test some other phenyltin compounds under the conditions of entry 3 in Table 6. Unfortunately, no satisfactory results were obtained. The best yield of **1** was only 41% when Ph_2SnBu_2 was employed as the nucleophile. The results are shown in Table 7.

Table 7. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Phenyltin Compounds[a]

entry	nucleophile	% yield[b]	
		1	**2**
1	Ph_4Sn	36	72
2	Ph_3SnOAc	20	98
3	Ph_3SnOH	34	50
4	Ph_2SnBu_2	41	117

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$, 1 equiv of *n*-Bu_4NCl and 2.5 equiv of $NaHCO_3$ at 100 °C.

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

Conclusion

The palladium-catalyzed coupling of aryl iodides, non-conjugated dienes and phenylmetallics has been systematically investigated. This process provides a useful method for making long chain hydrocarbons with an aromatic

group at each end. This process has been successfully applied to a variety of aromatic iodides and acyclic non-conjugated dienes. Modest to good yields of the coupling products are obtained, although there were four isomers present in the product. Fortunately, the regioselectivity can be controlled somewhat by the choice of the aryl iodide. The more sterically hindered the aryl iodides, the more attack there is on the less hindered carbon of the double bond.

In our investigation, palladium has been shown to have the ability to easily migrate along a carbon chain containing as many as 10 carbon atoms between the two double bonds of the starting diene to form a stable π-allylpalladium species. Palladium also can migrate around a ring; however, only low yields of the coupling products have been achieved in these cases. Finally, the palladium-catalyzed coupling proceeds under mild reaction conditions and many functional groups may be accommodated.

Experimental Section

Equipment. All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Digilab FTS-7 spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed on an HP 5890 chromatograph equipped with an HP-1 Megabore column. Flash chromatography was carried out on 230-400 mesh silica gel. Thin-layer chromatography was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F). 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).

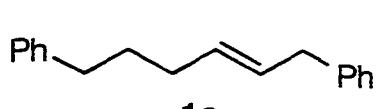
Reagents. Bis(dibenzylideneacetone)palladium was donated by Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride and ethyl 4-iodobenzoate were purchased from Lancaster Synthesis Inc. Iodobenzene, 2-iodoanisole, 4-iodoanisole, 4-iodoacetophenone, 1,5-hexadiene, 1,9-decadiene, 1,4-cyclohexadiene, phenylboronic acid and triphenyltin hydroxide were purchased from Aldrich Chemical Company, Inc. Dimethyl sulfoxide, *N*,*N*-dimethylformamide, and lithium chloride were purchased from Fisher Scientific Company. 1-Iodonaphthalene was purchased from Eastman Kodak Co. 2-Methyl-1,4-pentadiene and 2-methyl-1,5-hexadiene were purchased from Wiley Organics. 1,13-Tetradecadiene was purchased from Columbia Organic Chemical Co., Inc. Sodium tetraphenylborate was purchased from J. T. Baker Chemical Co. Tetraphenyltin was purchased from Pfaltz & Bauer, Inc.

General procedure for the palladium-catalyzed coupling of aryl iodides, non-conjugated dienes and phenylboron compounds.

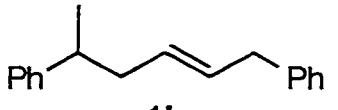
To a 2 dram vial with a micromagnetic stirring bar were added 0.25 or 0.5 mmol of aryl iodide, 1.25 or 2.5 mmol of non-conjugated diene, 0.5 or 1.0 mmol of nucleophile, 5 mol % of bis(dibenzylideneacetone)palladium, 0.25 or 0.5 mmol of tetra-*n*-butylammonium chloride, 0.625 or 1.25 mmol of sodium bicarbonate and 2 or 4 ml of DMF respectively. The vial was capped with a screw-cap containing a Teflon liner. The resulting mixture was stirred at 100 °C for 3 days. The mixture was then allowed to cool to room temperature, diluted with

saturated NaCl solution and extracted with hexane or ether. The organic layer was dried over anhydrous $MgSO_4$ and then evaporated under reduced pressure to remove the solvent. The crude products were isolated by flash chromatography on a silica gel column.

Preparation of Compounds **1a**, **1b**, **1c** and **1d**

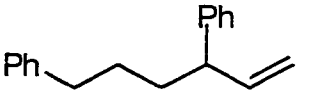


1a



1b

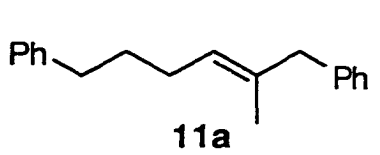
1c



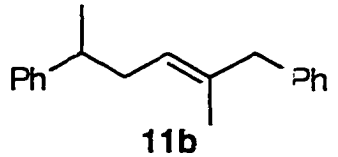
1d

Compounds **1a**, **1b**, **1c** and **1d** were obtained as an inseparable 66:14:12:8 mixture of isomers in 65% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **1b**), 1.71 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.07 (dt, J = 6.3 Hz, J = 6.9 Hz, 2 H, CH_2C=), 2.61 (t, J = 7.8 Hz, 2 H, $PhCH_2$), 2.74 (m, 1 H, PhCH in **1b**), 3.27 (d, J = 6.6 Hz, 2 H, $=CCH_2Ph$ in **1c**), 3.33 (d, J = 5.7 Hz, 2 H, $=CCH_2Ph$), 5.00 (m, 2 H, $=CH_2$ in **1d**), 5.52 (dt, J = 15.6 Hz, J = 6.0 Hz, 1 H, vinyl), 5.58 (dt, J = 15.6 Hz, J = 6.0 Hz, 1 H, vinyl), 7.15-7.30 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 31.3, 32.1, 35.5, 39.1, 125.7, 125.9, 127.1, 128.3, 128.4, 128.5, 129.4, 130.4, 131.5, 142.5; IR (neat) 3080, 3024, 2926, 2854, 1601, 1451, 1028 cm^{-1}; HRMS for $C_{18}H_{20}$: calcd 236.1565, found 236.1566.

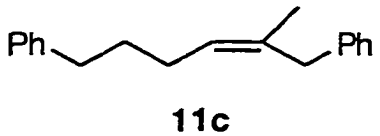
Preparation of Compounds **11a**, **11b**, **11c** and **11d**



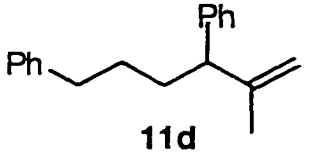
11a



11b



11c

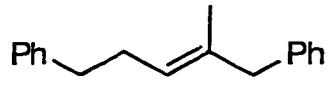


11d

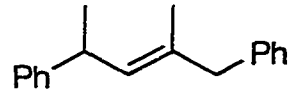
Compounds **11a**, **11b**, **11c** and **11d** were obtained as an inseparable 62:16:13:9 mixture of isomers in 57% combined yield from the coupling of iodobenzene, 5 equiv. of 2-methyl-1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.6 Hz, 3 H, $PhCCH_3$ in **11b**), 1.51 (s, 3 H, CH_3 in **11a**), 1.70 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.07 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.18 (q, J = 7.2 Hz, 2 H, CH_2C= in **11c**), 2.62 (t, J = 7.8 Hz, 2 H, $PhCH_2$), 2.77 (sextet, J = 7.2 Hz, 1 H, PhCH in **11b**), 3.23 (s, 2 H, =CCH_2Ph in **11c**), 3.29 (s, 2 H, =CCH_2Ph in **11a**), 3.34 (s, 2 H, =CCH_2Ph in **11b**), 4.81 (m, 1 H, =C<u>H</u>H in **11d**), 4.89 (m, 1 H, =CH<u>H</u> in **11d**), 5.22 (t, J = 7.2 Hz, 1 H, HC= in **11c**), 5.28 (tq, J = 7.2 Hz, J = 0.9 Hz, 1 H, HC= in **11a**), 5.33 (t, J = 7.2 Hz, 1 H, HC= in **11b**), 7.15-7.29 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.8, 27.6, 31.5, 35.5, 46.2, 125.5, 125.8, 126.2, 128.1, 128.3, 128.4, 128.7, 134.7, 140.3, 142.5; IR (neat) 3084, 3063, 3026, 2930, 2856, 1603, 1452, 1076 cm^{-1}; HRMS for $C_{19}H_{22}$: calcd 250.1722, found 250.1720.

Preparation of Compounds **12a**, **12b**, **12c** and **12d**

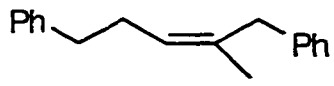
Compounds **12a**, **12b**, **12c** and **12d** were obtained as an inseparable 66:13:12:9 mixture of isomers in 56% combined yield from the coupling of



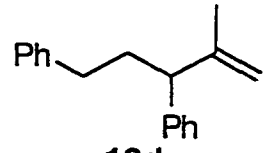
12a



12b



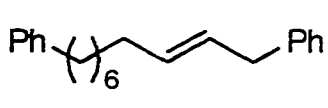
12c



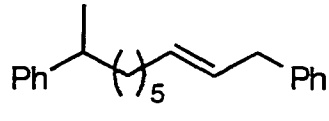
12d

iodobenzene, 5 equiv. of 2-methyl-1,4-pentadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 7.2 Hz, 3 H, $PhCCH_3$ in **12b**), 1.47 (s, 3 H, CH_3 in **12a**), 2.35 (q, J = 7.2 Hz, 2 H, $PhCCH_2$ in **12a**), 2.46 (q, J = 7.2 Hz, 2 H, $PhCCH_2$ in **12c**), 2.67 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 3.26 (s, 2 H, $=CCH_2Ph$ in **12a**), 3.29 (s, 2 H, $=CCH_2Ph$ in **12c**), 3.32 (s, 2 H, $=CCH_2Ph$ in **12b**), 4.86 (s, 1 H, =CHH in **12d**), 4.95 (s, 1 H, =CHH in **12d**), 5.29 (tq, J = 7.2 Hz, J = 0.9 Hz, 1 H, HC= in **12a**), 5.36 (t, J = 7.2 Hz, 1 H, HC= in **12c**), 5.45 (m, 1 H, HC= in **12b**), 7.12-7.27 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.8, 30.0, 36.0, 46.2, 125.7, 125.9, 128.2, 128.5, 128.8, 135.1, 140.2, 142.2 (two peaks overlapped); IR (neat) 3079, 3024, 2956, 2922, 2853, 1600, 1450, 1074 cm^{-1}; HRMS for $C_{18}H_{20}$: calcd 236.1565, found 236.1571.

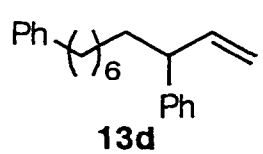
Preparation of Compounds **13a**, **13b** and **13d**



13a



13b

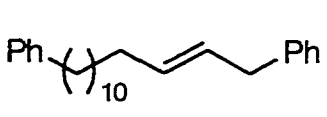


13d

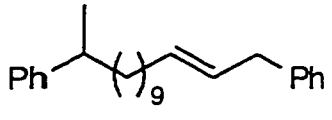
Compounds **13a**, **13b** and **13d** were obtained as an inseparable 78:15:7 mixture of isomers in 46% combined yield from the coupling of iodobenzene, 5 equiv. of 1,9-decadiene and 2 equiv. of phenylboronic acid using the procedure

above: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **13b**), 1.25-36 (br m, 8 H, CH_2's), 1.60 (m, 2 H, $PhCCH_2$), 2.00 (q, J = 6.6 Hz, 2 H, CH_2C=), 2.59 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.66 (m, 1 H, PhCH in **13b**), 3.32 (d, J = 5.4 Hz, 2 H, $=CCH_2Ph$ in **13a**), 3.41 (d, 2 H, J = 5.4 Hz, $=CCH_2Ph$ in **13b**), 5.01 (m, 2 H, $=CH_2$ in **13d**), 5.49 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.55 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 7.16-7.30 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 29.1, 29.2, 29.3, 29.4, 31.5, 32.5, 36.0, 39.1, 125.5, 125.8, 128.2, 128.3, 128.4, 128.5, 128.7, 132.0, 141.1, 142.9; IR (neat) 3080, 3024, 2925, 2852, 1601, 1452, 1029 cm^{-1}; HRMS for $C_{22}H_{28}$: calcd 292.2191, found 292.2184.

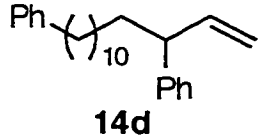
Preparation of Compounds **14a**, **14b** and **14d**



14a



14b

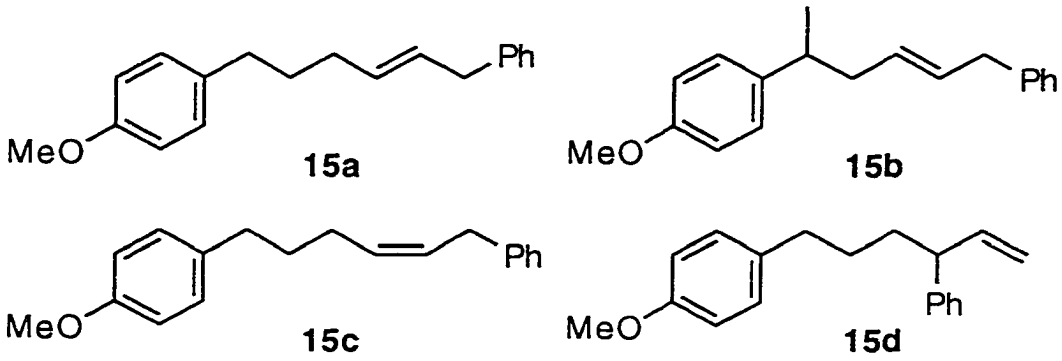


14d

Compounds **14a**, **14b** and **14d** were obtained as an inseparable 81:10:9 mixture of isomers in 43% combined yield from the coupling of iodobenzene, 5 equiv. of 1,13-tetradecadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3 H, $PhCCH_3$ in **14b**), 1.23-32 (br m, 16 H, CH_2's), 1.60 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.00 (q, J = 6.0 Hz, 2 H, CH_2C=), 2.59 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.65 (m, 1 H, PhCH in **14b**), 3.32 (d, J = 5.4 Hz, 2 H, $=CCH_2Ph$ in **14a**), 3.39 (d, 2 H, J = 6.0 Hz, $=CCH_2Ph$ in **14b**), 5.00 (m, 2 H, $=CH_2$ in **14d**), 5.49 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H, vinyl), 5.55 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 7.15-7.29 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.4, 29.5, 29.6, 31.6, 32.5, 36.0, 39.1, 125.5, 125.8, 128.2, 128.3, 128.4, 128.5, 128.6, 132.1, 141.1, 142.9 (four peaks

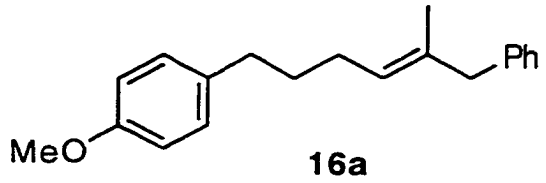
overlapped); IR (neat) 3061, 3026, 2925, 2853, 1603, 1453, 1030 cm^{-1}; HRMS for $C_{26}H_{36}$: calcd 348.2817, found 348.2825.

Preparation of Compounds **15a**, **15b**, **15c** and **15d**

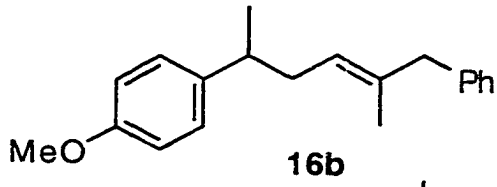


Compounds **15a**, **15b**, **15c** and **15d** were obtained as an inseparable 60:13:17:10 mixture of isomers in 57% combined yield from the coupling of 4-iodoanisole, 5 equiv. of 1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **15b**), 1.66 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.05 (dt, J = 6.3 Hz, J = 6.9 Hz, 2 H, CH_2C=), 2.27 (m, 2 H, CH_2C= in **15c**), 2.55 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 2.68 (m, 1 H, ArCH in **15b**), 3.27 (d, J = 6.0 Hz, 2 H, $=CCH_2Ph$ in **15c**), 3.33 (d, J = 5.7 Hz, 2 H, $=CCH_2Ph$ in **15a**), 3.37 (d, J = 5.7 Hz, 2 H, $=CCH_2Ph$ in **15b**), 3.77 (s, 3 H, CH_3O), 5.01 (m, 2 H, $=CH_2$ in **15d**), 5.51 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.58 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H, vinyl), 6.80-7.30 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.7, 32.0, 34.4, 39.1, 55.2, 113.6, 125.8, 127.9, 128.3, 128.4, 129.2, 131.5, 134.6, 141.0, 157.6; IR (neat) 3060, 2954, 2925, 2856, 1610, 1462, 1245 (C–O), 1039 cm^{-1}; HRMS for $C_{19}H_{22}O$: calcd 266.1671, found 266.1670.

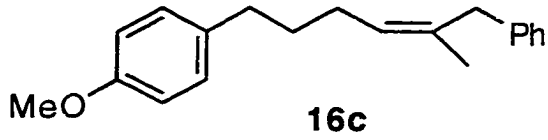
Preparation of Compounds **16a**, **16b**, **16c** and **16d**



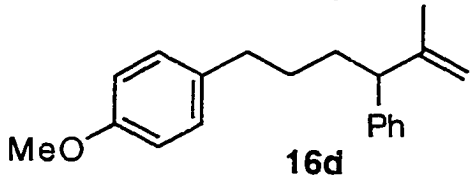
16a



16b



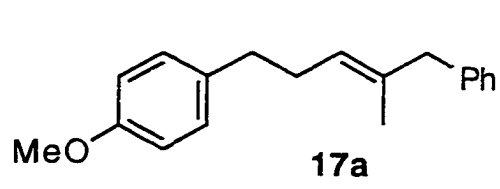
16c



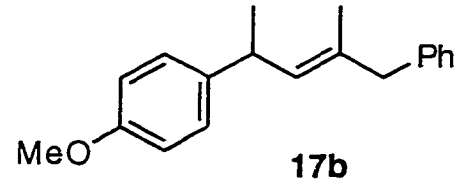
16d

Compounds **16a**, **16b**, **16c** and **16d** were obtained as an inseparable 62:14:15:9 mixture of isomers in 63% combined yield from the coupling of 4-iodoanisole, 5 equiv. of 2-methyl-1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **16b**), 1.51 (s, 3 H, CH_3 in **16a**), 1.66 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.05 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.16 (m, 2 H, CH_2C= in **16c**), 2.56 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 2.72 (sextet, J = 7.2 Hz, 1 H, ArCH in **16b**), 3.23 (s, 2 H, $=CCH_2Ph$ in **16c**), 3.28 (s, 2 H, $=CCH_2Ph$ in **16a**), 3.34 (s, 2 H, $=CCH_2Ph$ in **16b**), 3.77 (s, 3 H, CH_3O), 4.80 (m, 1 H, =C<u>H</u>H in **16d**), 4.88 (m, 1 H, =CH<u>H</u> in **16d**), 5.20 (tq, J = 7.2 Hz, J = 0.9 Hz, 1 H, HC= in **16c**), 5.27 (tq, J = 7.2 Hz, J = 0.9 Hz, 1 H, HC= in **16a**), 5.32 (t, J = 7.2 Hz, 1 H, HC= in **16b**), 6.80-7.29 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.9, 27.6, 31.8, 34.6, 46.3, 55.2, 113.6, 125.8, 126.4, 128.2, 128.5, 128.8, 129.3, 134.7, 140.4, 157.6; IR (neat) 3062, 3026, 2931, 2855, 1611, 1463, 1247 (C–O), 1038 cm^{-1}; HRMS for $C_{20}H_{24}O$: calcd 280.1827, found 280.1827.

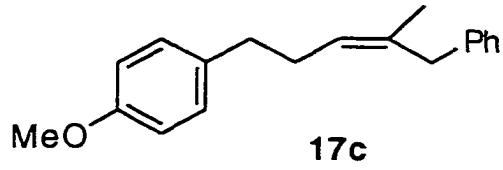
Preparation of Compounds **17a**, **17b**, **17c** and **17d**



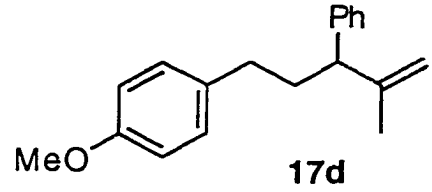
17a



17b



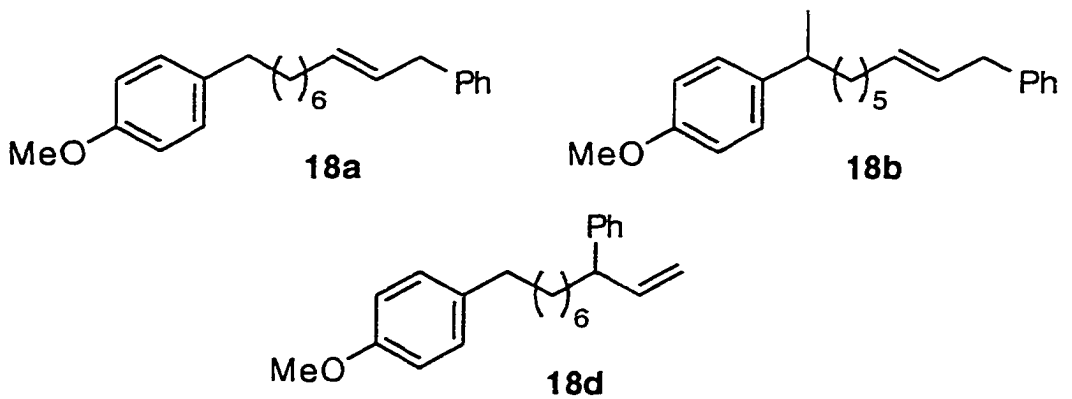
17c



17d

Compounds **17a**, **17b**, **17c** and **17d** were obtained as an inseparable 65:15:11:9 mixture of isomers in 53% combined yield from the coupling of 4-iodoanisole, 5 equiv. of 2-methyl-1,4-pentadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 7.2 Hz, 3 H, $ArCCH_3$ in **17b**), 1.47 (s, 3 H, CCH_3 in **17a**), 2.32 (q, J = 7.5 Hz, 2 H, $ArCCH_2$ in **17a**), 2.44 (m, 2 H, $ArCCH_2$ in **17c**), 2.62 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 3.27 (s, 2 H, $=CCH_2Ph$ in **17a**), 3.29 (s, 2 H, $=CCH_2Ph$ in **17c**), 3.32 (s, 2 H, $=CCH_2Ph$ in **17b**), 3.77 (s, 3 H, CH_3O), 4.86 (s, 1 H, =C<u>H</u>H in **17d**), 4.94 (s, 1 H, =CH<u>H</u> in **17d**), 5.28 (t, J = 6.9 Hz, 1 H, HC= in **17a**), 5.35 (t, J = 7.2 Hz, 1 H, HC= in **17c**), 5.44 (m, 1 H, HC= in **17b**), 6.80-7.29 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.8, 30.2, 35.1, 46.2, 55.2, 113.6, 125.7, 125.8, 128.1, 128.2, 128.8, 129.3, 134.2, 140.3, 157.6; IR (neat) 3057, 3024, 2949, 2924, 2852, 1609, 1461, 1245 (C–O), 1037 cm^{-1}; HRMS for $C_{19}H_{22}O$: calcd 266.1671, found 266.1664.

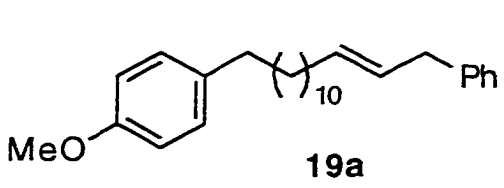
Preparation of Compounds **18a**, **18b** and **18d**



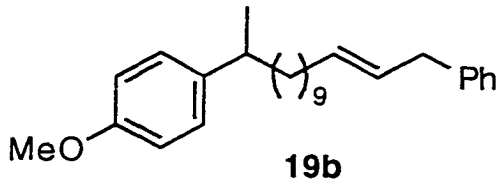
Compounds **18a**, **18b** and **18d** were obtained as an inseparable 81:11:8 mixture of isomers in 42% combined yield from the coupling of 4-iodoanisole, 5 equiv. of 1,9-dodecadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 7.2 Hz, 3 H, $ArCCH_3$ in **18b**), 1.25-1.34 (br m, 8 H, CH_2's), 1.56 (m, 2 H, $ArCCH_2$), 2.00 (q, J = 6.0 Hz, 2 H, CH_2C=), 2.53 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.60 (m, 1 H, ArCH in **18b**), 3.32 (d, J = 5.1 Hz, 2 H, $=CCH_2Ph$ in **18a**), 3.41 (d, 2 H, J = 6.0 Hz, $=CCH_2Ph$ in **18b**), 5.00 (m, 2 H, $=CH_2$ in **18d**), 5.48 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.55 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 6.79-7.29 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.1, 29.2, 29.3, 29.4, 31.7, 32.5, 35.0, 39.0, 55.2, 113.6, 125.8, 127.7, 128.3, 128.4, 128.9, 129.2, 134.9, 141.1, 157.5; IR (neat) 3059, 2925, 2852, 1610, 1461, 1245 (C–O), 1038 cm^{-1}; HRMS for $C_{23}H_{30}O$: calcd 322.2297, found 322.2292.

Preparation of Compounds **19a**, **19b** and **19d**

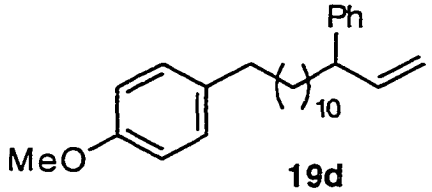
Compounds **19a**, **19b** and **19d** were obtained as an inseparable 80:9:11 mixture of isomers in 42% combined yield from the coupling of 4-iodoanisole, 5



19a



19b

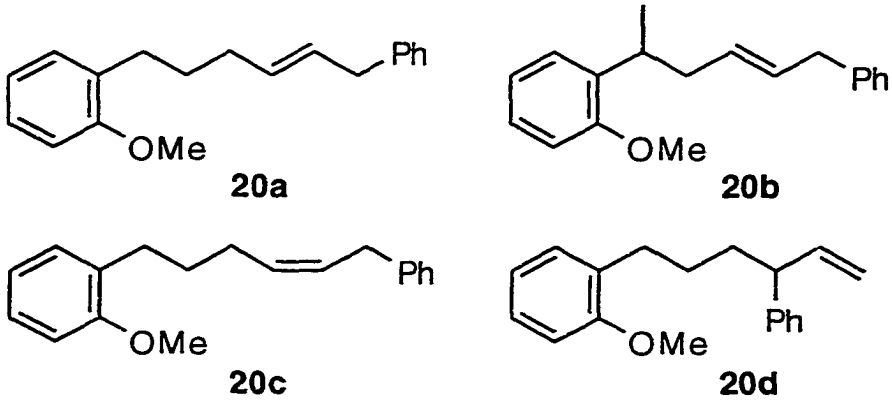


19d

equiv. of 1,13-tetradecadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **19b**), 1.22-1.30 (br m, 16 H, CH_2's), 1.55 (m, 2 H, $ArCCH_2$), 2.00 (dt, J = 6.6 Hz, J = 6.0 Hz, 2 H, CH_2C=), 2.53 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 2.60 (m, 1 H, ArCH in **19b**), 3.32 (d, J = 5.4 Hz, 2 H, $=CCH_2Ph$ in **19a**), 3.39 (d, 2 H, J = 6.0 Hz, $=CCH_2Ph$ in **19b**), 3.77 (s, 3 H, CH_3O), 5.00 (m, 2 H, $=CH_2$ in **19d**), 5.49 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H, vinyl), 5.56 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H, vinyl), 6.79-7.29 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.3, 29.5, 29.6, 29.9, 31.8, 32.5, 35.1, 39.1, 55.2, 113.6, 125.8, 127.7, 128.3, 128.4, 128.6, 129.2, 132.1, 141.1, 157.5 (three peaks overlapped); IR (neat) 3060, 2926, 2853, 1611, 1463, 1246 (C–O), 1039 cm^{-1}; HRMS for $C_{27}H_{38}O$: calcd 378.2923, found 378.2924.

Preparation of Compounds **20a**, **20b**, **20c** and **20d**

Compounds **20a**, **20b**, **20c** and **20d** were obtained as an inseparable 72:6:11:11 mixture of isomers in 53% combined yield from the coupling of 2-iodoanisole, 5 equiv. of 1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in

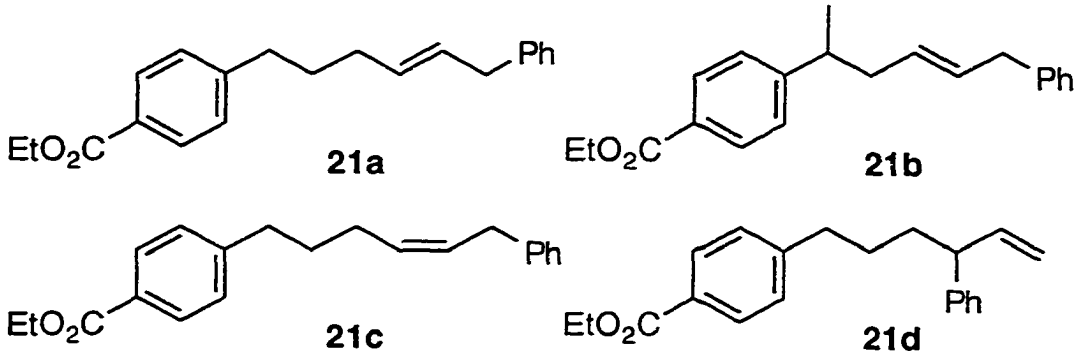


20a **20b** **20c** **20d**

20b), 1.66 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.07 (dt, J = 6.6 Hz, J = 6.0 Hz, 2 H, CH_2C=), 2.20 (m, 2 H, CH_2C= in **20c**), 2.61 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.72 (m, 1 H, ArCH in **20b**), 3.27 (m, 2 H, $=CCH_2Ph$ in **20c**), 3.33 (d, J = 4.8 Hz, 2 H, $=CCH_2Ph$ in **20a**), 3.38 (d, J = 5.4 Hz, 2 H, $=CCH_2Ph$ in **20b**), 3.78 (s, 3 H, CH_3O), 5.00 (m, 2 H, $=CH_2$ in **20d**), 5.52 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H, vinyl), 5.59 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H, vinyl), 6.79-7.31 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.6, 29.7, 32.4, 39.1, 55.2, 110.1, 120.2, 125.8, 126.8, 128.3, 128.4, 128.9, 129.8, 130.9, 131.8, 141.0, 157.4; IR (neat) 3060, 2940, 2834, 1601, 1454, 1243 (C–O), 1029 cm^{-1}; HRMS for $C_{19}H_{22}O$: calcd 266.1671, found 266.1671.

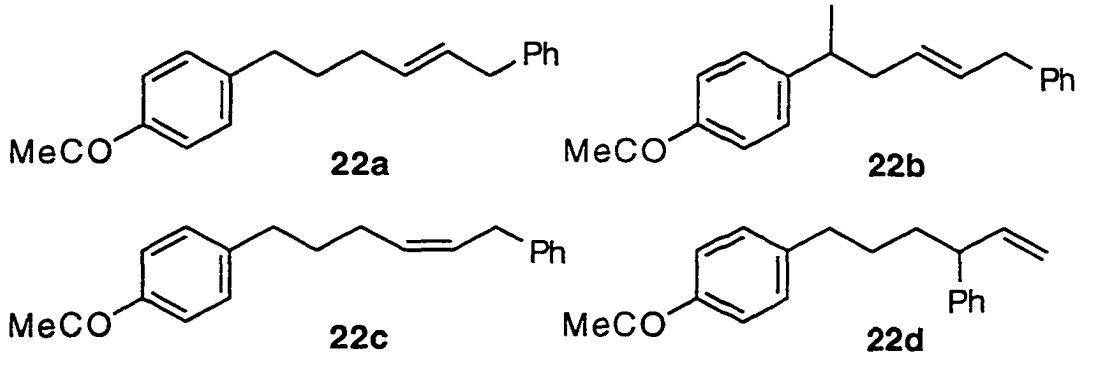
Preparation of Compounds **21a**, **21b**, **21c** and **21d**

Compounds **21a**, **21b**, **21c** and **21d** were obtained as an inseparable 67:11:12:10 mixture of isomers in 72% combined yield from the coupling of ethyl 4-iodobenzoate, 5 equiv. of 1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **21b**), 1.38 (t, J = 7.2 Hz, 3 H, $OCCH_3$), 1.71 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.06 (dt, J = 6.9 Hz, J = 7.2 Hz, 2 H, CH_2C=), 2.33 (m, 2 H,



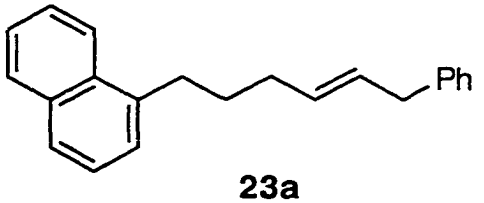
CH_2C= in **21c**), 2.66 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.79 (m, 1 H, ArCH in **21b**), 3.26 (d, J = 6.3 Hz, 2 H, $=CCH_2Ph$ in **21c**), 3.33 (d, J = 6.0 Hz, 2 H, $=CCH_2Ph$ in **21a**), 3.36 (d, J = 6.0 Hz, 2 H, $=CCH_2Ph$ in **21b**), 3.35 (q, J = 7.2 Hz, 2 H, OCH_2), 5.02 (m, 2 H, $=CH_2$ in **21d**), 5.50 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.59 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H, vinyl), 7.16-7.30 (m, 7 H, aryl), 7.96 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.4, 30.8, 31.9, 35.4, 39.1, 60.7, 125.8, 128.0, 128.4, 129.6, 131.1, 140.8, 147.9, 166.6 (three peaks overlapped); IR (neat) 3056, 2980, 2928, 2857, 1717 (C=O), 1609, 1452, 1277 (C–O), 1106 cm^{-1}; HRMS for $C_{21}H_{24}O_2$: calcd 308.1776, found 308.1776.

Preparation of Compounds **22a**, **22b**, **22c** and **22d**

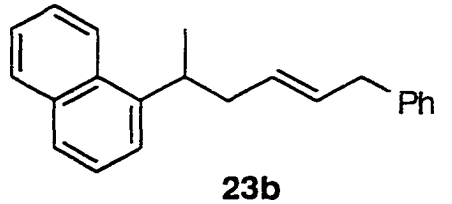


Compounds **22a**, **22b**, **22c** and **22d** were obtained as an inseparable 68:11:12:9 mixture of isomers in 70% combined yield from the coupling of 4-iodoacetophenone, 5 equiv. of 1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **22b**), 1.71 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.06 (dt, J = 6.9 Hz, J = 7.2 Hz, 2 H, CH_2C=), 2.56 (s, 3 H, CH_3), 2.66 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.77 (m, 1 H, ArCH in **22b**), 3.25 (d, J = 6.3 Hz, 2 H, $=CCH_2Ph$ in **22c**), 3.33 (d, J = 6.0 Hz, 2 H, $=CCH_2Ph$ in **22a**), 3.36 (d, J = 6.0 Hz, 2 H, $=CCH_2Ph$ in **22b**), 5.02 (m, 2 H, $=CH_2$ in **22d**), 5.50 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.59 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H, vinyl), 7.16-7.30 (m, 7 H, aryl), 7.87 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 26.5, 30.7, 31.9, 35.3, 39.0, 125.8, 128.3, 128.4, 128.5, 129.6, 131.0, 134.8, 140.7, 148.3, 197.7 (one peak overlapped); IR (neat) 3060, 2954, 2925, 2856, 1654 (C=O), 1605, 1451, 1268 cm^{-1}; HRMS for $C_{20}H_{22}O$: calcd 278.1671, found 278.1663.

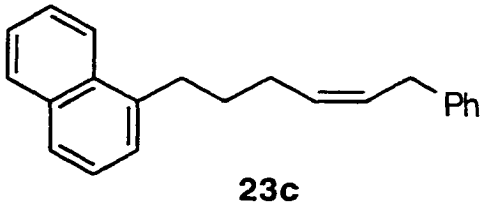
Preparation of Compounds **23a**, **23b**, **23c** and **23d**



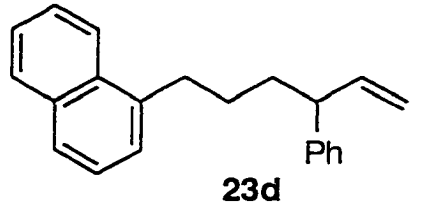
23a



23b



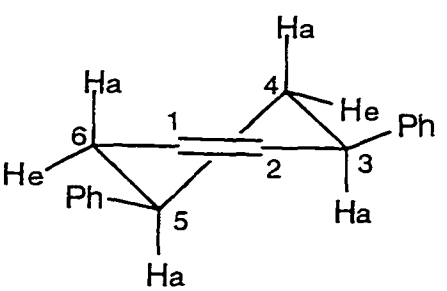
23c



23d

Compounds **23a**, **23b**, **23c** and **23d** were obtained as an inseparable 75:6:11:8 mixture of isomers in 56% combined yield from the coupling of 1-iodonaphthalene, 5 equiv. of 1,5-hexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **23b**), 1.82 (quintet, J = 7.8 Hz, 2 H, $ArCCH_2$), 2.15 (dt, J = 6.3 Hz, J = 7.2 Hz, 2 H, CH_2C=), 2.28 (m, 2 H, CH_2C= in **23c**), 3.05 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 3.18 (m, 1 H, ArCH in **23b**), 3.27 (d, J = 5.7 Hz, 2 H, $=CCH_2Ph$ in **23c**), 3.34 (d, J = 6.0 Hz, 2 H, $=CCH_2Ph$), 3.40 (d, J = 6.6 Hz, 2 H, $=CCH_2Ph$ in **23b**), 4.98 (m, 2 H, $=CH_2$ in **23d**), 5.54 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.63 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 7.15-8.01 (m, 12 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.5, 32.5, 39.1, 123.8, 125.3, 125.5, 125.6, 125.9, 126.4, 128.3, 128.4, 128.7, 129.5, 131.4, 131.8, 133.8, 138.6, 140.9 (two peaks overlapped); IR (neat) 3059, 2925, 2856, 1597, 1452, 1029 cm^{-1}; HRMS for $C_{22}H_{22}$: calcd 286.1722, found 286.1729.

Preparation of Compound **7**

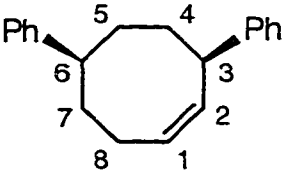


7

Compound **7** was obtained in 31% yield from the coupling of iodobenzene, 5 equiv. of 1,4-cyclohexadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.76 (ddd, J = 12.6 Hz, J = 12.6 Hz, J =

11.7 Hz, 1 H, 4-Ha), 2.17-2.42 (br m, 3 H, 4-He, 6-Ha, 6-He), 3.01 (dddd, J = 12.3 Hz, J = 11.7 Hz, J = 5.4 Hz, J = 2.4 Hz, 1 H, 5-Ha), 3.60 (dddd, J = 12.6 Hz, J = 5.4 Hz, J = 5.1 Hz, J = 2.4 Hz, 1 H, 3-Ha), 5.80 (m, 1 H, vinyl), 5.95 (dddd, J = 9.9 Hz, J = 5.1 Hz, J = 2.4 Hz, J = 2.4 Hz, 1 H, vinyl), 7.16-7.34 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 33.8, 40.3, 40.9, 44.0, 126.1, 126.2, 126.7, 127.3, 127.7, 128.4, 130.6, 146.1, 146.6 (one peak overlapped); IR (neat) 3024, 2915, 2836, 1599, 1452, 1028 cm^{-1}; HRMS for $C_{18}H_{18}$: calcd 234.1409, found 234.1404.

Preparation of Compound 8



8

Compound **8** was obtained in 23% yield from the coupling of iodobenzene, 5 equiv. of 1,5-cyclooctadiene and 2 equiv. of phenylboronic acid using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.60 (ddt, J = 13.5 Hz, J = 2.1 Hz, J = 11.7 Hz, 1 H), 1.75 (m, 1 H), 1.83-2.15 (br m, 4 H), 2.30 (dddd, J = 13.8 Hz, J = 7.5 Hz, J = 6.3 Hz, J = 2.7 Hz, 1 H), 2.48 (m, 1 H), 2.72 (m, 1 H), 3.96 (ddd, J = 12.6 Hz, J = 9.3 Hz, J = 5.1 Hz, 1 H, 3-H), 5.62 (ddd, J = 10.2 Hz, J = 9.3 Hz, J = 1.5 Hz, 1 H, 2-H), 5.89 (ddt, J = 10.2 Hz, J = 0.6 Hz, J = 7.8 Hz, 1 H, 1-H), 7.15-7.33 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.3, 34.0, 35.6, 38.5, 41.2, 46.2, 125.5, 126.0, 126.4, 127.3, 128.4, 129.3, 133.3, 145.5, 151.2 (one peak overlapped); IR (neat) 3060, 3024, 2926, 2857, 1600, 1450, 1030 cm^{-1}; HRMS for $C_{20}H_{22}$: calcd 262.1722, found 262.1720.

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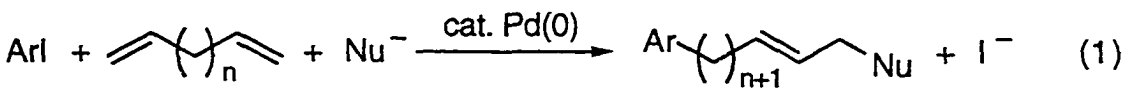
PALLADIUM–CATALYZED COUPLING OF ARYL IODIDES, NONCONJUGATED DIENES AND AMINES

A paper submitted to the *Journal of Organic Chemistry*

Richard C. Larock and Yao Wang

Introduction

Palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and nucleophiles (eq. 1) has successfully been applied to carbon nucleophiles.[1]

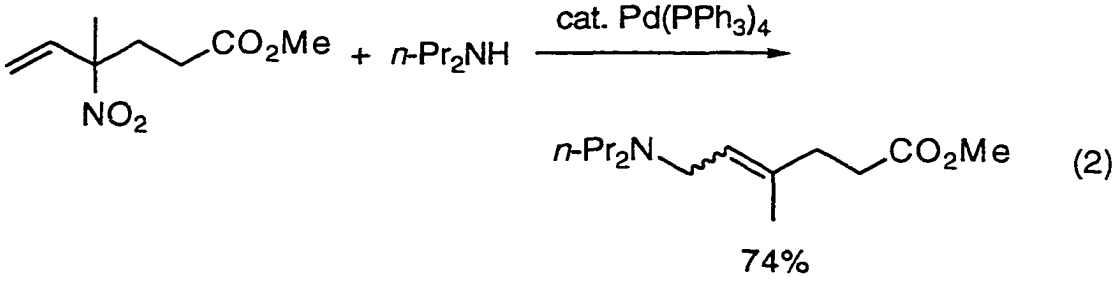


(1)

The application of this process to heteroatom nucleophiles could provide a very interesting and synthetically useful process. The most common and useful heteroatom nucleophiles employed in the displacement of π-allylpalladium compounds are primary and secondary amines.

Tamura *et al.*[2] have reported that allylic nitro compounds undergo Pd(0)-catalyzed allylic substitution by secondary amines to afford good yields of allylic amines (eq. 2). Generally, substitution occurred at the less hindered or least substituted site.

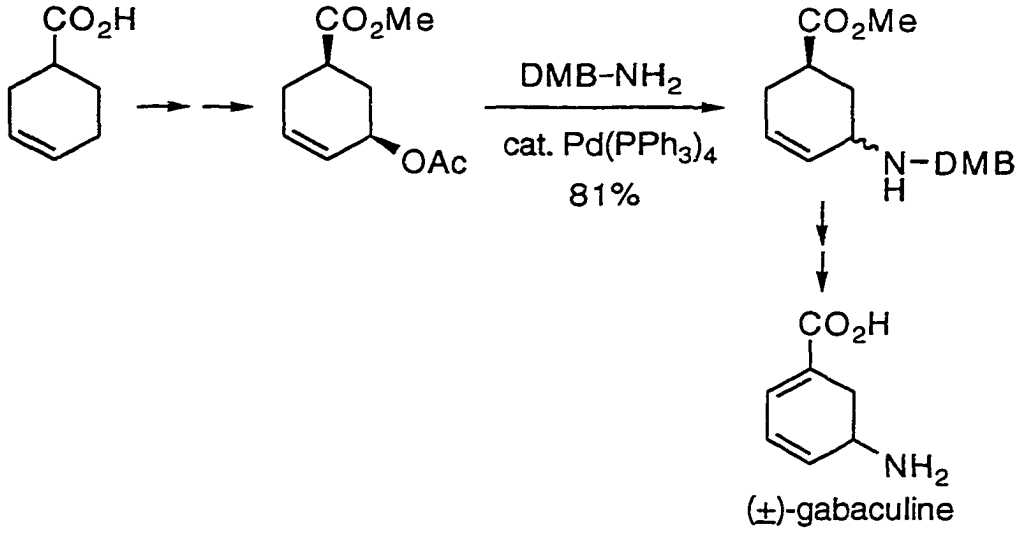
Trost and Keinan[3] developed the reaction of allylic acetates with a primary amine, 4,4'-dimethoxybenzhydrylamine (DMB–NH_2), catalyzed by palladium(0). A regiocontrolled synthesis of the naturally-occurring amino acid



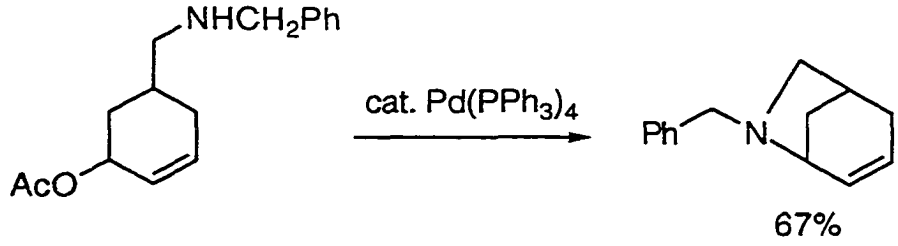
(2)

(±)-gabaculine in 45% overall yield from 3-cyclohexenecarboxylic acid was achieved using this key amination procedure (Scheme 1).

