Synthesis of Aryl-Substituted Allylic Amines via Palladium-Catalyzed Coupling of Aryl Iodides, Nonconjugated Dienes, and Amines

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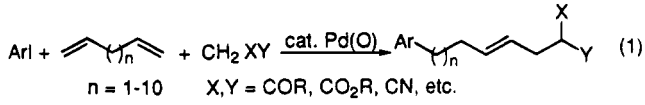
The palladium-catalyzed coupling of aryl iodides, nonconjugated dienes, and primary and secondary amines provides ω-aryl allylic amines in good yields by a process involving arylpalladium formation and addition to the less-substituted C–C double bond of the diene, palladium migration to form a π-allylpalladium intermediate, and nucleophilic displacement of palladium by the amine.

Aryl halides, nonconjugated dienes, and carbon nucleophiles can be coupled in high yields using a palladium catalyst (eq 1).[1] This process apparently proceeds via (1) arylpalladium formation and addition to the less hindered of the C–C double bonds, (2) palladium migration by a series of palladium hydride β-eliminations and readditions to form a π-allylpalladium intermediate, and (3) nucleophilic displacement of palladium by the carbanion generated *in situ*. It would appear that a variety of nucleophiles known to effect π-allylpalladium displacement[2] should also undergo this process. The reaction of amines would appear quite useful, but displacement of the palladium hydride from intermediate palladium hydride–olefin π complexes formed during palladium migration and the resulting formation of aryl-substituted dienes would appear to be a major concern. Indeed, Heck has previously studied the coupling of bromo- and iodobenzene with a couple of representative 1,4-dienes and reported generally low yields of several isomeric allylic amines and substantial amounts of dienes (eq 2).[3] One might anticipate even greater difficulties with longer chain nonconjugated dienes where each additional carbon inserted between the two C–C double bonds dramatically 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. 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.



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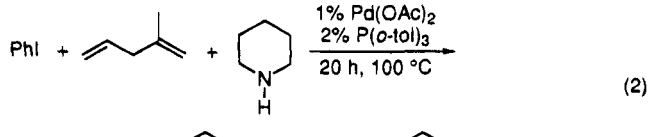

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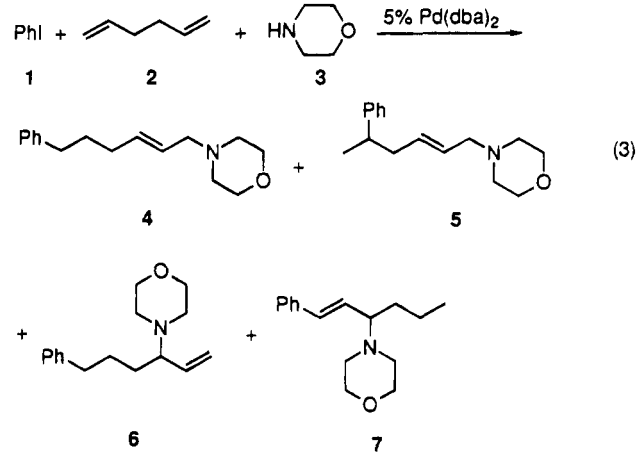
Results and Discussion

The reaction of iodobenzene (**1**), 1,5-hexadiene (**2**), and morpholine (**3**) was chosen as a model system in which to optimize yields (eq 3). We began our studies employing



(3)

a five fold exess of both diene and amine, and one 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 **4** and **5** was obtained, alongside what appeared to be a small amount of isomeric amines, which were easily separated from **4** and **5** (Table 1, entry 1). By doubling the amount of n-Bu_4NCl, the yield of compounds **4** plus **5** 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 7). A detailed analysis of this reaction indicated that amines **4** and **5** were formed in a ratio of 87:13, alongside 7% of a 56:44 mixture of two amines which appeared to possess the structures **6** and **7**. 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 regioselec-

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(1) Larock, R. C.; Lu, Y.; Bain, A. C.; Russell, C. E. *J. Org. Chem.* **1991**, *56*, 4589.

(2) (a) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (b) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1982; Vol. 8, p 799. (c) Tsuji, J. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 3, p 163. (d) Godleski, S. A. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Chap. 3.2.

(3) Bender, D. B.; Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1982**, *47*, 1278.