Scheme 1

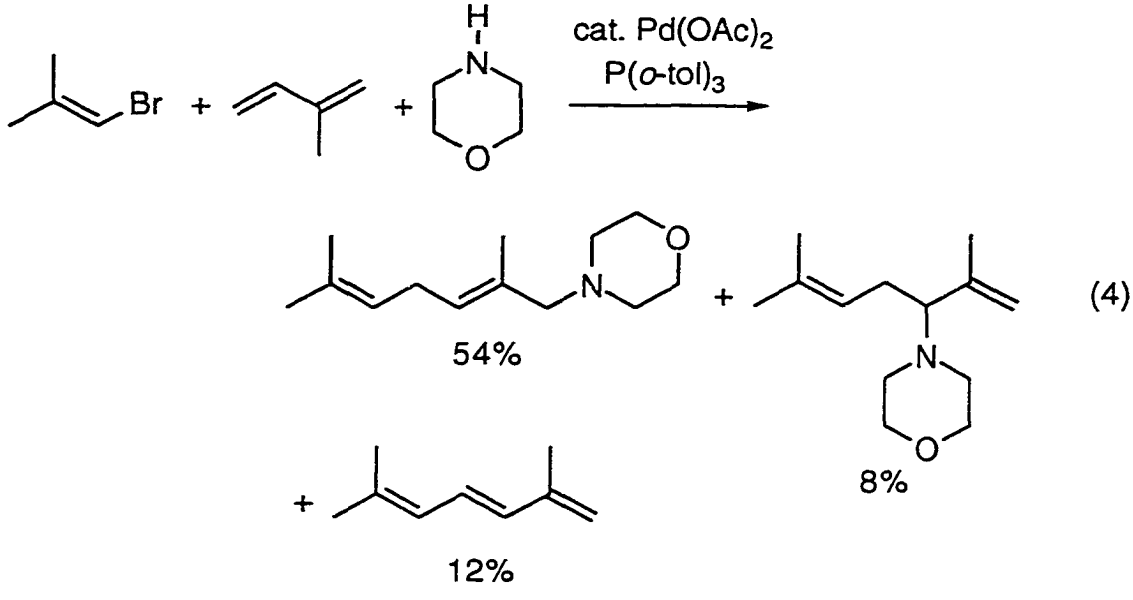


Palladium-catalyzed allylation of amines can be also accomplished in an intramolecular sense. For example, the cyclization of amino allylic acetates has been reported by Trost and Genêt (eq. 3).[4] They have synthesized the basic ring system of three different classes of alkaloids (e.g., actinobolamine, ibogamine and mesembrine).



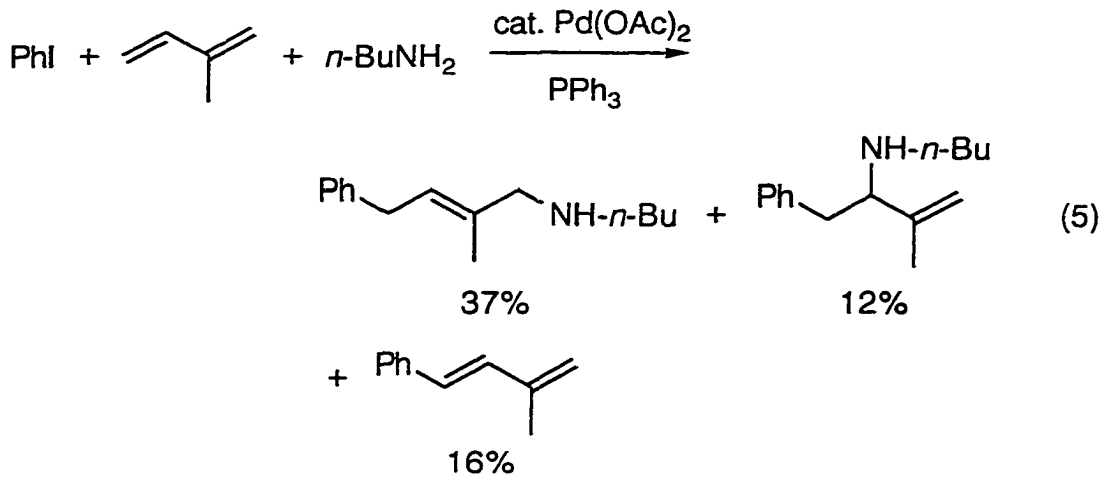
(3)

Three component coupling of amines with conjugated dienes and vinylic halides (eq. 4)[5] or aryl halides (eq. 5)[6] in the presence of a palladium catalyst has been reported. In many cases, both terminal and internal allylic amine products were formed, and the Heck products were also obtained in significant amounts.



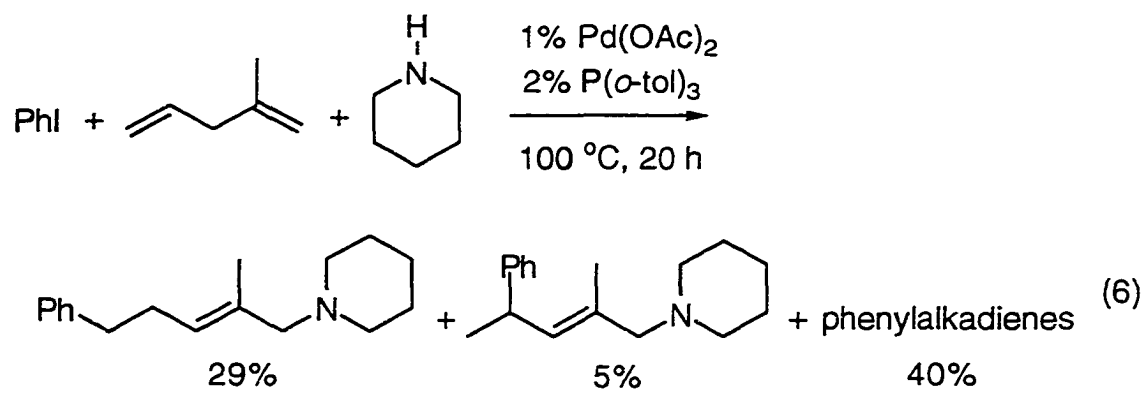
(4)

Our interest is the coupling of aryl halides, nonconjugated long chain dienes and amines catalyzed by palladium. Indeed, Heck has previously studied the coupling of bromo- and iodobenzene with a couple of representative 1,4-dienes and amines, and reported generally low yields of several isomeric



(5)

allylic amines and substantial amounts of dienes (eq. 6).[7] One might anticipate even greater difficulties with longer chain nonconjugated dienes where each additional carbon inserted between the two C–C double bonds dramatically

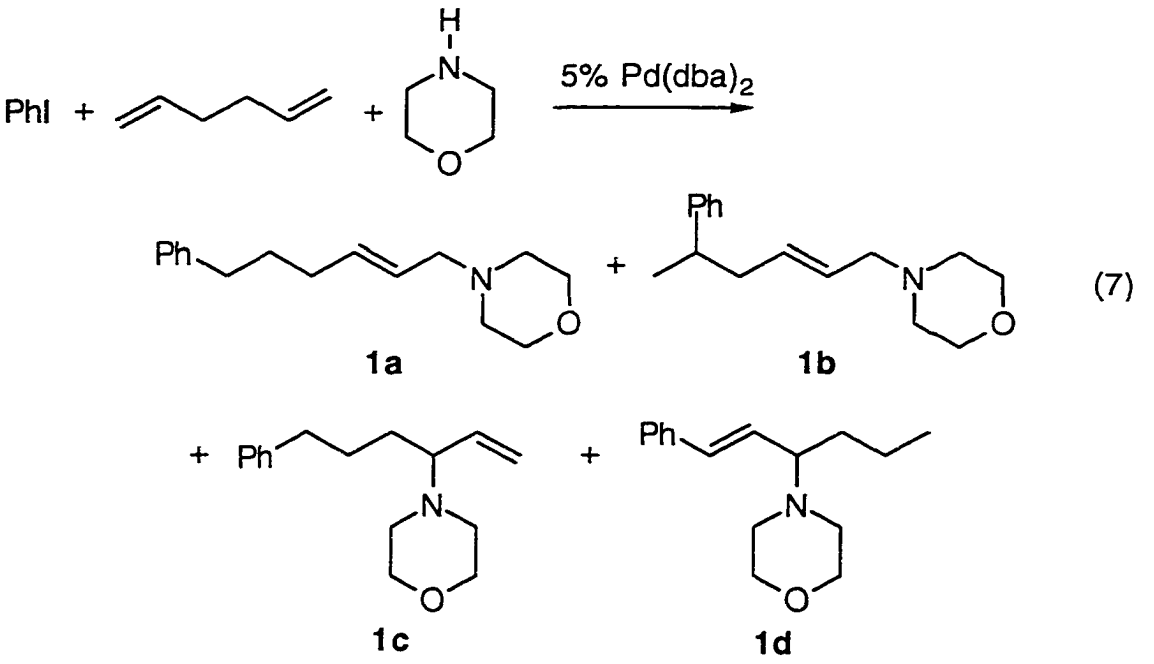


(6)

increases the number of palladium hydride elimination and readdition steps required to produce the allylic amine if one assumes migration proceeds by a random walk process. In this paper, we wish to report that despite such potential complications, under appropriate reaction conditions the coupling of aryl iodides, nonconjugated dienes and amines can be effected in high yields.

Results and Discussion

The reaction of iodobenzene, 1,5-hexadiene and morpholine was chosen as a model system in which to optimize yields (eq. 7). We began our studies



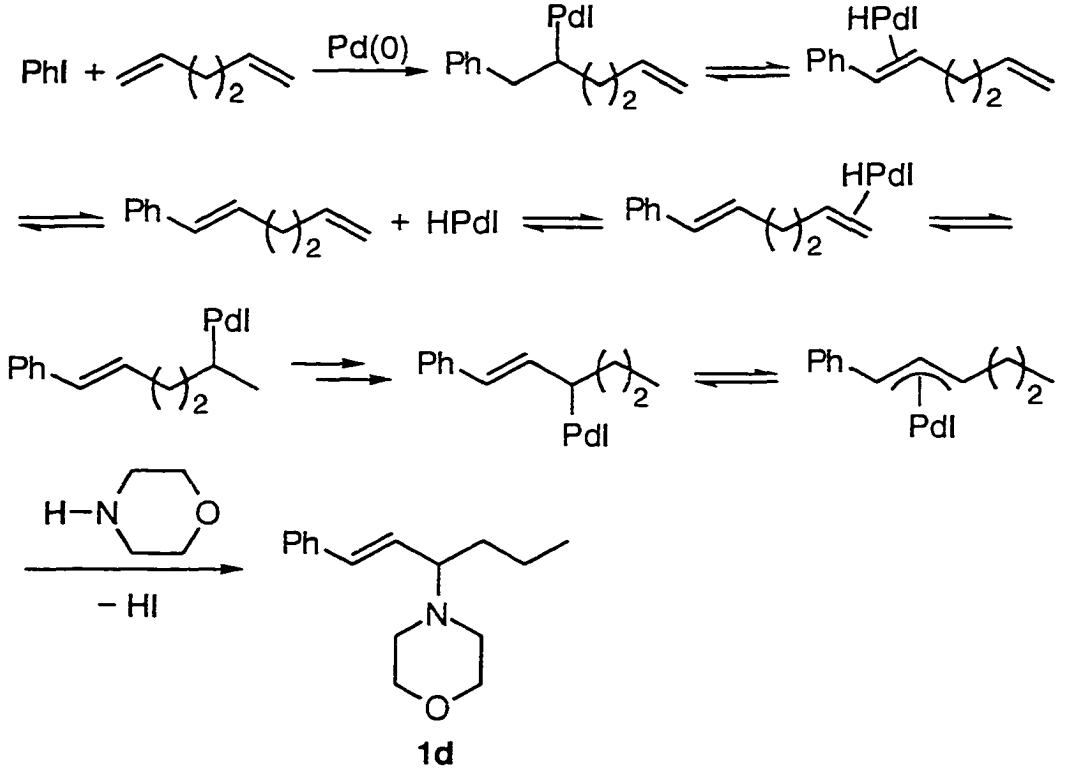
employing a five fold excess of both diene and amine, and 1 equivalent of *n*-Bu_4NCl, a procedure similar to that used earlier in the analogous reaction with carbon nucleophiles.[1] A 64% isolated yield of a mixture of allylic amines **1a** and **1b** was obtained, alongside what appeared to be a small amount of isomeric amines, which were easily separated from **1a** and **1b** (Table I, entry 1). By doubling the amount of *n*-Bu_4NCl, the yield of compounds **1a** and **1b** was raised to 79% (entry 2). Analogous reactions in *N,N*-dimethylacetamide (DMA) or DMSO as solvent gave somewhat lower yields (entries 3 and 4). The use of LiCl in place of *n*-Bu_4NCl also gave somewhat lower yields. The number of equivalents of amine could be reduced to two without lowering the yield (entry

Table 1. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Morpholine (Eq. 7)

entry	ratio PhI/diene/Nu	Cl^- source (equiv.)	solvent	temp (°C)	% yield (**1a+1b**) (ratio **1a**:**1b**)	% yield (**1c+1d**) (ratio **1c**:**1d**)
1	1/5/5	*n*-Bu_4NCl (1.0)	DMF	100	64	
2	1/5/5	*n*-Bu_4NCl (2.0)	DMF	100	79	
3	1/5/5	*n*-Bu_4NCl (2.0)	DMA	100	75	
4	1/5/5	*n*-Bu_4NCl (2.2)	DMSO	100	64	
5	1/5/5	LiCl (1.3)	DMF	100	71	
6	1/5/5	LiCl (2.0)	DMF	100	65	
7	1/5/2	*n*-Bu_4NCl (2.0)	DMF	100	80 (87:13)	7 (56:44)
8	1/5/2	*n*-Bu_4NCl (2.0)	DMF	80	77 (87:13)	
9	1/5/2	*n*-Bu_4NCl (2.0)	DMF	60	58 (88:12)	
10	1/5/2	LiCl (2.0)	DMF	100	81 (85:15)	--
11	1/5/2	--	DMF	100	75 (79:21)	15 (15:85)
12	1/2.5/2	*n*-Bu_4NCl (2.0)	DMF	100	68	
13	1/2.5/2	LiCl (1.3)	DMF	100	68	

7). A detailed analysis of this reaction indicated that amines **1a** and **1b** were formed in a ratio of 87:13, alongside 7% of a 56:44 mixture of two amines which appeared to possess the structures **1c** and **1d**. From the mechanism described in Scheme 1 in Paper I, one can see that **1a**, **1b** and **1c** are reasonable products of this coupling reaction. The formation of the fourth product **1d** can be rationalized as follows (Scheme 2). The reaction between iodobenzene and 1,5-hexadiene forms the Heck product 1-phenyl-1,5-hexadiene and a palladium hydride which apparently then react so as to add the hydride to the terminal double bond and migrate the palladium towards the phenyl group to produce a π-allylpalladium intermediate, which undergoes displacement by morpholine to produce the observed side product **1d**.

Scheme 2

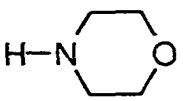
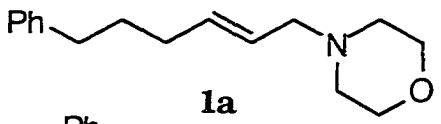
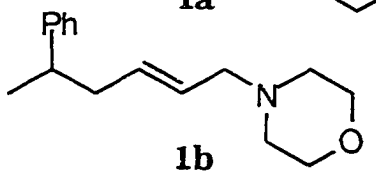
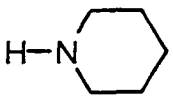
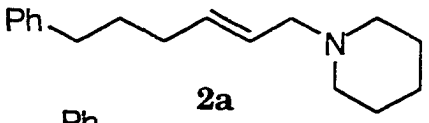
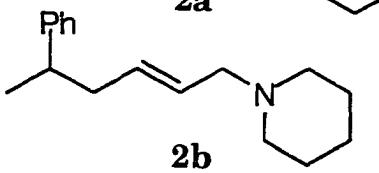
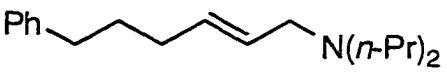
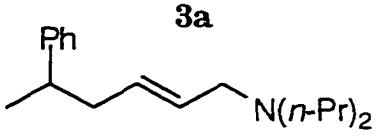
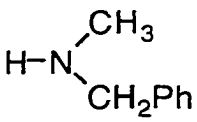
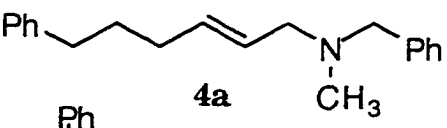
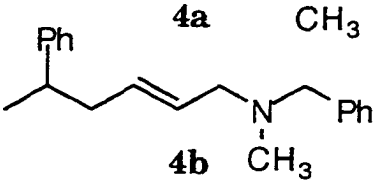


Efforts to reduce the temperature from 100 °C to 80 °C and 60 °C produced lowered yields of the desired amines with no increase in the regioselectivity (entries 8 and 9). Later on the use of LiCl at 100 °C was observed to give yields of **1a** and **1b** comparable to *n*-Bu_4NCl (entry 10). Failure to employ any chloride reagent resulted in a slight reduction in both the yield of **1a** plus **1b** and the regioselectivity of their formation, plus a significant increase in the undesired compounds **1c** and **1d** (entry 11). Efforts to reduce the amount of diene to 2.5 equivalents resulted in a modest reduction in the yield of the desired amines to 68% (entries 12 and 13).

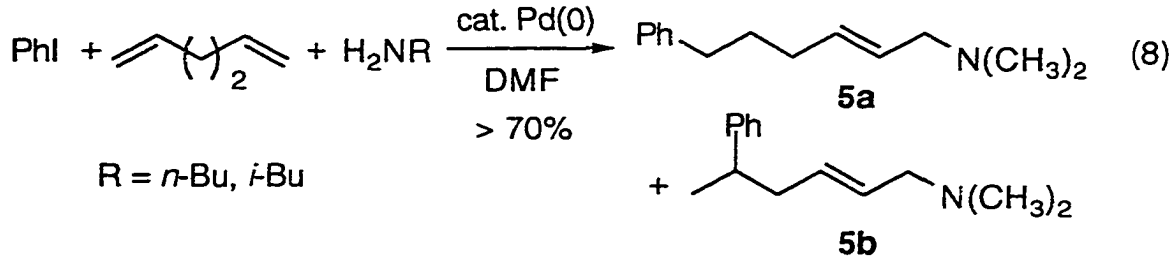
After the optimization of the reaction conditions, we examined a wide variety of aryl iodides, nonconjugated dienes and amines in this coupling reaction. As demonstrated in the model system (eq. 7), two minor isomers **c** and **d** were only formed in a very small amount, and were easily separated from the major isomers **a** and **b**. Therefore, in the following investigation, we just studied the yield and the ratio of **a** and **b**.

Several secondary amines were first employed in the coupling of iodobenzene and 1,5-hexadiene under the optimized conditions. The results are shown in Table 2. All the secondary aliphatic amines appeared to be excellent nucleophiles in this type of coupling. We expected primary amines would give similar results to those of secondary amines. Unfortunately, when employed in the same coupling, primary amines (e.g., *n*-butylamine and *i*-butylamine) failed to produce the desired products. Instead, dimethylamine coupling products (**5a** and **5b**) were formed in over 70% combined yields (eq. 8). Apparently, the solvent DMF was the source of the side products. Transamidation of DMF by primary amines released dimethylamine, a secondary amine, which reacted

Table 2. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Secondary Amines[a]

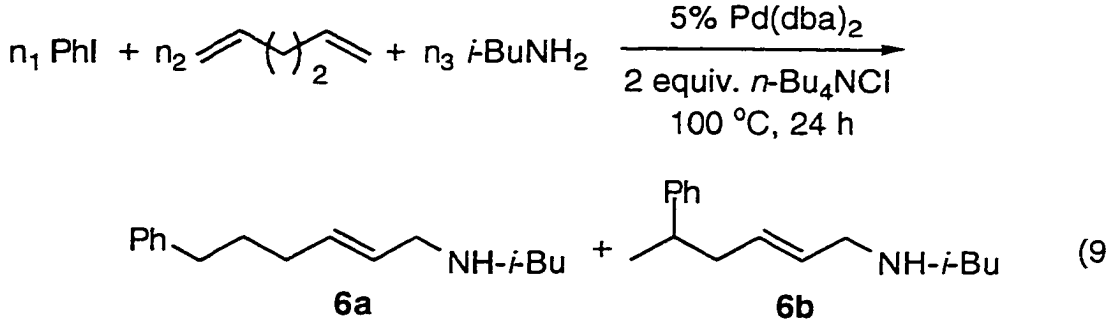
entry	amine	products	% yield (ratio **a**:**b**)
1		 **1a**  **1b**	87 (85:15)
2		 **2a**  **2b**	80 (90:10)
3	$HN(n\text{-}Pr)_2$	 **3a**  **3b**	87 (92:8)
4		 **4a**  **4b**	83 (87:13)

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$ and 2 equiv. of $n\text{-}Bu_4NCl$ at 100 °C for 24 hours, using 5 equiv. of 1,5-hexadiene and 2 equiv. of amine.



(8)

with iodobenzene and 1,5-hexadiene to generate **5a** and **5b**. To solve this problem, apparently, we simply had to change the solvent. DMA and DMSO were then tested in the coupling of isobutylamine with iodobenzene and 1,5-hexadiene (eq. 9). In order to soak up the HI produced during the coupling process, 2 equivalents of an additional base were added in some cases. The results are summarized in Table 3. A 48% combined yield of the desired coupling products **6a** and **6b** was obtained (entry 1) by simply changing the solvent from DMF to DMSO under the conditions described in Table 2. An increase of the amount of amine from 2 equivalents to 5 slightly raised the yield (entry 3). Addition of a base gave somewhat lower yields (entries 2 and 4). The addition of 5% Ph_3P analogous to the work of Heck[7] significantly reduced the yield of the desired product (entry 5). As a solvent, DMA appeared to be worse than DMSO in this reaction. A 40% yield was obtained only in the presence of 2 equivalents of Na_2CO_3 (entry 7).



(9)

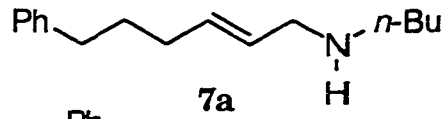
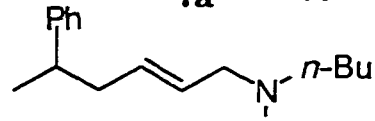
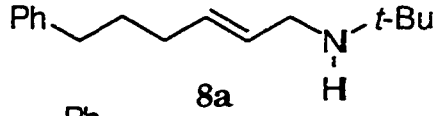
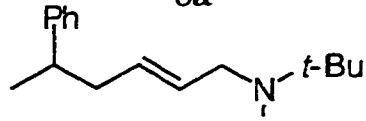
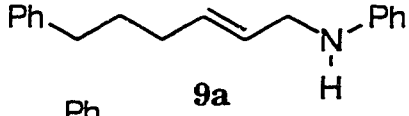
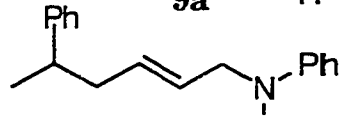
Table 3. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Isobutylamine (Eq. 9)

entry	n_1 / n_2 / n_3	solvent	base (2 equiv.)	% yield (ratio **6a**:**6b**)
1	1 / 5 / 2	DMSO	--	48
2	1 / 5 / 2	DMSO	KOAc	34
3	1 / 5 / 5	DMSO	--	51 (92:8)
4	1 / 5 / 5	DMSO	Na_2CO_3	45
5[a]	1 / 5 / 5	DMSO	--	17
6	1 / 5 / 5	DMA	--	trace
7	1 / 5 / 5	DMA	Na_2CO_3	40 (89:11)
8	1 / 5 / 5	DMA	Et_3N	trace

[a] 5 Mol % of Ph_3P added.

The reaction conditions of entry 3 in Table 3 were then applied to several other primary amines. Generally, primary amines provided fair to good yields of the desired products under these coupling conditions, which are shown in Table 4. Although aniline is substantially less basic than aliphatic amines, a comparable result was obtained under the same conditions (entry 3). A higher yield was achieved for the coupling of aniline when 2 equivalents of Na_2CO_3 were added (entry 4). Interestingly, in the reaction of aniline with iodobenzene and 1,5-hexadiene, a side product believed to be $CH_3(CH_2)_2CH{=}CHCH_2NHPh$ was isolated. This side product appears to be formed by the addition of a palladium hydride formed in a Heck reaction to the double bond of 1,5-hexadiene, the formation of a π-allylpalladium intermediate after the palladium migration, and, finally, the displacement of palladium by aniline.

Table 4. Palladium-catalyzed Coupling of Iodobenzene, 1,5-Hexadiene and Primary Amines[a]

entry	amine	products	% yield (ratio **a**:**b**)
1	n-$BuNH_2$	 **7a**  **7b**	35 (81:19)
2	t-$BuNH_2$	 **8a**  **8b**	58 (85:15)
3	$PhNH_2$	 **9a**  **9b**	53 (87:13)[b]
4[c]			67 (88:12)[d]

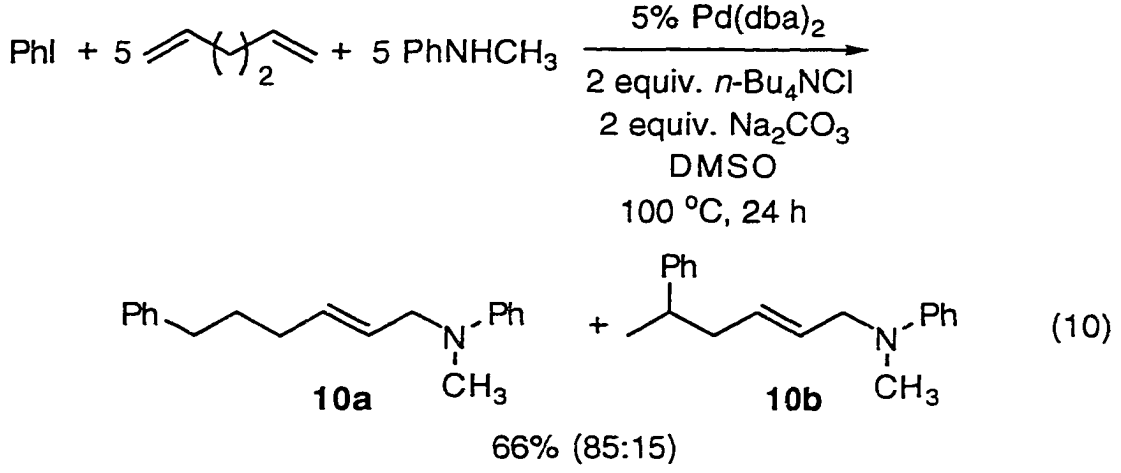
[a] Reactions were run in DMSO in the presence of 5 mol % $Pd(dba)_2$ and 2 equiv. of n-Bu_4NCl at 100 °C for 24 hours, using 5 equiv. of 1,5-hexadiene and 5 equiv. of amines.

[b] $CH_3(CH_2)_2CH{=}CHCH_2NHPh$ was isolated in 27% yield.

[c] 2 Equiv. of Na_2CO_3 was added.

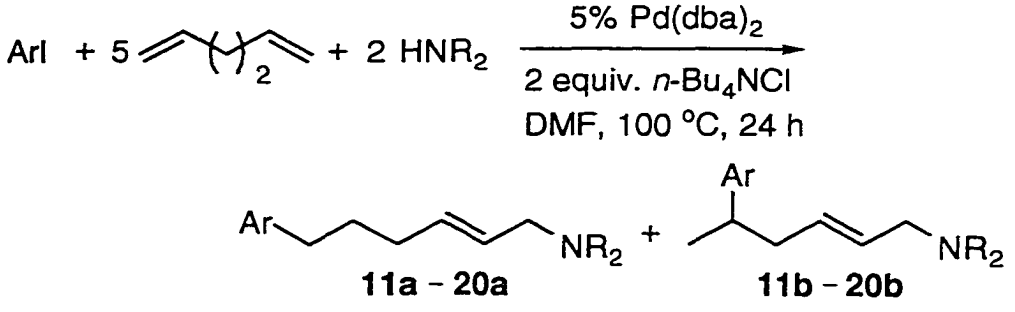
[d] $CH_3(CH_2)_2CH{=}CHCH_2NHPh$ was isolated in 9% yield.

N-Methylaniline, a secondary aniline, which gave only a 15% yield of the coupling product when DMF was used as the solvent was tested again because of the success of aniline. Therefore, *N*-methylaniline was allowed to react with iodobenzene and 1,5-hexadiene under the same conditions as that in entry 4 of Table 4. The desired products (**10a** and **10b**) were obtained in a 66% combined yield (eq. 10).



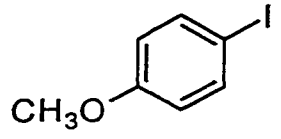
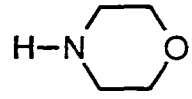
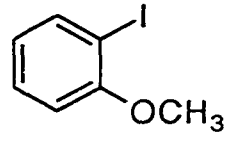
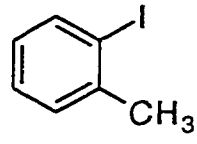
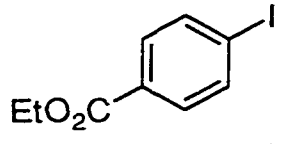
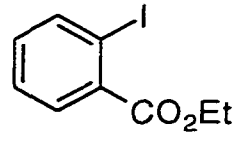
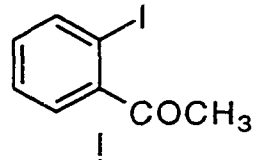
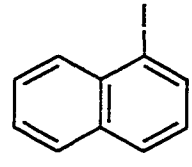
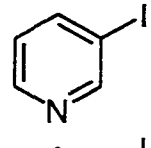
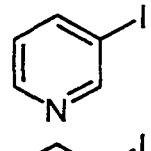
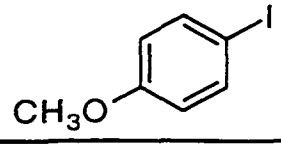
(10)

A variety of aromatic iodides were next investigated in this coupling process. The results from the coupling of a wide variety of aromatic iodides with 1,5-hexadiene and amines under our optimized conditions are summarized in eq. 11 and Table 5. In general, all the aryl iodides so far tested have provided



(11)

Table 5. Palladium-catalyzed Coupling of Aryl Iodides, 1,5-Hexadiene and Amines

entry	aryl iodide	amine	products	% yield (ratio **a**:**b**)
1			**11a, 11b**	89 (80:20)
2			**12a, 12b**	91 (93:7)
3			**13a, 13b**	90 (95:5)
4			**14a, 14b**	85 (89:11)
5			**15a, 15b**	92 (99:1)
6			**16a, 16b**	70 (~100:0)
7			**17a, 17b**	90 (92:8)
8			**18a, 18b**	67 (89:11)
9		*n*-Pr_2NH	**19a, 19b**	56 (91:9)
10		*n*-Pr_2NH	**20a, 20b**	67 (86:14)

very good results. Simple aryl iodides bearing electron-donating or electron-withdrawing substituents anywhere on the aromatic ring may be employed with little variation in overall yield. Even ketone and ester functionality may be accommodated. Polycyclic and heterocyclic iodides have also been successfully employed.

The most interesting thing here to us is the regioselectivity. From the results shown in Table 5, one can see that the location of the substituent on the aromatic ring influences the regioselectivity remarkably. For example, when a methoxy group was moved from the *para* position (entry 1) to the *ortho* position (entry 2) of iodobenzene, the ratio of **a**:**b** was increased from 80:20 to 93:7. Also, an increase of the ratio of **a**:**b** from 89:11 to 99:1 was observed when moving an ester group from the *para* to the *ortho* position (entries 4 and 5). Apparently, a substituent in the *ortho* position of iodobenzene makes this aryl group more sterically hindered, and the hindered aryl group prefers to add to the less hindered carbon of the double bond to produce more isomer **a**. In fact, all the *ortho*-substituted aryl iodides gave very high regioselectivity (entries 2, 3, 5–7).

Comparing entries 1 and 4 or entries 2 and 5, one can see that aryl iodides bearing electron-withdrawing groups give higher regioselectivity than those bearing electron-donating groups. To understand the reason, one must examine the nature of the C–C double bond when it coordinates with a transition metal. There are two types of bonds which can be formed between the double bond and the metal atom (Figure 1):[8] one is a σ-coordinate bond formed by interaction of the filled, bonding π orbital of the C–C double bond with an empty σ-acceptor orbital on the metal; another is a π-backbond formed

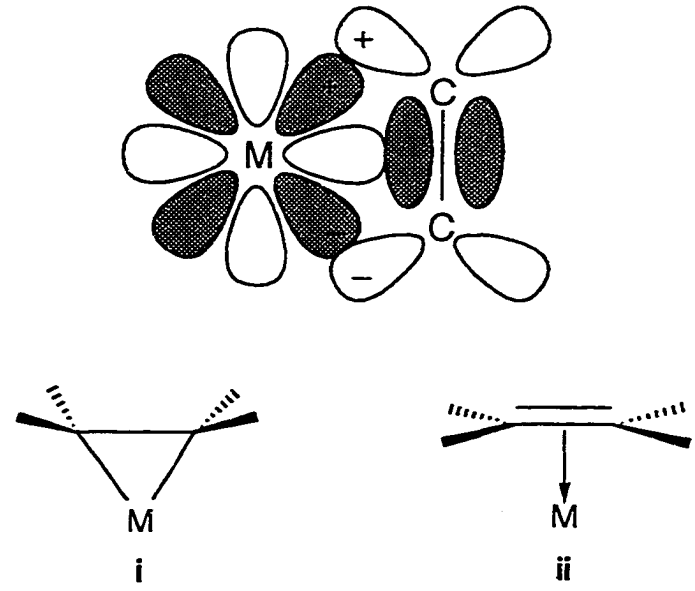


Figure 1

by interaction of a filled metal d-orbital with the vacant antibonding π^* orbital of the C–C double bond. The latter is the major factor in lengthening the C–C double bond. The stronger the π-backbonding, the longer the C–C bond. When the metal is strongly π basic and has a very high degree of back donation to the C–C double bond, the metal alkene system is considered as approaching the metallacyclopropane extreme (**i**), as contrasted with the extreme of minimal π back donation in the Dewar–Chatt model (**ii**).[9]

Here is an example of the influence of the electron density on the metal on the length of the C–C double bond (Figure 2). Platinum with two triphenyl-phosphine ligands (**iii**) possesses more electron density and has stronger π backbonding which makes the length of the coordinated C–C double bond much longer than the free alkene.[10] While in Zeise's salt (**iv**),[11] platinum possesses much less electron density and the length of the C–C double bond (1.37 Å) is very close to the free alkene.

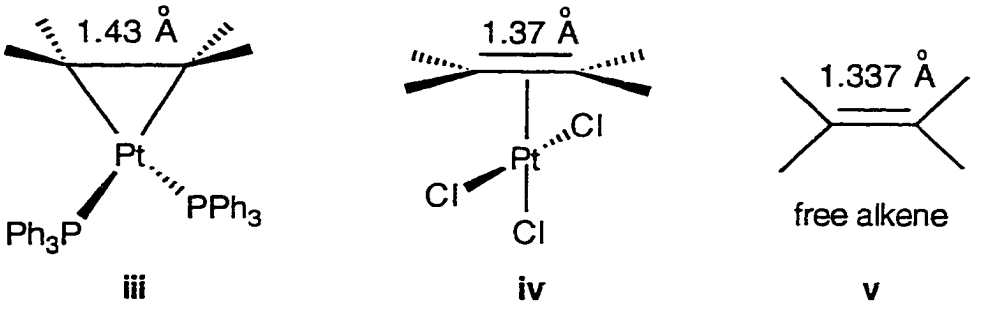


Figure 2

In the metallacyclopropane extreme (e.g., **iii**), the substituents on carbon are strongly folded back away from the metal as the carbons rehybridize from sp^2 to something more closely approaching sp^3. This is the key point to explain the regioselectivity of our coupling reaction. As we know, the first step of the coupling is oxidative addition of Pd(0) to an aryl iodide, followed by coordination with a C–C double bond of the diene. An aryl group bearing an electron-donating substituent somewhat increases the electron density on palladium, which makes the palladium-alkene complex (**vi** in Figure 3) more like **iii**. While an aryl group bearing an electron-withdrawing substituent reduces the electron density on palladium, which makes the complex (**vii**) more closely resemble **iv**. Figure 3 clearly shows that when an arylpalladium species coordinates to a C–C double bond of a diene, the substituent on the double bond is closer to

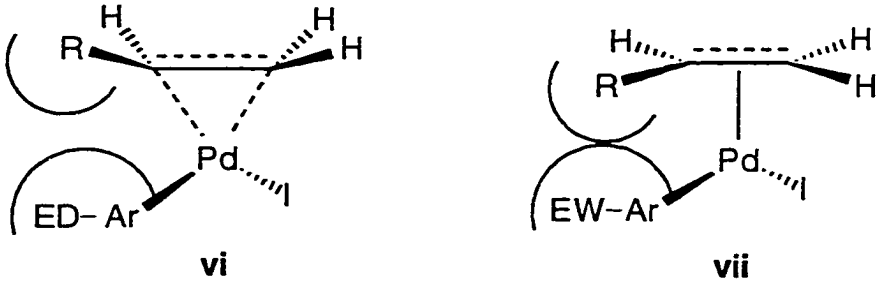
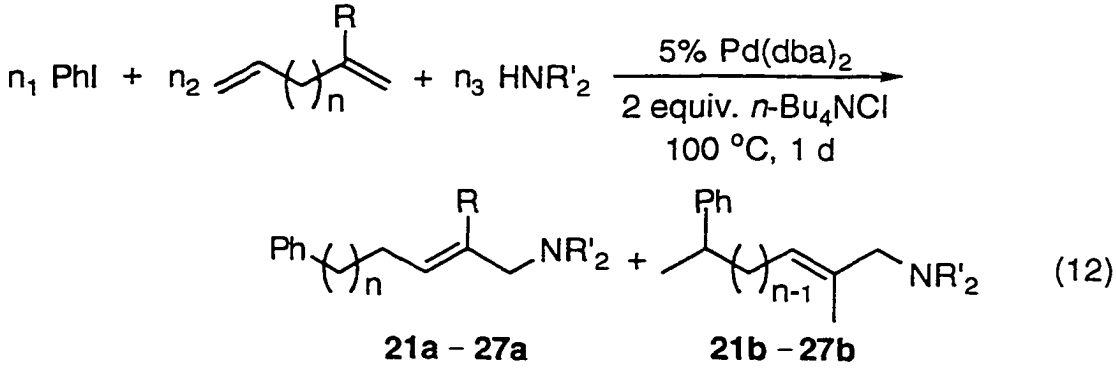


Figure 3

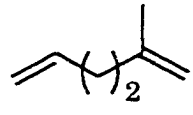
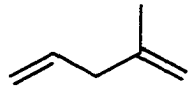
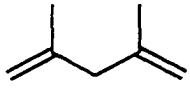
palladium in the case of the electron-withdrawing group on the aromatic ring and makes the complex more hindered (**vii**). Therefore, the aryl group will much prefer to add to the less hindered terminal carbon. In other words, higher regioselectivity should be observed. In the case of an electron-donating group on the aromatic ring (**vi**), the substituent on the double bond is further away from palladium, so it is less hindered than in the case of **vii**. Apparently, the regioselectivity is reduced due to the decreased steric effect. This is consistent with all the results from our coupling reactions.

Finally, a wide variety of nonconjugated dienes were examined in our palladium-catalyzed three component coupling. In general, the coupling is quite versatile with regard to the types of dienes one can utilize. The results from the coupling of iodobenzene, acyclic nonconjugated dienes and amines are summarized in eq. 12 and Table 6. Dienes with from one to ten carbons between the two C–C double bonds have been successfully coupled with only a modest reduction in overall yield as the chain length increases. Branched dienes, however, appear to be different from linear dienes. Compared with 1,5-hexadiene, 2-methyl-1,5-hexadiene gave only a 39% yield of the desired product, alongside a 41% yield of the dimethylamine coupling product under the same



(12)

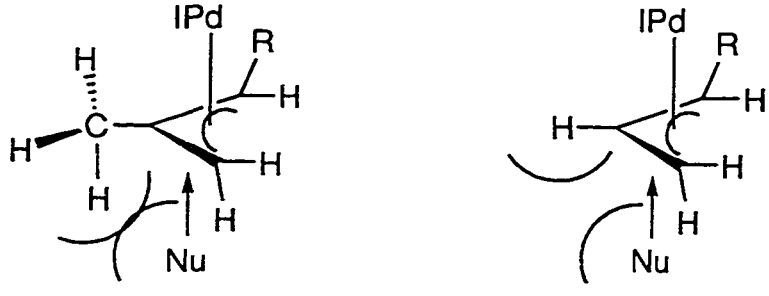
Table 6. Palladium-catalyzed Coupling of Iodobenzene, Nonconjugated diene and Amines

entry	diene	amine	$n_1 / n_2 / n_3$	solvent	products	% yield (ratio a:b)
1		morpholine	1 / 5 / 2	DMF	**1a, 1b**	87 (85:15)
2			1 / 5 / 2	DMF	**21a, 21b**	75 (82:18)
3		*n*-Pr_2NH	1 / 5 / 2	DMF	**22a, 22b**	78 (85:15)
4		morpholine	1 / 5 / 2	DMF	**23a, 23b**	67 (80:20)
5[a]			1 / 5 / 2	DMF	**24a, 24b**	39 (86:14)[b]
6			1 / 5 / 5	DMF	**24a, 24b**	58 (85:15)
7			1 / 5 / 5	DMA	**24a, 24b**	81 (86:14)
8			1 / 5 / 5	DMSO	**24a, 24b**	67 (85:15)
9			1 / 5 / 5	DMF	**25a, 25b**	61 (91:9)
10			1 / 5 / 5	DMA	**25a, 25b**	73 (89:11)
11		piperidine	1 / 5 / 5	DMA	**26a, 26b**	78 (93:7)
12		morpholine	1 / 5 / 5	DMA	**27a, 27b**	62 (100:0)

[a] Reaction was run for 3 days.

[b] Dimethylamine coupling product was isolated in 41% yield.

conditions using DMF as the solvent (entry 5). Apparently, the transamidation of DMF occurred again. The only factor allowing the transamidation to once again become a competing reaction here is the presence of the methyl group on the diene. The arylpalladium is observed to add cleanly to the less substituted C–C double bond of the diene, followed by palladium migration towards the more substituted C–C double bond to form a π-allylpalladium intermediate (**viii**) as shown in Figure 4. Compared with the case of linear diene (**ix**), the methyl group makes the π-allyl complex more hindered towards attack by a nucleophile. Therefore, the nucleophilic displacement of palladium becomes slower, which gives enough time for the transamidation of the DMF solvent by the amine.



viii **ix**

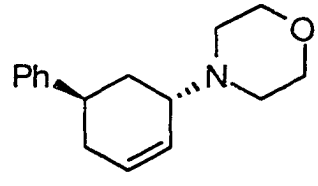
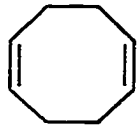
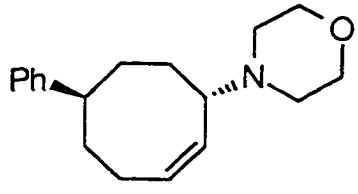
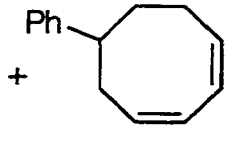
Figure 4

It has been proven that increasing the amount of the nucleophile can somewhat overcome the transamidation (entry 6). By changing the solvent to DMA or DMSO, the reaction was greatly improved. DMA gave the best result for the coupling reaction involving a branched diene (entries 7, 10–12). The coupling of iodobenzene, 2,4-dimethyl-1,4-pentadiene and morpholine produced only a single isomer (**27a**) in 62% yield (entry 12). With this diene the aryl group exclusively adds to the terminal carbon of the double bond because the

disubstituted internal carbon of the double bond is much more sterically hindered than the terminal carbon. In addition, our reaction of iodobenzene, 2-methyl-1,4-pentadiene and piperidine provides a 78% yield (entry 11), while the previous procedure of Heck with these same reagents gave only a 34% combined yield of the expected allylic amines (eq. 6).

When employed in the coupling reaction, cyclic dienes gave different results according to the ring size. The results are shown in Table 7. 1,4-

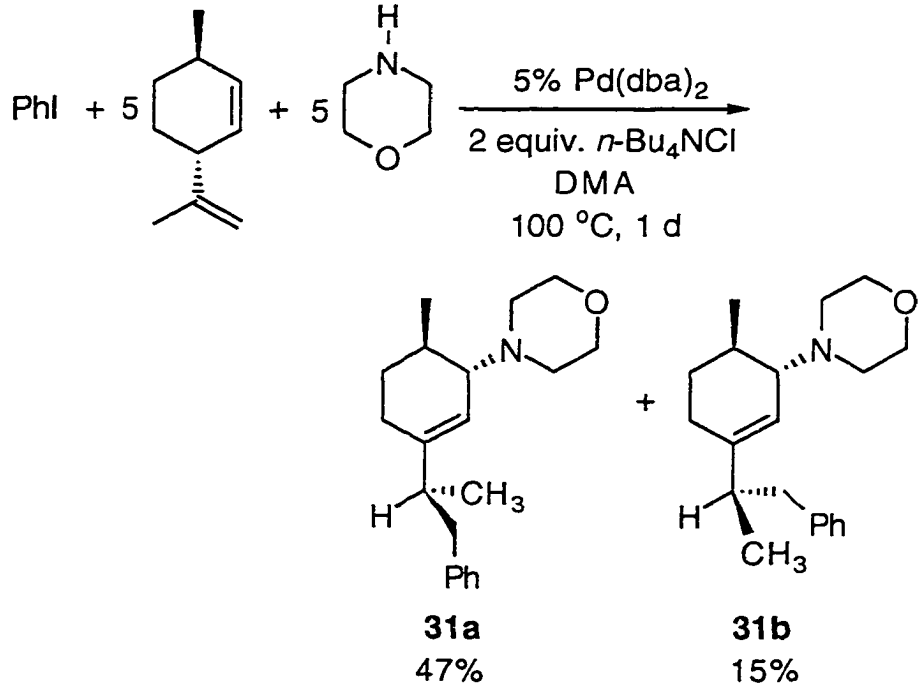
Table 7. Palladium-catalyzed Coupling of Iodobenzene, Nonconjugated Cyclic Dienes and Morpholine

entry	diene	PhI/diene/Nu	solvent	product, % yield
1		1/5/2	DMF	 **28**, 70
2		1/5/2	DMF	 **29**, 0
3		1/5/5	DMA	**29**, trace
4[a]		1/5/5	DMSO	**29**, 30
				 **30**, 58

[a] 2 Equiv. of Na_2CO_3 were added.

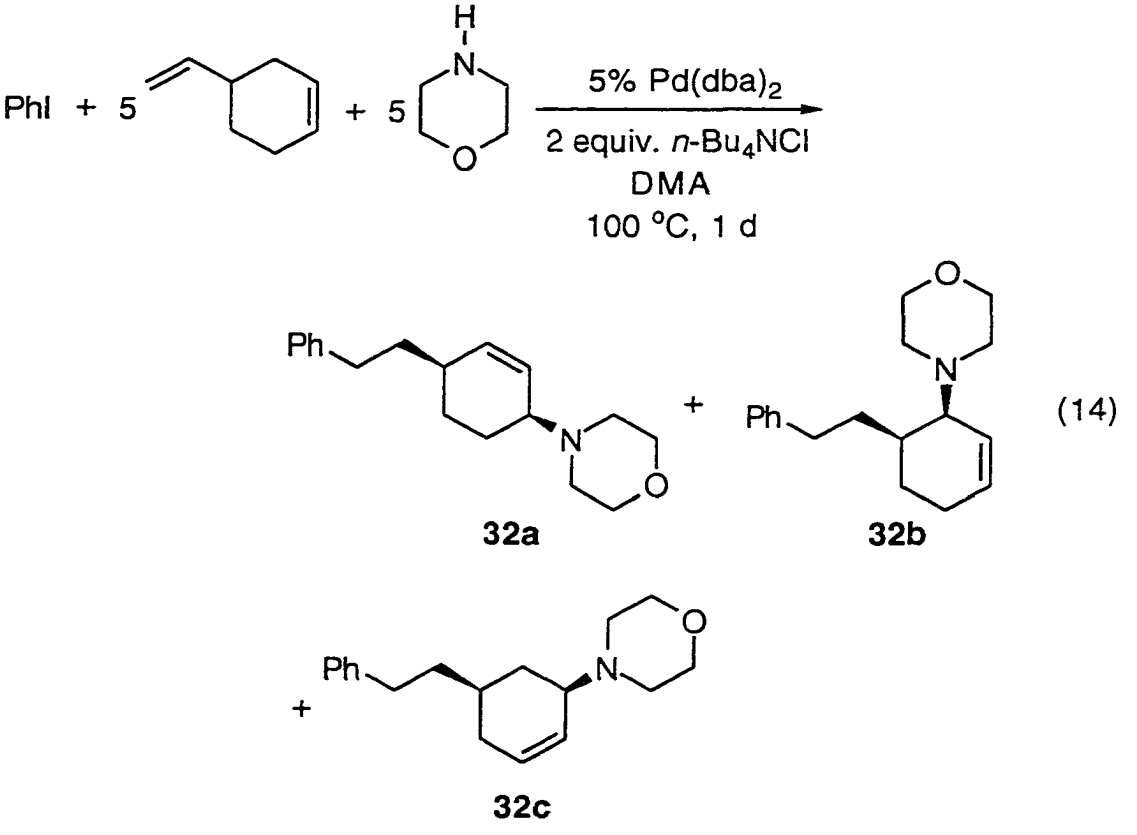
Cyclohexadiene coupled with iodobenzene and morpholine to afford a high yield of a single allylic amine (entry 1) in which phenylpalladium addition has taken place on one face of the diene and the amine is introduced from the opposite face. 1,5-Cyclooctadiene, however, failed to give the desired product under the same conditions (entry 2). By using additional base and running the reaction in DMSO, the desired product **29** was obtained in only 30% yield, alongside a 58% yield of a side product believed to be the conjugated diene **30** (entry 4).[12]

The optically active 1,4-diene (1*R*)-(+)-*trans*-isolimonene in which both acyclic and cyclic C–C double bonds exist couples cleanly with iodobenzene and morpholine to afford two separable diastereomeric amines in 47% and 15% yields respectively (eq. 13).



(13)

In the same procedure as above, 4-vinylcyclohexene, however, produces a 58% yield of an inseparable 73:17:10 mixture of three isomeric amines believed to be compounds **32a–32c** respectively (eq. 14). Apparently, migration involving the least number of hydride eliminations and readditions is favored, resulting in products **32a** and **32b** being favored over **32c**.



Conclusion

The palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and amines has been successfully achieved. Secondary amines have proven to be excellent nucleophiles in this coupling process, while primary amines give relatively lower yields of the desired products. A wide variety of aryl iodides tested have provided good to excellent yields of the expected allylic amines. Both acyclic and cyclic nonconjugated dienes are successfully employed in this coupling process. Even long chain dienes (10 carbons between two double bonds) give good yields of the desired products.

The regiochemistry of this process is quite interesting. Generally, the aryl group adds predominantly to the less hindered end of the less hindered C–C double bond, but significant amounts of internal addition are observed. In the coupling of monosubstituted C–C double bonds the ratio of ~85:15 is not significantly affected by the nature of the diene, but hindered aryl groups, such as *ortho*-substituted aryl iodides do provide greater regioselectivity as expected. The functional groups present on the aromatic ring also influence the regiochemistry. Electron-withdrawing groups provide higher regioselectivity than electron-donating groups. Terminal disubstituted C–C double bonds undergo arylation exclusively on the unsubstituted carbon.

The stereochemistry of the C–C double bond of the acyclic allylic amines produced by the process is found to be exclusively *E*, even when that double bond is trisubstituted.

Experimental Section

Equipment. All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Digilab FTS-7 spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed on an HP 5890 chromatograph equipped with an HP-1 Megabore column. Flash chromatography was carried out on 230-400 mesh silica gel. Thin-layer chromatography was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F). 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. Bis(dibenzylideneacetone)palladium was donated by Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride, ethyl 2-iodobenzoate and ethyl 4-iodobenzoate were purchased from Lancaster Synthesis Inc. Iodobenzene, 2-iodotoluene, 2-iodoanisole, 4-iodoanisole, di-*n*-propylamine, 1,5-hexadiene, 2-methyl-1,5-hexadiene, 1,4-cyclohexadiene, 1,9-decadiene, *t*-butylamine and *N*,*N*-dimethylacetamide were purchased from Aldrich Chemical Company, Inc. Morpholine, piperidine, dimethyl sulfoxide, *N*,*N*-dimethylformamide, and lithium chloride were purchased from Fisher Scientific Company. Aniline, *N*-methylaniline and *n*-butylamine were purchased from J. T. Baker Chemical Co. 1-Iodonaphthalene, *i*-butylamine and benzylmethylamine were purchased from Eastman Kodak Co. 2-Methyl-

1,4-pentadiene and 2,4-dimethyl-1,4-pentadiene were purchased from Wiley Organics. 1,13-Tetradecadiene was purchased from Columbia Organic Chemical Co., Inc. (1*R*)-(+)-*trans*-Isolimonene was purchased from Fluka Chemika.

General procedure for the palladium-catalyzed coupling of aryl iodides, non-conjugated dienes and amines.

Procedure A:

To a 2 dram vial with a micromagnetic stirring bar were added 0.25 or 0.5 mmol of aryl iodide, 1.25 or 2.5 mmol of non-conjugated diene, 0.5 or 1.0 mmol of amine, 5 mol % of bis(dibenzylideneacetone)palladium, 0.5 or 1.0 mmol of tetra-*n*-butylammonium chloride (Lancaster, anhydrous) and 1 or 2 ml of DMF respectively. The vial was capped with a screw-cap containing a Teflon liner. The resulting mixture was stirred at 100 °C for 24 hours. The mixture was then allowed to cool down to room temperature, diluted with saturated NaCl solution and extracted with ethyl ether. The ether layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to remove the solvent. The crude products were isolated by flash chromatography on a silica gel column.

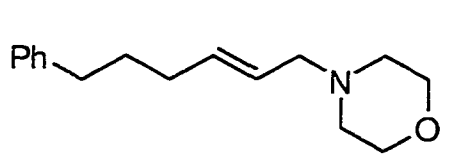
Procedure B:

Procedure B is identical to that of procedure A except that 5 equiv. of amine in DMSO is employed.

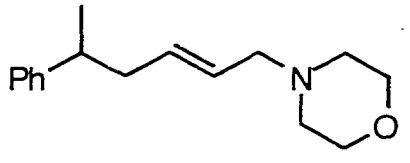
Procedure C:

Procedure C is identical to that of procedure B except that *N,N*-dimethylacetamide is employed as the solvent.

Preparation of Compounds **1a** and **1b**



1a

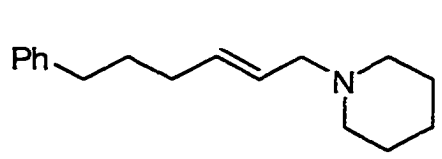


1b

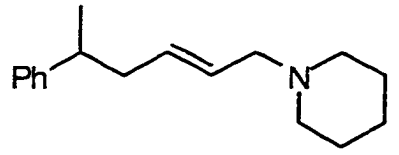
Compounds **1a** and **1b** were obtained as an inseparable 85:15 mixture of isomers in 87% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **1b**), 1.70 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.08 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.43 (br s, 4 H, ring NCH_2), 2.60 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.95 (d, J = 6.3 Hz, 2 H, =CCH_2N), 3.64 (t, J = 4.5 Hz, 4 H, ring CH_2O in **1b**), 3.71 (t, J = 4.5 Hz, 4 H, ring CH_2O), 5.50 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.60 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 7.14-7.29 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 30.9, 31.8, 35.3, 53.4, 61.2, 66.9, 125.6, 126.2, 128.2, 128.3, 134.5, 142.2; IR (neat) 3084, 3026, 2926, 1685, 1452, 1119 cm^{-1}; HRMS for $C_{16}H_{23}NO$: calcd 245.1780, found 245.1781.

Preparation of Compounds **2a** and **2b**

Compounds **2a** and **2b** were obtained as an inseparable 90:10 mixture of isomers in 80% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2 equiv. of piperidine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.24



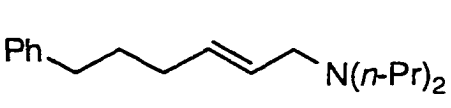
2a



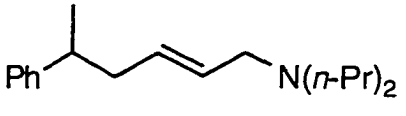
2b

(d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **2b**), 1.40-1.45 (br m, 2 H, $NCH_2CH_2C\underline{H}_2$), 1.54-1.62 (br m, 4 H, $NCH_2C\underline{H}_2CH_2$), 1.70 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.07 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.33-2.38 (br m, 4 H, $NC\underline{H}_2CH_2C\underline{H}_2$), 2.61 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.90 (d, J = 5.1 Hz, 2 H, $=CCH_2N$), 5.52 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H, vinyl), 5.58 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H, vinyl), 7.15-7.29 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 24.3, 25.9, 31.0, 31.9, 35.3, 54.3, 61.7, 125.6, 127.1, 128.2, 128.3, 133.7, 142.4; IR (neat) 3084, 3026, 2933, 1604, 1453, 1154 cm^{-1}; HRMS for $C_{17}H_{25}N$: calcd 243.1987, found 243.1986.

Preparation of Compounds **3a** and **3b**



3a

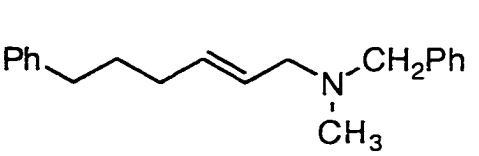


3b

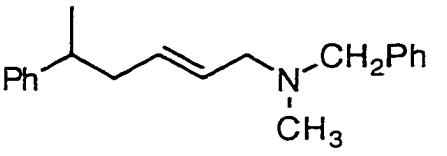
Compounds **3a** and **3b** were obtained as an inseparable 92:8 mixture of isomers in 87% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2 equiv. of di-*n*-propylamine using procedure A: ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6 H, $CH_2C\underline{H}_3$), 1.24 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **3b**), 1.46 (sextet, J = 7.5 Hz, 4 H, $C\underline{H}_2CH_3$), 1.70 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.07 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.38 (t, J = 7.5 Hz, 4 H, $NC\underline{H}_2CH_2$), 2.61 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 3.04 (d, J = 5.1 Hz, 2 H,

=CCH_2N), 5.45-5.62 (m, 2 H, vinyl), 7.15-7.30 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 12.0, 19.9, 31.0, 31.9, 35.3, 55.5, 56.1, 125.6, 127.1, 128.2, 128.4, 133.5, 142.4; IR (neat) 3084, 3026, 2957, 2931, 1603, 1454, 1189 cm^{-1}; HRMS for $C_{18}H_{29}N$: calcd 259.2300, found 259.2298.

Preparation of Compounds **4a** and **4b**



4a

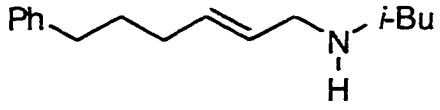


4b

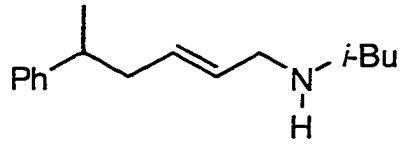
Compounds **4a** and **4b** were obtained as an inseparable 87:13 mixture of isomers in 83% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2 equiv. of benzylmethylamine using procedure A: ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.6 Hz, 3 H, $PhCCH_3$ in **4b**), 1.71 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.05-2.12 (br m, 2 H, CH_2C=), 2.17 (s, 3 H, CH_3N), 2.61 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.98 (d, J = 5.4 Hz, 2 H, =CCH_2N), 3.38 (s, 2 H, NCH_2Ph in **18**), 3.48 (s, 2 H, NCH_2Ph), 5.48-5.66 (m, 2H, vinyl), 7.15-7.31 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 31.0, 31.9, 35.4, 41.9, 59.6, 61.5, 125.6, 126.9, 127.5, 128.2, 128.2, 128.4, 129.1, 133.8, 138.9, 142.4; IR (neat) 3085, 3026, 2929, 1603, 1453, 1131 cm^{-1}; Anal. Calcd for $C_{20}H_{25}N$: C, 85.97; H, 9.02. Found: C, 85.31; H, 9.04.

Preparation of Compounds **6a** and **6b**

Compounds **6a** and **6b** were obtained as an inseparable 92:8 mixture of isomers in 51% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-



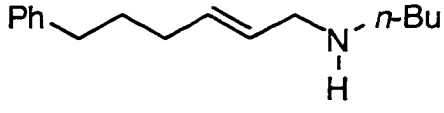
6a



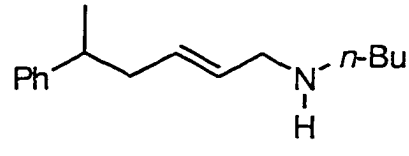
6b

hexadiene and 5 equiv. of isobutylamine using procedure B: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.9 Hz, 6 H, $NCC(CH_3)_2$), 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **6b**), 1.70 (quintet, J = 7.2 Hz, 2 H, $PhCCH_2$), 1.85 (nontet, J = 6.9 Hz, 1 H, $NCH_2C\underline{H}$), 2.08 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.47 (d, J = 6.9 Hz, 2 H, $NC\underline{H_2}CH$), 2.61 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 3.27 (d, J = 5.7 Hz, 2 H, $=CCH_2N$), 3.62 (br s, 1 H, NH), 5.57 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.67 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 7.15-7.30 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.7, 28.4, 30.9, 31.9, 35.3, 51.9, 57.4, 125.6, 128.2, 128.3, 128.8, 132.0, 142.4; IR (neat) 3360 (N-H), 3084, 3024, 2966, 1603, 1477, 1231 cm^{-1}; HRMS for $C_{16}H_{25}N$: calcd 231.1987, found 231.1983.

Preparation of Compounds **7a** and **7b**



7a

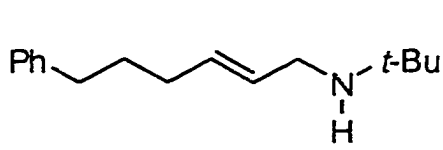


7b

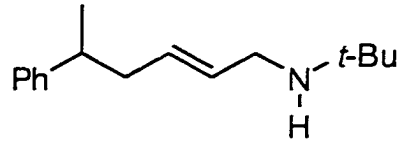
Compounds **7a** and **7b** were obtained as an inseparable 81:19 mixture of isomers in 35% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 5 equiv. of *n*-butylamine using procedure B: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3 H, $CH_2C\underline{H_3}$ in **7b**), 0.91 (t, J = 7.2 Hz, 3 H, $CH_2C\underline{H_3}$), 1.24 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **7b**), 1.34 (sextet, J = 7.2 Hz, 2 H, $C\underline{H_2}CH_3$),

1.52 (quintet, J = 7.2 Hz, 2 H, $NCH_2C\underline{H_2}$), 1.70 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.07 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.53 (t, J = 7.2 Hz, 2 H, $NC\underline{H_2}CH_2$ in **7b**), 2.61 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.62 (t, J = 7.2 Hz, 2 H, NCH_2), 2.89 (br s, 1 H, NH), 3.23 (d, J = 5.4 Hz, 2 H, =CCH_2N), 5.55 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.64 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 7.15-7.29 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.8, 20.3, 28.9, 30.8, 32.0, 35.4, 46.1, 49.6, 123.3, 125.7, 128.3, 128.3, 137.3, 142.0; IR (neat) 3403 (N-H), 3084, 3026, 2934, 1603, 1454, 1128 cm^{-1}; HRMS for $C_{16}H_{25}N$: calcd 231.1987, found 231.1988.

Preparation of Compounds **8a** and **8b**



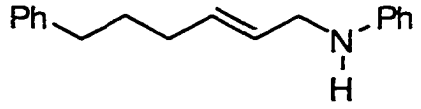
8a



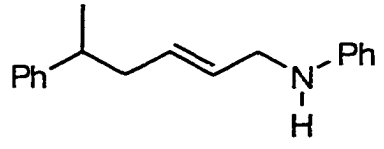
8b

Compounds **8a** and **8b** were obtained as an inseparable 85:15 mixture of isomers in 58% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 5 equiv. of *t*-butylamine using procedure B: ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, $NC(CH_3)_3$ in **8b**), 1.14 (s, 9 H, $NC(CH_3)_3$), 1.23 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **8b**), 1.69 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.02-2.09 (m, 2 H, CH_2C=), 2.15-2.32 (br m, 1 H, NH), 2.60 (t, J = 7.8 Hz, 2 H, $PhCH_2$), 2.75 (sextet, J = 6.9 Hz, 1 H, PhCH in **8b**), 3.17 (d, J = 4.8 Hz, 2 H, =CCH_2N), 5.51-5.67 (m, 2 H, vinyl), 7.15-7.29 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.8, 30.9, 31.9, 35.3, 44.8, 50.7, 125.6, 128.2, 128.3, 128.8, 132.1, 142.3; IR (neat) 3360 (N-H), 3084, 3024, 2966, 1603, 1477, 1231 cm^{-1}; HRMS for $C_{16}H_{25}N$: calcd 231.1987, found 231.1983.

Preparation of Compounds **9a** and **9b**



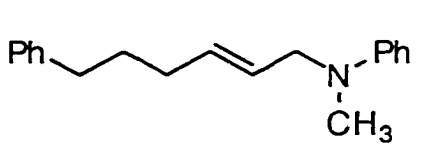
9a



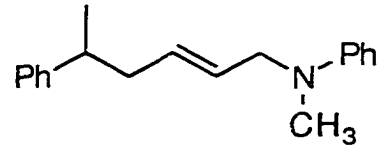
9b

Compounds **9a** and **9b** were obtained as an inseparable 88:12 mixture of isomers in 67% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 5 equiv. of aniline in the presence of 2.0 equiv. of Na_2CO_3 using procedure B: ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **9b**), 1.70 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.07 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.60 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.70-2.80 (m, 1 H, PhCH in **9b**), 3.69 (d, J = 5.7 Hz, 2 H, $=CCH_2N$), 5.57 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H, vinyl), 5.70 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 6.55-6.72 (m, 3 H, aryl), 7.14-7.29 (m, 7 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.9, 31.8, 35.3, 46.0, 112.9, 117.3, 125.6, 127.3, 128.2, 128.4, 129.1, 132.7, 142.3, 148.1; IR (neat) 3412 (N-H), 3083, 3024, 2929, 1602, 1504, 1319, 1251 cm^{-1}; HRMS for $C_{18}H_{21}N$: calcd 251.1674, found 251.1674.

Preparation of Compounds **10a** and **10b**



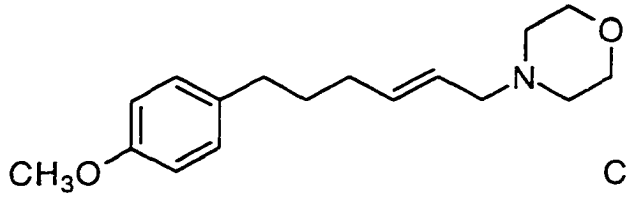
10a



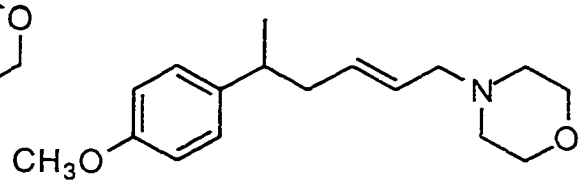
10b

Compounds **10a** and **10b** were obtained as an inseparable 85:15 mixture of isomers in 66% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 5 equiv. of *N*-methylaniline in the presence of 2.0 equiv. of Na_2CO_3 using procedure B: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **10b**), 1.67 (quintet, J = 7.8 Hz, 2 H, $PhCCH_2$), 2.05 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.57 (t, J = 7.8 Hz, 2 H, $PhCH_2$), 2.87 (s, 3 H, NCH_3 in **10b**), 2.89 (s, 3 H, NCH_3), 3.85 (d, J = 5.1 Hz, 2 H, $=CCH_2N$), 5.45 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H, vinyl), 5.59 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 6.66-6.74 (m, 3 H, aryl), 7.12-7.28 (m, 7 H, aryl); ^{13}C NMR ($CDCl_3$) δ 31.0, 31.8, 35.3, 37.8, 54.5, 112.6, 116.3, 125.6, 128.2, 128.4, 129.0, 132.4, 142.4, 149.5 (one peak overlapped); IR (neat) 3084, 3061, 3025, 2930, 1600, 1502, 1358, 1205 cm^{-1}; HRMS for $C_{19}H_{23}N$: calcd 265.1831, found 265.1831.

Preparation of Compounds **11a** and **11b**



11a

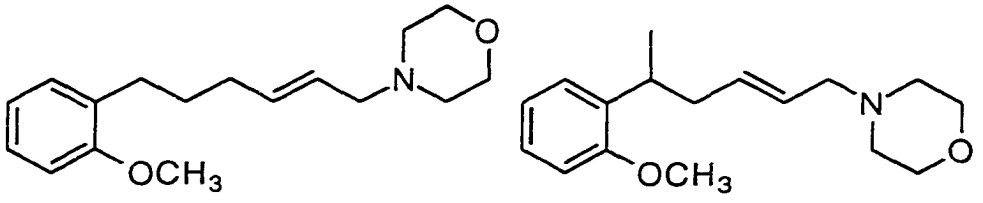


11b

Compounds **11a** and **11b** were obtained as an inseparable 80:20 mixture of isomers in 89% combined yield from the coupling of 4-iodoanisole, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 7.2 Hz, 3 H, $ArCCH_3$ in **11b**), 1.66 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.06 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.43 (br t, J = 4.2 Hz, 4 H, ring NCH_2), 2.55 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.94 (d, J = 6.0 Hz, 2 H, $=CCH_2N$),

3.64 (t, J = 4.8 Hz, 4 H, ring CH_2O in **11b**), 3.71 (t, J = 4.8 Hz, 4 H, ring CH_2O), 3.76 (s, 3 H, CH_3O in **11b**), 3.77 (s, 3 H, CH_3O), 5.48 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.61 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 6.81 (d, J = 8.4 Hz, 2 H, aryl), 7.07 (d, J = 8.4 Hz, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 31.2, 31.8, 34.4, 53.5, 55.2, 61.3, 66.9, 113.6, 126.1, 127.4, 129.2, 134.6, 157.6; IR (neat) 3058, 3028, 2953, 2926, 1611, 1453, 1244, 1117 cm^{-1}; HRMS for $C_{17}H_{25}NO_2$: calcd 275.1885, found 275.1891.

Preparation of Compounds **12a** and **12b**

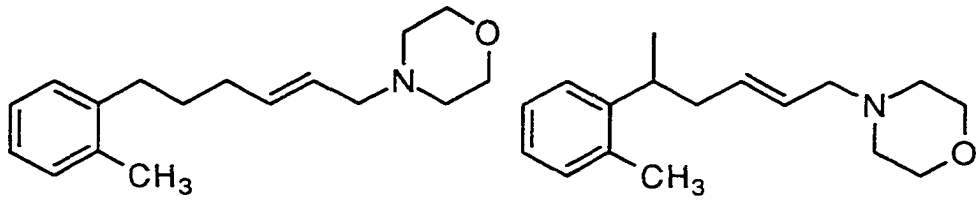


12a **12b**

Compounds **12a** and **12b** were obtained as an inseparable 93:7 mixture of isomers in 91% combined yield from the coupling of 2-iodoanisole, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 7.5 Hz, 3 H, $ArCCH_3$ in **12b**), 1.66 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.09 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.43 (br s, 4 H, ring NCH_2), 2.60 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.93 (d, J = 6.6 Hz, 2 H, $=CCH_2N$), 3.71 (t, J = 4.8 Hz, 4 H, ring CH_2O), 3.80 (s, 3 H, CH_3O), 5.49 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.63 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 6.81-6.89 (m, 2 H, aryl), 7.09-7.19 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.4, 29.7, 32.2, 53.5, 55.2, 61.4, 67.0, 110.1, 120.2, 125.9, 126.9, 129.7, 130.7, 135.0, 157.3; IR (neat) 3103,

3063, 3018, 2956, 2927, 1601, 1463, 1243, 1118 cm^{-1}; HRMS for $C_{17}H_{25}NO_2$: calcd 275.1885, found 275.1893.

Preparation of Compounds **13a** and **13b**

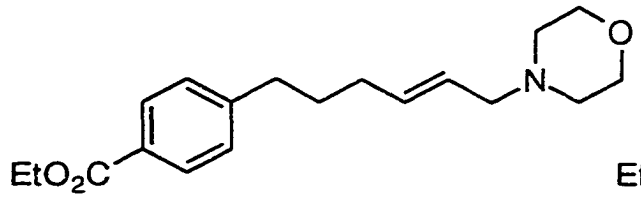


13a **13b**

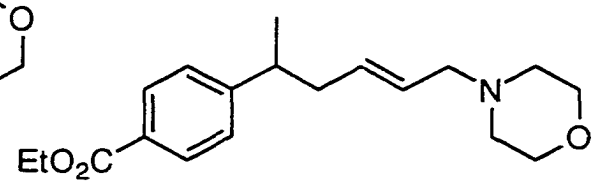
Compounds **13a** and **13b** were obtained as an inseparable 95:5 mixture of isomers in 90% combined yield from the coupling of 2-iodotoluene, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^1H NMR ($CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **13b**), 1.65 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.12 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.28 (s, 3 H, CH_3), 2.43 (br s, 4 H, ring NCH_2), 2.59 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.94 (d, J = 6.3 Hz, 2 H, $=CCH_2N$), 3.71 (t, J = 4.8 Hz, 4 H, ring CH_2O), 5.51 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.64 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.10 (br s, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 19.3, 29.7, 32.3, 32.8, 53.5, 61.3, 66.9, 125.8, 126.2, 128.7, 130.1, 134.6, 135.7, 140.5 (one peak overlapped); IR (neat) 3100, 3061, 3014, 2948, 2926, 1603, 1453, 1117 cm^{-1}; HRMS for $C_{17}H_{25}NO$: calcd 259.1936, found 259.1937.

Preparation of Compounds **14a** and **14b**

Compounds **14a** and **14b** were obtained as an inseparable 86:14 mixture of isomers in 85% combined yield from the coupling of ethyl 4-iodobenzoate, 5



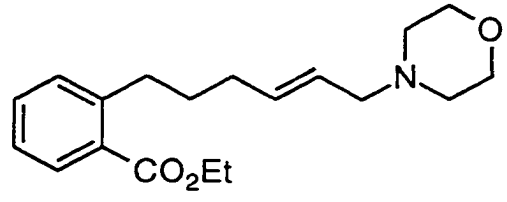
14a



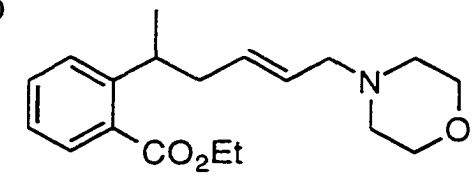
14b

equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **14b**), 1.38 (t, J = 7.2 Hz, 3 H, CH_3), 1.72 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.08 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.43 (br s, 4 H, ring NCH_2), 2.66 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.94 (d, J = 6.6 Hz, 2 H, =CCH_2N), 3.63 (t, J = 4.8 Hz, 4 H, ring CH_2O in **14b**), 3.71 (t, J = 4.8 Hz, 4 H, ring CH_2O), 4.36 (q, J = 7.2 Hz, 2 H, $CH_3C\underline{H_2}O$), 5.49 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.61 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 7.22 (d, J = 8.1 Hz, 2 H, aryl), 7.95 (d, J = 8.1 Hz, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.4, 30.6, 31.8, 35.4, 53.5, 60.7, 61.3, 66.9, 126.5, 128.1, 128.4, 129.6, 134.2, 147.7, 166.6; IR (neat) 3032, 2954, 2930, 1714 (C=O), 1611, 1453, 1277, 1118 cm^{-1}; HRMS for $C_{19}H_{27}NO_3$: calcd 317.1991, found 317.1988.

Preparation of Compounds **15a** and **15b**



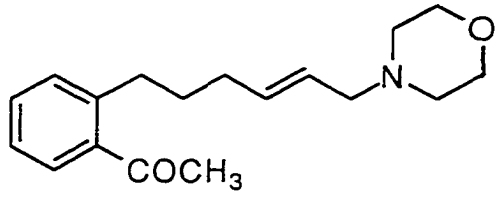
15a



15b

Compounds **15a** and **15b** were obtained as an inseparable 99:1 mixture of isomers in 92% combined yield from the coupling of ethyl 2-iodobenzoate, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3 H, CH_3), 1.69 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.12 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.43 (br s, 4 H, ring NCH_2), 2.93 (d, J = 6.6 Hz, 2 H, =CCH_2N), 2.94 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 3.71 (t, J = 4.8 Hz, 4 H, ring CH_2O), 4.35 (q, J = 7.2 Hz, 2 H, $CH_3C\underline{H_2}O$), 5.49 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.63 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.21-7.28 (m, 2 H, aryl), 7.40 (dt, J = 1.2 Hz, J = 7.2 Hz, 1 H, aryl), 7.85 (dd, J = 7.8 Hz, J = 1.2 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.4, 31.3, 32.4, 34.1, 53.5, 60.7, 61.3, 67.0, 125.8, 126.1, 129.8, 130.5, 130.9, 131.7, 134.7, 144.0, 167.7; IR (neat) 3063, 3021, 2956, 2929, 1718 (C=O), 1601, 1453, 1256, 1118 cm^{-1}; HRMS for $C_{19}H_{27}NO_3$: calcd 317.1991, found 317.1993.

Preparation of Compound **16a**

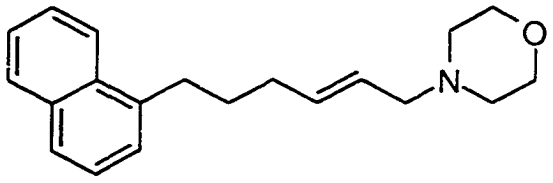


16a

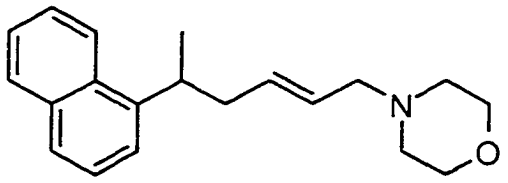
Compound **16a** was obtained in 70% yield from the coupling of 2-iodoacetophenone, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.66 (quintet, J = 7.8 Hz, 2 H, $ArCCH_2$), 2.11 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.43 (br t, J = 4.2 Hz, 4 H, ring NCH_2), 2.57 (s, 3 H, CH_3), 2.84 (t, J = 8.1 Hz, 2 H, $ArCH_2$), 2.94 (d, J = 6.3 Hz, 2 H, =CCH_2N),

3.71 (t, J = 4.5 Hz, 4 H, ring CH_2O), 5.49 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.63 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.23-7.28 (m, 2 H, aryl), 7.39 (dt, J = 1.2 Hz, J = 7.5 Hz, 1 H, aryl), 7.64 (dd, J = 7.8 Hz, J = 1.2 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.9, 31.3, 32.4, 33.6, 53.5, 61.3, 67.0, 125.7, 126.1, 129.1, 131.2, 131.3, 134.7, 137.8, 142.5, 201.9; IR (neat) 3096, 3062, 3013, 2955, 2926, 1686 (C=O), 1599, 1453, 1117 cm^{-1}; HRMS for $C_{18}H_{25}NO_2$: calcd 287.1885, found 287.1888.

Preparation of Compounds **17a** and **17b**



17a

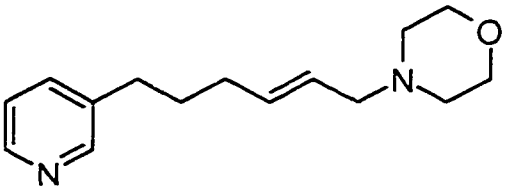


17b

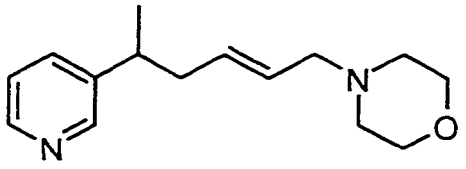
Compounds **17a** and **17b** were obtained as an inseparable 92:8 mixture of isomers in 90% combined yield from the coupling of 1-iodonaphthalene, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^1H NMR ($CDCl_3$) δ 1.37 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **17b**), 1.83 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.16 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.41 (br s, 4 H, ring NCH_2), 2.93 (d, J = 6.6 Hz, 2 H, $=CCH_2N$), 3.05 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 3.61 (t, J = 4.8 Hz, 4 H, ring CH_2O in **17b**), 3.69 (t, J = 4.5 Hz, 4 H, ring CH_2O), 5.51 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.64 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.27-8.01 (m, 7 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.2, 32.4, 32.5, 53.5, 61.3, 66.9, 123.7, 125.4, 125.4, 125.6, 125.9, 126.4, 126.5, 128.7, 131.8, 133.8, 134.5,

138.3; IR (neat) 3041, 2929, 1596, 1452, 1117 cm^{-1}; HRMS for $C_{20}H_{25}NO$: 295.1936, found 295.1942.

Preparation of Compounds **18a** and **18b**



18a

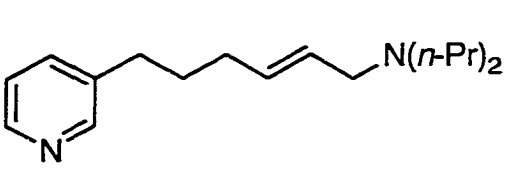


18b

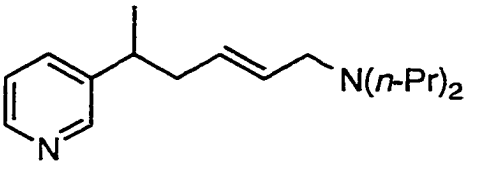
Compounds **18a** and **18b** were obtained as an inseparable 89:11 mixture of isomers in 67% combined yield from the coupling of 3-iodopyridine, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using procedure A: ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 3 H, $PyCCH_3$ in **18b**), 1.71 (quintet, J = 7.8 Hz, 2 H, $PyCCH_2$), 2.09 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.43 (br s, 4 H, ring NCH_2), 2.61 (t, J = 7.8 Hz, 2 H, $PyCH_2$), 2.95 (d, J = 6.3 Hz, 2 H, $=CCH_2N$), 3.66 (t, J = 4.5 Hz, 4 H, ring CH_2O in **18b**), 3.72 (t, J = 4.5 Hz, 4 H, ring CH_2O), 5.50 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.62 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 7.20 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.48 (d, J = 7.8 Hz, 1 H, Py), 8.43 (br m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 30.6, 31.7, 32.4, 53.5, 61.2, 66.9, 123.2, 126.6, 134.0, 135.7, 137.4, 147.3, 149.9; IR (neat) 3083, 3027, 2926, 1574, 1454, 1118 cm^{-1}; HRMS for $C_{15}H_{22}N_2O$: calcd 246.1732, found 246.1729.

Preparation of Compounds **19a** and **19b**

Compounds **19a** and **19b** were obtained as an inseparable 91:9 mixture of isomers in 56% combined yield from the coupling of 3-iodopyridine, 5 equiv. of



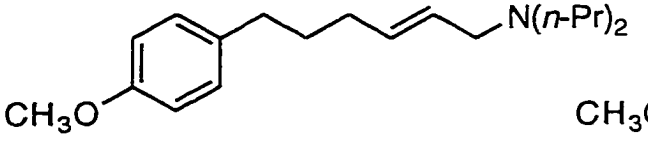
19a



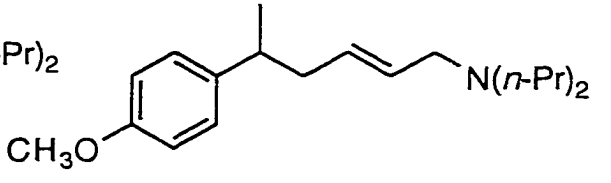
19b

1,5-hexadiene and 2 equiv. of di-*n*-propylamine using procedure A: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.5 Hz, 6 H, $CH_2C\underline{H}_3$), 1.27 (d, *J* = 6.9 Hz, 3 H, $ArCCH_3$ in **19b**), 1.47 (sextet, *J* = 7.5 Hz, 4 H, $C\underline{H}_2CH_3$), 1.71 (quintet, *J* = 7.5 Hz, 2 H, $ArCCH_2$), 2.09 (m, 2 H, CH_2C=), 2.38 (t, *J* = 7.5 Hz, 4 H, $NC\underline{H}_2CH_2$), 2.61 (t, *J* = 7.5 Hz, 2 H, $ArCH_2$), 3.06 (d, *J* = 5.7 Hz, 2 H, $=CCH_2N$), 5.51 (dt, *J* = 15.3 Hz, *J* = 5.7 Hz, 1 H, vinyl), 5.58 (dt, *J* = 15.3 Hz, *J* = 5.7 Hz, 1 H, vinyl), 7.20 (dd, *J* = 7.8 Hz, *J* = 4.8 Hz, 1 H, Ar), 7.48 (d, *J* = 7.8 Hz, 1 H, Ar), 8.42-8.45 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.0, 20.1, 30.7, 31.8, 32.4, 55.7, 56.3, 123.3, 128.1, 132.7, 135.8, 137.6, 147.3, 150.0; IR (neat) 3082, 3025, 2953, 2928, 1574, 1457, 1186 cm^{-1}; HRMS for $C_{17}H_{28}N_2$: calcd 260.2253, found 260.2258.

Preparation of Compounds **20a** and **20b**



20a

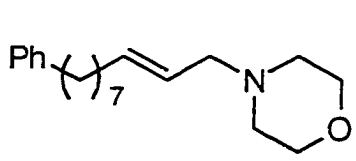


20b

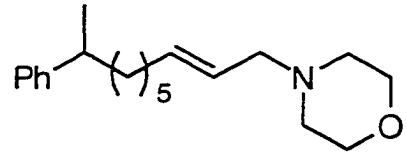
Compounds **20a** and **20b** were obtained as an inseparable 86:14 mixture of isomers in 67% combined yield from the coupling of 4-iodoanisole, 5 equiv. of 1,5-hexadiene and 2 equiv. of di-*n*-propylamine using procedure A: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.5 Hz, 6 H, $CH_2C\underline{H}_3$), 1.21 (d, *J* = 6.9 Hz, 3 H, $ArCCH_3$

in **20b**), 1.46 (sextet, J = 7.5 Hz, 4 H, $C\underline{H_2}CH_3$), 1.66 (quintet, J = 7.5 Hz, 2 H, $ArCCH_2$), 2.05 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.37 (t, J = 7.5 Hz, 4 H, $NC\underline{H_2}CH_2$), 2.55 (t, J = 7.5 Hz, 2 H, $ArCH_2$), 2.75 (m, 1 H, ArCH in **20b**), 3.04 (d, J = 5.7 Hz, 2 H, $=CCH_2N$), 3.77 (s, 3 H, OCH_3), 5.49 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.57 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 6.81 (d, J = 8.7 Hz, 2 H, Ar), 7.08 (d, J = 8.7 Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.0, 20.1, 31.3, 31.9, 34.4, 55.2, 55.7, 56.3, 113.6, 127.6, 129.3, 133.1, 134.5, 157.6; IR (neat) 3028, 2957, 2931, 1613, 1464, 1246, 1177 cm^{-1}; HRMS for $C_{19}H_{31}NO$: calcd 289.2406, found 289.2414.

Preparation of Compounds **21a** and **21b**



21a

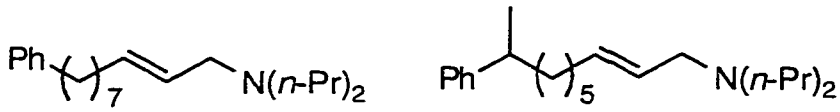


21b

Compounds **21a** and **21b** were obtained as an inseparable 82:18 mixture of isomers in 75% combined yield from the coupling of iodobenzene, 5 equiv. of 1,9-decadiene and 2 equiv. of morpholine using procedure A: ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **21b**), 1.26-1.37 (br m, 8 H, CH_2's), 1.55-1.62 (br m, 2 H, $PhCCH_2$), 2.01 (q, J = 6.6 Hz, 2 H, CH_2C=), 2.42 (br s, 4 H, ring NCH_2), 2.59 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.64 (m, 1 H, PhCH in **21b**), 2.92 (d, J = 6.6 Hz, 2 H, $=CCH_2N$), 3.70 (t, J = 4.5 Hz, 4 H, ring CH_2O), 5.45 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.58 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.14-7.28 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 29.1, 29.2, 29.3, 31.5, 32.4, 36.0, 39.9, 53.5, 61.4, 67.0, 125.7, 126.9, 128.2, 128.3, 135.1, 142.8; IR (neat) 3085,

3026, 2925, 1604, 1453, 1119 cm^{-1}; HRMS for $C_{20}H_{31}NO$: calcd 301.2406, found 301.2397.