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Table 1. Palladium-Catalyzed Coupling of Iodobenzene, 1,5-Hexadiene, and Morpholine (Eq 3)

entry	ratio **1/2/3**	chloride source (equiv)	solvent	temp (°C)	% isolated yield (**4** + **5**) (ratio **4**:**5**)	% isolated yield (**6** + **7**) (ratio **6**:**7**)
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)	~0
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	

Table 2. Palladium-Catalyzed Coupling of Aryl Iodides, Nonconjugated Dienes, and Amines (Eq 4)

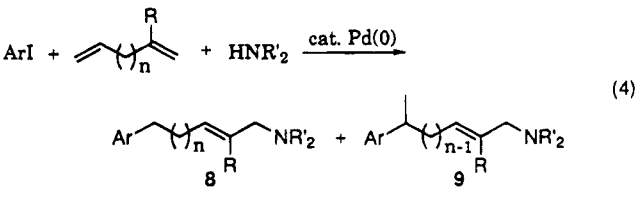
entry	aryl iodide	diene	amine	procedure[a]	% isolated yield	ratio[b] **8**:**9**
1	PhI	1,5-hexadiene	morpholine	A	87	85:15
2	PhI	1,5-hexadiene	piperidine	A	80	90:10
3	PhI	1,5-hexadiene	di-*n*-propylamine	A	87	92:8
4	PhI	1,5-hexadiene	benzylmethylamine	A	83	87:13
5	PhI	1,5-hexadiene	*N*-methylaniline	B[c]	66	85:15
6	PhI	1,5-hexadiene	aniline	B[c]	67	88:12
7	PhI	1,5-hexadiene	*n*-butylamine	B	35	81:19
8	PhI	1,5-hexadiene	*i*-butylamine	B	51	92:8
9	PhI	1,5-hexadiene	*t*-butylamine	B	58	85:15
10	PhI	1,9-decadiene	morpholine	A	75	82:18
11	PhI	1,9-decadiene	di-*n*-propylamine	A	78	85:15
12	PhI	1,13-tetradecadiene	morpholine	A	67	80:20
13	PhI	2-methyl-1,4-pentadiene	morpholine	C	73	89:11
14	PhI	2-methyl-1,4-pentadiene	piperidine	C	78	93:7
15	PhI	2-methyl-1,5-hexadiene	morpholine	C	81	86:14
16	PhI	2,4-dimethyl-1,4-pentadiene	morpholine	C	62	~100:0
17	*o*-$MeOC_6H_4I$	1,5-hexadiene	morpholine	A	91	93:7
18	*o*-$MeOC_6H_4I$	1,5-hexadiene	morpholine	A	90	95:5
19	*o*-AcC_6H_4I	1,5-hexadiene	morpholine	A	70	~100:0
20	*o*-$EtO_2CC_6H_4I$	1,5-hexadiene	morpholine	A	92	99:1
21	*p*-$MeOC_6H_4I$	1,5-hexadiene	morpholine	A	89	80:20
22	*p*-$EtO_2CC_6H_4I$	1,5-hexadiene	morpholine	A	85	86:14
23	*p*-$MeOC_6H_4I$	1,5-hexadiene	di-*n*-propylamine	A	67	86:14
24	1-iodonaphthalene	1,5-hexadiene	morpholine	A	90	92:8
25	3-iodopyridine	1,5-hexadiene	morpholine	A	67	89:11
26	3-iodopyridine	1,5-hexadiene	di-*n*-propylamine	A	56	91:9

[a] See the text and Experimental Section for the procedures. [b] All compounds gave appropriate ^1H and ^{13}C NMR, IR and mass spectral data. [c] Two equiv of Na_2CO_3 was also added.

tivity (entries 8 and 9). Later on the use of LiCl at 100 °C was observed to give yields of **4** and **5** comparable to *n*-Bu_4NCl, but with no formation of the side products **6** and **7** (entry 10). Failure to employ any chloride reagent resulted in a slight reduction in both the yield of **4** plus **5** and the regioselectivity of their formation, plus a significant increase in the undesired compounds **6** and **7** (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). The addition of 5% Ph_3P analogous to the work of Heck[3] resulted in sharply reduced yields of the desired products.