Preparation of Compounds **22a** and **22b**

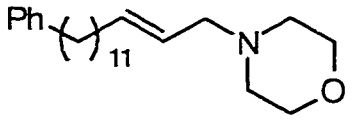


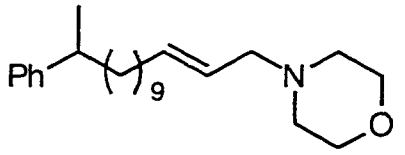
22a **22b**

Compounds **22a** and **22b** were obtained as an inseparable 85:15 mixture of isomers in 78% combined yield from the coupling of iodobenzene, 5 equiv. of 1,9-decadiene and 2 equiv. of di-*n*-propylamine using procedure A; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.5 Hz, 6 H, $CH_2C\underline{H}_3$), 1.22 (d, *J* = 6.9 Hz, 3 H, $PhCCH_3$ in **22b**), 1.30 (br s, 8 H, CH_2's), 1.45 (sextet, *J* = 7.5 Hz, 4 H, $C\underline{H}_2CH_3$), 1.55-1.63 (m, 2 H, $PhCCH_2$), 2.01 (q, *J* = 6.3 Hz, 2 H, CH_2C=), 2.36 (t, *J* = 7.5 Hz, 4 H, $NC\underline{H}_2CH_2$), 2.59 (t, *J* = 7.5 Hz, 2 H, $PhCH_2$), 3.02 (d, *J* = 5.7 Hz, 2 H, $=CCH_2N$), 5.45 (dt, *J* = 15.3 Hz, *J* = 6.3 Hz, 1 H, vinyl), 5.53 (dt, *J* = 15.3 Hz, *J* = 6.3 Hz, 1 H, vinyl), 7.15-7.28 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 12.1, 20.1, 29.1, 29.4 (2 carbon peaks), 31.6, 32.4, 36.0, 40.0, 55.7, 56.4, 125.6, 127.1, 128.2, 128.4, 133.7, 142.9; IR (neat) 3084, 3026, 2956, 2926, 1604, 1454, 1165 cm^{-1}; HRMS for $C_{22}H_{37}N$: calcd 315.2926, found 315.2931.

Preparation of Compounds **23a** and **23b**

Compounds **23a** and **23b** were obtained as an inseparable 80:20 mixture of isomers in 67% combined yield from the coupling of iodobenzene, 5 equiv. of 1,13-tetradecadiene and 2 equiv. of morpholine using procedure A: ^1H NMR

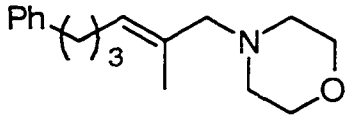


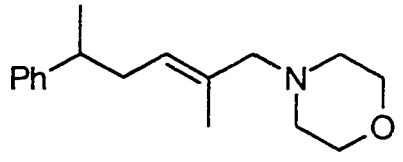


23a **23b**

($CDCl_3$) δ 1.22-1.30 (br m, 16 H, CH_2's), 1.55-1.64 (br m, 2 H, $PhCCH_2$), 2.02 (q, J = 6.6 Hz, 2 H, CH_2C=), 2.42 (br s, 4 H, ring NCH_2), 2.59 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.92 (d, J = 6.6 Hz, 2 H, $=CCH_2N$), 3.71 (t, J = 4.5 Hz, 4 H, ring CH_2O), 5.45 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.59 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.15-7.28 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.3, 29.4, 29.5, 29.6, 31.6, 32.4, 36.0, 40.0, 53.6, 61.4, 67.0, 125.7, 127.0, 128.2, 128.4, 135.2, 142.9 (3 peaks overlapped); IR (neat) 3083, 3025, 2917, 1603, 1452, 1117 cm^{-1}; HRMS for $C_{24}H_{39}NO$: calcd 357.3032, found 357.3026.

Preparation of Compounds **24a** and **24b**



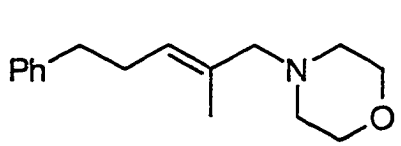


24a **24b**

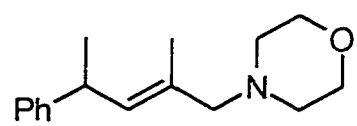
Compounds **24a** and **24b** were obtained as an inseparable 86:14 mixture of isomers in 81% combined yield from the coupling of iodobenzene, 5 equiv. of 2-methyl-1,5-hexadiene and 5 equiv. of morpholine using procedure C: ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **24b**), 1.56 (s, 3 H, $=CCH_3$ in **24b**), 1.62 (s, 3 H, $=CCH_3$), 1.67 (quintet, J = 7.8 Hz, 2 H, $PhCCH_2$), 2.06 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.33 (t, J = 4.5 Hz, 4 H, ring NCH_2), 2.60 (t, J = 7.8 Hz,

2 H, $PhCH_2$), 2.82 (s, 2 H, $=CCH_2N$), 3.62 (t, J = 4.5 Hz, 4 H, ring CH_2O in **24b**), 3.69 (t, J = 4.5 Hz, 4 H, ring CH_2O), 5.23 (t, J = 6.9 Hz, 1 H, vinyl in **24b**), 5.33 (t, J = 6.9 Hz, 1 H, vinyl), 7.15-7.29 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.7, 27.4, 31.4, 35.6, 58.5, 67.0, 67.8, 125.6, 127.0, 128.2, 128.3, 130.1, 142.4; IR (neat) 3084, 3026, 2957, 1452, 1119 cm^{-1}; HRMS for $C_{17}H_{25}NO$: calcd 259.1936, found 259.1939.

Preparation of Compounds **25a** and **25b**



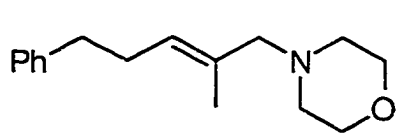
25a

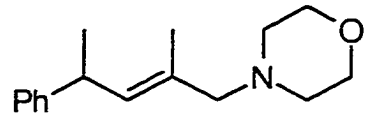


25b

Compounds **25a** and **25b** were obtained as an inseparable 89:11 mixture of isomers in 73% combined yield from the coupling of iodobenzene, 5 equiv. of 2-methyl-1,4-pentadiene and 5 equiv. of morpholine using procedure C: ^1H NMR ($CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **25b**), 1.57 (s, 3 H, $=CCH_3$), 1.71 (s, 3 H, $=CCH_3$ in **25b**), 2.26 (t, J = 4.5 Hz, 4 H, ring NCH_2), 2.35 (q, J = 7.5 Hz, 2 H, $CCH_2C=$), 2.66 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.78 (s, 2 H, $=CCH_2N$), 3.65 (t, J = 4.5 Hz, 4 H, CH_2O), 5.32 (tq, J = 7.2 Hz, J = 0.9 Hz, 1 H, vinyl), 5.47 (dq, J = 9.6 Hz, J = 0.9 Hz, 1 H, vinyl in **25b**), 7.15-7.28 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.9, 29.6, 35.8, 53.4, 67.0, 67.7, 125.7, 127.4, 128.1, 128.4, 132.4, 141.9; IR (neat) 3084, 3061, 3026, 2956, 2920, 1603, 1453, 1118 cm^{-1}; HRMS for $C_{16}H_{23}NO$: calcd 245.1780, found 245.1779.

Preparation of Compounds **26a** and **26b**

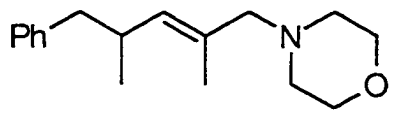




26a **26b**

Compounds **26a** and **26b** were obtained as an inseparable 93:7 mixture of isomers in 78% combined yield from the coupling of iodobenzene, 5 equiv. of 2-methyl-1,4-pentadiene and 5 equiv. of piperidine using procedure C: ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **26b**), 1.38-1.43 (br m, 2H, $NCH_2CH_2C\underline{H}_2$), 1.53 (quintet, J = 5.4 Hz, 4 H, $NCH_2C\underline{H}_2CH_2$), 1.58 (s, 3 H, $=CCH_3$), 2.21 (br s, 4 H, $NC\underline{H}_2CH_2CH_2$), 2.35 (q, J = 7.5 Hz, 2 H, $CCH_2C=$), 2.65 (t, J = 7.8 Hz, 2 H, $PhCH_2$), 2.76 (s, 2 H, $=CCH_2N$), 5.31 (t, J = 7.2 Hz, 1 H, vinyl), 7.15-7.29 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.1, 24.6, 26.0, 29.7, 35.9, 54.5, 68.1, 125.6, 126.5, 128.2, 128.4, 133.4, 142.2; IR (neat) 3084, 3026, 2932, 1603, 1453, 1153 cm^{-1}; HRMS for $C_{17}H_{25}N$: calcd 243.1987, found 243.1989.

Preparation of Compound **27a**

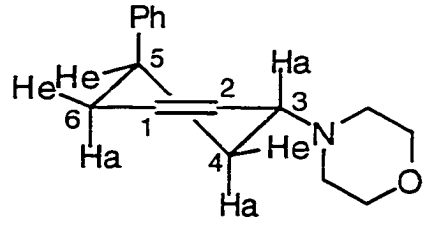


27a

Compound **27a** was obtained in 62% yield from the coupling of iodobenzene, 5 equiv. of 2,4-dimethyl-1,4-pentadiene and 5 equiv. of morpholine using procedure C: ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.3 Hz, 3 H, $PhCCCH_3$),

1.46 (d, J = 1.2 Hz, 3 H, =CCH_3), 2.08-2.22 (m, 4 H, ring NCH_2), 2.48 (dd, J = 13.2 Hz, J = 8.4 Hz, 1 H, PhCH), 2.62 (dd, J = 13.2 Hz, J = 6.0 Hz, 1 H, PhCH), 2.65 (d, J = 12.0 Hz, 1 H, =CCHN), 2.69-2.75 (m, 1 H, PhCCH), 2.80 (d, J = 12.0 Hz, 1 H, =CCHN), 3.61 (t, J = 4.5 Hz, 4 H, CH_2O), 5.10 (dq, J = 9.3 Hz, J = 1.2 Hz, 1 H, vinyl), 7.10-7.25 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.0, 20.8, 34.4, 43.8, 53.3, 67.0, 67.8, 125.5, 127.9, 129.1, 130.7, 134.0, 140.9; IR (neat) 3084, 3026, 2956, 2924, 1604, 1453, 1118 cm^{-1}; HRMS for $C_{17}H_{25}NO$: calcd 259.1936, found 259.1938.

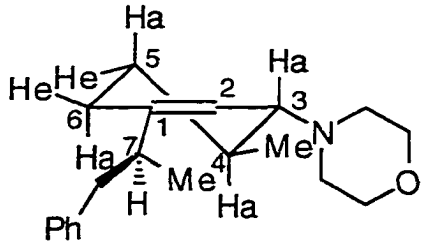
Preparation of *trans*-3-morpholino-5-phenylcyclohexene (**28**)



28

Compound **28** was obtained in 70% yield from the coupling of iodobenzene, 5 equiv. of 1,4-cyclohexadiene and 2 equiv. of morpholine using procedure A: ^1H NMR ($CDCl_3$) δ 1.73 (ddd, J = 13.8 Hz, J = 11.4 Hz, J = 5.7 Hz, 1 H, 4-Ha), 2.09-2.18 (m, 2 H, 4-He and 6-Ha), 2.37 (dt, J = 18.0 Hz, J = 4.5 Hz, 1 H, 6-He), 2.50-2.69 (m, 4 H, ring NCH_2), 2.95-3.08 (m, 2 H, 5-He and 3-Ha), 3.70 (br s, 4 H, ring CH_2O), 5.79 (d, J = 9.9 Hz, 1 H, vinyl), 6.01 (ddd, J = 9.9 Hz, J = 4.5 Hz, J = 2.4 Hz, 1 H, vinyl), 7.18-7.33 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 31.2, 32.7, 36.3, 50.5, 58.2, 67.5, 126.1, 126.9, 127.5, 128.4, 130.4, 146.4; IR (neat) 3081, 3024, 2952, 1651, 1601, 1451, 1118 cm^{-1}; HRMS for $C_{16}H_{21}NO$: calcd 243.1623, found 243.1617.

Preparation of Compound **31a**

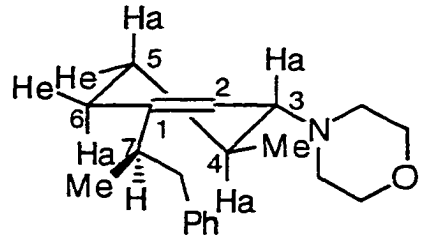


31a

Compound **31a** was obtained in 47% yield from the coupling of iodobenzene, 5 equiv. of (1*R*)-(+)-*trans*-isolimonene and 5 equiv. of morpholine using procedure C: $[\alpha]^{26}_{D}$ –32.0° (c 0.10, CH_3COCH_3); ^{1}H NMR ($CDCl_3$) δ 0.94 (d, *J* = 6.6 Hz, 3 H, 4-CH_3), 1.05 (d, *J* = 6.6 Hz, 3 H, 7-CH_3), 1.22-1.34 (m, 1 H, 5-Ha), 1.54 (ddt, *J* = 16.8 Hz, *J* = 3.0 Hz, *J* = 6.9 Hz, 1 H, 5-He), 1.65 (ddd, *J* = 12.6 Hz, *J* = 8.1 Hz, *J* = 4.8 Hz, 1 H, 6-Ha), 1.89-1.94 (br m, 2 H, 4-Ha and 6-He), 2.16 (dt, *J* = 11.4 Hz, *J* = 4.5 Hz, 2 H, ring NCH), 2.34 (dt, *J* = 11.7 Hz, *J* = 4.5 Hz, 2 H, ring NCH), 2.44 (dd, *J* = 15.0 Hz, *J* = 6.6 Hz, 1 H, 3-Ha), 2.55 (m, 1 H, 7-H), 2.58 (dd, *J* = 13.2 Hz, *J* = 6.6 Hz, 2 H, PhCH), 2.63 (dd, *J* = 13.2 Hz, *J* = 8.7 Hz, 2 H, PhCH), 3.56 (t, *J* = 4.5 Hz, 4 H, ring OCH_2), 5.26 (br s, 1 H, vinyl), 7.09-7.25 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.5, 23.6, 29.9, 41.8, 43.6, 49.2, 67.2, 67.7, 120.5, 125.5, 128.0, 128.9, 141.3, 144.0 (two peaks overlapped); IR (neat) 3082, 3025, 2954, 2924, 1660, 1604, 1451, 1117 cm^{-1}; HRMS for $C_{20}H_{29}NO$: calcd 299.2249, found 299.2257.

Preparation of Compound **31b**

Compound **31b** was obtained in 15% yield from the coupling of iodobenzene, 5 equiv. of (1*R*)-(+)-*trans*-isolimonene and 5 equiv. of morpholine



31b

using procedure C: $[\alpha]^{26}_D$ –10.0° (c 0.10, CH_3COCH_3); ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3 H, 4-CH_3), 0.99 (d, J = 6.6 Hz, 3 H, 7-CH_3), 1.24-1.37 (m, 1 H, 5-Ha), 1.60-1.67 (m, 1 H, 5-He), 1.71 (ddd, J = 12.6 Hz, J = 8.4 Hz, J = 4.8 Hz, 1 H, 6-Ha), 1.92-1.99 (br m, 2 H, 4-Ha and 6-He), 2.33-2.43 (m, 3 H, 7-H and ring NCH_2), 2.51-2.60 (m, 4 H, $PhCH_2$ and ring NCH_2), 2.74 (dd, J = 13.2 Hz, J = 6.6 Hz, 1 H, 3-Ha), 3.64 (t, J = 4.5 Hz, 4 H, ring OCH_2), 5.35 (br s, 1 H, vinyl), 7.10-7.27 (m, 5 H, Ph). Other spectra were not taken because of a lack of material.

References and Notes

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12. ^{1}H NMR ($CDCl_3$) spectrum of compound **30**: δ 1.66 (m, 1 H), 1.88 (ddd, J = 10.2 Hz, J = 4.2 Hz, J = 1.5 Hz, 1 H), 2.11 (m, 1 H), 2.43–2.56 (m, 3 H), 2.77 (m, 1 H), 5.71 (dt, J = 10.8 Hz, J = 6.9 Hz, 2 H), 5.86 (dd, J = 10.8 Hz, J = 3.9 Hz, 1 H), 5.93 (dd, J = 10.8 Hz, J = 3.9 Hz, 1 H), 7.17–7.31 (m, 5 H).

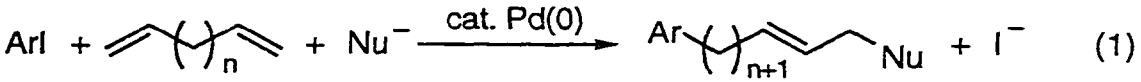
SYNTHESIS OF NATURALLY–OCCURRING PYRIDINE ALKALOIDS VIA PALLADIUM–CATALYZED COUPLING

A paper to be submitted to the *Journal of Organic Chemistry*

Richard C. Larock and Yao Wang

Introduction

Palladium-based migration chemistry has provided a very efficient approach to the synthesis of long chain aromatic substrates.[1,2] It allows the generation of more than one carbon-carbon or carbon-heteroatom bond and combines three components in a single step (eq. 1). This is one of the more

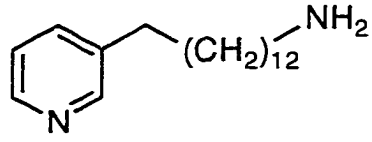


(1)

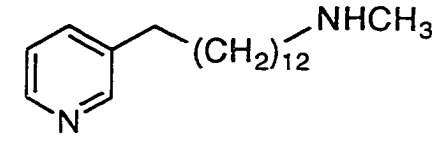
efficient ways to rapidly increase molecular complexity. The success of the palladium-catalyzed coupling of aryl iodides, non-conjugated dienes and nitrogen nucleophiles[2] has prompted us to apply this methodology to the synthesis of naturally-occurring, biologically active pyridine alkaloids.

Recently many pyridine-derived alkaloids have been isolated from marine organisms and shown to exhibit interesting biological activities. Some of them are particularly interesting to us, because they might be synthesized using our palladium-catalyzed coupling as a key step, for example, anitleukemic and

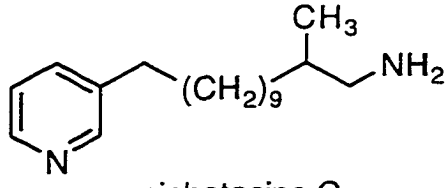
antineoplastic theonelladins C and D isolated from the Okinawan marine sponge *Theonella swinhoei*,[3] antileukemic niphatesines C and D isolated from the Okinawan marine sponge *Niphates* sp.,[4] cytotoxic ikimines A-C isolated from the Micronesian sponge,[5] antimicrobial xestamine C isolated from Caribbean sponge *Xestospongia wiedenmayeri*,[6] antimicrobial xestamines D-H isolated from Bahamas sponge *Calyx podatypa*[7] and cytotoxic and antimicrobial niphatesine G isolated from the Okinawan sponge *Niphates* sp.[8]



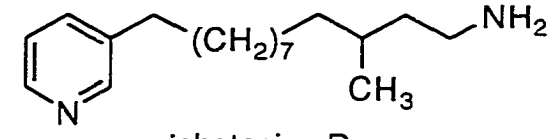
theonelladin C



theonelladin D



niphatesine C



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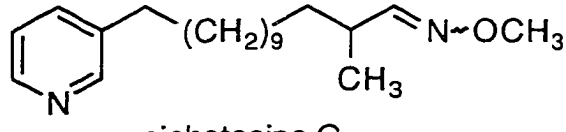
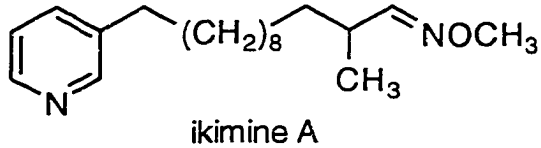
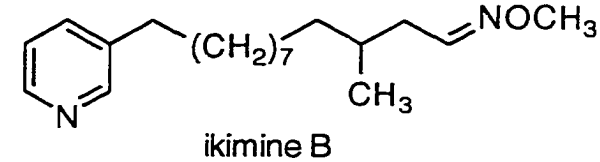


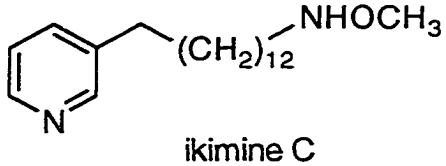
niphatesine G



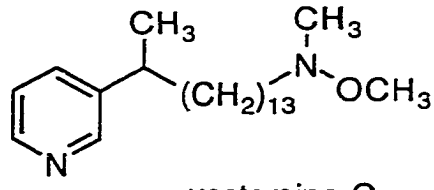
ikimine A



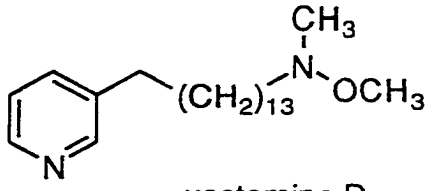
ikimine B



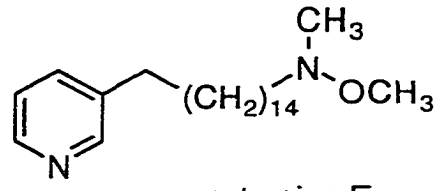
ikimine C



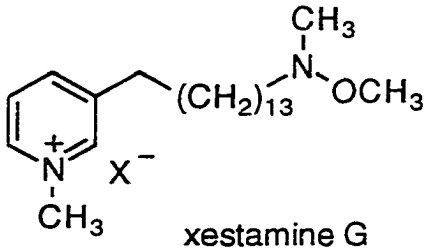
xestamine C



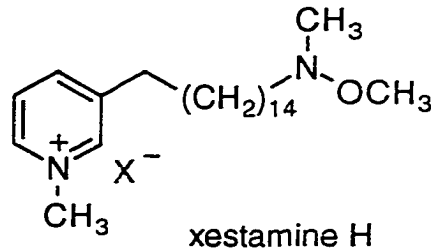
xestamine D



xestamine E



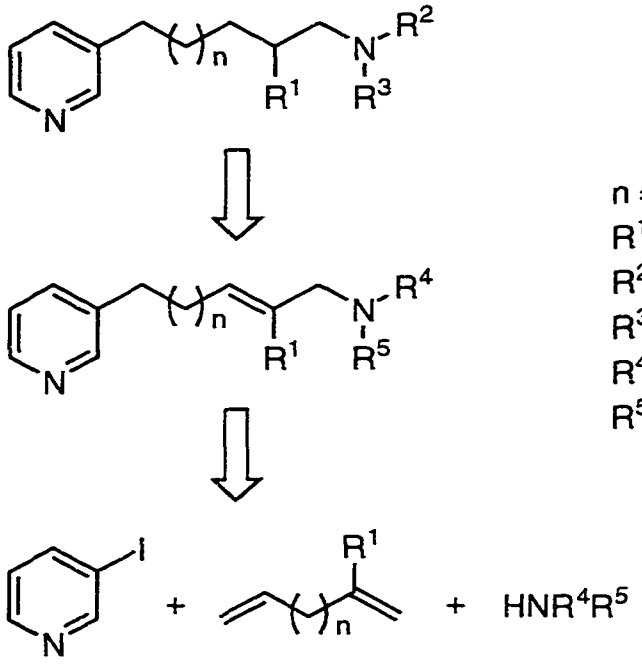
xestamine G



xestamine H

Some of these alkaloids have been synthesized. Rao *et al.* have reported the first total synthesis of theonelladins A–D.[9] They used a Wittig reaction for construction of the carbon skeleton and several other reactions for the interconversion of functional groups. Six steps were required to complete the total synthesis of theonelladins C and D. Our strategy for the synthesis of theonelladins and other alkaloids is more efficient (Scheme 1). All the compounds listed above have similar structures: long chain hydrocarbons bearing functional groups at each end, one is a pyridine group and another is an amino or imino group. Our palladium-catalyzed three component coupling process would appear to be able to construct the whole entire skeleton of these alkaloids in just one step.

Scheme 1



Here we describe our successful approach to the synthesis of natural products theonelladins C and D, niphatesine C and xestamine D using the palladium-catalyzed coupling of 3-iodopyridine, non-conjugated dienes and nitrogen nucleophiles as a key step.

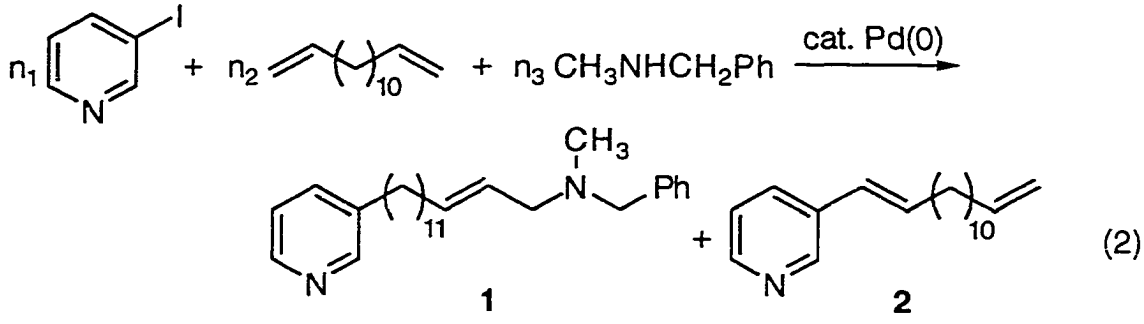
Results and Discussion

Total synthesis of theonelladins C and D

As shown in Scheme 1, to make theonelladins C and D we should start with three major components 3-iodopyridine, 1,12-tridecadiene and a nitrogen nucleophile. Choosing the best nitrogen nucleophile is the key issue here. Lu[10] has reported that methylamine (an ideal nucleophile for preparing theonelladin

D) is an unsuccessful nucleophile in the palladium-catalyzed coupling of iodobenzene and 1,5-hexadiene. However, we have proven that 2° amines are very good nucleophiles in this type of reaction.[2] We also know that the benzyl group ($PhCH_2$) is often used as a protecting group for amines.[11] Therefore, benzylmethylamine and dibenzylamine were chosen as the most appropriate nucleophiles for our approach to the synthesis of theonelladins.

In our exploratory studies, 1,13-tetradecadiene which is commercially available was used as a substitute for 1,12-tridecadiene. Based on our previous work, the coupling of 3-iodopyridine, 1,13-tetradecadiene and benzylmethylamine was examined. The results are summarized in equation 2 and Table 1.



(2)

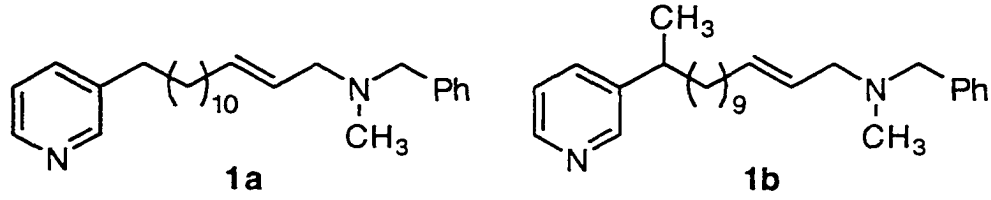
The reaction run in DMSO gave a very low yield of the coupling product **1**. As a solvent, DMF was much better than DMSO in this reaction. This is consistent with our previous work. Increasing the amount of diene only yielded more Heck product (**2**) (entry 4). One equivalent and two equivalents of LiCl gave similar results. The best result was obtained when the reaction was run in DMF in the presence of 1 equiv. of LiCl at 100 °C for 24 hours with a 1:2.5:2 ratio of the starting materials (entry 6). The isolated product **1** was examined

Table 1. Palladium-catalyzed Coupling of 3-Iodopyridine, 1,13-Tetradecadiene and Benzylmethylamine (Eq. 2)[a]

entry	$n_1/n_2/n_3$	LiCl (equiv)	solvent	time (h)	% isolated yield 1	2
1	1 / 2.5 / 2	1	DMSO	18	28	58
2	1 / 2.5 / 2	1	DMF	18	53	41
3	1 / 2.5 / 2	2	DMF	18	55	36
4	1 / 5 / 2	1	DMF	18	50	48
5	1 / 2.5 / 2	1	DMF	12	49	30
6	1 / 2.5 / 2	1	DMF	24	66	31
7	1 / 2.5 / 2	1	DMF	36	52	41
8	1 / 2.5 / 2	2	DMF	24	54	34

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ at 100 °C.

by GC-MS and ^1H NMR spectroscopy and proven to be a mixture of two isomers in a ratio of 86:14. The minor isomer (**1b**) was formed by the addition of pyridine to the more hindered internal carbon of one of the double bonds of the diene.

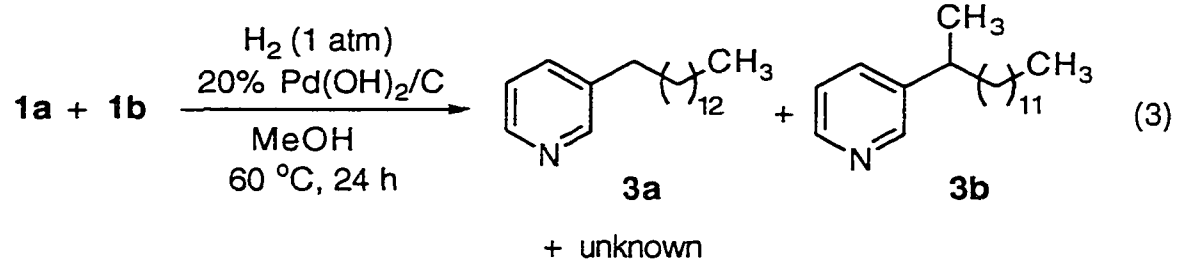


1a **1b**

1a : **1b** = 86 : 14

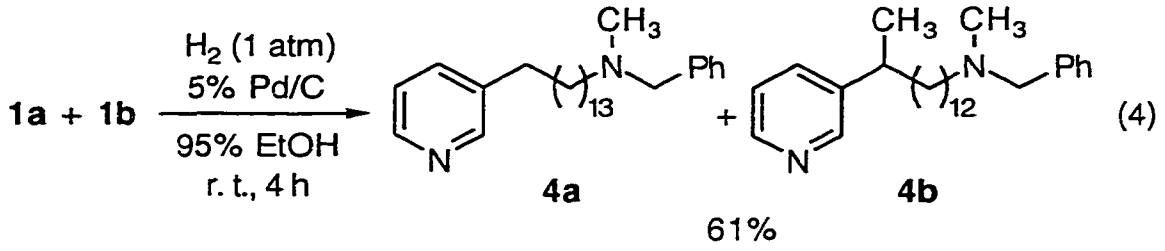
It appeared that a carbon analogue of theonelladin D bearing one more methylene unit could be easily obtained simply by hydrogenation of the double bond and debenzylation of compound **1a**. The traditional procedure for debenzylation of benzylamines is heterogeneous catalytic hydrogenation.[12-14] It was hoped that compound **1a** would undergo hydrogenation of the double bond and debenzylation simultaneously under the same reaction conditions.

Pearlman's catalyst,[15] 20% $Pd(OH)_2$ on charcoal, has proven to be an effective catalyst for debenzylation, even when other palladium catalysts have failed.[16] So we chose Pearlman's catalyst in our first try. Compounds **1a** and **1b** were hydrogenated under the conditions shown in equation 3. Unexpectedly, none of the desired theonelladin D analogue was formed. 3-*n*-Tetradecylpyridine (**3a**) and its isomer **3b** were isolated along with



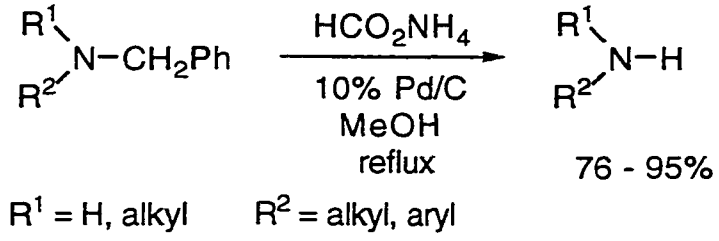
(3)

an unknown, which proved to be a major component. Apparently, compounds **3a** and **3b** were formed by cleavage of the allylic C-N bond. Allylic amines, quite similar to benzylic amines, can be cleaved at the C-N bond by catalytic hydrogenation.[17] To avoid this situation, we decided to saturate the double bond first, then remove the benzyl group. Hydrogenation of the C-C double bond in compounds **1a** and **1b** proceeded smoothly under mild conditions as shown in equation 4.



(4)

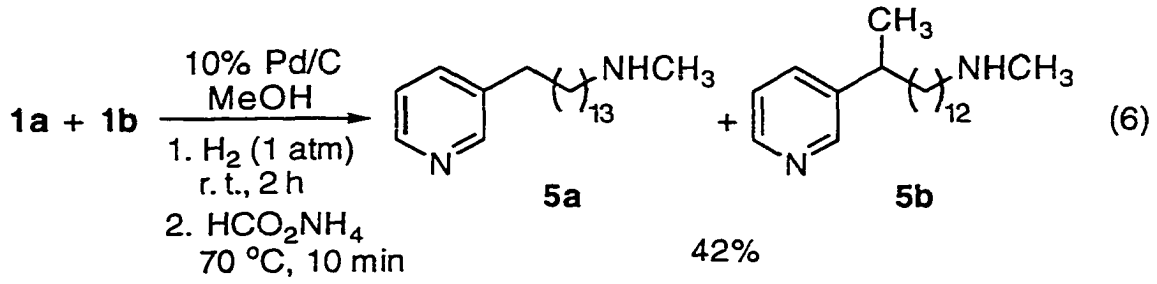
Debenzylation, in most cases, is carried out by high pressure catalytic hydrogenation.[13,14,18] This did not appear particularly attractive to us. Ram *et al.*[19] have reported a more convenient debenzylation procedure for *N*-benzylamino derivatives using ammonium formate as a hydrogen source catalyzed by 10% Pd/C (eq. 5).



(5)

We have successfully applied Ram's procedure to the conversion of compound **4a** to the analogue **5a** of theonelladin D. To simplify the procedure, the same catalyst and solvent were used for both hydrogenation of the double bond and debenzylation. Therefore, hydrogenation of the double bond was followed by debenzylation without purification or separation of the intermediates. The first example is shown in equation 6. Compounds **1a** and **1b** were dissolved in methanol and flushed with 1 atmosphere of H_2 gas in the presence of 10% Pd/C at room temperature for 2 hours; then, to the reaction

mixture was added 6 equivs. of HCO_2NH_4. The mixture was stirred at 70 °C for 10 minutes and the products **5a** and **5b** were obtained in 42% combined yield.



(6)

To get better yields of the products, several different palladium catalysts were examined in the reaction described in equation 6. The results given in Table 2 indicate that Pearlman's catalyst (20% $Pd(OH)_2/C$) was the best and the amount of Pd required was at least 0.35 equiv. in order to get a good yield.

Table 2. Effects of Pd-catalyst on Hydrogenation and Debenzylation

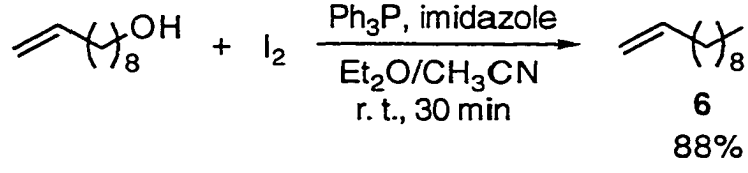
entry	catalyst	Pd content (equiv)	% isolated yield (**5a** + **5b**)
1	10% Pd/C	0.35	42
2	5% Pd/C	0.10	54
3	20% $Pd(OH)_2/C$	0.75	75
4	20% $Pd(OH)_2/C$	0.35	76
5	20% $Pd(OH)_2/C$	0.20	46

We even tried to simplify this procedure further. For example, compounds **1a** and **1b** were mixed with HCO_2NH_4 in methanol and flushed with 1 atmosphere of H_2 at room temperature (eq. 7), or the mixture of **1a** and **1b** with HCO_2NH_4 in methanol was simply refluxed without flushing with H_2 (eq. 8). Unfortunately, neither effort provided a better result.

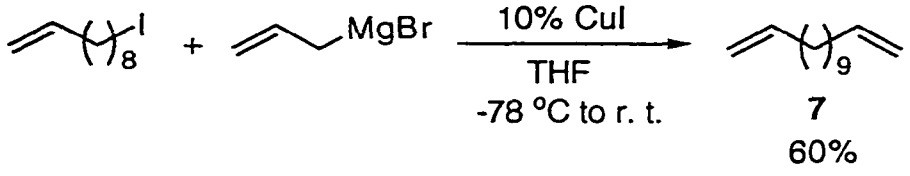
$$\mathbf{1a} + \mathbf{1b} + HCO_2NH_4 + H_2 \xrightarrow[\text{MeOH, r. t.}\\ 53\%]{20\%\ Pd(OH)_2/C} \mathbf{5a} + \mathbf{5b} \qquad (7)$$

$$\mathbf{1a} + \mathbf{1b} + HCO_2NH_4 \xrightarrow[\text{MeOH, 70 °C}\\ 43\%]{20\%\ Pd(OH)_2/C} \mathbf{5a} + \mathbf{5b} \qquad (8)$$

With proven procedures for the palladium-catalyzed coupling, hydrogenation and debenzylation in hand, we could now easily synthesize the natural product theonelladin D by changing the diene in the coupling reaction from 1,13-tetradecadiene to 1,12-tridecadiene. Although it is not commercially available, 1,12-tridecadiene can be easily made from 9-decen-1-ol in two steps. Therefore, 9-decen-1-ol was allowed to react with iodine in the presence of triphenylphosphine and imidazole[20, 21] to give 10-iodo-1-decene (**6**) in 88% yield (eq. 9). The copper-catalyzed coupling of 10-iodo-1-decene with allylmagnesium bromide[22] afforded a 60% yield of 1,12-tridecadiene (**7**) (eq. 10).

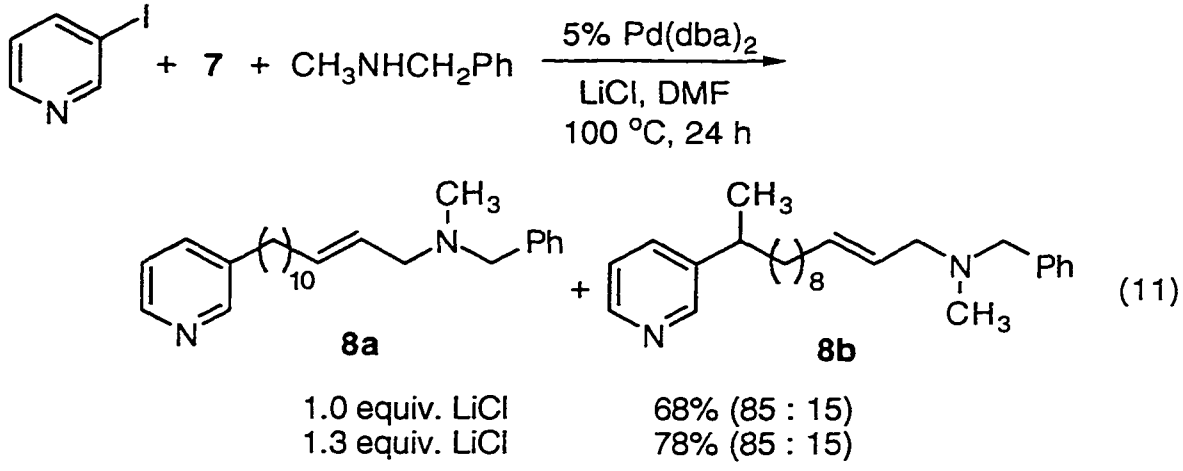


6
88% (9)



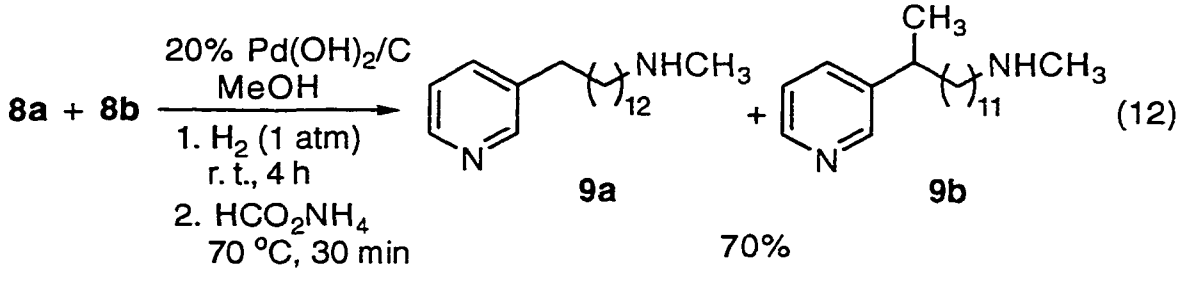
(10)

1,12-Tridecadiene was then employed in the palladium-catalyzed coupling reaction under the conditions described in entry 6, Table 1. The desired coupling products (**8a** and **8b**) were isolated in a 68% combined yield in a ratio of 85:15 (eq. 11). We found that slightly increasing the amount of LiCl afforded a still better yield.



(11)

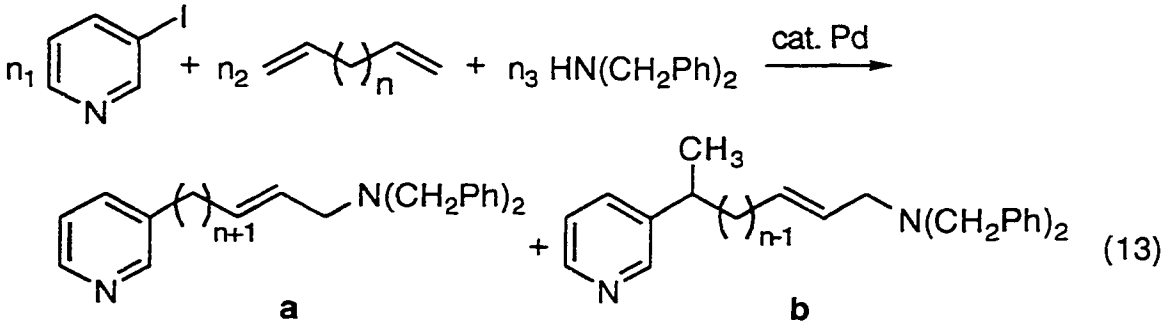
Finally, by the hydrogenation and debenzylation of compounds **8a** and **8b**, the natural product theonelladin D (**9a**) and its isomer (**9b**) were obtained in 70% combined yield (eq. 12).



(12)

Theonelladin C having an NH_2 group at the end of the carbon chain was our next target molecule. As in the synthesis of theonelladin D, the key issue here is to find an appropriate nucleophile. Based on the success of our debenzylation process, benzylamine and dibenzylamine were first chosen as the nucleophiles. In the exploratory investigation, commercially available 1,13-tetradecadiene was again used as a substitute for 1,12-tridecadiene.

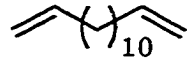
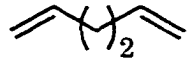
When employed in the palladium-catalyzed coupling, benzylamine failed to give the desired product. Our previous work indicated that 1° amines as nucleophiles were generally not as good as 2° amines. Therefore, we hoped that dibenzylamine would lead to the desired product. Surprisingly, dibenzylamine did not work well in this coupling either. We tried to improve this reaction by changing the chloride, adding a base, extending the reaction time and using a short- chain diene. Unfortunately, no satisfactory results were achieved. Some results are summarized in equation 13 and Table 3.



(13)

It appeared that other protecting groups were necessary. The protecting group, of course, not only is just a protecting group, but also makes the nitrogen a better nucleophile. The tosyl group is known as a useful protecting group for amines,[11] and tosylamides are generally good nucleophiles in π-

Table 3. Palladium-catalyzed Coupling of 3-Iodopyridine, Non-conjugated Diene and Dibenzylamine (Eq. 13)[a]

entry	diene	$n_1/n_2/n_3$	base (equiv)	time (d)	% yield (**a**+**b**)
1[b]		1/2.5/2	–	2	0
2[b]		1/2.5/2	$NaHCO_3$ (1)	2	0
3		1/5/2	Na_2CO_3 (4)	4	–[c]
4		1/5/1.5	Na_2CO_3 (4)	4	–[c]
5		1/2.5/1	Na_2CO_3 (4)	4	–[c]
6		1/2.5/2	Na_2CO_3 (2)	5	38[d]
7		1/5/2	Na_2CO_3 (4)	4	49[e]

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$ and 1 equiv. of *n*-Bu_4NCl at 100 °C.