As a result of these types of studies, we have arrived at three procedural variations which affect the overall process in high yield. In most cases the use of one equivalent of aryl iodide, five equivalents of diene and two equivalents of amine in DMF (4 mL per mmol of aryl iodide) in the presence of 5 mol % $Pd(dba)_2$ (dba = dibenzylideneacetone) and two equivalents of *n*-Bu_4NCl (Lancaster, anhydrous) at 100 °C for 24 h (procedure A) affords excellent yields of coupled products. However, for primary amines this procedure affords substantial amounts of dimethylamine derivatives via transamidation of the DMF solvent by the primary amine. By switching to DMSO as the solvent and increasing the amount of the amine to five equivalents to improve the yield (procedure B), good yields can be obtained from primary amines. The reactions of branched dienes turned out to be rather sluggish using procedure A. To facilitate reaction in these cases, a procedure C using *N*,*N*-dimethylacetamide (DMA) as the solvent and five equivalents of amine has been employed. In much later work it was observed that the *n*-Bu_4NCl can be replaced by LiCl and/or the temperature can be reduced to 80 °C with virtually identical results as far as yields and regioselectivity are concerned.

The results from the coupling of a wide variety of aryl iodides, nonconjugated dienes and amines are summarized in eq 4 and Table 2. In general, a wide variety



(4)

of aromatic iodides can be employed successfully in this process. Simple aryl iodides bearing electron-donating

or electron-withdrawing substituents anywhere on the aromatic ring may be employed with little variation in overall yield and little interference by the functionality (entries 17–22). Even ketone and ester functionality may be accommodated. Polycyclic and heterocyclic iodides have also been successfully employed (entries 24–26). Surprisingly, no more than a 16% combined yield of compounds **4** and **5** (ratio 92:8) could be obtained under a variety of reaction conditions when iodobenzene was replaced by phenyl triflate in the reaction with 1,5-hexadiene and morpholine.

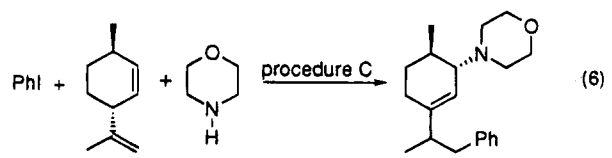
The coupling is quite versatile with regard to the types of dienes one can utilize. Dienes with from 1 to 10 carbons between the two C–C double bonds have been successfully coupled with only a modest reduction in overall yield as the chain length increases (compares entries 1, 10 and 12). This is quite remarkable when one considers that the coupling of iodobenzene, 1,13-tetradecadiene and morpholine which proceeds in 67% overall yield (entry 12) is estimated to take 484 mechanistic steps (see the mechanistic discussion later where each palladium hydride elimination and each palladium hydride addition are considered separate steps) if one assumes that the migration involves a random walk process. In effect each step of this particular transformation is proceeding in an average yield of 99.92%!

Branching in the diene does not significantly affect the coupling process (entries 13–16). Although the rate of reaction is reduced sufficiently that we have been forced to employ a different procedure, procedure C, the yields are still quite good. Our reaction of iodobenzene, 2-methyl-1,4-pentadiene and piperidine gives a 78% yield (entry 14), while the previous procedure of Heck with these same reagents gave only a 34% combined yield of the expected allylic amines (see eq 2). The aryl group is observed to add cleanly to the less-substituted C–C double bond and the amine adds to the terminal carbon of the more substituted C–C double bond. Even arylpalladium addition to a disubstituted terminal double bond as in Table 2, entry 16 results in good yields of allylic amine products.

We have also briefly examined the coupling of cyclic dienes. The reaction of iodobenzene, 1,4-cyclohexadiene and morpholine affords a high yield of a single allylic amine in which phenylpalladium addition has taken place on one face of the diene and the amine is introduced from the opposite face (eq 5). The optically active 1,4-

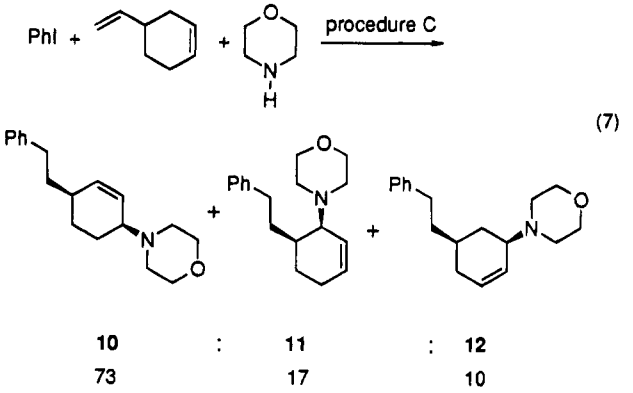
(5)

diene (1R)-(+)-*trans*-isolimonene in which both acyclic and cyclic C–C double bonds exist couples cleanly to afford two separable diastereomeric amines in 47% and 15% yields respectively (eq 6). However, 4-vinylcyclo-



(6)

hexene produces a 58% yield of an inseparable 73:17:10 mixture of three isomeric amines believed to be compounds **10**–**12** respectively (eq 7). Apparently migration



(7)

involving the least number of hydride eliminations and readditions is favored, resulting in products **10** and **11** being favored over amine **12**.