[b] 1.3 Equiv. of LiCl were used instead of *n*-Bu_4NCl.

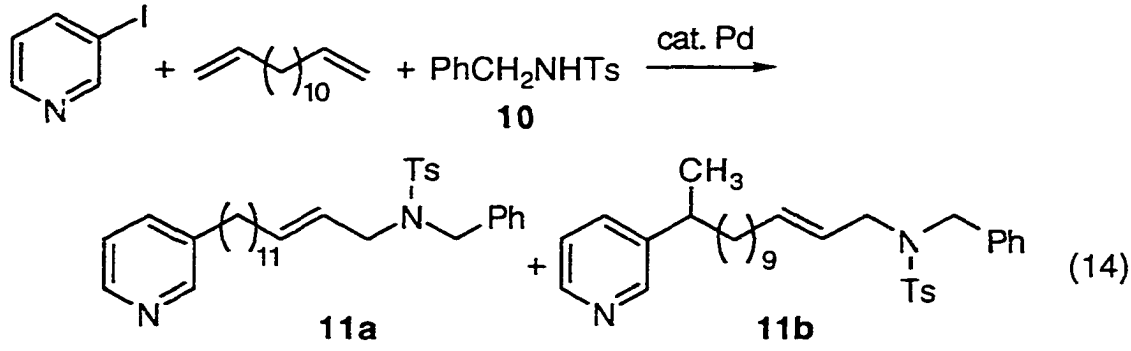
[c] Coupling products were found only in very small amounts.

[d] Purity of products: > 60%

[e] Purity of products: 70%

allylpalladium coupling processes.[23] *N*-Benzyl tosylamide was therefore examined in our palladium-catalyzed three-component coupling. The results from the coupling of 3-iodopyridine, 1,13-tetradecadiene and *N*-benzyl tosylamide are summarized in equation 14 and Table 4.

From Table 4, one can see that *N*-benzyl tosylamide is a good nucleophile in this coupling reaction as expected. There is one thing, however, unexpected but exciting and valuable. The coupling products **11a** and **11b** could be separated by flash chromatography. This permits the synthesis of pure



(14)

Table 4. Palladium-catalyzed Coupling of 3-Iodopyridine, 1,13-Tetradecadiene and *N*-Benzyl Tosylamide (Eq. 14)[a]

entry	*n*-Bu_4NCl (equiv.)	Na_2CO_3 (equiv.)	temp. (°C)	time (h)	% isolated yield **11a**	**11b**
1	1	4	100	24	50[b]	
2	–[c]	0	100	24	–[d]	
3	1	2	100	48	46[b]	
4	1	–[e]	100	48	23	5
5[f]	1	4	100	48	37	7
6	1	4	80	48	23	5
7	2	4	100	24	58	11

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ in DMF using 2.5 equiv. of 1,13-tetradecadiene and 2 equiv. of *N*-benzyl tosylamide.

[b] Combined yield of **11a** and **11b**.

[c] 1 Equiv. of LiCl used.

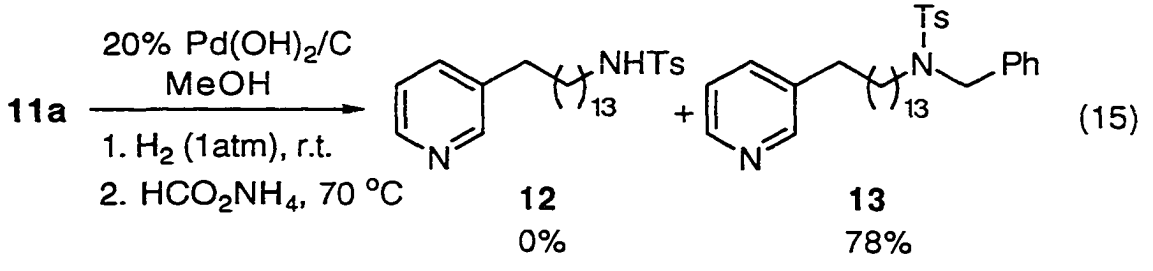
[d] The reaction was very slow, and the yield was not determined.

[e] 4 Equiv. of $NaHCO_3$ used.

[f] 5 Mol % Ph_3P added.

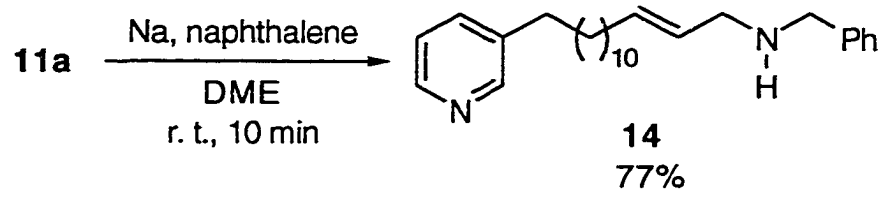
theonelladin C. The results in Table 4 indicate that an excess of base was required to get a good yield and Na_2CO_3 was better than $NaHCO_3$. The use of LiCl slowed the reaction considerably. No improvement was observed by either adding Ph_3P or lowering the temperature.

It now appeared that an analogue of theonelladin C as a single isomer could be obtained from compound **11a** through deprotection and hydrogenation. We first tried to apply our earlier procedure for hydrogenation and debenzylation to compound **11a**. Unfortunately, debenzylation did not occur and only the hydrogenation product **13** was formed in 78% yield (eq. 15). This

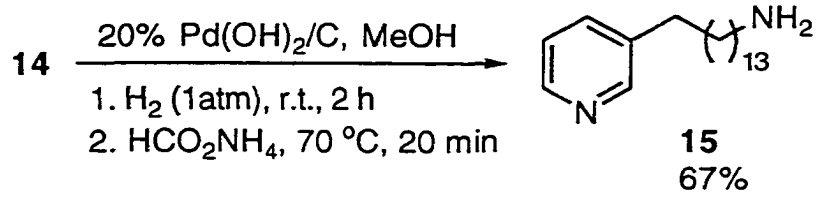


(15)

suggests that this debenzylation procedure is only effective on *N*-benzylamines, not on *N*-benzyl tosylamides. So, the tosyl group must be removed first. Ji *et al.* have reported a very efficient method for the cleavage of sulfonamides.[24] The N-S bond in sulfonamides is cleaved by the anion radical formed from sodium and naphthalene under very mild conditions. We applied their procedure to our tosylamide coupling product. Compound **11a** was treated with 8 equiv. of sodium naphthalene in dimethoxyethane at room temperature for 10 minutes to give the detosylation product **14** in 77% yield (eq. 16). Compound **14**, a benzylamine, was then hydrogenated and debenzylated to give the theonelladin C analogue **15** in 67% yield (eq. 17).



(16)

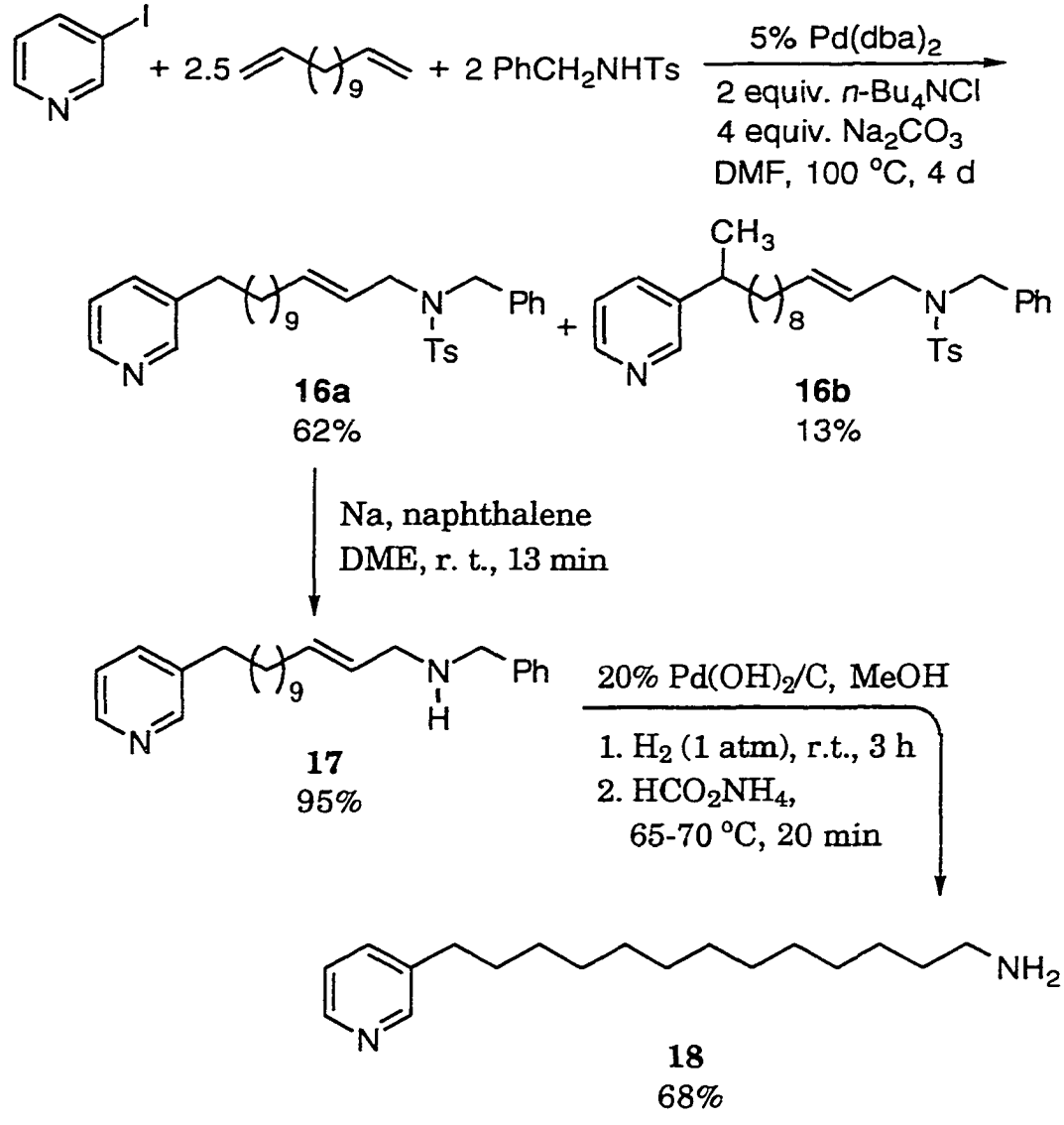


(17)

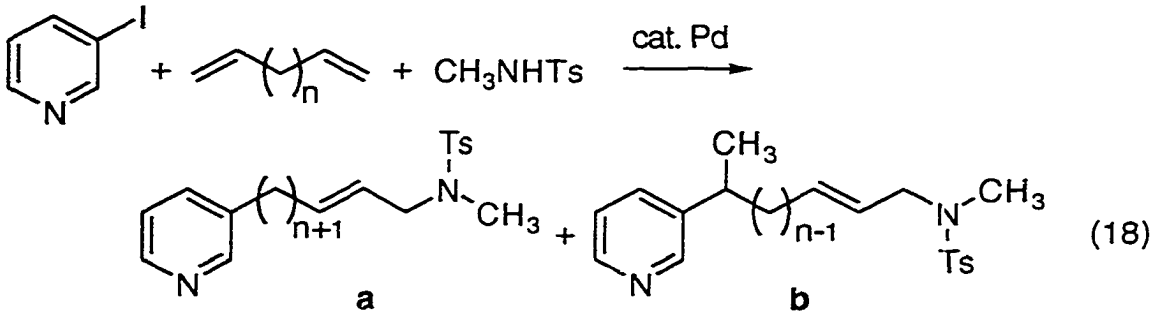
With those successful procedures for preparing compound **15**, the natural product theonelladin C (**18**) was then synthesized simply by using 1,12-tridecadiene instead of 1,13-tetradecadiene in the palladium-catalyzed coupling, followed by deprotection and hydrogenation (Scheme 2). The coupling of 3-iodopyridine, 1,12-tridecadiene and *N*-benzyl tosylamide afforded the desired product **16a** and its isomer **16b** in 62% and 13% yields respectively. Compound **16a** was converted into benzylamine **17** in 95% yield upon treatment with sodium naphthalene. Finally, theonelladin C was obtained in 68% yield from the hydrogenation and debenzylation of **17**.

The success of the synthesis of theonelladin C using a tosylamide as a nucleophile in the palladium-catalyzed coupling prompted us to try to approach theonelladin D by a similar process. Commercially available *N*-methyl tosylamide was therefore chosen as the nucleophile for the coupling reaction. It was expected that *N*-methyl tosylamide would be a good nucleophile and the desired coupling product could be easily separated from its isomer.

Scheme 2



Some results from the palladium-catalyzed coupling of 3-iodopyridine, 1,12-tridecadiene or 1,13-tetradecadiene, and *N*-methyl tosylamide are summarized in equation 18 and Table 5 (on page 108). First, 1,13-tetradecadiene was again used as a substitute for 1,12-tridecadiene (entries 1 and 2). Compared with *N*-benzyl tosylamide (Table 4), *N*-methyl tosylamide



(18)

Table 5. Palladium-catalyzed Coupling of 3-Iodopyridine, Non-conjugated Dienes and *N*-Methyl Tosylamide (Eq. 18)[a]

entry	n	base (equiv.)	time (d)	product, % yield	
1	10	Na_2CO_3 (4)	1	**19a**, 28	**19b**, –[b]
2	10	Na_2CO_3 (4)	2	**19a**, 42	**19b**, –[b]
3[c]	9	Na_2CO_3 (4)	4	**20a**, 50	**20b**, –[b]
4[d]	9	Na_2CO_3 (4)	4	**20a**, 59	**20b**, 11
5	9	NaH (2)	4	**20a**, 40	**20b**, 8

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$ and 2 equivs. of *n*-Bu_4NCl using 2.5 equiv. of diene and 2.0 equiv. of *N*-methyl tosylamide at 100 °C.

[b] Not determined.

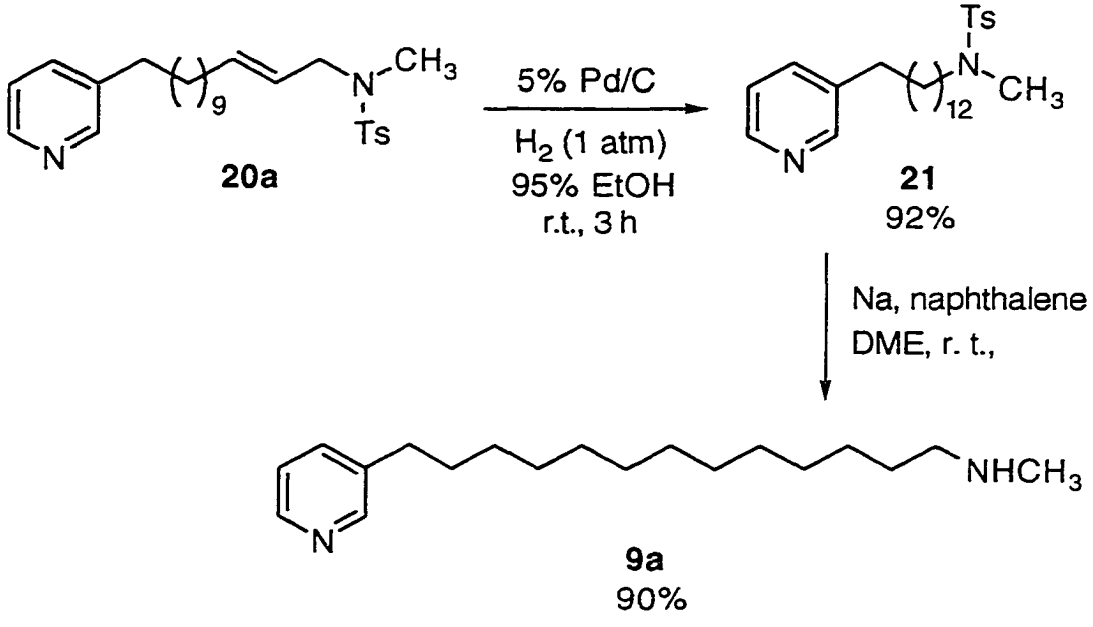
[c] Crude products treated with NaH to remove excess CH_3NHTs.

[d] Crude products treated with NaOH to remove excess CH_3NHTs.

underwent a slower coupling reaction, and 4 days were required to get good results. The desired product (**20a**) was obtained in 59% isolated yield as a single isomer from the coupling of 3-iodopyridine, 1,12-tridecadiene and *N*-methyl tosylamide (entry 4).

Theonelladin D was finally obtained through the hydrogenation and subsequent detosylation of compound **20a**. As shown in Scheme 3, the C–C double bond of compound **20a** was saturated by H_2 using 5% Pd/C as a catalyst to give 92% a yield of compound **21**, which, in turn, was treated with fresh radical anion formed from sodium and naphthalene to afford theonelladin D in 90% yield.

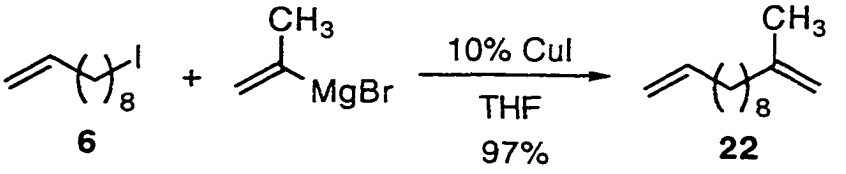
Scheme 3



Total synthesis of niphatesine C

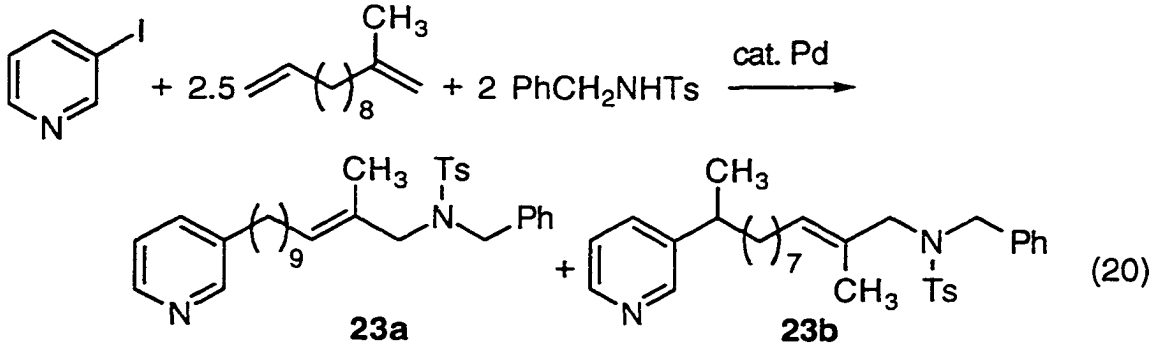
Niphatesine C has a very similar structure to theonelladin C. They both have the same amino and pyridyl groups at the ends of a long carbon chain. Niphatesine C contains a saturated 12 carbon chain with a methyl group on the second carbon from the amine, while theonelladin C contains a straight, saturated 13 carbon chain. Therefore, all the procedures for making theonelladin C should be applicable to the synthesis of niphatesine C simply by changing the diene from 1,12-tridecadiene to 2-methyl-1,11-dodecadiene (**22**).

Diene **22** was easily prepared by the copper-catalyzed reaction of 10-iodo-1-decene with isopropenylmagnesium bromide in an excellent yield (eq. 19).



6 **22** (19)

Diene **22** was then employed in the palladium-catalyzed coupling with 3-iodopyridine and *N*-benzyl tosylamide. The results shown in Table 6 indicate that the reaction was very slow and 5 days were needed to afford a satisfactory yield of the desired product.



23a **23b** (20)

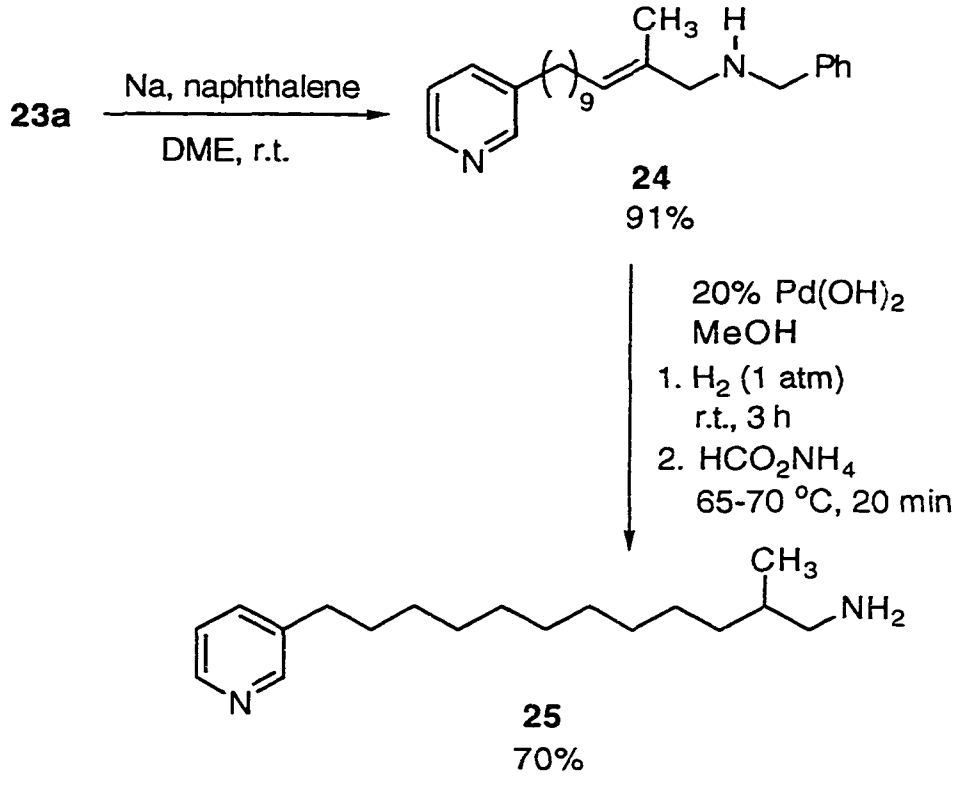
Table 6. Palladium-catalyzed Coupling of 3-Iodopyridine, 2-Methyl-1,11-dodecadiene and *N*-Benzyl Tosylamide (Eq. 20)[a]

entry	reaction time (d)	% isolated yield **23a**	**23b**
1	1	20	4
2	2	29	–
3	4	58	11
4	5	61	13

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$, 2 equiv. of *n*-Bu_4NCl and 4 equiv. of Na_2CO_3 at 100 °C.

With the coupling product **23a** readily separable from **23b**, it would appear that niphatesine C could be readily prepared by detosylation, hydrogenation and debenzylation (Scheme 4). Indeed, compound **23a** was treated with fresh radical anion formed from sodium and naphthalene to give the detosylated product **24** in 91% yield. Then, compound **24** underwent hydrogenation and debenzylation catalyzed by 20% $Pd(OH)_2$ in MeOH to afford the natural product niphatesine C (**25**) in 70% yield.

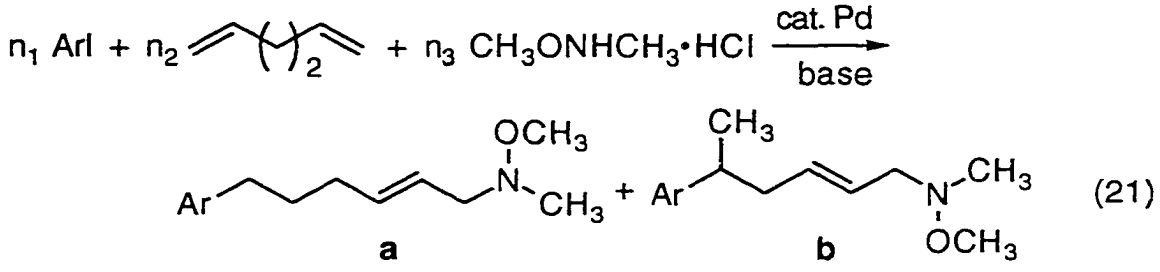
Scheme 4



Total synthesis of xestamine D

Another interesting alkaloid, xestamine D, has a structure containing a 14 carbon chain bearing two functional groups at the ends. One is a pyridine and the other is an *N*-(methoxyl)methylamine. It appeared that this natural product might be easily synthesized using our palladium-catalyzed coupling as a key step. Three major components, *N,O*-dimethylhydroxylamine, 1,13-tetradecadiene and 3-iodopyridine are all readily available. The key point is whether *N,O*-dimethylhydroxylamine will work well as a nucleophile in the palladium-catalyzed coupling.

In our initial investigation of this question, a short-chain diene was used in order to simplify the reaction. In addition to 3-iodopyridine, iodobenzene was also examined. The results are summarized in equation 21 and Table 7.



(21)

Since *N,O*-dimethylhydroxylamine is only available as the hydrochloride salt, comparable amounts of a base are needed in the reaction system to release the hydroxylamine. From Table 7, one can see that DMSO was a suitable solvent for this coupling reaction, and the temperature was a crucial factor. The reaction was very slow at room temperature (entry 4), but a high temperature (100 °C) gave only a very low yield of the product. The reaction run at 60 °C, however, gave a better yield, although it was still not very satisfactory (entry 3). Fortunately, 3-iodopyridine gave somewhat better results than iodobenzene in this coupling process, and generally afforded a modest yield of the desired product. It was observed that Na_2CO_3 did not completely dissolve in the solvent (DMSO) during the reaction. Li_2CO_3 was therefore used, because (1) it is more soluble in most organic solvents; and (2) neutralizing HCl would generate LiCl which might substitute for *n*-Bu_4NCl. The reaction run with Li_2CO_3 (entry 9) was faster than that of Na_2CO_3, but the yield of the product was about the same. Remarkably, *N,O*-dimethylhydroxylamine provided much better regioselectivity than alkyl

Table 7. Palladium-catalyzed Coupling of Aryl Iodides, 1,5-Hexadiene and *N,O*-Dimethylhydroxylamine (Eq. 21)[a]

entry	ArI	$n_1/n_2/n_3$	solvent	base (equiv)	temp (°C)	time (d)	% yield (ratio)
1	PhI	1/5/2	DMF	Na_2CO_3 (2)	100	2	trace
2		1/5/5	DMSO	Na_2CO_3 (5)	100	1	14[b]
3		1/5/5	DMSO	Na_2CO_3 (5)	60	2	39[b]
4		1/5/5	DMSO	Na_2CO_3 (5)	r.t.	4	< 20[b]
5		1/5/5	DMF	Na_2CO_3 (5)	60	2	trace
6		1/5/5	DMA	Na_2CO_3 (5)	60	2	trace
7	PyI[c]	1/5/5	DMSO	Na_2CO_3 (5)	60	2	46 (95:5)
8		1/5/2	DMSO	Na_2CO_3 (2)	60	2	45[b]
9[d]		1/5/5	DMSO	Li_2CO_3 (5)	60	1	43 (97:3)

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ and 2 equiv. of *n*-Bu_4NCl.

[b] Ratios were not determined.

[c] 3-Iodopyridine.

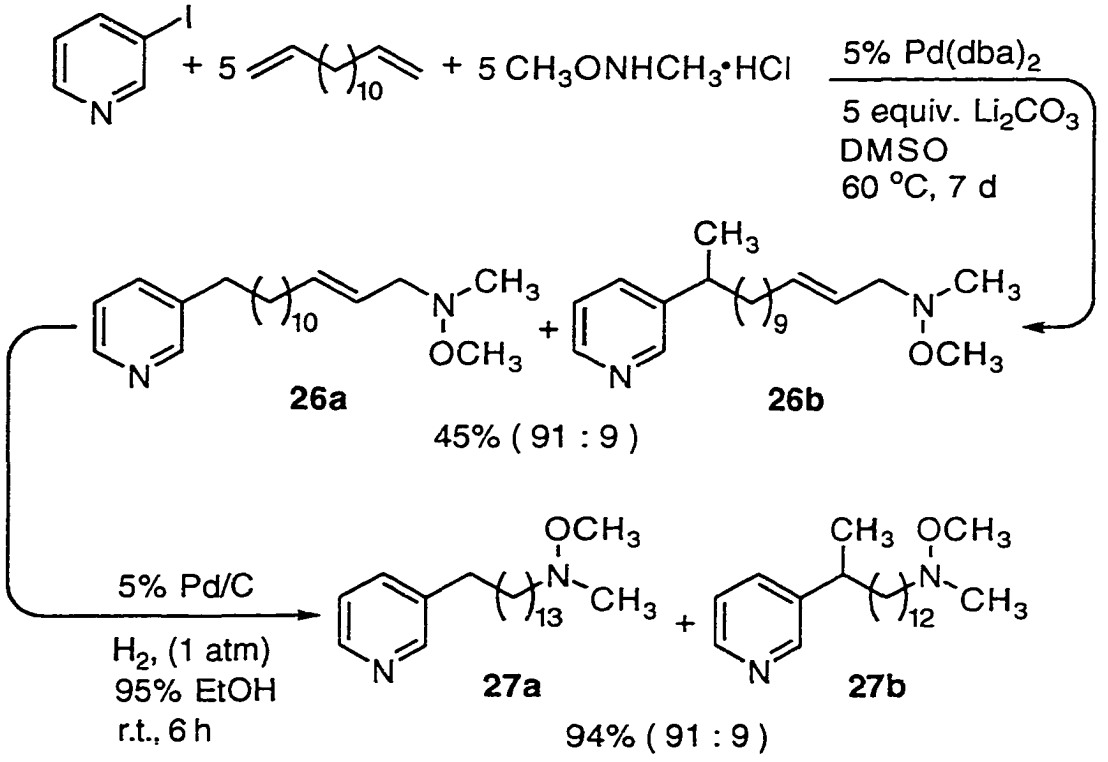
[d] *n*-Bu_4NCl was not added.

amines or tosylamides.

The reaction conditions described in entry 9 of Table 7 were then applied to the coupling of 3-iodopyridine, 1,13-tetradecadiene and *N,O*-dimethylhydroxylamine and the desired product **26a** was obtained in 45% yield, alongside a small amount of an isomer **26b** (Scheme 5). Interestingly, the

reaction became much slower with the long chain diene. The efficient catalytic hydrogenation of **26a** afforded xestamine D in 94% yield.

Scheme 5



Conclusion

The palladium-catalyzed coupling of 3-iodopyridine, non-conjugated dienes and nitrogen nucleophiles has been successfully applied to the synthesis of the naturally-occurring alkaloids theonelladins C and D, niphatesine C and xestamine D. Only two to three steps were needed to accomplish the total synthesis of these natural products from readily available starting materials.

In most cases, palladium-catalyzed coupling provided good yields of the desired products. Benzyl and tosyl groups were chosen as the protecting groups for the nitrogen nucleophiles, because they could be easily removed by appropriate procedures and the benzylamines and tosylamides were usually very good nucleophiles for the palladium-catalyzed coupling process.

It has been proven that our palladium-catalyzed coupling procedure is a very efficient and general method quite useful in organic synthesis. It can be used not only for the synthesis of many natural products like the theonelladins, but also for preparing biologically interesting compounds which contain a saturated carbon chain with an aryl group at one end and another functional group at the other end. This can be achieved by simply changing the number of carbons present in the diene and using different aryl groups and/or nucleophiles in the palladium-catalyzed coupling according to requirements.

Experimental Section

Equipment. All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Digilab FTS-7 spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed on an HP 5890 chromatograph equipped with an HP-1 Megabore column. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Flash chromatography was carried out on 230-400 mesh silica gel.

Reagents. Bis(dibenzylideneacetone)palladium and 5% palladium on charcoal were donated by Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride was purchased from Lancaster Synthesis Inc. 20% Palladium hydroxide on carbon, cuprous iodide, ammonium formate, allylmagnesium bromide, 2-bromopropene, 9-decen-1-ol, benzylamine, 3-aminopyridine, iodobenzene, and 1,5-hexadiene were purchased from Aldrich Chemical Company, Inc. Dimethyl sulfoxide, *N*,*N*-dimethylformamide, and lithium chloride were purchased from Fisher Scientific Company. Benzylmethylamine and *N*-methyl tosylamide were purchased from Eastman Kodak Co. 1,13-Tetradecadiene was purchased from Columbia Organic Chemical Co., Inc.

Preparation of 3-iodopyridine

3-Iodopyridine was prepared using the literature procedure.[25] To 500 mg (5.3 mmol) of 3-aminopyridine in 1.8 ml of concentrated HCl and 1.8 ml of H_2O was added dropwise 403 mg (5.83 mmol) of $NaNO_2$ in 0.8 ml of H_2O at 0-2 °C. The resulting mixture was stirred at 0-2 °C for 15 minutes. Then, 970 mg (5.83 mmol) of KI in 2.4 ml of H_2O was added dropwise over 10 minutes. The reaction was maintained at this temperature for an additional 20 minutes, then warmed to room temperature and left for 3 hours. The reaction mixture was neutralized with 42% NaOH solution to pH > 8 and extracted with ethyl ether. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified on a silica gel column to give 490 mg (45%) of product as colorless crystals: mp 53-54 °C (lit.[25] mp 52.5 °C, brown solid);

^{1}H NMR ($CDCl_3$) δ 7.09 (dd, J = 8.1 Hz, J = 4.8 Hz, 1 H, H-5), 8.00 (d, J = 8.1 Hz, 1 H, H-4), 8.55 (d, J = 4.5 Hz, 1 H, H-6), 8.84 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 93.6, 125.2, 144.2, 148.1, 155.8; IR ($CDCl_3$) 3068, 3044, 1566, 1461, 1409, 1007, 908 cm^{-1}; HRMS for C_5H_4NI: calcd 204.9389, found 204.9392.

Preparation of 10-iodo-1-decene (**6**)

Triphenylphosphine (25.15 g, 96.0 mmol) and imidazole (8.70 g, 128 mmol) were dissolved in 200 ml of 3:1 Et_2O/CH_3CN at room temperature. To the resulting mixture was added 24.4 g (96.0 mmol) of iodine at 0-5 °C. After the addition was complete, the mixture was kept stirring at this temperature for an additional 20 minutes. Then, to the mixture was added dropwise 11.1 g (64.0 mmol) of 9-decen-1-ol (90% purity) over 15 minutes. The reaction mixture was warmed to room temperature and left for 1 hour. After a normal work-up, the product was purified on a silica gel column and obtained in 88% yield: ^{1}H NMR ($CDCl_3$) δ 1.29-1.38 (br m, 10 H, CH_2's), 1.82 (quintet, J = 7.2, Hz, 2 H, CH_2CI), 2.03 (q, J = 7.2 Hz, 2 H, =CCH_2), 3.19 (t, J = 7.2 Hz, 2 H, CH_2I), 4.93 (ddt, J = 10.2 Hz, J = 1.8 Hz, J = 0.9 Hz, 1 H, Z-H_2C=), 4.99 (ddt, J = 17.1 Hz, J = 1.8 Hz, J = 1.5 Hz, 1 H, E-H_2C=), 5.81 (ddt, J = 17.1 Hz, J = 10.2 Hz, J = 6.6 Hz, 1 H, =CHC); ^{13}C NMR ($CDCl_3$) δ 7.3, 28.6, 28.9, 29.1, 29.3, 30.6, 33.6, 33.8, 114.2, 139.1; IR (neat) 3074, 2925, 2852, 1640, 1462, 909 cm^{-1}; HRMS for $C_{10}H_{19}I$: calcd 266.0532, found 266.0530.

Preparation of 1,12-tridecadiene (**7**)

To 4.39 g (16.5 mmol) of 10-iodo-1-decene and 0.42 g (2.2 mmol) of CuI (purchased from Aldrich and used without further purification) in anhydrous

THF (40 ml) was added 22 ml (1.0 N, 22 mmol) of allylmagnesium bromide under N_2 at -78 °C. After the addition was complete, the reaction mixture was allowed to warm to 0 °C and maintained at this temperature for 2 hours. Then, the mixture was kept at room temperature overnight. After filtration, the filtrate was diluted with saturated NaCl solution and extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to remove the solvent. The residue was distillated at 76-80 °C/2 mm Hg to give 1.78 g (60%) of **7**: ^{1}H NMR ($CDCl_3$) δ 1.27-1.37 (br m, 14 H, CH_2's), 2.03 (dt, J = 7.5 Hz, J = 6.9 Hz, 4 H, $=CCH_2C$), 4.92 (ddt, J = 10.2 Hz, J = 1.8 Hz, J = 0.9 Hz, 2 H, Z-$H_2C=$), 4.99 (ddt, J = 17.1 Hz, J = 1.8 Hz, J = 1.5 Hz, 2 H, E-$H_2C=$), 5.81 (ddt, J = 17.1 Hz, J = 10.2 Hz, J = 6.6 Hz, 2 H, =CHC); ^{13}C NMR ($CDCl_3$) δ 29.0, 29.2, 29.5, 29.6, 33.9, 114.1, 139.3; IR (neat) 3076, 2924, 2853, 1641, 1464, 1439, 909 cm^{-1}; HRMS for $C_{13}H_{24}$: calcd 180.1878, found 180.1880.

Preparation of 2-methyl-1,11-dodecadiene (**22**)

To 1.07 g (44 mmol) of magnesium metal (turnings) in 40 ml of anhydrous THF was added 4.89 g (40 mmol) of 2-bromopropene in 10 ml of THF at room temperature under N_2. After the addition was complete, the reaction mixture was refluxed for 8 hours. The resulting Grignard solution was transferred by a syringe to a suspension of CuI (purchased from Aldrich and used without further purification) (0.40 g, 2.1 mmol) in 30 ml of anhydrous THF at -78 °C and stirred for 10 minutes. The mixture was allowed to warm to 0 °C and maintained at this temperature for 2 hours, then kept at room temperature overnight. After filtration, the filtrate was poured into 150 ml of

saturated NH_4Cl solution and extracted with hexane. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified on a silica gel column to give 2.79 g (97%) of **22**: ^1H NMR ($CDCl_3$) δ 1.28 (br s, 8 H, CH_2's), 1.39 (m, 4 H, CH_2CC=), 1.70 (s, 3 H, CH_3), 2.01 (m, 4 H, =CCH_2), 4.65 (s, 1 H, HHC=CMe), 4.68 (s, 1 H, HHC=CMe), 4.92 (d, J = 10.2 Hz, 1 H, *Z*-H_2C=), 4.98 (d, J = 17.1 Hz, 1 H, *E*-H_2C=), 5.81 (ddt, J = 17.1 Hz, J = 10.2 Hz, J = 6.6 Hz, 1 H, =CHC); ^{13}C NMR ($CDCl_3$) δ 22.5, 27.7, 29.1, 29.3, 29.4, 29.6, 33.9, 37.9, 109.6, 114.1, 139.3, 146.3 (one peak overlapped); IR (neat) 3075, 2969, 2924, 2853, 1642, 1456, 909 cm^{-1}; HRMS for $C_{13}H_{24}$: calcd 180.1878, found 180.1878.

Preparation of N-benzyl tosylamide (**10**)

N-Benzyl tosylamide was prepared using the literature procedure.[26] To 10.7 g (0.1 mol) of benzylamine in 32 ml of pyridine was gradually added 19.2 g (0.1 mol) of tosyl chloride at 0-5 °C. After the addition was complete, the resulting mixture was allowed to warm to room temperature and maintained at that temperature for 2 hours, then raised to 70 °C for 4 hours. After cooling to room temperature, the mixture was diluted with ethyl ether (500 ml) and washed with 10% HCl solution. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the product **10** was formed as crystals in 87% yield (22.7 g): mp 113-114 °C; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3 H, CH_3), 2.12 (d, J = 6.0 Hz, 2 H, CH_2), 4.74 (t, J = 6.0 Hz, 1 H, NH), 7.17-7.28 (m, 5 H, Ph), 7.30 (d, J = 7.8 Hz, 2 H, Ts), 7.75 (d, J = 7.8 Hz, 2 H, Ts); ^{13}C NMR ($CDCl_3$) δ 21.6, 47.3, 127.2, 127.9, 128.7, 129.7, 136.3, 136.9, 143.5 (one peak

overlapped); IR ($CDCl_3$) 3361, 3284, 3033, 2925, 2872, 1599, 1456, 1330, 1162 cm^{-1}; HRMS for $C_{14}H_{14}NO_2S$ ($M^+ - H$): calcd 260.0745, found 260.0744.

General procedure for the palladium-catalyzed coupling of aryl iodides, non-conjugated dienes and amines.

To a 2 dram vial with a micromagnetic stirring bar were added 0.25 or 0.5 mmol of aryl iodide, 0.625 or 1.25 mmol of nonconjugated diene, 0.5 or 1.0 mmol of nucleophile, 5 mol % of bis(dibenzylideneacetone)palladium, 0.5 or 1.0 mmol of tetra-*n*-butylammonium chloride (only for reactions with tosylamides), 1.0 or 2.0 mmol of sodium carbonate (only for reactions with tosylamides) and 1 or 2 ml of DMF respectively unless indicated otherwise. The vial was capped with a screw-cap containing a Teflon liner. The resulting mixture was stirred at 100 °C or 60 °C for the required period of time. The mixture was then allowed to cool down to room temperature, diluted with saturated NaCl solution and extracted with ethyl ether. The ether layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to remove the solvent. The crude products were isolated by flash chromatography on a silica gel column.

Preparation of Compounds **1a** and **1b**

Compounds **1a** and **1b** were obtained as an inseparable 86:14 mixture of isomers in 66% combined yield from the coupling of 3-iodopyridine, 2.5 equiv. of 1,13-tetradecadiene and 2 equiv. of benzylmethylamine in the presence of 1.0 equiv. of LiCl at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 1.25-1.30 (br m, 14 H, CH_2's), 1.36 (quintet, J = 7.0 Hz, 2 H, CH_2CC=), 1.60 (quintet, J = 7.5 Hz, 2 H,

$PyCCH_2$), 2.02 (q, J = 7.0 Hz, 2 H, CH_2C=), 2.17 (s, 3 H, NCH_3), 2.59 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.69 (sextet, J = 7.5 Hz, 1 H, PyCH in **1b**), 2.96 (d, J = 6.5 Hz, 2 H, CH_2N), 3.03 (d, J = 6 Hz, 2 H, CH_2N in **1b**), 3.47 (s, 2 H, NCH_2Ph), 5.52 (dt, J = 15.5 Hz, J = 6.5 Hz, 1 H, vinyl), 5.58 (dt, J = 15.5 Hz, J = 6.5 Hz, 1 H, vinyl), 7.19 (dd, J = 7.5 Hz, J = 4.5 Hz, 1 H, Py), 7.24 (m, 1 H, Ph), 7.30 (m, 4 H, Ph), 7.47 (dt, J = 7.5 Hz, J = 1.5 Hz, 1 H, Py), 8.42 (dd, J = 4.5 Hz, J = 1.5 Hz, 1 H, Py), 8.44 (d, J = 1.5 Hz, 1 H, Py); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.4, 29.5, 29.6, 29.6, 29.7, 29.8, 31.2, 32.5, 33.1, 42.0, 59.8, 61.6, 123.2, 126.9, 127.0, 128.2, 129.2, 134.4, 135.8, 138.0, 139.1, 147.2, 150.0 (one peak overlapped); IR (neat) 3082, 3058, 3026, 2924, 1682, 1454, 1128, 1024 cm^{-1}; HRMS for $C_{27}H_{39}N_2$ (M^+ – H): calcd 391.3113, found 391.3107.

Preparation of Compounds **8a** and **8b**

Compounds **8a** and **8b** were obtained as an inseparable 85:15 mixture of isomers in 78% combined yield from the coupling of 3-iodopyridine, 2.5 equiv. of 1,12-tridecadiene and 2 equiv. of benzylmethylamine in the presence of 1.3 equiv. of LiCl at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 1.23-1.35 (br m, 14 H, CH_2's), 1.60 (quintet, J = 7.2 Hz, 2 H, $PyCCH_2$), 2.03 (q, J = 6.3 Hz, 2 H, CH_2C=), 2.16 (s, 3 H, NCH_3), 2.58 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.67 (sextet, J = 6.9 Hz, 1 H, PyCH in **8b**), 2.96 (d, J = 6.0 Hz, 2 H, CH_2N), 3.47 (s, 2 H, NCH_2Ph), 5.51 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.59 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 7.18 (dd, J = 7.5 Hz, J = 5.1 Hz, 1 H, Py), 7.22-7.34 (m, 5 H, Ph), 7.47 (d, J = 7.8 Hz, 1 H, Py), 8.43 (s, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.2, 29.3, 29.4, 29.5, 29.6, 31.1, 32.4, 33.0, 37.4, 42.0, 59.7, 61.6, 123.2, 126.8, 127.0, 128.1, 129.1, 134.3, 135.7, 137.9, 139.1, 147.2, 149.9; IR (neat) 3083,

3024, 2924, 2852, 1681, 1454, 1024 cm^{-1}; HRMS for $C_{26}H_{37}N_2$ ($M^+ - H$): calcd 377.2957, found 377.2955.

Preparation of Compound **11a**

Compound **11a** was obtained in 58% yield from the coupling of 3-iodopyridine, 2.5 equiv. of 1,13-tetradecadiene and 2 equiv. of *N*-benzyl tosylamide using the procedure above at 100 °C for 24 hours: ^1H NMR ($CDCl_3$) δ 1.20-1.30 (br m, 16 H, CH_2's), 1.60 (quintet, J = 7.2 Hz, 2 H, $PyCCH_2$), 1.86 (m, 2 H, CH_2C=), 2.43 (s, 3 H, CH_3), 2.59 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.69 (d, J = 6.9 Hz, 2 H, $=CCH_2N$), 4.32 (s, 2 H, NCH_2Ph), 5.06 (dt, J = 15.3 Hz, J = 6.9 Hz, 1 H, vinyl), 5.37 (dt, J = 15.3 Hz, J = 6.9 Hz, 1 H, vinyl), 7.19 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.23-7.35 (m, 5 H in Ph, 2 H in Ts), 7.48 (d, J = 7.8 Hz, 1 H, Py), 7.73 (d, J = 8.1 Hz, 2 H, Ts), 8.43 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 21.5, 28.9, 29.0, 29.1, 29.4, 29.6, 31.1, 32.1, 33.0, 48.9, 50.0, 123.3, 127.2, 127.5, 128.3, 128.4 129.6, 135.8, 136.2, 136.4, 137.6, 138.0, 143.1, 147.2, 150.0 (four peaks overlapped); IR (neat) 3084, 3029, 2926, 2853, 1598, 1455, 1340, 1159 cm^{-1}; HRMS for $C_{33}H_{43}N_2O_2S$ ($M^+ - H$): calcd 531.3045, found 531.3050.

Preparation of Compound **16a**

Compound **16a** was obtained in 62% yield from the coupling of 3-iodopyridine, 2.5 equiv. of 1,12-tridecadiene and 2 equiv. of *N*-benzyl tosylamide using the procedure above at 100 °C for 4 days: ^1H NMR ($CDCl_3$) δ 1.20-1.31 (br m, 14 H, CH_2's), 1.61 (quintet, J = 6.9 Hz, 2 H, $PyCCH_2$), 1.86 (q, J = 6.0 Hz, 2 H, CH_2C=), 2.43 (s, 3 H, CH_3), 2.59 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.69 (d, J

= 6.9 Hz, 2 H, $=CCH_2N$), 4.32 (s, 2 H, NCH_2Ph), 5.07 (dt, J = 15.3 Hz, J = 6.9 Hz, 1 H, vinyl), 5.37 (dt, J = 15.3 Hz, J = 6.9 Hz, 1 H, vinyl), 7.19 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.23-7.35 (m, 5 H in Ph, 2 H in Ts), 7.47 (d, J = 7.8 Hz, 1 H, Py), 7.73 (d, J = 8.1 Hz, 2 H, Ts), 8.43 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 21.6, 28.9, 29.2, 29.5, 29.6, 31.2, 32.1, 33.0, 49.0, 50.0, 123.2, 123.3, 127.2, 127.6, 128.4, 129.6, 135.8, 136.3, 136.4, 137.7, 138.0, 143.1, 147.2, 150.0 (four peaks overlapped); IR (neat) 3083, 3027, 2925, 2853, 1597, 1455, 1340, 1160 cm^{-1}; HRMS for $C_{32}H_{42}N_2O_2S(M^+ - H)$: calcd 518.2967, found 518.2960.

Preparation of Compound **20a**

Compound **20a** was obtained in 59% yield from the coupling of 3-iodopyridine, 2.5 equiv. of 1,12-tridecadiene and 2 equiv. of *N*-methyl tosylamide using the procedure above at 100 °C for 4 days: ^1H NMR ($CDCl_3$) δ 1.20-1.30 (br m, 14 H, CH_2's), 1.61 (m, 2 H, $PyCCH_2$), 1.97 (q, J = 6.3 Hz, 2 H, $CH_2C=$), 2.42 (s, 3 H, CH_3 in Ts), 2.60 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.63 (s, 3 H, NCH_3), 3.55 (d, J = 6.6 Hz, 2 H, $=CCH_2N$), 5.31 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.56 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.20 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.31 (d, J = 8.1 Hz, 2 H, Ts), 7.48 (d, J = 7.8 Hz, 1 H, Py), 7.66 (d, J = 8.1 Hz, 2 H, Ts), 8.43 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 21.5, 29.0, 29.1, 29.2, 29.4, 29.5, 31.1, 32.1, 33.0, 33.9, 52.4, 58.8, 123.2, 123.8, 127.4, 129.5, 134.5, 135.7, 136.2, 137.9, 143.1, 147.0, 149.8 (one peak overlapped); IR (neat) 3083, 3027, 2923, 2853, 1598, 1455, 1343, 1163 cm^{-1}; HRMS for $C_{26}H_{38}N_2O_2S$: calcd 442.2654, found 442.2655.

Preparation of Compound **23a**

Compound **23a** was obtained in 61% yield from the coupling of 3-iodopyridine, 2.5 equiv. of 2-methyl-1,11-dodecadiene and 2 equiv. of *N*-benzyl tosylamide using the procedure above at 100 °C for 5 days: ^{1}H NMR ($CDCl_3$) δ 1.15-1.32 (br m, 12 H, CH_2's), 1.36 (s, 3 H, $=CCH_3$), 1.60 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 1.84 (m, 2 H, $CH_2C=$), 2.42 (s, 3 H, CH_3 in Ts), 2.59 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.65 (s, 2 H, $=CCH_2N$), 4.26 (s, 2 H, NCH_2Ph), 5.10 (t, J = 6.9 Hz, 1 H, vinyl), 7.15-7.24 (m, 5 H in Ph, 1 H in Py), 7.28 (d, J = 8.1 Hz, 2 H, Ts), 7.47 (d, J = 7.5 Hz, 1 H, Py), 7.69 (d, J = 8.1 Hz, 2 H, Ts), 8.42 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.5, 27.8, 29.1, 29.2, 29.3, 29.4, 29.5, 31.1, 33.0, 50.8, 56.1, 123.2, 127.2, 127.3, 128.1, 128.5, 129.5, 130.6, 135.7, 136.5, 137.4, 137.9, 143.0, 147.1, 149.9 (two peaks overlapped); IR (neat) 3087, 3031, 2921, 2853, 1599, 1455, 1338, 1160 cm^{-1}; HRMS for $C_{32}H_{42}N_2O_2S$: calcd 518.2967, found 518.2960.

Preparation of Compounds **26a** and **26b**

Compounds **26a** and **26b** were obtained as an inseparable mixture of isomers (91:9) in 45% combined yield from the coupling of 3-iodopyridine, 5 equiv. of 1,13-tetradecadiene and 5 equiv. of *N,O*-dimethylhydroxylamine hydrochloride in the presence of 5 equiv. of Li_2CO_3 in DMSO at 60 °C for 7 days: ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7.2 Hz, 3 H, $PyCCH_3$ in **26b**), 1.24-1.31 (br m, 16 H, CH_2's), 1.61 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 2.02 (q, J = 6.9 Hz, 2 H, $CH_2C=$), 2.55 (s, 3 H, NCH_3), 2.60 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.24 (m, 2 H, CH_2N), 3.51 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3 in **26b**), 5.51 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.63 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl),

7.19 (dd, J = 7.8 Hz, J = 5.1 Hz, 1 H, Py), 7.47 (d, J = 7.8 Hz, 1 H, Py), 8.43 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 29.1, 29.4, 29.5, 29.6, 31.1, 32.4, 33.0, 44.5, 59.8, 62.5, 123.1, 125.1, 135.1, 135.7, 137.9, 147.1, 149.9 (four peaks overlapped); IR (neat) 3083, 3026, 2924, 2853, 1574, 1460, 1361, 1049 cm^{-1}; HRMS for $C_{21}H_{36}N_2O$: calcd 332.2828, found 332.2834.

Preparation of Compound **21**

To 115 mg of compound **20a** in 3 ml of 95% EtOH was added 11.5 mg (10% by weight) of 5% Pd/C. The resulting mixture was stirred and flushed with H_2 (1 atm) at room temperature for 4 hours. After filtration and removal of the solvent, compound **21** was obtained in 92% yield: ^1H NMR ($CDCl_3$) δ 1.22-1.32 (br m, 18 H, CH_2's), 1.50 (m, 2 H, CH_2CN), 1.61 (m, 2 H, $PyCCH_2$), 2.42 (s, 3 H, CH_3 in Ts), 2.60 (t, J = 7.8 Hz, 2 H, $PyCH_2$), 2.69 (s, 3 H, NCH_3), 2.96 (t, J = 7.2 Hz, 2 H, CH_2N), 7.19 (dd, J = 7.5 Hz, J = 4.2 Hz, 1 H, Py), 7.30 (d, J = 7.8 Hz, 2 H, Ts), 7.48 (d, J = 7.5 Hz, 1 H, Py), 7.66 (d, J = 7.8 Hz, 2 H, Ts), 8.43 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.5, 27.6, 29.1, 29.2, 29.4, 29.5, 31.1, 33.0, 34.5, 50.1, 59.1, 123.2, 127.3, 129.5, 134.5, 135.7, 137.9, 143.1, 147.0, 149.8 (three peaks overlapped); IR (neat) 3082, 3027, 2920, 2851, 1598, 1462, 1342, 1161 cm^{-1}; HRMS for $C_{26}H_{39}N_2O_2S$ ($M^+ - H$): calcd 443.2732, found 443.2733.

General procedures for the deprotection of tosylamides.

Procedure A: To a 0.5 M solution of naphthalene in 1,2-dimethoxyethane (DME) was added 3 equiv. of sodium. The resulting mixture was stirred under N_2 at 25 °C for approximately 1 to 2 hours. After becoming dark, the mixture

was stirred for an additional 2 hours at this temperature. The resulting radical anion solution was added dropwise into the tosylamide in DME until a brown color lasted over 10 seconds. The reaction mixture was immediately poured into a saturated $NaHCO_3$ solution and extracted with methylene chloride or ether. The organic layer was then dried over anhydrous Na_2SO_4. After removal of the solvent, the product was purified on a silica gel column.

Procedure B: The fresh radical anion was prepared as in method A. The tosylamide in DME was added to this radical anion solution. The resulting mixture was stirred under N_2 at room temperature for about 10 minutes, then poured into a saturated salt solution and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the product was purified on a silica gel column.

Preparation of Compound **14**

Compound **14** was obtained in 77% yield from the detosylation of compound **11a** using procedure B: ^1H NMR ($CDCl_3$) δ 1.20-1.30 (br m, 16 H, CH_2's), 1.60 (quintet, J = 7.2 Hz, 2 H, $PyCCH_2$), 2.02 (q, J = 6.6 Hz, 2 H, CH_2C=), 2.58 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.26 (d, J = 5.7 Hz, 2 H, =CCH_2N), 3.83 (s, 2 H, NCH_2Ph), 4.74 (br s, 1 H, NH), 5.55 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 5.65 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H, vinyl), 7.19 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.26-7.38 (m, 5 H, Ph), 7.48 (d, J = 7.8 Hz, 1 H, Py), 8.40 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.5, 29.6, 31.1, 32.4, 33.0, 49.9, 51.8, 123.2, 125.2, 127.6, 128.5, 128.8, 135.6, 135.8, 137.2, 138.0, 147.0, 149.8 (five peaks overlapped); IR (neat) 3293 (N-H), 3084, 3028, 2922, 2850, 1681, 1455, 1360, 1112 cm^{-1}; HRMS for $C_{26}H_{37}N_2(M^+ - H)$: calcd 377.2957, found 377.2953.

Preparation of Compound **17**

Compound **17** was obtained in 95% yield from the detosylation of compound **16a** using procedure B: ^{1}H NMR ($CDCl_3$) δ 1.21-1.30 (br m, 14 H, CH_2's), 1.60 (m, 2 H, $PyCCH_2$), 2.01 (q, J = 6.6 Hz, 2 H, CH_2C=), 2.59 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.23 (d, J = 5.7 Hz, 2 H, $=CCH_2N$), 3.81(s, 2 H, NCH_2Ph), 3.90-4.05 (br m, 1 H, NH), 5.52 (dt, J = 15.6 Hz, J = 6.0 Hz, 1 H, vinyl), 5.62 (dt, J = 15.6 Hz, J = 6.0 Hz, 1 H, vinyl), 7.19 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.24-7.36 (m, 5 H, Ph), 7.47 (dt, J = 7.8 Hz, J = 1.8 Hz, 1 H, Py), 8.41 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.3, 29.6, 29.8, 31.2, 32.4, 33.1, 51.0, 53.1, 123.2, 127.0, 127.7, 128.3, 128.4, 133.4, 135.8, 138.0, 140.0, 147.1, 149.9 (three peaks overlapped); IR (neat) 3288 (N-H), 3083, 3027, 2922, 2852, 1681, 1454, 1360, 1114 cm^{-1}; HRMS for $C_{25}H_{35}N_2(M^+ - H)$: calcd 363.2800, found 363.2797.

Preparation of Compound **24**

Compound **24** was obtained in 91% yield from the detosylation of compound **23a** using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.27 (br s, 12 H, CH_2's), 1.60 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 1.65 (s, 3 H, CH_3), 2.01 (m, 2 H, CH_2C=), 2.58 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.16 (s, 2 H, $=CCH_2N$), 3.72 (s, 2 H, NCH_2Ph), 5.31 (t, J = 7.2 Hz, 1 H, vinyl), 7.18 (dd, J = 7.5 Hz, J = 4.8 Hz, 1 H, Py), 7.22-7.32 (m, 5 H, Ph), 7.47 (d, J = 7.5 Hz, 1 H, Py), 8.42 (s, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 14.8, 27.8, 29.2, 29.3, 29.4, 29.5, 29.7, 31.2, 33.0, 52.8, 57.0, 123.2, 126.8, 128.2, 128.3, 132.9, 135.7, 137.9, 140.4, 147.1, 149.9 (two peaks overlapped); IR (neat) 3304 (N-H), 3084, 3027, 2921, 2852, 1682, 1454, 1359, 1106 cm^{-1}; HRMS for $C_{25}H_{36}N_2$: calcd 364.2879, found 364.2873.

Preparation of Compound **9a**

Compound **9a** was obtained in 90% yield from the detosylation of compound **21** using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.25 (br s, 18 H, CH_2's), 1.47 (m, 2 H, CH_2CN), 1.60 (m, 2 H, $PyCCH_2$), 2.43 (s, 3 H, CH_3), 2.56 (t, J = 7.2 Hz, 2 H, CH_2N), 2.59 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 7.19 (dd, J = 7.5 Hz, J = 4.8 Hz, 1 H, Py), 7.48 (d, J = 7.8 Hz, 1 H, Py), 8.43 (s, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 27.3, 29.1, 29.4, 29.6, 29.8, 29.9, 31.1, 33.0, 36.5, 52.2, 123.1, 135.7, 137.9, 147.1, 149.9 (four peaks overlapped); IR (neat) 3301 (N-H), 3081, 3025, 2924, 2852, 1574, 1465, 1369, 1126 cm^{-1}; HRMS for $C_{19}H_{33}N_2(M^+ - H)$: calcd 289.2644, found 289.2642.

General procedure for the hydrogenation and debenzylation of allylic benzylamines.

To 1.0 equiv. of an allylic benzylamine in MeOH (0.05-0.1 M solution) was added 0.35 equiv. of Pearlman's catalyst 20% $Pd(OH)_2/C$. The resulting mixture was flushed with H_2 (1 atm) at room temperature for 2 to 4 hours. Then, to the mixture was added 5.0 equiv. of ammonium formate (HCO_2NH_4). The mixture was heated at 65-70 °C for 10 to 20 minutes. After filtration and removal of the solvent, the product was purified on a silica gel column.

Preparation of Compounds **5a** and **5b**

Compounds **5a** and **5b** were obtained as an inseparable 86:14 mixture of isomers in 76% combined yield from the hydrogenation and debenzylation of compounds **1a** and **1b** using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J

= 6.3 Hz, 3 H, CH_3 in **5b**), 1.21-1.29 (br m, 20 H, CH_2's), 1.59 (m, 2 H, CH_2CN), 1.71 (m, 2 H, $PyCCH_2$), 2.59 (s, 3 H, NCH_3), 2.60 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.84 (t, J = 7.5 Hz, 2 H, CH_2N), 5.80-6.10 (br m, 1 H, NH), 7.20 (dd, J = 7.8 Hz, J = 5.1 Hz, 1 H, Py), 7.49 (d, J = 7.8 Hz, 1 H, Py), 8.42 (s, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 26.1, 26.8, 29.1, 29.2, 29.5, 29.6, 30.1, 31.2, 32.7, 33.1, 37.5, 49.3, 123.3, 135.9, 138.1, 147.3, 150.1 (three peaks overlapped); IR (neat) 3388 (N-H), 2925, 2853, 1592, 1465, 1362, 1047 cm^{-1}; HRMS for $C_{20}H_{35}N_2(M^+ - H)$: calcd 303.2879, found 303.2796.

Preparation of Compound **15**

Compound **15** was obtained in 67% yield from the hydrogenation and debenzylation of compound **14** using the procedure above: ^1H NMR (CD_3OD) δ 1.26-1.33 (br m, 20 H, CH_2's), 1.48 (m, 2 H, CH_2CN), 1.62 (m, 2 H, $PyCCH_2$), 2.64 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.67 (t, J = 6.3 Hz, 2 H, CH_2N), 7.34 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.67 (d, J = 7.8 Hz, 1 H, Py), 8.34 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 26.9, 29.2, 29.5, 29.7, 29.9, 31.2, 33.1, 33.3, 41.9, 123.2, 135.8, 138.0, 147.2, 150.0 (five peaks overlapped); IR (neat) 3350 (N-H), 3264 (N-H) , 3028, 2927, 2854, 1576, 1464, 1026 cm^{-1}; HRMS for $C_{19}H_{34}N_2$: calcd 290.2722, found 290.2720.

Preparation of Compound **18**

Compound **18** was obtained in 68% yield from the hydrogenation and debenzylation of compound **17** using the procedure above: ^1H NMR ($CDCl_3$) δ 1.23-1.30 (br m, 18 H, CH_2's), 1.43 (m, 2 H, CH_2CN), 1.61 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 2.60 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.67 (t, J = 6.6 Hz, 2 H,

CH_2N), 7.19 (dd, J = 7.5 Hz, J = 4.8 Hz, 1 H, Py), 7.47 (d, J = 7.5 Hz, 1 H, Py), 8.42 (m, 2 H, Py) (NH_2 peak overlapped); ^{13}C NMR ($CDCl_3$) δ 26.9, 29.1, 29.4, 29.5, 29.6, 31.1, 33.0, 33.8, 42.2, 123.1, 135.8, 138.0, 147.1, 149.9 (four peaks overlapped); IR (neat) 3363 (N-H), 3290 (N-H), 3028, 2927, 2854, 1575, 1466, 1309, 1026 cm^{-1}; HRMS for $C_{18}H_{32}N_2$: calcd 276.2566, found 276.2559.

Preparation of Compound **25**

Compound **25** was obtained in 70% yield from the hydrogenation and debenzylation of compound **24** using the procedure above: ^1H NMR (CD_3OD) δ 0.93 (d, J = 6.6 Hz, 3 H, CH_3), 1.30-1.40 (br m, 16 H, CH_2's), 1.50 (m, 1 H, CHCN), 1.66 (m, 2 H, $PyCCH_2$), 2.43 (dd, J = 12.3 Hz, J = 7.2 Hz, 1 H, CHN), 2.60 (dd, J = 12.3 Hz, J = 5.7 Hz, 1 H, CHN), 2.68 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 7.37 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.71 (d, J = 7.8 Hz, 1 H, Py), 8.37 (dd, J = 5.1 Hz, J = 1.2 Hz, 1 H, Py), 8.39 (d, J = 1.2 Hz, 1 H, Py); ^{13}C NMR ($CDCl_3$) δ 17.4, 27.0, 29.1, 29.4, 29.5, 29.6, 29.9, 31.1, 33.0, 34.3, 36.2, 48.3, 123.1, 135.7, 137.9, 147.1, 149.9 (one peak overlapped); IR (neat) 3365 (N-H), 3300 (N-H) , 3025, 2925, 2853, 1574, 1464, 1026 cm^{-1}; HRMS for $C_{18}H_{31}N_2$ (M^+ – H): calcd 275.2487, found 275.2480.

Preparation of Compounds **4a** and **4b**

To 33.4 mg of a mixture of compounds **1a** and **1b** (86:14) in 2 ml of 95% EtOH was added 5 mg of 5% Pd/C. The resulting mixture was stirred and flushed with H_2 (1 atm) at room temperature for 4 hours. After filtration and removal of the solvent, compounds **4a** and **4b** were obtained in 61% combined yield: ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 6.6 Hz, 3 H, $PyCCH_3$ in **4b**), 1.22-1.30 (br

m, 20 H, CH_2's), 1.05 (m, 2 H, CH_2CN), 1.61 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 2.18 (s, 3 H, NCH_3), 2.35 (t, *J* = 7.5 Hz, 2 H, CH_2N), 2.60 (t, *J* = 7.5 Hz, 2 H, $PyCH_2$), 3.48 (s, 2 H, NCH_2Ph), 7.19 (dd, *J* = 7.8 Hz, *J* = 4.8 Hz, 1 H, Py), 7.23-7.31 (m, 5 H, Ph), 7.48 (d, *J* = 7.8 Hz, 1 H, Py), 8.43 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 27.5, 29.2, 29.4, 29.5, 29.7, 29.9, 31.2, 33.1, 42.2, 57.6, 62.3, 123.2, 126.9, 128.2, 129.1, 135.8, 138.0, 139.2, 147.2, 150.0 (five peaks overlapped); IR (neat) 3082, 3026, 2924, 2852, 1576, 1454, 1363, 1027 cm^{-1}; HRMS for $C_{27}H_{41}N_2$ ($M^+ - H$): calcd 393.3269, found 393.3274.

Preparation of Compounds **27a** and **27b**

To 39 mg of a mixture of compounds **26a** and **26b** (91:9) in 3 ml of 95% EtOH was added 7.7 mg of 5% Pd/C. The resulting mixture was stirred and flushed with H_2 (1 atm) at room temperature for 6 hours. After filtration and removal of the solvent, compounds **27a** and **27b** were obtained in 92% combined yield: ^1H NMR ($CDCl_3$) δ 1.25-1.30 (br m, 20 H, CH_2's), 1.58 (m, 4 H, CH_2CN, $PyCCH_2$), 2.56 (s, 3 H, NCH_3), 2.60 (m, 4 H, CH_2N, $PyCH_2$), 3.51 (s, 3 H, OCH_3), 7.19 (dd, *J* = 7.5 Hz, *J* = 4.8 Hz, 1 H, Py), 7.48 (d, *J* = 7.5 Hz, 1 H, Py), 8.43 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 27.3, 27.4, 29.1, 29.4, 29.6, 31.1, 33.0, 45.2, 60.0, 61.0, 123.1, 135.7, 137.9, 147.0, 149.9 (six peaks overlapped); IR (neat) 3082, 3026, 2923, 2853, 1576, 1461, 1048 cm^{-1}; HRMS for $C_{21}H_{38}N_2O$: calcd 334.2984, found 334.2992.

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PALLADIUM–CATALYZED COUPLING OF ARYL IODIDES, NONCONJUGATED DIENES AND HETEROATOM NUCLEOPHILES

A paper to be submitted to the *Journal of Organic Chemistry*

Richard C. Larock and Yao Wang

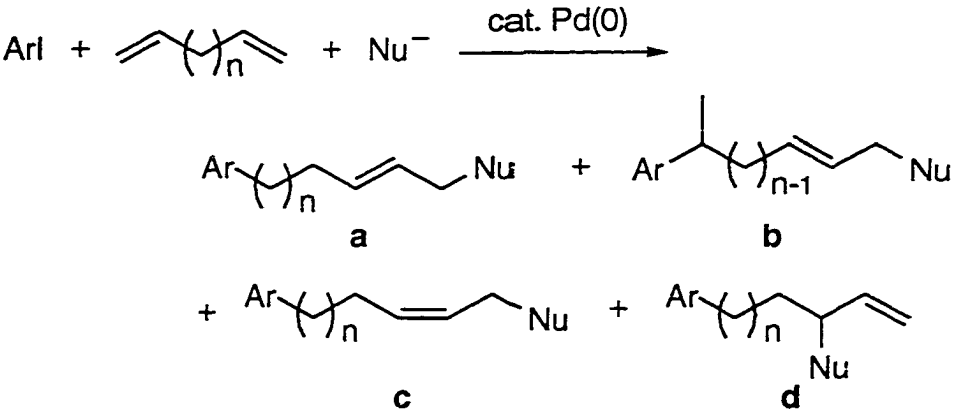
Introduction

We have proven, in previous papers, that the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and nucleophiles is a very efficient method to rapidly construct relatively complex molecules. Amines (see Paper II) and phenylboron compounds (see Paper I) have successfully been applied as nucleophiles to this type of coupling. This process, as described in Paper I, involves arylpalladium formation and addition to the less-substituted C–C double bond of the diene, palladium migration to form a π-allylpalladium intermediate, and displacement of palladium by the nucleophile. It would appear that a variety of nucleophiles known to effect π-allylpalladium displacement should also undergo this process.

We here present our work on other heteroatom nucleophiles, such as sulfonamide,[1] imide,[2] azide,[3] acetate[4] and phenol[5] in the palladium-catalyzed three-component coupling. The coupling products from these nucleophiles are potentially quite useful intermediates in organic synthesis. For example, an allylic amide or imide product can be easily converted to a primary or secondary allylic amine by hydrolysis.[2b,6] An allylic azide can be readily

reduced to form a primary amine.[7] As intermediates, allylic acetates or allylic phenyl ethers may be converted to other functionalized allylic compounds by displacement of the acetate or phenoxy group by other functional groups, such as alkoxy groups.[8]

The palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and nucleophiles generally provides a mixture of several isomers of the coupling product (eq. 1; also see Scheme 1 in Paper I). The number and ratio of the



(1)

isomers depends on the nature and/or the structure of the aryl iodides, dienes and nucleophiles. It has been proven that steric effects are very important for the selectivity of this coupling reaction. In this paper, one will see that the nucleophile also influences the reaction selectivity very much (some nucleophiles provide two isomers of the product, and some provide 3 or 4 isomers) although the reason why is still not very clear. It is probably because of coordination between the nucleophile and palladium.

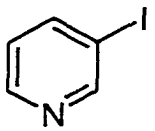
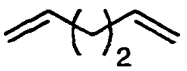
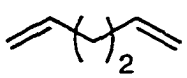
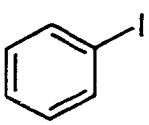
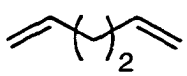
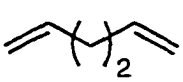
Results and Discussion

Carbon nucleophiles[9] and amines[10] employed in the palladium-catalyzed three-component coupling have provided very good results, and optimized procedures have been achieved. Other heteroatom nucleophiles described in this paper have basically been examined using these earlier optimized procedures. In some cases, reaction conditions were changed a little to achieve better results.

All of the reaction conditions and results are summarized in Table 1. Tosylamides have been used as nucleophiles in the palladium-catalyzed coupling of 3-iodopyridine and 1,12-tridecadiene for the synthesis of the natural products theonelladins C and D. To establish the generality of this process, a tosylamide was tested in the coupling with a short chain diene and an aryl iodide. For example, *N*-benzyl tosylamide was allowed to react with 1,5-hexadiene and iodobenzene or 3-iodopyridine (entries 1–4). As expected, two isomers of the product were obtained in good yields. Increasing the amount of 1,5-hexadiene from 2.5 equiv. to 5 equiv. provided higher yields. This may be due to the volatility of the diene.

Benzenesulfonamide was also tested in the coupling with 1,5-hexadiene and iodobenzene under the same reaction conditions used for *N*-benzyl tosylamide (entry 5). Unfortunately, no desired products were observed. We subsequently changed the solvent from DMF to DMSO to improve the reaction in the same manner employed successfully in the case of primary amines. As a result, the desired coupling product was obtained in 41% yield when the reaction was run for 3 days (entry 7). A third isomer (*Z* isomer **3c**) was

Table 1. Palladium-catalyzed Coupling of Aryl Iodides, Non-conjugated Dienes and Various Nucleophiles[a]

entry	aryl iodide	diene	nucleophile	Cl^- source (equiv)	base (equiv)
1		2.5 	2 $PhCH_2NHTs$	*n*-Bu_4NCl (2)	Na_2CO_3 (4)
2		5 		*n*-Bu_4NCl (2)	Na_2CO_3 (2)
3		2.5 	2 $PhCH_2NHTs$	*n*-Bu_4NCl (2)	Na_2CO_3 (4)
4		5 		*n*-Bu_4NCl (2)	Na_2CO_3 (2)

[a] All reactions were run in the presence of 5 mol % $Pd(dba)_2$ at 100 °C.

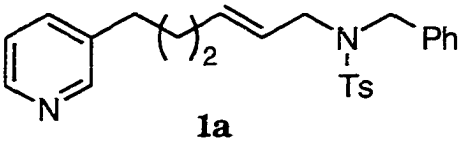
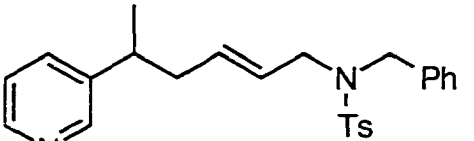
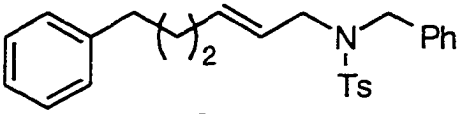
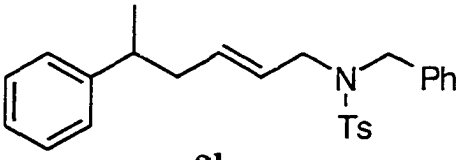
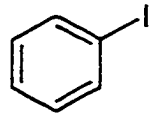
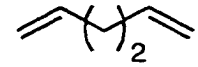
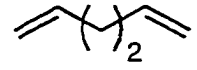
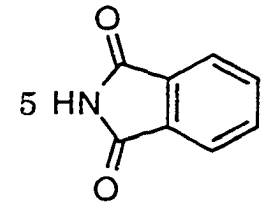
solvent	time (h)	product(s)	% isolated yield (ratio)
DMF	24	 **1a**  **1b**	67 (89:11)
DMF	24		80 (88:12)
DMF	24	 **2a**  **2b**	41 (90:10)
DMF	24		68 (87:13)

Table 1. (continued)

entry	aryl iodide	diene	nucleophile	Cl^- source (equiv)	base (equiv)
5		5 	2 H_2NSO_2Ph	*n*-Bu_4NCl (2)	Na_2CO_3 (2)
6			5 H_2NSO_2Ph	*n*-Bu_4NCl (2)	Na_2CO_3 (2)
7			2.5 H_2NSO_2Ph	*n*-Bu_4NCl (2)	Na_2CO_3 (2)
8		5 	5 	*n*-Bu_4NCl (2)	Na_2CO_3 (2)

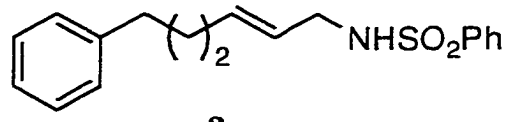
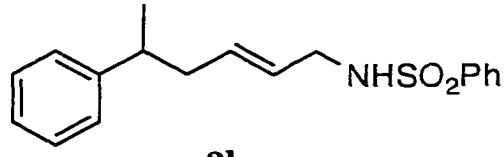
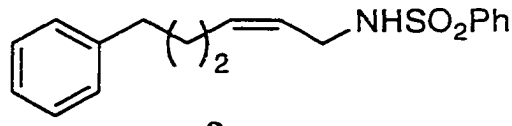
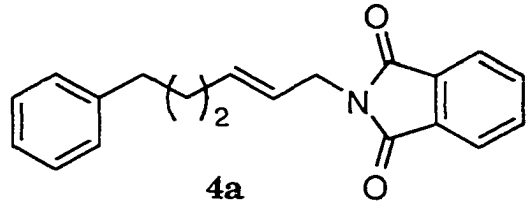
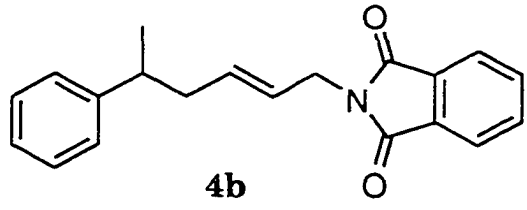
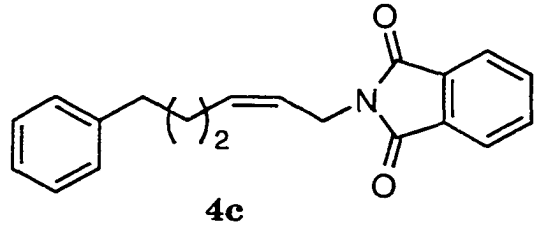
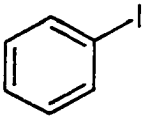
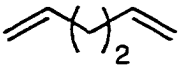
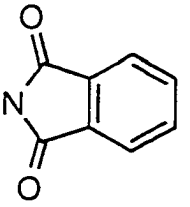
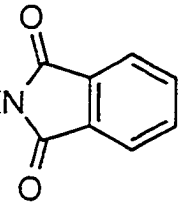
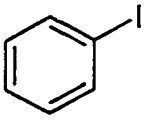
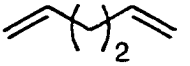
solvent	time (h)	product(s)	% isolated yield (ratio)
DMF	24	 **3a**  **3b**  **3c**	0
DMSO	24		15 (--)
DMSO	72		41 (73:13:14)
DMSO	24	 **4a**  **4b**  **4c**	7 (--)

Table 1. (continued)

entry	aryl iodide	diene	nucleophile	Cl^- source (equiv)	base (equiv)
9		5 	2.5 	*n*-Bu_4NCl (2)	Na_2CO_3 (2)
10			2.5 	*n*-Bu_4NCl (2)	--
11				LiCl (2)	--
12		5 	2 $HN(CO_2\text{-}t\text{-}Bu)_2$	*n*-Bu_4NCl (1)	$NaHCO_3$ (2.5)
13			5 $HN(CO_2\text{-}t\text{-}Bu)_2$	*n*-Bu_4NCl (2)	Na_2CO_3 (2)

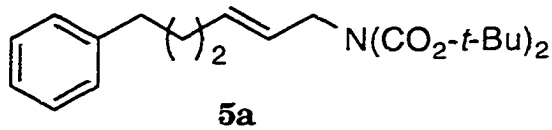
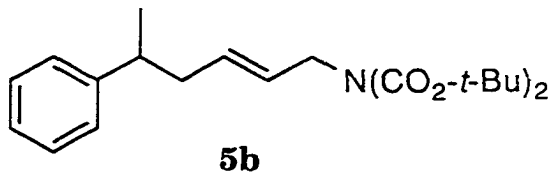
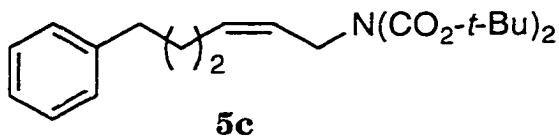
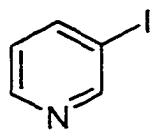
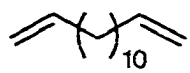
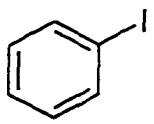
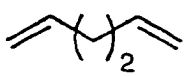
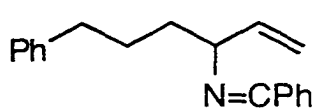
solvent	time (h)	product(s)	% isolated yield (ratio)
DMSO	24		17 (74:19:7)
DMSO	48		20 (--)
DMSO	48		64 (70:15:15)
DMF	72	 **5a**  **5b**  **5c**	0
DMSO	24		72 (81:9:10)

Table 1. (continued)

entry	aryl iodide	diene	nucleophile	Cl^- source (equiv)	base (equiv)
14		5 	5 $HN(CO_2\text{-}t\text{-}Bu)_2$	n-Bu_4NCl (2)	Na_2CO_3 (2)
15		5 	2 $HN{=}CPh_2$	n-Bu_4NCl (2)	--
16			5 $HN{=}CPh_2$	n-Bu_4NCl (2)	--
17				n-Bu_4NCl (2)	--
18				n-Bu_4NCl (2)	Na_2CO_3 (2)
19				n-Bu_4NCl (2)	Na_2CO_3 (2)

[b] The *N,N*-dimethylamino product was isolated in 44% yield.

[c] A third isomer was isolated in 8% yield with the structure



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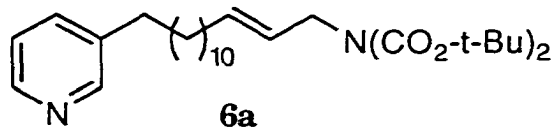
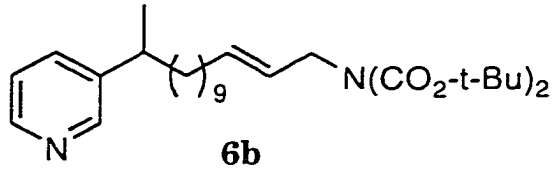
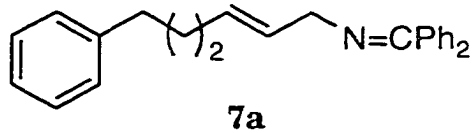
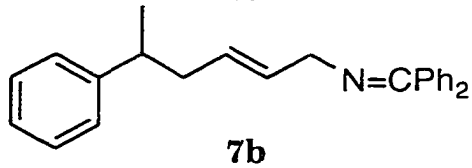
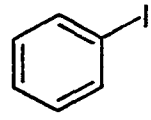
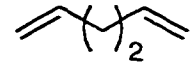
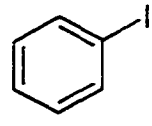
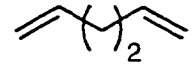
solvent	time (h)	product(s)	% isolated yield (ratio)
DMSO	48	 **6a**  **6b**	44 (87:13)
DMF	48	 **7a**  **7b**	0[b]
DMA	48		0
DMSO	48		0
DMSO	48		7 (87:13)[c]
DMA	48		trace

Table 1. (continued)

entry	aryl iodide	diene	nucleophile	Cl^- source (equiv)	base (equiv)
20		5 	2 	*n*-Bu_4NCl (2)	--
21				*n*-Bu_4NCl (2)	Na_2CO_3 (2)
22		5 	1.5 NaN_3	*n*-Bu_4NCl (2.2)	--
23			1.5 NaN_3	--	--
24			1.5 NaN_3	--	--

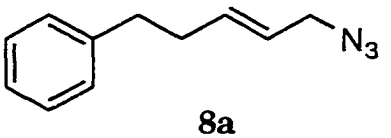
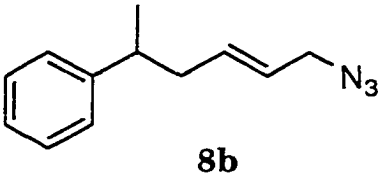
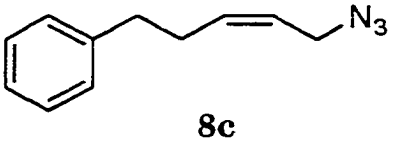
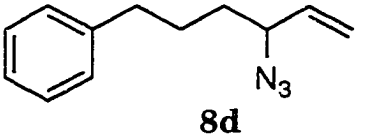
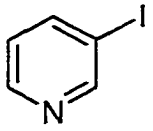
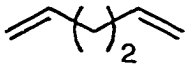
solvent	time (h)	product(s)	% isolated yield (ratio)
DMF	48		0
DMSO	48		0
DMSO	12	 **8a**  **8b**  **8c**  **8d**	41 (56:16:10:18)
DMSO	12		42 (--)
DMF	12		52 (46:26:12:16)

Table 1. (continued)

entry	aryl iodide	diene	nucleophile	Cl^- source (equiv)	base (equiv)
25		5 	1.5 LiN_3	LiCl (1)	--
26			1.5 LiN_3	LiCl (1)	--
27			1.5 NaN_3	LiCl (1)	--
28			1.5 NaN_3	LiCl (1)	--

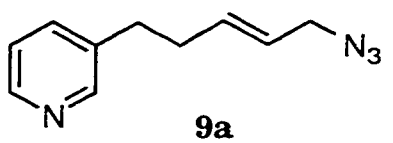
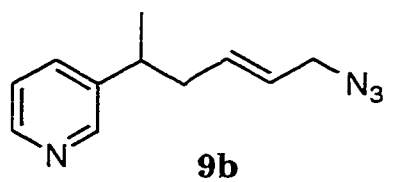
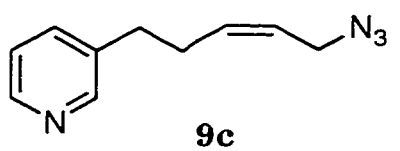
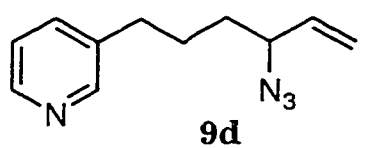
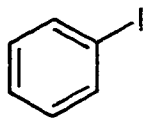
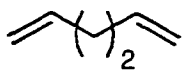
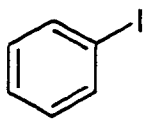
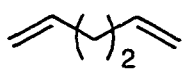
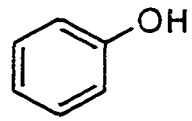
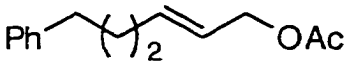
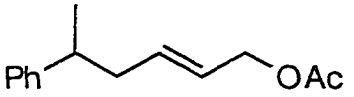
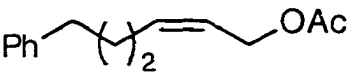
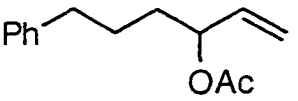
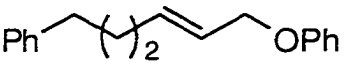
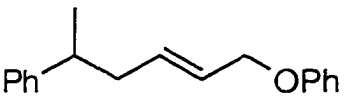
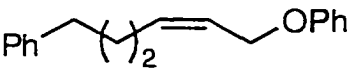
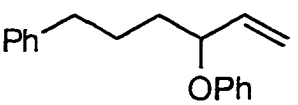
solvent	time (h)	product(s)	% isolated yield (ratio)
DMSO	12	 **9a**  **9b**  **9c**  **9d**	43 (--)
DMF	12		45 (58:12:11:19)
DMSO	12		30 (--)
DMF	12		50 (56:14:12:18)

Table 1. (continued)

entry	aryl iodide	diene	nucleophile	Cl^- source (equiv)	base (equiv)
29		5 	3 $LiOAc \cdot 2H_2O$	*n*-Bu_4NCl (1) + LiCl (1.5)	--
30		2.5 	3 	*n*-Bu_4NCl (1.1)	$NaHCO_3$ (2.5)

solvent	time (h)	product(s)	% isolated yield (ratio)
DMSO	48	 **10a**  **10b**  **10c**  **10d**	36 (53:14:9:24)
DMSO	24	 **11a**  **11b**  **11c**  **11d**	71 (56:16:10:18)

observed in a significant amount. The ratio of the three isomers present in the product was **3a**:**3b**:**3c** = 73:13:14.

Imide, another type of nitrogen nucleophile, was next examined. When coupled with iodobenzene and 1,5-hexadiene, phthalimide also provided three isomers of the coupling product (entry 9) just like benzenesulfonamide, but the yield was very low. By using potassium phthalimide as the nucleophile, instead of phthalimide plus a base, the yield of the product was improved. Interestingly, when 2 equiv. of LiCl was used instead of *n*-Bu_4NCl, the yield was dramatically increased to 64% (entry 11).

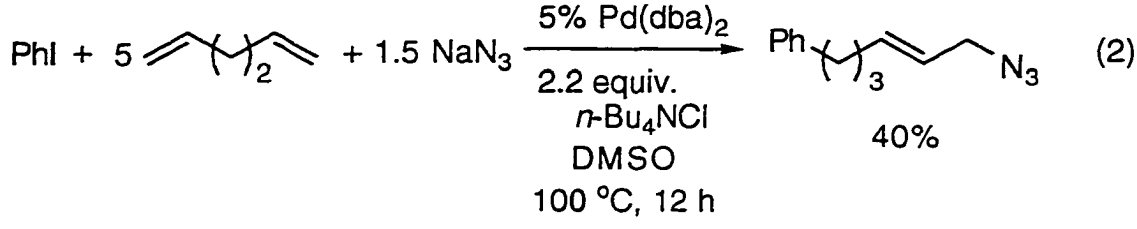
Di-*t*-butyl iminodicarboxylate has successfully been coupled with iodobenzene and 1,5-hexadiene when the reaction is run in DMSO in the presence of 2 equiv. of *n*-Bu_4NCl and 2 equiv. of Na_2CO_3 (entry 13). The coupling product was obtained in 72% yield as a mixture of three isomers (**5a**:**5b**:**5c** = 81:9:10). Since the BOC group has often been used as a protecting group for a free amine, if di-*t*-butyl iminodicarboxylate as a nucleophile works well in the coupling of 3-iodopyridine and a long chain diene, it should provide a nice way to synthesize natural products, such as theonelladin C and niphatesine C. However, the result was not very satisfactory. The coupling of 3-iodopyridine, 1,13-tetradecadiene and di-*t*-butyl iminodicarboxylate only afforded a 44% yield of the product as a mixture of two isomers (entry 14).