The coupling process is fairly versatile as far as the amine is concerned. Best results are generally obtained using secondary aliphatic amines (Table 2, entries 1–4). Primary amines give lower yields and require a variation in procedure as noted earlier (Table 2, entries 7–9). In general, the more hindered the primary amine, the higher the yield. Although anilines are substantially less basic than aliphatic amines, good yields have been obtained using either primary or secondary anilines provided procedure B is employed and two equivalents of Na_2CO_3 are added (entries 5 and 6).

The regio- and stereochemistry of this process is interesting. As with many other examples of the addition of arylpalladium species to C–C double bonds,[4] 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 this ratio of ~85:15 is not significantly affected by the nature of the diene, but hindered aryl groups, such as *ortho*-substituted aryl iodides (entries 17–20) do provide greater regioselectivity as expected. The regiochemistry of addition is also slightly affected by the nature of the amine, suggesting that the amines are serving as ligands on the palladium during arylpalladium addition to the carbon-carbon double bond. Terminal disubstituted C–C double bonds undergo arylation exclusively on the unsubstituted carbon (entry 16 and eq 6).

Like Heck,[3] we also find a minor amount (<5%) of product from displacement of the palladium at the more substituted carbon of the π-allylpalladium intermediate, but this product is usually easily separated from the products of terminal displacement. In our model system, we have also detected a few percent of a product believed to be compound **7**, which appears to arise by a Heck reaction between iodobenzene and 1,5-hexadiene to form 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 toward the phenyl group to produce a π-allylpalladium intermediate, which undergoes displacement by morpholine to produce the observed side product.

Where there is stereochemistry present (eqs 5–7), only displacement by backside attack on the π-allylpalladium

(4) (a) Heck, R. F. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Chap. 4.3. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985; Chap. 6.

intermediate is observed.[5] The stereochemistry of the C–C double bond of the acyclic allylic amines produced by this process is found to be exclusively *E*, even when that double bond is trisubstituted as in entries 13–16.

All products thus far observed are consistent with the mechanism set forth previously for the coupling of aryl halides, non-conjugated dienes and carbon nucleophiles.[1] The products from the dienes possessing cyclic double bonds (eqs 5–7) are all consistent with a process involving *syn* addition of an arylpalladium species to the double bond, followed by a series of *syn* β-hydride eliminations and additions,[6,7] and subsequent backside displacement of palladium from the less hindered end of the resulting π-allylpalladium intermediate.[5]

We believe this versatile three-component coupling process has considerable synthetic potential, particularly in the synthesis of long chain aromatic compounds possessing remote functionality, and are presently examining applications to pharmacologically interesting compounds of this nature.

Experimental Section

Equipment. All proton and carbon nuclear magnetic resonance spectra were recorded at 300 and 75.5 MHz respectively. Flash chromatography was carried out on 230–400 mesh silica gel.

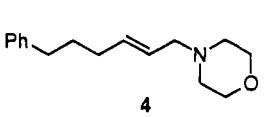
Reagents. Bis(dibenzylideneacetone)palladium was donated by Kawaken Fine Chemicals Co., Ltd. Tetra-*n*-butylammonium chloride, ethyl 2-iodobenzoate and ethyl 4-iodobenzoate were purchased from Lancaster Synthesis, Inc. Iodobenzene, 2-iodotoluene, 2-iodoanisole, 4-iodoanisole, di-*n*-propylamine, 1,5-hexadiene, 2-methyl-1,5-hexadiene, 1,4-cyclohexadiene, 1,9-decadiene, *t*-butylamine and *N,N*-dimethylacetamide were purchased from Aldrich Chemical Co., Inc. Morpholine, piperidine, dimethyl sulfoxide, *N,N*-dimethylformamide, and lithium chloride were purchased from Fisher Scientific Co. Aniline, *N*-methylaniline and *n*-butylamine were purchased from J. T. Baker Chemical Co. 1-Iodonaphthalene, isobutylamine 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, Nonconjugated 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 h. The mixture was then allowed to cool to rt, diluted with saturated NaCl solution and extracted with 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 4 and 5. Compounds **4** and