Unlike sulfonamides and imides, imine is not a good nucleophile in this type of coupling. Benzophenone imine was chosen as an example. When the coupling reaction was run in DMF, instead of the desired product, the *N*,*N*-dimethylamino product was obtained in 44% yield (entry 15). Apparently, the solvent DMF was involved in the reaction. DMA was then chosen as a

substitute for DMF in order to avoid the side product. Unfortunately, there was still no desired product formed, although the side product was avoided. It appears that DMSO helps benzophenone imine undergo the coupling reaction, but this reaction gave three isomers of the product in very low yield (entry 18).

Pyrrole was also tested as a nucleophile in the coupling reaction of iodobenzene and 1,5-hexadiene, and the reaction was checked by TLC analysis which showed that the reaction was very messy (entries 20 and 21).

Lu, a former student in the Larock research group, has explored the coupling of aryl iodides, nonconjugated dienes and azide,[11] and reported that the desired products were obtained in modest yields. The following is an example (eq. 2).



(2)

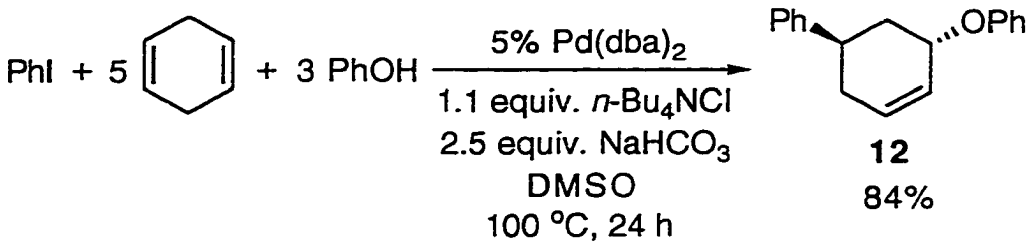
Since all of the reactions of the palladium-catalyzed three-component coupling process have been proven to form a mixture of several isomers of the products in our investigations, the reaction above was reexamined. The ^{1}H NMR spectrum of the product showed that there were four isomers present in the product with a ratio of **8a**:**8b**:**8c**:**8d** = 56:16:10:18 (entry 22). When DMF was used as a solvent instead of DMSO, the yield of the product was increased, but the selectivity was decreased (entry 24).

When coupled with 3-iodopyridine and 1,5-hexadiene, lithium and sodium azide also generated mixtures of four isomers of the products in modest yields (entries 25–28). DMF proved to be a better solvent than DMSO in this case.

The palladium-catalyzed coupling of iodobenzene, 1,5-hexadiene and oxygen nucleophiles like lithium acetate and phenol has been reported by Lu.[11] Here we reran two reactions shown in entries 29 and 30 under Lu's conditions and reexamined the composition of the products. According to Lu's report, these two reactions produced 56% and 62% yields of the coupling products respectively, and the products were mixtures of three isomers (**a**, **c** and **d**). However, we found that these oxygen nucleophiles were similar to azides in that they give mixtures of four isomers of the coupling products. Actually, from the ^{1}H NMR spectra of Lu's products one can easily tell that there was the other isomer **b** by two typical peaks around δ 1.25 ($PhCCH_3$) and 2.75 (PhCH).

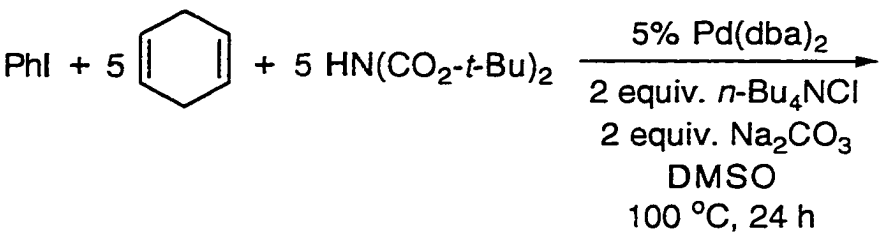
So far, it has been proven that all the nucleophiles tested in the coupling with acyclic dienes almost always give the **b** type regioisomers. With symmetrical cyclic dienes, one would expect a single isomer from this type of coupling (see equations 6 and 7 in Paper I and Table 7 in Paper II). We therefore examined a couple of different nucleophiles in coupling reactions with iodobenzene and 1,4-cyclohexadiene. Phenol (eq. 3) and di-*t*-butyl iminodicarboxylate (eq. 4) reacted as expected, generating single coupling products **12** and **13** respectively through direct attack on the π-allyl intermediate from the face opposite palladium; therefore, both products had *trans* structures. Interestingly, sodium azide coupled with iodobenzene and 1,4-cyclohexadiene to give two diastereomers **14a** and **14b**, although there were no regioisomers formed (eq. 5). It appears that the azide anion undergoes predominantly direct attack on the π-allyl system, but there is still 18% of azide product apparently proceeding through ligand exchange (see Scheme 2 in

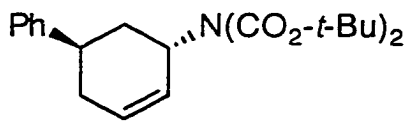
Paper I) to form a π-allylpalladium azide complex, followed by reductive elimination to give the *cis* isomer **14b**.



12
84%

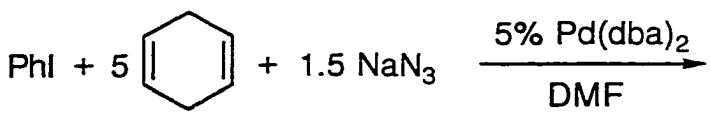
(3)

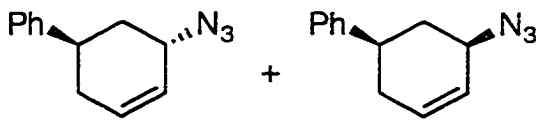




13
46%

(4)





14a **14b**

66% (82:18)

(5)

Conclusion

Several different types of heteroatom nucleophiles have been examined in the palladium-catalyzed coupling with aryl iodides and nonconjugated dienes. Sulfonamides and imides have proven to be good nucleophiles in this coupling process. Their coupling products were generated in good yields with two to three isomers present in the products. The major isomer generally existed in substantial amounts (70–90%). An imine has failed to give satisfactory yields in this coupling reaction. Azide anion as the nucleophile provides modest yields of the coupling products. However, the product is a mixture of four isomers and the major isomer was only present to the extent of about 50% in the mixture.

Phenol and lithium acetate as examples of oxygen nucleophiles have been reexamined in this palladium-catalyzed three-component coupling process. Phenol gave a good yield of the coupling product, but lithium acetate only afforded a 36% yield of the product. Very similar to azide, both oxygen nucleophiles provided low regio- and stereoselectivities and the products were mixtures of four isomers.

When a symmetric cyclic diene was used in this coupling process, only a single isomer or two diastereomers were formed.

Experimental Section

Equipment. All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Digilab FTS-7

spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed on an HP 5890 chromatograph equipped with an HP-1 Megabore column. Flash chromatography was carried out on 230-400 mesh silica gel. Thin-layer chromatography was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F). 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. Bis(dibenzylideneacetone)palladium was donated by Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride was purchased from Lancaster Synthesis Inc. Iodobenzene, 1,5-hexadiene, benzenesulfonamide, potassium phthalimide, di-*t*-butyl iminodicarboxylate, benzophenone imine, pyrrole, *N,N*-dimethylacetamide and lithium chloride were purchased from Aldrich Chemical Company, Inc. Dimethyl sulfoxide, *N,N*-dimethylformamide, sodium azide and lithium chloride were purchased from Fisher Scientific Company. Lithium azide was purchased from Eastman Kodak Co. Phthalimide was purchased from Eastman Organic Chemicals. 1,13-Tetradecadiene was purchased from Columbia Organic Chemical Co., Inc. Phenol was purchased from J. T. Baker Chemical Co. 3-Iodopyridine[12] and *N*-benzyl tosylamide[13] were prepared using literature procedures.

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

To a 1 dram vial with a micromagnetic stirring bar were added 0.25 mmol of aryl iodide, 0.625 or 1.25 mmol of nonconjugated diene, 0.375–1.25 mmol of nucleophile, 5 mol % of bis(dibenzylideneacetone)palladium, 0.25 or 0.5 mmol of tetra-*n*-butylammonium chloride or lithium chloride if required, a certain amount of base (Na_2CO_3 or $NaHCO_3$) if required and 1 ml of DMF or DMSO respectively. The vial was capped with a screw-cap containing a Teflon liner. The resulting mixture was stirred at 100 °C for 0.5–3 days. The mixture was then allowed to cool to room temperature, diluted with saturated NaCl solution and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to remove the solvent. The crude products were isolated by flash chromatography on a silica gel column.

Preparation of Compounds **1a** and **1b**

Compounds **1a** and **1b** were obtained as an 88:12 mixture of isomers in 80% combined yield from the coupling of 3-iodopyridine, 5 equiv. of 1,5-hexadiene and 2 equiv. of *N*-benzyl tosylamide in DMF in the presence of 2 equiv. of *n*-Bu_4NCl and 2 equiv. of Na_2CO_3 at 100 °C for 1 day: ^1H NMR ($CDCl_3$) δ 1.18 (d, J = 6.9 Hz, 3 H, $PyCCH_3$ in **1b**), 1.53 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 1.91 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.41 (s, 3 H, CH_3 in Ts), 2.50 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.70 (d, J = 6.6 Hz, 2 H, =CCH_2N), 4.32 (s, 2 H, NCH_2Ph), 5.12 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.38 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.20 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H, Py), 7.22-7.31 (m, 7 H, aryl), 7.42 (d, J = 7.8 Hz, 1 H, Py), 7.73 (d, J = 8.1 Hz, 2 H, Ts), 8.38 (d, J =

1.5 Hz, 1 H, Py), 8.43 (d, J = 4.5 Hz, 1 H, Py); ^{13}C NMR ($CDCl_3$) δ 21.3, 30.0, 31.2, 32.1, 48.9, 50.1, 123.1, 124.2, 127.0, 127.4, 128.1, 128.3, 129.5, 134.8, 135.6, 136.0, 137.1, 137.2, 143.0, 147.1, 149.6; IR (neat) 3028, 2924, 2859, 1598, 1495, 1339 (SO_2), 1159 (SO_2) cm^{-1}; HRMS for $C_{25}H_{28}N_2O_2S$: calcd 420.1872, found 420.1876.

Preparation of Compounds **2a** and **2b**

Compounds **2a** and **2b** were obtained as an 87:13 mixture of isomers in 68% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2 equiv. of *N*-benzyl tosylamide in DMF in the presence of 2 equiv. of *n*-Bu_4NCl and 2 equiv. of Na_2CO_3 at 100 °C for 1 day: ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **2b**), 1.54 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 1.91 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.39 (s, 3 H, CH_3 in Ts), 2.50 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 3.70 (d, J = 6.9 Hz, 2 H, =CCH_2N), 4.32 (s, 2 H, NCH_2Ph), 5.10 (dt, J = 15.6 Hz, J = 6.6 Hz, 1 H, vinyl), 5.39 (dt, J = 15.6 Hz, J = 6.6 Hz, 1 H, vinyl), 7.10-7.74 (m, 14 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.5, 30.5, 31.5, 35.2, 48.9, 50.0, 123.8, 125.7, 127.1, 127.5, 128.2, 128.3 (two carbon peaks), 128.4, 129.6, 135.6, 136.2, 137.5, 142.1, 143.1; IR (neat) 3027, 2925, 2857, 1600, 1495, 1340 (SO_2), 1159 (SO_2) cm^{-1}; HRMS for $C_{26}H_{29}NO_2S$: calcd 419.1919, found 419.1924.

Preparation of Compounds **3a**, **3b** and **3c**

Compounds **3a**, **3b** and **3c** were obtained as a 73:13:14 mixture of isomers in 41% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2.5 equiv. of benzenesulfonamide in DMSO in the presence of 2

equiv. of *n*-Bu_4NCl and 2 equiv. of Na_2CO_3 at 100 °C for 3 days: ^1H NMR ($CDCl_3$) δ 1.19 (d, *J* = 6.9 Hz, 3 H, CH_3 in **3b**), 1.62 (quintet, *J* = 7.5 Hz, 2 H, $PhCCH_2$), 1.99 (q, *J* = 7.2 Hz, 2 H, CH_2C=), 2.24 (m, 2 H, CH_2C= in **3b**), 2.55 (t, *J* = 7.5 Hz, 2 H, $PhCH_2$), 2.68 (m, 1 H, PhCH in **3b**), 3.76 (d, *J* = 6.6 Hz, 2 H, $=CCH_2N$), 5.22 (dt, *J* = 15.0 Hz, *J* = 6.6 Hz, 1 H, vinyl), 5.53 (dt, *J* = 15.0 Hz, *J* = 6.6 Hz, 1 H, vinyl), 7.11-7.82 (m, 10 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.7, 31.6, 35.3, 48.3, 124.4, 125.7, 126.9, 127.0, 128.2, 128.3, 128.9, 132.2, 135.2, 142.1; IR (neat) 3024, 2927, 2856, 1603, 1495, 1340 (SO_2), 1160 (SO_2) cm^{-1}; HRMS for $C_{18}H_{21}NO_2S$: calcd 315.1293, found 315.1338.

Preparation of Compounds **4a**, **4b** and **4c**

Compounds **4a**, **4b** and **4c** were obtained as a 70:15:15 mixture of isomers in 64% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 2.5 equiv. of potassium phthalimide in DMSO in the presence of 2 equiv. of LiCl at 100 °C for 2 days: ^1H NMR ($CDCl_3$) δ 1.22 (d, *J* = 6.9 Hz, 3 H, $PhCCH_3$ in **4b**), 1.68 (quintet, *J* = 7.5 Hz, 2 H, $PhCCH_2$), 2.05 (q, *J* = 7.2 Hz, 2 H, CH_2C=), 2.58 (t, *J* = 7.8 Hz, 2 H, $PhCH_2$), 2.74 (m, 1 H, PhCH in **4b**), 4.18 (d, *J* = 6.0 Hz, 2 H, $=CCH_2N$ in **4c**), 4.24 (dd, *J* = 6.3 Hz, *J*= 0.9 Hz, 2 H, $=CCH_2N$), 4.30 (dd, *J* = 6.3 Hz, *J*= 0.9 Hz, 2 H, $=CCH_2N$ in **4b**), 5.52 (dtt, *J* = 15.6 Hz, *J* = 6.0 Hz, *J* = 0.9 Hz, 1 H, vinyl), 5.75 (dt, *J* = 15.6 Hz, *J* = 6.6 Hz, 1 H, vinyl), 7.12-7.28 (m, 5 H, Ph), 7.70 (dd, *J* = 5.4 Hz, *J* = 3.0 Hz, 2 H, aryl), 7.84 (ddd, *J* = 5.4 Hz, *J* = 3.3 Hz, *J* = 1.2 Hz, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.5, 31.6, 35.3, 39.5, 123.2, 123.5, 125.6, 128.2, 128.4, 132.2, 133.8, 134.6, 142.2, 167.9; IR (neat) 3025, 2928, 2857, 1772 (C=O), 1715 (C=O), 1604, 1495, 1393 cm^{-1}; HRMS for $C_{20}H_{19}NO_2$: calcd 305.1416, found 305.1411.

Preparation of Compounds **5a**, **5b** and **5c**

Compounds **5a**, **5b** and **5c** were obtained as an 81:9:10 mixture of isomers in 72% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 5 equiv. of di-*t*-butyl iminodicarboxylate in DMSO in the presence of 2 equiv. of *n*-Bu_4NCl and 2 equiv. of Na_2CO_3 at 100 °C for 1 day: ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **5b**), 1.50 (s, 18 H, $OCCH_3$), 1.69 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.05 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.60 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.73 (m, 1 H, PhCH in **5b**), 4.07 (d, J = 5.1 Hz, 2 H, $=CCH_2N$ in **5c**), 4.11 (d, J = 5.7 Hz, 2 H, $=CCH_2N$), 4.20 (d, J = 5.7 Hz, 2 H, $=CCH_2N$ in **5b**), 5.48 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.63 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 7.14-7.29 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.1, 30.8, 31.7, 35.2, 48.0, 82.1, 125.6, 126.8, 128.2, 128.4, 133.1, 142.2, 152.3; IR (neat) 3026, 2979, 2933, 1748 (C=O), 1699 (C=O), 1455, 1227, 1141 cm^{-1}; HRMS for $C_{22}H_{33}NO_4$: calcd 375.2410, found 375.2414.

Preparation of Compounds **6a** and **6b**

Compounds **6a** and **6b** were obtained as an 87:13 mixture of isomers in 44% combined yield from the coupling of 3-iodopyridine, 5 equiv. of 1,13-tetradecadiene and 5 equiv. of di-*t*-butyl iminodicarboxylate in DMSO in the presence of 2 equiv. of *n*-Bu_4NCl and 2 equiv. of Na_2CO_3 at 100 °C for 2 days: ^1H NMR ($CDCl_3$) δ 1.24-1.35 (br m, 16 H, CH_2's plus CH_3 in **6b**), 1.50 (s, 18 H, $OCCH_3$), 1.61 (m, 2 H, $PyCCH_2$), 2.01 (m, 2 H, CH_2C=), 2.60 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 4.09 (d, J = 6.0 Hz, 2 H, $=CCH_2N$), 4.21 (d, J = 6.0 Hz, 2 H, $=CCH_2N$ in **6b**), 5.45 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.58 (dt, J = 15.3

Hz, J = 6.3 Hz, 1 H, vinyl), 7.19 (dd, J = 7.8 Hz, J = 5.1 Hz, 1 H, Py), 7.48 (d, J = 7.8 Hz, 1 H, Py), 8.41-8.44 (m, 2 H, Py); ^{13}C NMR ($CDCl_3$) δ 28.0, 29.1, 29.2, 29.4, 29.5, 29.7, 31.1, 32.2, 33.0, 48.0, 82.0, 123.1, 125.0, 133.7, 135.7, 137.9, 147.0, 149.8, 152.3 (three peaks overlapped); IR (neat) 2979, 2924, 2852, 1746 (C=O), 1700 (C=O), 1350, 1133 cm^{-1}; HRMS for $C_{29}H_{48}N_2O_4$: calcd 488.3614, found 488.3627.

Preparation of Compounds **8a**, **8b**, **8c** and **8d**

Compounds **8a**, **8b**, **8c** and **8d** were obtained as a 46:26:12:16 mixture of isomers in 52% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 1.5 equiv. of sodium azide in DMF at 100 °C for 12 hours: ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **8b**), 1.73 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.12 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.63 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 2.78 (m, 1 H, PhCH in **8b**), 3.64 (d, J = 6.6 Hz, 2 H, $=CCH_2N$ in **8c**), 3.70 (d, J = 6.6 Hz, 2 H, $=CCH_2N$), 3.75-3.85 (m, 3 H, $=CCH_2N$ in **8b** and =CCHN in **8d**), 5.24 (m, 2 H, $=CH_2$ in **8d**), 5.53 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.77 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.16-7.33 (m, 5 H, Ph). See Lu's thesis for other experimental data.[11]

Preparation of Compounds **9a**, **9b**, **9c** and **9d**

Compounds **9a**, **9b**, **9c** and **9d** were obtained as a 56:14:12:18 mixture of isomers in 50% combined yield from the coupling of 3-iodopyridine, 5 equiv. of 1,5-hexadiene and 1.5 equiv. of sodium azide in DMF in the presence of 1 equiv. of LiCl at 100 °C for 12 hours: ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 6.9 Hz, 3 H, $PyCCH_3$ in **9b**), 1.74 (quintet, J = 7.5 Hz, 2 H, $PyCCH_2$), 2.14 (q, J = 7.2 Hz, 2

H, CH_2C=), 2.63 (t, J = 7.5 Hz, 2 H, $PyCH_2$), 3.65 (d, J = 6.6 Hz, 2 H, =CCH_2N in **9c**), 3.71 (d, J = 6.3 Hz, 2 H, =CCH_2N), 3.84 (d, J = 6.3 Hz, 2 H, =CCH_2N in **9b**), 5.26 (m, 2 H, =CH_2 in **9d**), 5.55 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.75 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 7.21 (dd, J = 7.5 Hz, J = 4.8 Hz, 1 H, Py), 7.48 (d, J = 7.5 Hz, 1 H, Py), 8.44 (m, 2 H, Py). See Lu's thesis for other experimental data.[11]

Preparation of Compounds **10a**, **10b**, **10c** and **10d**

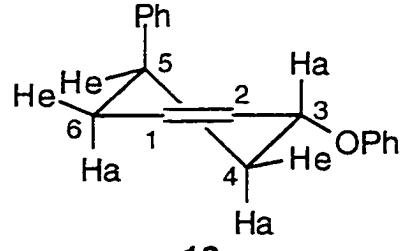
Compounds **10a**, **10b**, **10c** and **10d** were obtained as a 53:14:9:24 mixture of isomers in 36% combined yield from the coupling of iodobenzene, 5 equiv. of 1,5-hexadiene and 3 equiv. of lithium acetate in DMSO in the presence of 1 equiv. of n-Bu_4NCl and 1.5 equiv. of LiCl at 100 °C for 2 days: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **10b**), 1.72 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.06 (s, 3 H, CH_3CO), 2.10 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.62 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.77 (m, 1 H, PhCH in **10b**), 4.46 (d, J = 6.6 Hz, 2 H, =CCH_2O in **10c**), 4.51 (d, J = 6.3 Hz, 2 H, =CCH_2O), 4.59 (d, J = 6.3 Hz, 2 H, =CCH_2O in **10b**), 5.13-5.25 (m, 2 H, =CH_2 in **10d**), 5.58 (dt, J = 15.6 Hz, J = 6.6 Hz, 1 H, vinyl), 5.78 (dt, J = 15.6 Hz, J = 6.6 Hz, 1 H, vinyl), 7.15-7.31 (m, 5 H, Ph). See Lu's thesis for other experimental data.[11]

Preparation of Compounds **11a**, **11b**, **11c** and **11d**

Compounds **11a**, **11b**, **11c** and **11d** were obtained as a 56:16:10:18 mixture of isomers in 71% combined yield from the coupling of iodobenzene, 2.5 equiv. of 1,5-hexadiene and 3 equiv. of phenol in DMSO in the presence of 1.1 equiv. of n-Bu_4NCl and 2.5 equiv. of $NaHCO_3$ at 100 °C for 1 day: ^{1}H NMR

($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **11b**), 1.74 (quintet, J = 7.5 Hz, 2 H, $PhCCH_2$), 2.13 (q, J = 7.2 Hz, 2 H, CH_2C=), 2.62 (t, J = 7.5 Hz, 2 H, $PhCH_2$), 2.78 (m, 1 H, PhCH in **11b**), 4.42 (d, J = 4.5 Hz, 2 H, $=CCH_2O$ in **11c**), 4.47 (d, J = 5.7 Hz, 2 H, $=CCH_2O$), 4.53 (d, J = 4.8 Hz, 2 H, $=CCH_2O$ in **11b**), 4.59 (m, 1 H, =CCHO in **11d**), 5.16-5.26 (m, 2 H, $=CH_2$ in **11d**), 5.72 (dt, J = 14.7 Hz, J = 6.0 Hz, 1 H, vinyl), 5.85 (dt, J = 14.7 Hz, J = 6.0 Hz, 1 H, vinyl), 6.88-7.31 (m, 10 H, Ph). See Lu's thesis for other experimental data.[11]

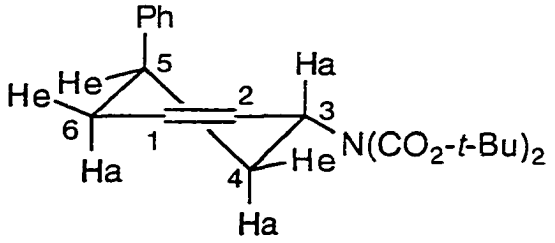
Preparation of Compound **12**



12

Compound **12** was obtained in 84% yield from the coupling of iodobenzene, 2.5 equiv. of 1,4-cyclohexadiene and 3 equiv. of phenol in DMSO in the presence of 1.1 equiv. of n-Bu_4NCl and 2.5 equiv. of $NaHCO_3$ at 100 °C for 1 day: ^1H NMR ($CDCl_3$) δ 1.93 (ddd, J = 13.2 Hz, J = 13.2 Hz, J = 4.2 Hz, 1 H, 4-Ha), 2.15 (dddd, J = 18.0 Hz, J = 11.1 Hz, J = 3.9 Hz, J = 2.1 Hz, 1 H, 6-Ha), 2.29 (d, J = 13.8 Hz, 1 H, 4-He), 2.42 (dt, J = 18.0 Hz, J = 5.1 Hz, 1 H, 6-He), 3.17 (m, 1 H, 5-He), 4.84 (br s, 1 H, 3-Ha), 6.00 (m, 1 H, vinyl), 6.13 (ddd, J = 9.9 Hz, J = 5.1 Hz, J = 1.8 Hz, 1 H, vinyl), 6.88–7.31 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 33.5, 34.7, 34.9, 69.8, 115.9, 120.7, 124.9, 126.2, 126.9, 128.4, 129.5, 132.7, 145.8, 157.6; IR (neat) 3068, 3031, 2915, 1598 (C=C), 1493, 1238 cm^{-1}; HRMS for $C_{18}H_{18}O$: calcd 250.1358, found 250.1357.

Preparation of Compound **13**

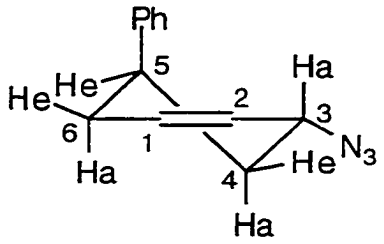


13

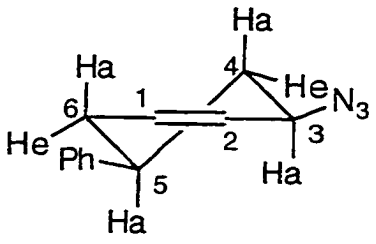
Compound **13** was obtained in 46% yield from the coupling of iodobenzene, 5 equiv. of 1,4-cyclohexadiene and 5 equiv. of di-*t*-butyl iminodicarboxylate in DMSO in the presence of 2 equiv. of *n*-Bu_4NCl and 2 equiv. of Na_2CO_3 at 100 °C for 1 day: ^1H NMR ($CDCl_3$) δ 1.44 (s, 18 H, CH_3) 2.00 (ddd, J = 12.9 Hz, J = 7.8 Hz, J = 6.3 Hz, 1 H, 4-Ha), 2.22 (dddd, J = 18.0 Hz, J = 5.7 Hz, J = 5.7 Hz, J = 3.0 Hz, 1 H, 6-Ha), 2.27 (ddd, J = 12.9 Hz, J = 6.6 Hz, J = 3.9 Hz, 1 H, 4-He), 2.45 (dddd, J = 18.0 Hz, J = 5.7 Hz, J = 5.7 Hz, J = 2.7 Hz, 1 H, 6-He), 3.32 (m, 1 H, 5-He), 4.55 (m, 1 H, 3-Ha), 5.69 (ddd, J = 10.2 Hz, J = 4.5 Hz, J = 2.1 Hz, 1 H, vinyl), 5.95 (ddd, J = 10.2 Hz, J = 6.3 Hz, J = 3.6 Hz, 1 H, vinyl), 7.18–7.31 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.9, 30.3, 34.8, 36.0, 50.8, 82.0, 126.0, 126.9, 127.6, 128.1, 128.2, 145.4, 152.6; IR (neat) 3028, 2980, 2932, 1744 (C=O), 1705 (C=O), 1603, 1454, 1340, 1237, 1148 cm^{-1}; HRMS for $C_{18}H_{23}O_4N$ ($M^+ - t$-Bu + H): calcd 317.1627, found 317.1626.

Preparation of Compounds **14a** and **14b**

Compounds **14a** and **14b** were obtained as an 82:18 mixture of isomers in 66% combined yield from the coupling of iodobenzene, 5 equiv. of 1,4-cyclohexadiene and 1.5 equiv. of sodium azide in DMF at 100 °C for 12 hours:



14a



14b

^{1}H NMR ($CDCl_3$) δ 1.83 (ddd, *J* = 12.6 Hz, *J* = 12.6 Hz, *J* = 10.5 Hz, 1 H, 4-Ha in **14b**), 1.96 (ddd, *J* = 13.5 Hz, *J* = 12.3 Hz, *J* = 4.5 Hz, 1 H, 4-Ha), 2.08 (ddd, *J* = 13.5 Hz, *J* = 2.1 Hz, *J* = 2.1 Hz, 1 H, 4-He), 2.18 (dddd, *J* = 18.3 Hz, *J* = 10.8 Hz, *J* = 4.5 Hz, *J* = 2.4 Hz, 1 H, 6-Ha), 2.28 (m, 1 H, 6-He in **14b**), 2.39 (dt, *J* = 18.3 Hz, *J* = 5.1 Hz, 1 H, 6-He), 2.89 (dddd, *J* = 12.6 Hz, *J* = 11.1 Hz, *J* = 5.4 Hz, *J* = 2.4 Hz, 1 H, 5-Ha in **14b**), 3.00 (m, 1 H, 5-He), 4.02 (br s, 1 H, 3-Ha), 4.10 (m, 1 H, 3-Ha in **14b**), 5.71 (m, 1 H, vinyl in **14b**), 5.84 (m, 1 H, vinyl), 5.97 (ddt, *J* = 10.2 Hz, *J* = 5.1 Hz, *J* = 2.4 Hz, 1 H, vinyl in **14b**), 6.14 (ddd, *J* = 9.9 Hz, *J* = 5.1 Hz, *J* = 2.1 Hz, 1 H, vinyl), 7.19–7.33 (m, 5 H, Ph) [4-He and 6-Ha peaks in **14b** overlapped]; ^{13}C NMR ($CDCl_3$) δ 33.0, 35.1, 35.6, 55.5, 123.3, 126.4, 126.9, 128.5, 133.0, 145.2 (small peaks corresponding to **14b**: δ 33.3, 35.3, 39.3, 58.5, 126.0, 126.5, 126.6, 128.6, 130.8, 144.9); IR (neat) 3031, 2917, 2097 (N_3), 1604 (C=C), 1453, 1230 cm^{-1}; M^+ was not found by HRMS, but the CI mass spectromerty proved the molecular weight (M + NH_3 + H: 217.1).

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SYNTHESIS OF C–5 SUBSTITUTED 2'–DEOXYURIDINES VIA PALLADIUM–CATALYZED COUPLING

A paper to be submitted to the *Journal of Organic Chemistry*

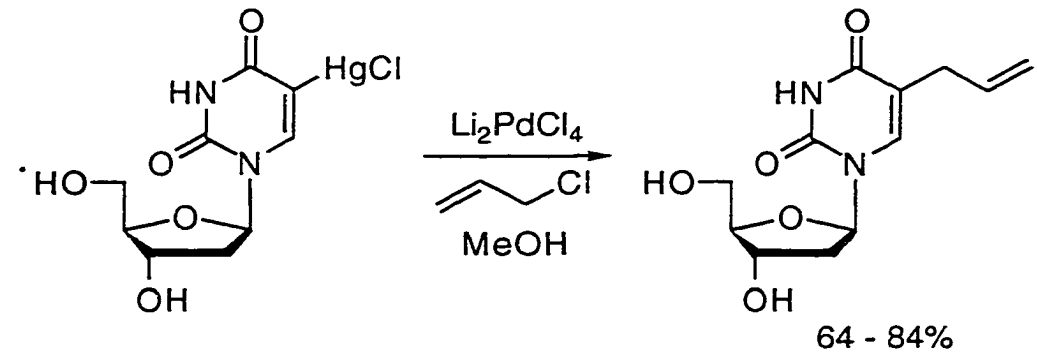
Richard C. Larock and Yao Wang

Introduction

Oligodeoxynucleotides have generated great interest in both antigene and antisense strategies.[1] Nucleosides modified at C-5 of the pyrimidine base have become important components of synthetic oligonucleotide probes. Modification of uridine C-5 in the transfer RNA (tRNA) anticodon wobble position occurs frequently.[2] DNA base hypermodification is much less prevalent, but the complexity of the C-5 substituents in some bacteriophages is noteworthy.[3]

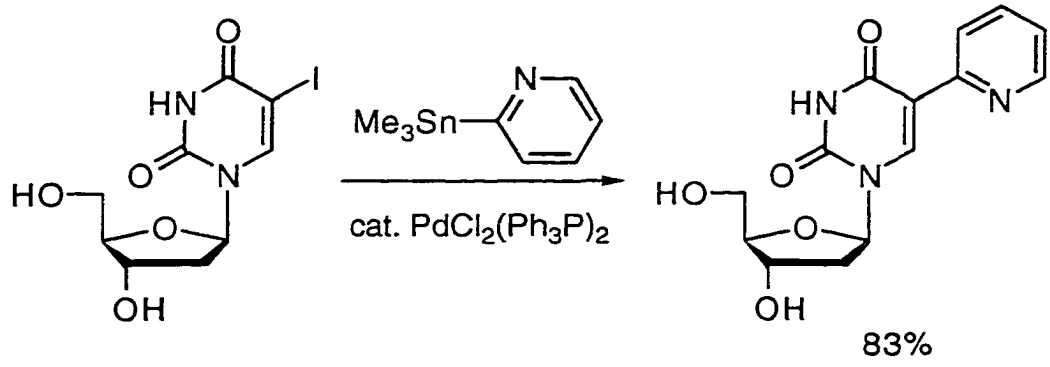
Over the past two decades numerous research papers on C-5 substituted pyrimidine nucleosides have been published.[4] Most procedures for modification of the nucleosides at C-5 have involved palladium-catalyzed coupling reactions. In the early studies, mercuriopyrimidine nucleosides were often used as starting materials.[5] For example, 5-allyl-2'-deoxyuridine was prepared by the palladium-mediated reaction of allyl chloride and 5-chloromercurio-2'-deoxyuridine (eq. 1).[5a]

To avoid the use of toxic organomercurial reagents, procedures have been developed involving palladium-catalyzed coupling of commercially available 5-



(1)

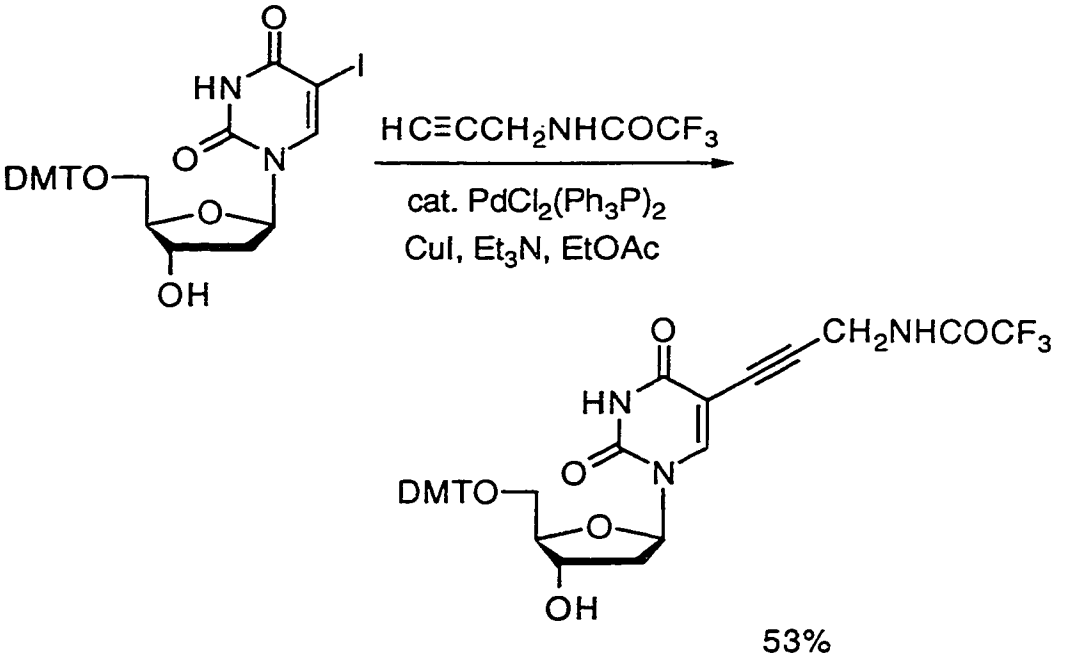
iodo-2'-deoxyuridine or 5-iodouridine.[4,6] Froehler and co-workers have recently reported the syntheses of a series of C-5 heteroaryl-2'-deoxyuridines by the palladium-catalyzed coupling of 5-iodo-2'-deoxyuridine with heteroaryl-stannanes (eq. 2).[7] Oligonucleotides containing heteroaryl (like pyridine) substituted 2'-deoxyuridine analogs have given enhanced thermal stability to complementary RNA relative to thymidine.



(2)

One of the interesting areas of oligonucleotide modifications is to devise C-5 amine "linker arm" analogs of 2'-deoxyuridine. The aliphatic amine groups have been used to covalently attach a variety of ligands, such as DNA affinity cleaving reagents,[8] enzymes,[9] paramagnetic spin probes[10] or affinity binding molecules such as biotin,[11] to the oligonucleotides.

Cruickshank and Stockwell[12] have reported an efficient method of preparing modified nucleosides valuable in oligonucleotide labelling studies. They used the palladium-catalyzed coupling of 5'-dimethoxytrityl-5-iodo-2'-deoxyuridine with a terminal alkyne bearing a potential amino group at the other end to provide a modified nucleoside (eq. 3).



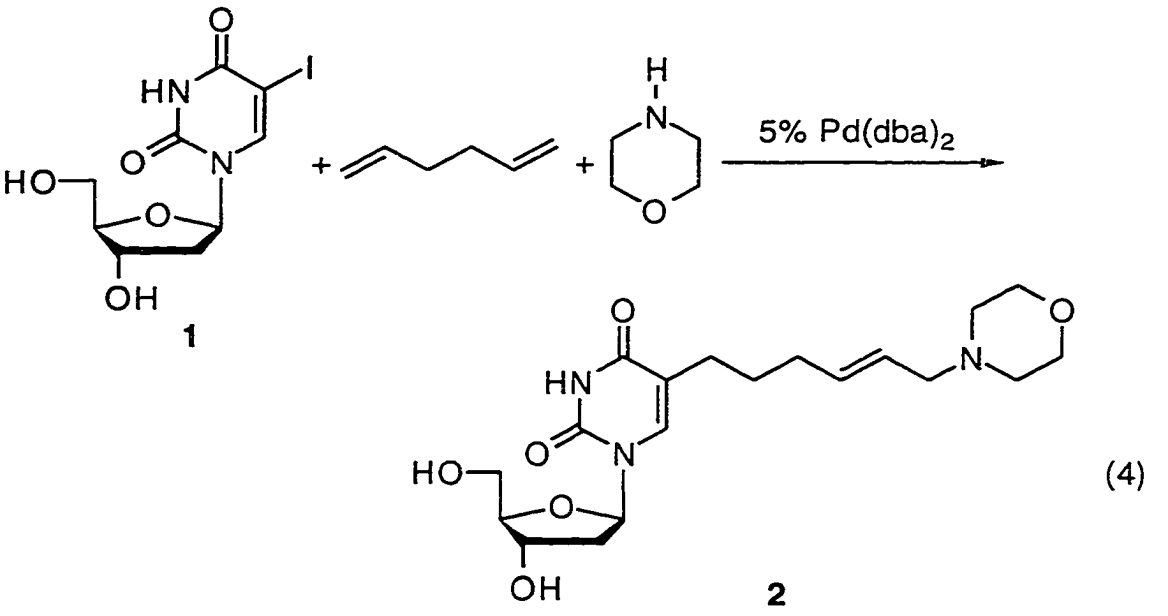
(3)

We have successfully developed the palladium-catalyzed three component coupling of aryl iodides, nonconjugated dienes and nucleophiles, especially amine nucleophiles.[13] In this paper, we present our efforts on the synthesis of C-5 substituted 2'-deoxyuridines using our palladium-catalyzed methodology. One of the biggest advantages of our methodology is that the length of the carbon chain and the functional groups introduced should be easily changed according to the requirements. This is particularly noteworthy for the modification of the nucleosides, since it has been found that increasing the

length of the side chain at C-5, while retaining substituents, such as halogen, increased the antiviral activity, but at the same time substantially decreased toxicity.[14]

Results and Discussion

Based on the success of the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and amines (Paper II in this thesis), the reaction of 5-iodo-2'-deoxyuridine (**1**), 1,5-hexadiene and morpholine was chosen as a model system in which to optimize yields (eq. 4). First, the reaction was run under



(4)

the best conditions for secondary amines described in Paper II. Unfortunately, no desired product was obtained (Table 1, entry 1). Then we increased the amount of morpholine to 5 equivalents, extended the reaction time to 2 days

and used LiCl instead of *n*-Bu_4NCl, but still no coupling product was formed.

Table 1. Palladium-catalyzed Coupling of 5-Iodo-2'-deoxyuridine, 1,5-Hexadiene and Morpholine (Eq. 4)[a]

entry	solvent	chloride source (equiv.)	temp. (°C)	time (d)	% isolated yield
1[b]	DMF	*n*-Bu_4NCl (2)	100	1	0
2	DMF	LiCl (2)	100	2	0
3	CH_3CN	LiCl (2)	80	2	0
4	MeOH	*n*-Bu_4NCl (2)	80	2	25
5	MeOH	LiCl (2)	80	2	> 18
6	DMSO	LiCl (2)	80	2	41
7	DMSO	LiCl (2)	100	2	38
8	DMSO	LiCl (2)	60	2	28
9	DMSO	LiCl (3)	80	2	28
10	DMSO	*n*-Bu_4NCl (2)	80	2	30
11	DMSO	*n*-Bu_4NCl (3)	80	2	43 (35)[c]
12[d]	DMSO	*n*-Bu_4NCl (3)	80	2	21
13	DMSO	*n*-Bu_4NCl (3)	80	4	30
14	MeOH + CH_2Cl_2 (1 : 1)	*n*-Bu_4NCl (2)	80	4	29
15	$HOCH_2CH_2OH$	*n*-Bu_4NCl (2)	80	2	4
16	dioxane	*n*-Bu_4NCl (2)	100	1	0
17	DMSO + H_2O (4 : 1)	*n*-Bu_4NCl (2)	100	1	30
18	DMSO + H_2O (1 : 4)	*n*-Bu_4NCl (2)	100	1	trace
19	CH_3CN + H_2O (4 : 1)	*n*-Bu_4NCl (2)	100	1	21

Table 1. (continued)

entry	solvent	chloride source (equiv.)	temp. (°C)	time (d)	% isolated yield
20	$CH_3CN + H_2O$ (1 : 4)	*n*-Bu_4NCl (2)	100	1	0
21	H_2O	*n*-Bu_4NCl (2)	100	1	0

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ using 5 equiv. of 1,5-hexadiene and 5 equiv. of morpholine.

[b] 2 Equiv. of morpholine used.

[c] Same reaction ran twice and gave different yields of the product.

[d] 2 Equiv. of Na_2CO_3 added.

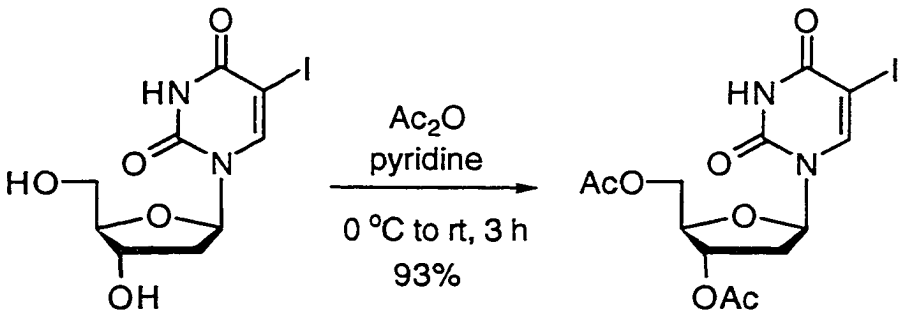
Other solvents were next tested. At the same time, the temperature was lowered to 80 °C since the starting material 5-iodo-2'-deoxyuridine (**1**) might not be very stable at higher temperatures (it decomposed during GC analysis). When MeOH or DMSO was used as the solvent, the desired coupling product **2** was formed (entries 4–13). That might be due to the higher solubility of **1** in MeOH or DMSO than in DMF or CH_3CN. The reaction was examined at different temperatures (compare entries 6–8), and it appeared that the reaction when run at 80 °C gave the highest yield of the product. To further improve the yield, the amount of the chloride source was increased to 3 equivalents (entries 9, 11–13). However, no significant change in yields was observed, although 3 equivalents of *n*-Bu_4NCl appeared to give the highest yield (43%), but this result was not very reproducible. Only a 35% yield of the product was obtained when the reaction was rerun under the same conditions

(entry 11). The addition of an inorganic base Na_2CO_3 gave a lower yield (entry 12).

Interestingly, there is only one isomer **2** present in the product while two isomers have normally been observed in the product in our previous studies of this amine coupling system. The possible reason for this is that the functional groups at *ortho* and *meta* positions make the iodide **1** more sterically hindered and therefore produce a very high regioselectivity.

Since the solubility of **1** in the reaction system appeared to be a critical factor, several other solvents were examined (entries 14–21), especially aqueous media. Unfortunately, none of them gave satisfactory results. Water failed to give the desired product, although it is a good solvent for compound **1**.

Because of its polarity, compound **1** only dissolves easily in a few very polar solvents, such as DMSO, MeOH and water. To solve this solubility problem, the hydroxyl groups in compound **1** were converted into acetoxy groups as shown in equation 5.[15] The obtained acetyl 5-iodo-2'-deoxyuridine (**3**)



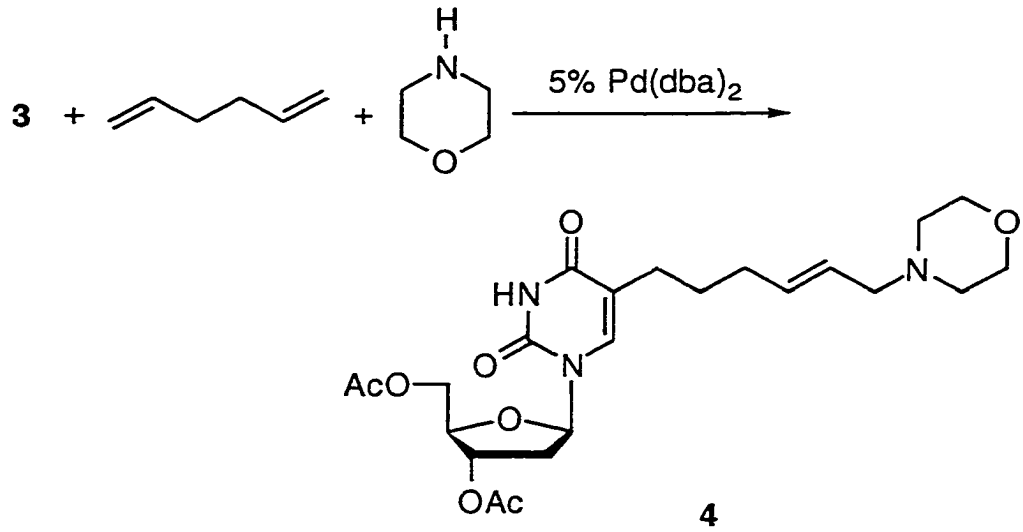
1 **3** (5)

was then employed in the coupling with 1,5-hexadiene and morpholine (eq. 6). The results shown in Table 2 were unexpected. No more than a 40% yield of the coupling product **4** could be obtained under a variety of reaction conditions. Among all the solvents tested, DMSO appeared to be the best for this coupling

Table 2. Palladium-catalyzed Coupling of Acetyl 5-Iodo-2'-Deoxyuridine (3), 1,5-Hexadiene and Morpholine[a]

entry	solvent	chloride source	temp. (°C)	time (d)	% isolated yield
1	DMF	*n*-Bu_4NCl	80	2	25
2	DMF	LiCl	80	2	15
3	DMF	LiCl	100	2	29
4	DMSO	*n*-Bu_4NCl	80	2	40
5	DMSO	*n*-Bu_4NCl	100	1	40
6	DMSO	LiCl	80	2	26
7	DMSO	LiCl	100	2	35
8	MeOH	LiCl	100	2	messy
9	dioxane	*n*-Bu_4NCl	100	1	0
10	DMSO + H_2O (4 : 1)	*n*-Bu_4NCl	100	1	25
11	DMSO + H_2O (1 : 4)	*n*-Bu_4NCl	100	1	0
12	CH_3CN + H_2O (4 : 1)	*n*-Bu_4NCl	100	1	38
13	CH_3CN + H_2O (1 : 4)	*n*-Bu_4NCl	100	1	0

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ and 2 equiv. of chloride salt using 5 equiv. of 1,5-hexadiene and 5 equiv. of morpholine.



(6)

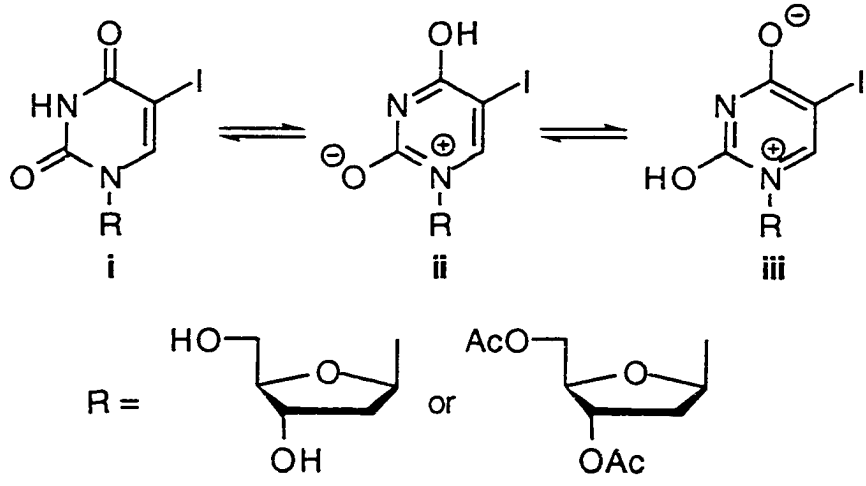
process. Surprisingly, MeOH, a relatively good solvent for the coupling of 5-iodo-2'-deoxyuridine, produced a messy mixture in this case (entry 8). Aqueous solutions were also tested, but water appeared to make the reaction worse (entries 10–13). The reactions run at 100 °C gave somewhat higher yields than those run at 80 °C in most cases. As a chloride source, *n*-Bu_4NCl was better than LiCl for this coupling reaction.

So far, the coupling reactions involving 5-iodo-2'-deoxyuridine or acetyl 5-iodo-2'-deoxyuridine had not provided satisfactory results (no more than a 43% yield of the product was obtained). However, our previous work on the coupling of aryl iodides, nonconjugated dienes and amines was very successful. The reactions of aryl iodides with 1,5-hexadiene and morpholine often gave excellent yields (up to 92%) of the coupling products. Apparently, C-5 iodopyrimidine nucleosides are different from normal aryl iodides, although they may be considered as aromatic iodides (Scheme 1).

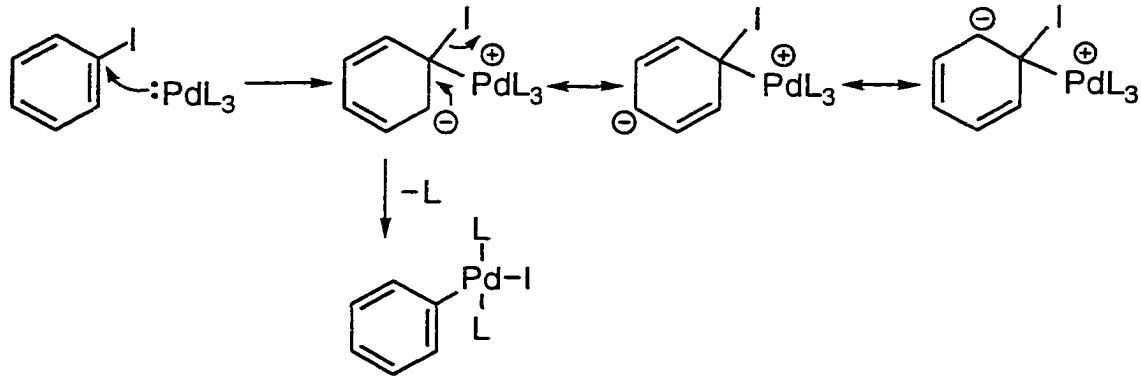
We believe that the first step of the coupling process, oxidative addition of palladium(0) to the aryl iodide, is the key step. As shown in Scheme 2, the

oxidative addition involves the nucleophilic attack of Pd(0) at the carbon bonded to iodine. Obviously, positive charge (or less electron density) on this carbon would favor the reaction. In the case of the pyrimidine nucleosides, the predominant species **i** has an enone structure which disfavors palladium

Scheme 1

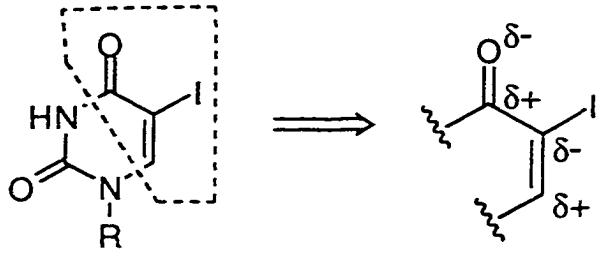


Scheme 2



nucleophilic attack on C-5, because of the partial negative charge (Scheme 3). The aromatic structures **ii** and **iii** are relatively favorable for nucleophilic attack. Apparently, stabilizing **ii** and **iii** (or in other words reducing the electron density on C-5) is the way to solve the problem. We decided to use a

Scheme 3



i **iv**

Lewis acid to stabilize **ii** and **iii**. After testing several common Lewis acids, we found that the use of zinc chloride ($ZnCl_2$) significantly improved the reaction described in equation 4. Some results are summarized in Table 3. Acetonitrile was chosen as the solvent in order to avoid possible strong coordination between $ZnCl_2$ and the solvent (such as DMSO). The coupling reaction run without Lewis acids provided only a 30% yield of the desired product (entry 1), while the reaction run in the presence of 1 equivalent of $ZnCl_2$ gave a 61% yield (entry 2). To confirm this contribution is due to Zn^{2+}, not Cl^-, we used 2 equivalents of LiCl, instead of 1 equivalent of $ZnCl_2$, in the reaction (entry 3), and we also ran a reaction with 4 equivalents of LiCl (entry 4). The fact is that LiCl failed to give the desired product, which is consistant with the result described in entry 3 of Table 1. Therefore, Zn^{2+} does play a role in the improvement of the reaction. An aqueous solution of acetonitrile (4 CH_3CN + 1 H_2O) was also tested for this reaction and the yield was reduced (entry 5).

Table 3. Palladium-catalyzed Coupling of 5-Iodo-2'-deoxyuridine, 1,5-Hexadiene and Morpholine[a]

entry	$ZnCl_2$ (equiv.)	chloride source (equiv.)	solvent	% isolated yield
1	0	*n*-Bu_4NCl (2)	CH_3CN	30
2	1	*n*-Bu_4NCl (2)	CH_3CN	61
3	0	*n*-Bu_4NCl (2) + LiCl (2)	CH_3CN	trace
4	0	LiCl (4)	CH_3CN	0
5	1	*n*-Bu_4NCl (2)	$CH_3CN + H_2O$ (4 : 1)	38
6	1	*n*-Bu_4NCl (2)	DMSO	55

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ using 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine at 100 °C for 1 day.

It was thought that DMSO might not be a proper solvent in this case since it might strongly coordinate with $ZnCl_2$. Surprisingly, the reaction run in DMSO gave a fair yield of the product (entry 6).

Since $ZnCl_2$ might tie up the base morpholine, it was of interest to examine the stoichiometry of this reaction. The results shown in Table 4 indicate that more $ZnCl_2$ is not better for the reaction. Increasing the amount of $ZnCl_2$, while keeping the amount of morpholine constant, reduced the yield of the product dramatically (entries 1–4). Interestingly, the best results were obtained when the amount of morpholine used in the reaction was 1 equivalent more than that of $ZnCl_2$ (entries 1, 6, 8 and 9).

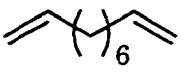
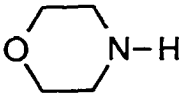
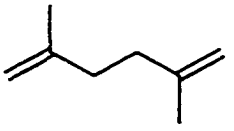
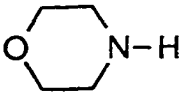
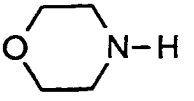
Table 4. Effects of the Amounts of Morpholine and $ZnCl_2$ on the Coupling Reaction (Eq. 4)[a]

entry	morpholine (equiv.)	$ZnCl_2$ (equiv.)	% isolated yield
1	1.5	0.5	52
2	1.5	1.0	42
3	1.5	2.0	trace
4	1.5	4.0	0
5	2.0	0.5	45
6	2.0	1.0	61
7	2.0	2.0	< 5
8	3.0	2.0	60
9	4.0	3.0	54
10	5.0	4.0	15

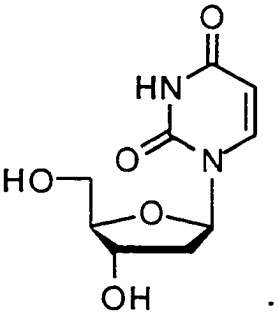
[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$, 2 equiv. of *n*-Bu_4NCl and 5 equiv. of 1,5-hexadiene in CH_3CN at 100 °C for 1 day.

The best reaction conditions described in entry 6 in Table 4 were then applied to several other nonconjugated dienes and amine nucleophiles. The results are summarized in equation 7 and Table 5. When coupled with 5-iodo-2'-deoxyuridine and 1,5-hexadiene, benzylmethylamine provided a 62% yield of the desired product (entry 1). This is as good as the reaction of morpholine. Di-*n*-propylamine, however, gave a somewhat lower yield (entry 2). The primary

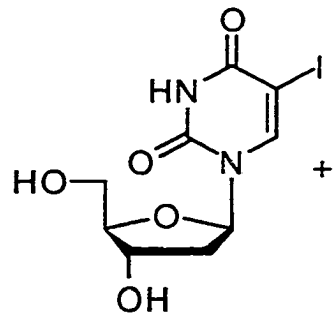
Table 5. Palladium-catalyzed Coupling of 5-Iodo-2'-deoxyuridine, Nonconjugated Dienes and Amines (Eq. 7)

entry	diene	amine	product, % yield
1		CH_3NHCH_2Ph	**5**, 62[a]
2		*n*-Pr_2NH	**6**, 42
3		*t*-$BuNH_2$	**7**, 0
4			**8**, 31
5			**9**, 8[b]
6			**10**, 30[c]

[a] Accompanied by benzylmethylamine (40% recovered).

[b] Accompanied by a 43% yield of side product **11** with the structure  .

[c] Side product **11** was isolated in 40% yield.



+ 5 diene + 2 amine $\xrightarrow[\text{1 equiv. } ZnCl_2]{\text{5\% } Pd(dba)_2}$ product (7)

$\xrightarrow[\text{2 equiv. } n\text{-}Bu_4NCl]{}$

$\xrightarrow[CH_3CN]{}$

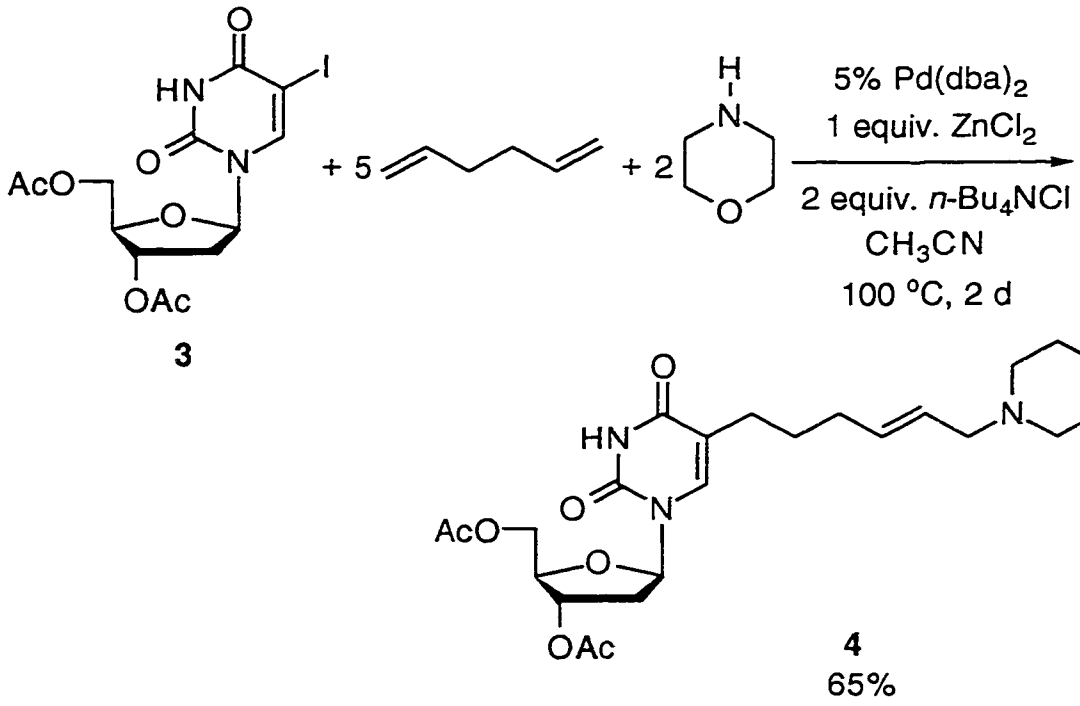
$\xrightarrow[100\ ^\circ C,\ 2\ d]{}$

amine *t*-butylamine was also examined in this coupling reaction, but no desired product was obtained (entry 3).

Different dienes yielded quite different results in this coupling system. Compared with 1,5-hexadiene, the longer chain diene 1,9-decadiene gave a much lower yield of the desired product (entry 4). Surprisingly, only a very small amount of the coupling product was obtained from the branched diene 2,5-dimethyl-1,5-hexadiene (entry 5), and the product was contaminated with a 43% yield of a side product **11**.[16] Compound **11** was also obtained in 40% yield when the cyclic diene 1,4-cyclohexadiene was employed in this coupling. The desired product was isolated in 30% yield (entry 6).

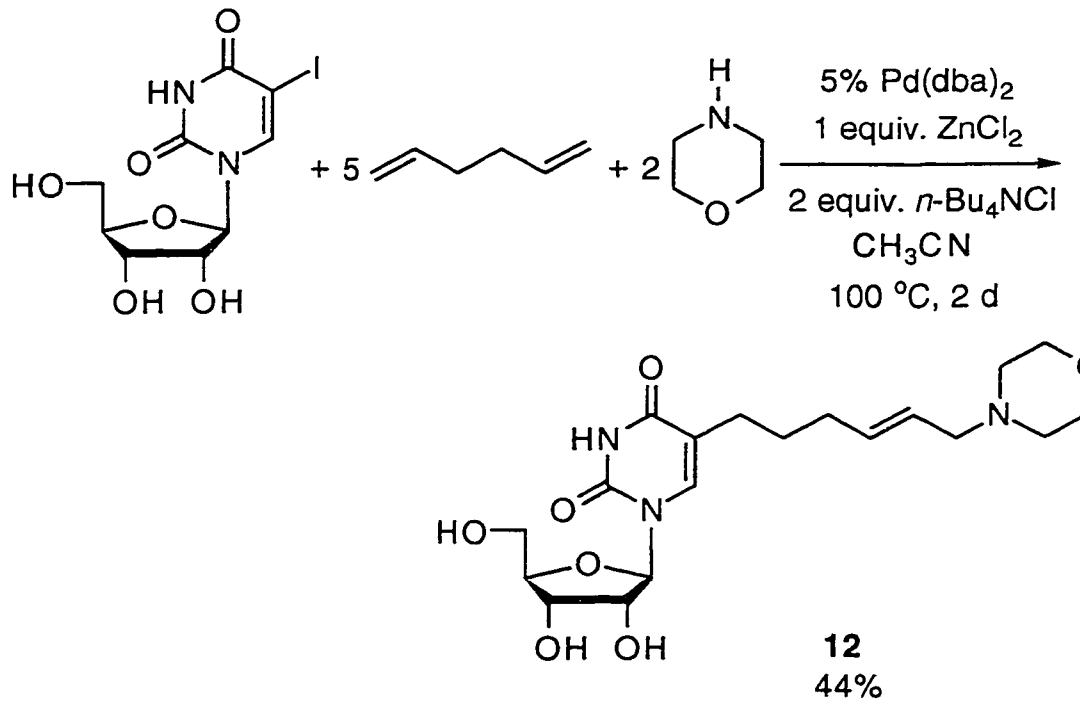
Besides 5-iodo-2'-deoxyuridine, two other nucleosides, acetyl 5-iodo-2'-deoxyuridine **3** (eq. 8) and 5-iodouridine (eq. 9), were also examined in the model reaction in the presence of $ZnCl_2$. As shown in equations 8 and 9, a 65% yield of the desired product **4** was obtained from acetyl 5-iodo-2'-deoxyuridine **3**. However, 5-iodouridine produced a somewhat lower yield, and the product **12** was contaminated with morpholine, which was recovered in 46% yield.

Finally, a wide variety of Lewis acids were examined in the coupling of 5-iodo-2'-deoxyuridine, 1,5-hexadiene and morpholine. The results are summarized in Table 6 (on page 184). Among all of the Lewis acids examined,


5% Pd(dba)2
1 equiv. ZnCl2
2 equiv. n-Bu4NCl
CH3CN
100 °C, 2 d

3 **4**
65%

(8)


5% Pd(dba)2
1 equiv. ZnCl2
2 equiv. n-Bu4NCl
CH3CN
100 °C, 2 d

12
44%

(9)

Table 6. Effects of Different Lewis Acids on the Coupling Reaction (Eq. 4)[a]

entry	Lewis acid	% isolated yield
1	$ZnCl_2$	61
2	$Zn(OAc)_2 \cdot 2H_2O$	68
3	ZnO	64
4	$CdCl_2$	63
5	$BaCl_2 \cdot 2H_2O$	60
6	$CoCl_2 \cdot 6H_2O$	46
7	CuCl	37
8	$FeCl_3 \cdot 6H_2O$	35
9	$NiCl_2$	26
10	$CuCl_2 \cdot 2H_2O$	trace
11	$CrCl_2$	0
12	$MgCl_2$	0
13	$HgCl_2$	0
14	$SnCl_2 \cdot 2H_2O$	0
15	$SnCl_4 \cdot 5H_2O$	0
16	$AlCl_3$	0
17	$BF_3 \cdot Et_2O$	0

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$, 2 equiv. of *n*-Bu_4NCl and 1 equiv. of Lewis acid using 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine in CH_3CN at 100 °C for 2 days.

Zn^{2+}, Cd^{2+} and Ba^{2+} are the best providing yields comparable to $ZnCl_2$. A couple of moisture-sensitive and hydrolyzable Lewis acids, such as $AlCl_3$ and BF_3-Et_2O, failed to give any products, because the reaction system was not kept anhydrous.

The work described above is just an exploratory investigation. This type of palladium-catalyzed coupling in the presence of a Lewis acid has never been reported. We believe that this coupling process could be applied to other types of nucleophiles, and it might be worth further establishing the generality of this process for the iodides having a basic enone structure like **iv** (Scheme 3).

Conclusion

We have successfully applied our palladium-catalyzed coupling process to the preparation of C-5 substituted pyrimidine nucleosides. Although commercially available 5-iodo-2'-deoxyuridine is different from normal aromatic iodides and produces only a very low yield of the desired product when coupled with 1,5-hexadiene and morpholine under our earlier, general coupling conditions, we have found that adding certain Lewis acids, particularly $ZnCl_2$, $Zn(OAc)_2$, ZnO, $CdCl_2$ and $BaCl_2$, can improve this type of coupling significantly. The stoichiometry of the Lewis acid and amine has been investigated. Interestingly, the best result is achieved when one more equivalent of amine than Lewis acid is employed.

The palladium-catalyzed coupling of C-5 iodopyrimidine nucleosides with nonconjugated dienes and amine nucleophiles in the presence of a Lewis acid, such as $ZnCl_2$, has been proven a novel and efficient method for the

preparation of a wide variety of C-5 substituted nucleosides which may exhibit potent antiviral activities and/or be valuable "linker arms" in oligonucleotide labeling studies.

Experimental Section

Equipment. All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Digilab FTS-7 spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed on an HP 5890 chromatograph equipped with an HP-1 Megabore column. Flash chromatography was carried out on 230-400 mesh silica gel. Thin-layer chromatography was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F). 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. Bis(dibenzylideneacetone)palladium was donated by Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride was purchased from Lancaster Synthesis Inc. (+)-5-Iodo-2'-deoxyuridine, 5-iodouridine, 1,5-hexadiene, 1,4-cyclohexadiene, 1,9-decadiene, di-*n*-propylamine, *t*-butylamine, $BF_3{\cdot}Et_2O$ and $CrCl_2$ were purchased from Aldrich Chemical Company, Inc. Morpholine, dimethyl sulfoxide, *N*,*N*-dimethylformamide, acetonitrile, methanol, acetic anhydride, LiCl, $ZnCl_2$, $CoCl_2{\cdot}6H_2O$, $HgCl_2$ and

$AlCl_3$ were purchased from Fisher Scientific Company. $Zn(OAc)_2 \cdot 2H_2O$, $BaCl_2 \cdot 2H_2O$, CuCl, $CdCl_2$, $MgCl_2$, $FeCl_3 \cdot 6H_2O$ and $SnCl_2 \cdot 2H_2O$ were purchased from J. T. Baker Chemical Co. ZnO, $CuCl_2 \cdot 2H_2O$ and $SnCl_4 \cdot 5H_2O$ were purchased from Mallinckrodt Chemical Works. $NiCl_2$ was purchased from Research Organic/Inorganic Chemical Corp. Benzylmethylamine was purchased from Eastman Kodak Co.

Preparation of Acetyl 5-Iodo-2'-Deoxyuridine (3)[15]

To the solution of 5-iodo-2'-deoxyuridine (3.0 g, 8.5 mmol) in 30 ml of pyridine was slowly added 8.0 ml (85 mmol) of acetic anhydride at 0 °C. The resulting mixture was stirred at room temperature for 3 hours, then poured into 200 ml of cold 2 N HCl and extracted with ethyl acetate three times. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl solutions respectively, then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the product was obtained as white solid in 93% yield: mp 161–162 °C (lit. mp 160.5–162 °C,[17] 158–160 °C[18]); ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H, CH_3), 2.18 (m, 1 H, H-2'), 2.21 (s, 3 H, CH_3), 2.55 (ddd, J = 14.1 Hz, J = 5.7 Hz, J = 2.1 Hz, 1 H, H-2'), 4.30 (m, 1 H, H-4'), 4.33 (dd, J = 12.0 Hz, J = 2.7 Hz, 1 H, H-5'), 4.42 (dd, J = 12.0 Hz, J = 3.0 Hz, 1 H, H-5'), 5.23 (dt, J = 6.6 Hz, J = 1.8 Hz, 1 H, H-3'), 6.30 (dd, J = 8.1 Hz, J = 5.7 Hz, 1 H, H-1'), 7.97 (s, 1 H, H-6), 8.86 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.1, 38.3, 63.8, 68.9, 74.1, 82.6, 85.4, 143.7, 149.8, 159.6, 170.1, 170.3.

General procedure for the palladium-catalyzed coupling of C-5 iodopyrimidine nucleosides, nonconjugated dienes and amines.

To a 1 dram vial with a micromagnetic stirring bar were added 0.125 or 0.25 mmol of C-5 iodopyrimidine nucleoside, 0.625 or 1.25 mmol of nonconjugated diene, 0.25 or 0.50 mmol of amine, 5 mol % of bis(dibenzylidene-acetone)palladium, 0.25 or 0.50 mmol of tetra-*n*-butylammonium chloride, 0.125 or 0.25 mmol of zinc chloride and 0.5 or 1 ml of CH_3CN respectively. The vial was capped with a screw-cap containing a Teflon liner. The resulting mixture was stirred at 100 °C for 1 to 2 days. The mixture was then allowed to cool down to room temperature. After removal of solvent, the residue was purified by flash chromatography on a silica gel column.

Preparation of Compound **2**

Compound **2** was obtained in 61% yield from the coupling of (+)-5-iodo-2'-deoxyuridine, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using the procedure above; ^{1}H NMR (CD_3SOCD_3) δ 1.47 (quintet, J = 7.5 Hz, 2 H, CH_2CC=), 1.97 (q, J = 6.9 Hz, 2 H, CH_2C=), 2.07 (m, 2 H, H-2'), 2.16 (t, J = 7.5 Hz, 2 H, CH_2CCC=), 2.29 (br s, 4 H, ring NCH_2), 2.84 (d, J = 6.0 Hz, 2 H, =CCH_2N), 3.37 (m, 1 H, OH), 3.51–3.57 (m, 7 H, H-5', OH and ring OCH_2), 3.75 (dd, J = 6.0 Hz, J = 3.0 Hz, 1 H, H-3'), 4.23 (m, 1 H, H-4'), 5.23 (m, 1 H, NH), 5.39 (dt, J = 15.6 Hz, J = 6.3 Hz, 1 H, vinyl), 5.54 (dt, J = 15.6 Hz, J = 6.3 Hz, 1 H, vinyl), 6.15 (t, J = 6.6 Hz, 1 H, H-1'), 7.68 (s, 1 H, H-6); ^{13}C NMR (CD_3SOCD_3) δ 25.9, 27.3, 31.3, 42.9, 52.2, 61.2, 63.4, 65.3, 70.4, 83.9, 87.3, 113.3, 124.2, 135.8, 136.3, 150.3, 163.3; IR (neat) 3402 (OH), 3196 (NH),

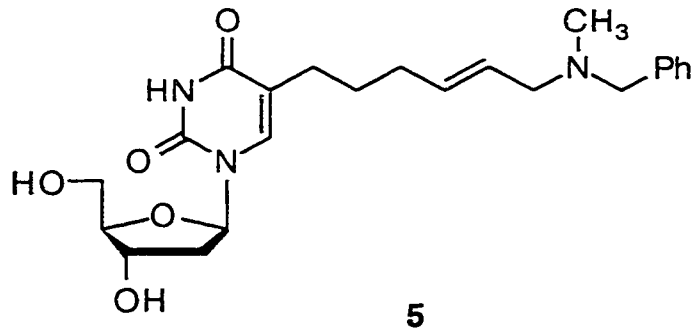
2934, 2860, 1704 (C=O), 1669 (C=O), 1462, 1278, 1110 cm^{-1}; HRMS for $C_{19}H_{29}N_3O_6$: calcd 395.2056, found 395.2051.

Preparation of Compound 4

Compound **4** was obtained in 65% yield from the coupling of acetyl 5-iodo-2'-deoxyuridine **3**, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using the procedure above; ^1H NMR ($CDCl_3$) δ 1.59 (quintet, J = 7.5 Hz, 2 H, CH_2CC=), 2.08 (m, 2 H, CH_2C=), 2.11 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO), 2.16 (m, 1 H, H-2'), 2.31 (m, 2 H, CH_2CCC=), 2.45 (t, J = 4.5 Hz, 4 H, ring NCH_2), 2.50 (m, 1 H, H-2'), 2.94 (d, J = 6.0 Hz, 2 H, $=CCH_2N$), 3.72 (t, J = 4.5 Hz, 4 H, ring OCH_2), 4.25 (m, 1 H, H-3'), 4.33 (dd, J = 12.3 Hz, J = 3.3 Hz, 1 H, AcOC<u>H</u>H), 4.39 (dd, J = 12.3 Hz, J = 4.5 Hz, 1 H, AcOCH<u>H</u>), 5.21 (dt, J = 6.6 Hz, J = 1.8 Hz, 1 H, H-4'), 5.49 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 5.60 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H, vinyl), 6.31 (dd, J = 8.7 Hz, J = 5.7 Hz, 1 H, H-1'), 7.22 (s, 1 H, H-6), the peak for NH was not observed; ^{13}C NMR ($CDCl_3$) δ 20.8 (two carbon peaks), 26.8, 31.9, 37.4, 40.8, 53.3, 61.0, 63.8, 66.8, 74.1, 82.0, 84.8, 115.5, 126.3, 133.9, 134.3, 150.2, 163.2, 170.0, 170.3; IR (neat) 3181 (NH), 2958, 2933, 2857, 1745 (C=O), 1709 (C=O), 1685 (C=O), 1458, 1236, 1116 cm^{-1}; HRMS for $C_{23}H_{33}N_3O_8$: calcd 479.2268, found 479.2275.

Preparation of Compound **5**

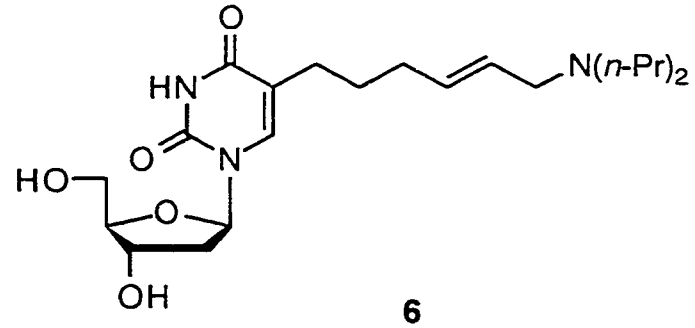
Compound **5** was obtained in 62% yield from the coupling of (+)-5-iodo-2'-deoxyuridine, 5 equiv. of 1,5-hexadiene and 2 equiv. of benzylmethylamine using the procedure above; ^1H NMR (CD_3OD) δ 1.64 (quintet, J = 7.5 Hz, 2 H, CH_2CC=), 2.15 (q, J = 6.6 Hz, 2 H, CH_2C=), 2.22 (m, 2 H, H-2'), 2.32 (t, J = 7.5



5

Hz, 2 H, CH_2CCC=), 2.70 (s, 3 H, CH_3), 3.54 (d, J = 6.9 Hz, 2 H, =CCH_2N), 3.76 (m, 2 H, H-5'), 3.92 (dd, J = 6.0 Hz, J = 3.0 Hz, 1 H, H-3'), 4.18 (s, 2 H, NCH_2Ph), 4.42 (m, 1 H, H-4'), 5.65 (dt, J = 15.3 Hz, J = 7.2 Hz, 1 H, vinyl), 5.97 (dt, J = 15.6 Hz, J = 6.9 Hz, 1 H, vinyl), 6.27 (t, J = 6.3 Hz, 1 H, H-1'), 7.41–7.52 (m, 5 H, Ph), 7.88 (s, 1 H, H-6), the OH and NH peaks overlapped with the water peak at δ 4.94; ^{13}C NMR (CD_3OD) δ 27.1, 28.5, 33.2, 41.3, 53.6, 59.1, 60.6, 62.7, 72.2, 86.3, 88.8, 115.3, 121.7, 130.0, 130.2, 130.8, 131.7, 133.1, 142.1, 152.1, 165.8; IR (neat) 3370 (OH), 3026, 2925, 2500, 1686 (C=O), 1669 (C=O), 1459, 1277, 1097 cm^{-1}; HRMS for $C_{23}H_{31}N_3O_5$: calcd 429.2264, found 429.2264.

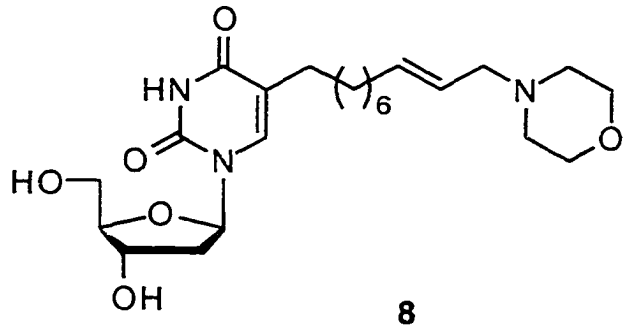
Preparation of Compound 6



6

Compound **6** was obtained in 42% yield from the coupling of (+)-5-iodo-2'-deoxyuridine, 5 equiv. of 1,5-hexadiene and 2 equiv. of di-*n*-propylamine using the procedure above; ^{1}H NMR (CD_3SOCD_3) δ 0.86 (t, J = 7.5 Hz, 6 H, CH_3), 1.51 (m, 2 H, CH_2CC=), 1.64 (sextet, J = 7.5 Hz, 4 H, $NCCH_2$), 2.06 (m, 4 H, CH_2C=, H-2'), 2.18 (t, J = 7.5 Hz, 2 H, CH_2CCC=), 2.75 (t, J = 7.5 Hz, 4 H, NCH_2), 2.86 (m, 2 H, =CCH_2N), 3.40 (br s, 2 H, OH overlapped with H_2O), 3.58 (m, 2 H, H-5'), 3.76 (m, 1 H, H-3'), 4.26 (m, 1 H, H-4'), 5.33 (m, 1 H, NH), 5.61 (dt, J = 15.0 Hz, J = 6.6 Hz, 1 H, vinyl), 5.94 (dt, J = 15.0 Hz, J = 6.6 Hz, 1 H, vinyl), 6.15 (t, J = 6.6 Hz, 1 H, H-1'), 7.75 (s, 1 H, H-6). Other spectra were not taken because of a lack of material.

Preparation of Compound 8

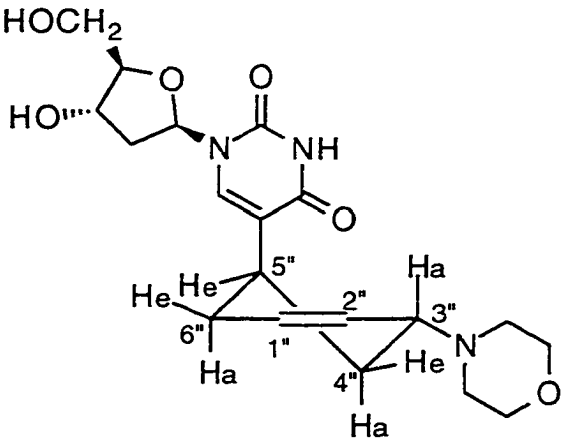


8

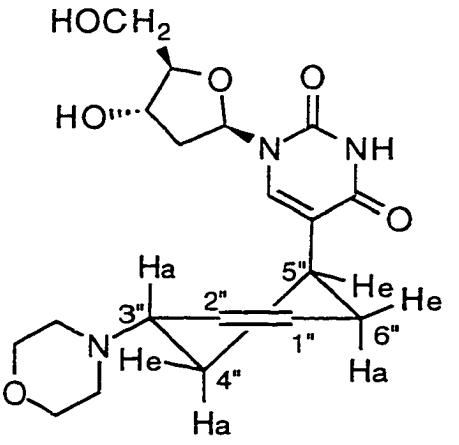
Compound **8** was obtained in 31% yield from the coupling of (+)-5-iodo-2'-deoxyuridine, 5 equiv. of 1,9-decadiene and 2 equiv. of morpholine using the procedure above; ^{1}H NMR (CD_3OD) δ 1.31–1.40 (m, 8 H, CH_2's), 1.48 (m, 2 H, CH_2CC=), 2.08 (m, 2 H, CH_2C=), 2.24 (m, 2 H, H-2'), 2.28 (t, J = 7.2 Hz, 2 H, $C\underline{H}_2(CH_2)_6C$=), 2.84 (br s, 4 H, ring NCH_2), 3.33 (m, 2 H, =CCH_2N), 3.78 (br s, 6 H, H-5', ring OCH_2), 3.92 (s, 1 H, H-3'), 4.42 (s, 1 H, H-4'), 5.53 (dt, J = 15.6 Hz, J = 6.9 Hz, 1 H, vinyl), 5.85 (dt, J = 15.6 Hz, J = 6.3 Hz, 1 H, vinyl), 6.15

(m, 1 H, H-1'), 7.82 (s, 1 H, H-6), the OH and NH peaks are overlapped with the water peak at δ 4.87; IR (neat) 3452 (OH), 2928, 2856, 2542, 1693 (C=O), 1668 (C=O), 1462, 1279 cm^{-1}. Other spectra were not taken because of a lack of material.

Preparation of Compound **10a** and **10b**



10a



10b

Compounds **10a** and **10b** were obtained as an inseparable 50:50 mixture of diastereomers in 30% combined yield from the coupling of (+)-5-iodo-2'-deoxyuridine, 5 equiv. of 1,4-cyclohexadiene and 2 equiv. of morpholine using the procedure above: ^{1}H NMR (CD_3OD) δ 1.85 (m, 1 H, Ha-4"), 2.22–2.42 (m, 5 H, H-2', He-4", Ha-6" and He-6"), 3.00 (m, 1 H, He-5"), 3.10–3.21 (m, 4 H, ring NCH_2), 3.56 (m, 1 H, Ha-3"), 3.74 (dd, J = 12.0 Hz, J = 3.3 Hz, 1 H, H-5'), 3.80 (dd, J = 12.0 Hz, J = 2.7 Hz, 1 H, H-5'), 3.85 (t, J = 4.8 Hz, 4 H, ring OCH_2), 3.93 (m, 1 H, H-3'), 4.41(m, 1 H, H-4'), 5.88 (m, 1 H, vinyl), 6.25 (m, 1 H, vinyl), 6.30 (t, J = 6.6 Hz, 1 H, H-1' in **10a** or **10b**), 6.31 (t, J = 6.6 Hz, 1 H, H-1' in **10b** or **10a**), 7.86 (s, 1 H, H-6 in **10a** or **10b**), 7.89 (s, 1 H, H-6 in **10b** or **10a**), the

OH and NH peaks overlapped with the water peak at δ 4.89. Other spectra were not taken because of a lack of material.

Preparation of Compound **12**

Compound **12** was obtained in 44% yield from the coupling of 5-iodouridine, 5 equiv. of 1,5-hexadiene and 2 equiv. of morpholine using the procedure above; ^{1}H NMR (CD_3OD) δ 1.57 (quintet, J = 7.2 Hz, 2 H, CH_2CC=), 2.06 (q, J = 6.6 Hz, 2 H, CH_2C=), 2.27 (t, J = 7.2 Hz, 2 H, CH_2CCC=), 2.67 (br s, 4 H, ring NCH_2), 3.19 (m, 2 H, =CCH_2N), 3.71–3.79 (m, 6 H, H-5', ring OCH_2), 3.99 (m, 1 H, H-2'), 4.15–4.21 (m, 2 H, H-3', H-4'), 5.50 (dt, J = 15.3 Hz, J = 6.9 Hz, 1 H, vinyl), 5.77 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H, vinyl), 5.89 (d, J = 4.2 Hz, 1 H, H-1'), 7.86 (s, 1 H, H-6), the OH and NH peaks overlapped with the water peak at δ 4.96; ^{13}C NMR (CD_3OD) δ 27.1, 28.5, 32.6, 53.7, 61.3, 62.2, 66.7, 71.4, 75.6, 86.5, 90.1, 115.4, 124.1, 138.5, 139.1, 152.5, 165.8; IR (neat) 3325 (OH), 3180 (NH), 2933, 2866, 2479, 1703 (C=O), 1668 (C=O), 1457, 1271, 1107 cm^{-1}; HRMS for $C_{19}H_{29}N_3O_7$: calcd 411.2006, found 411.2003.

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16. ^{1}H NMR (CD_3OD) spectrum of compound **11**: δ 2.21 (dd, *J* = 13.5 Hz, *J* = 6.9 Hz, 1 H, H-2'), 2.28 (ddd, *J* = 13.8 Hz, *J* = 6.3 Hz, *J* = 3.6 Hz, 1 H, H-2'), 3.70 (dd, *J* = 12.0 Hz, *J* = 3.9 Hz, 1 H, H-5'), 3.77 (dd, *J* = 12.0 Hz, *J* = 3.3 Hz, 1 H, H-5'), 3.92 (dd, *J* = 6.6 Hz, *J* = 3.3 Hz, 1 H, H-3'), 4.38 (ddd, *J* = 6.0 Hz, *J* = 3.6 Hz, *J* = 3.3 Hz, 1 H, H-4'), 5.70 (d, *J* = 8.1 Hz, 1 H, H-5), 6.26 (t, *J* = 6.6 Hz, 1 H, H-1'), 7.97 (d, *J* = 8.1 Hz, 1 H, H-6), the OH and NH peaks overlapped with the water peak at δ 4.87.
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GENERAL SUMMARY

The scope of the palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and nucleophiles has been investigated. This process has proven to be a very efficient, useful method in the area of organic synthesis. It allows two new bonds (carbon-carbon and/or carbon-heteroatom) to be formed in a single step to generate a relatively complex molecule.

A variety of nucleophiles, such as phenylmetallics, amines and other heteroatom nucleophiles, have been successfully employed in this coupling process. The regioselectivity can be controlled by the choice of the aryl iodide. Hindered aryl groups bearing electron-withdrawing substituents provide greater regioselectivity.

The total synthesis of the naturally-occurring alkaloids theonelladins C and D, niphatesine C and xestamine D has been successfully achieved using the palladium-catalyzed coupling of 3-iodopyridine, nonconjugated dienes and nitrogen nucleophiles as the key step.

Our palladium-catalyzed coupling process has also been applied to the synthesis of C-5 substituted pyrimidine nucleosides. We have found that adding a Lewis acid, such as $ZnCl_2$, significantly improves the coupling reaction of 5-iodo-2'-deoxyuridine, nonconjugated dienes and amine nucleophiles.

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