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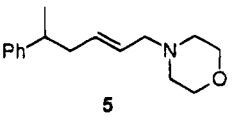
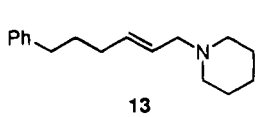


5

5 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 **5**), 1.70 (quintet, J = 7.5 Hz, 2 H), 2.08 (q, J = 7.2 Hz, 2 H), 2.43 (br s, 4 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.95 (d, J = 6.3 Hz, 2 H), 3.64 (t, J = 4.5 Hz, 4 H, ring CH_2O in **5**), 3.71 (t, J = 4.5 Hz, 4 H), 5.50 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 5.60 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 7.14–7.29 (m); ^{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 13 and 14. Compounds **13**



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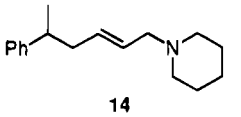
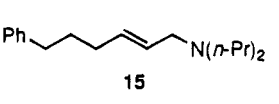


14

and **14** 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 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **14**), 1.40–1.45 (br m, 2 H), 1.54–1.62 (br m, 4 H), 1.70 (quintet, J = 7.5 Hz, 2 H), 2.07 (q, J = 6.9 Hz, 2 H), 2.33–2.38 (br m, 4 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.90 (d, J = 5.1 Hz, 2 H), 5.52 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H), 5.58 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H), 7.15–7.29 (m, 5 H); ^{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, 1496, 1453, 1154 cm^{-1}; HRMS for $C_{17}H_{25}N$: calcd 243.1987, found 243.1986.

Preparation of Compounds 15 and 16. Compounds **15**



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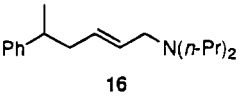
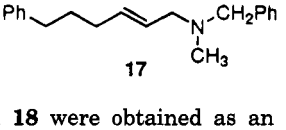


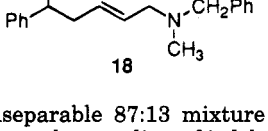
16

and **16** 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: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6 H), 1.24 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **16**), 1.46 (sextet, J = 7.5 Hz, 4 H), 1.70 (quintet, J = 7.5 Hz, 2 H), 2.07 (q, J = 6.9 Hz, 2 H), 2.38 (t, J = 7.5 Hz, 4 H), 2.61 (t, J = 7.5 Hz, 2 H), 3.04 (d, J = 5.1 Hz, 2 H), 5.45–5.62 (m, 2 H), 7.15–7.30 (m, 5 H); ^{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 17 and 18. Compounds **17**



17



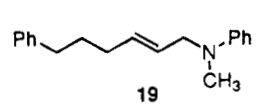
18

and **18** 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: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.6 Hz, 3 H, $PhCCH_3$ in **18**), 1.71 (quintet, J = 7.5 Hz, 2 H), 2.05–2.12 (br m, 2 H), 2.17 (s, 3 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.98 (d, J = 5.4 Hz, 2 H), 3.38 (s, 2 H, NCH_2Ph in **18**), 3.48 (s, 2 H),

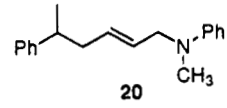
(5) Åkermark, B.; Zetterberg, K. *Tetrahedron Lett.* **1975**, 3733.
(6) Larock, R. C.; Song, H.; Kim, S.; Jacobson, R. A. *J. Chem. Soc., Chem. Commun.* **1987**, 834.
(7) For some recent references to palladium migration processes, see ref. 1 and: (a) Larock, R. C.; Leung, W.-Y. *J. Org. Chem.* **1990**, *55*, 6244. (b) Söderberg, B. C.; Åkermark, B.; Chen, Y.-H.; Hall, S. S. *J. Org. Chem.* **1990**, *55*, 1344. (c) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1992**, *57*, 2528.

5.48–5.66 (m, 2 H), 7.15–7.31 (m, 10 H); ^{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, 3062, 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 19 and 20. Compounds **19**



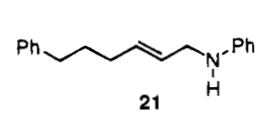
19



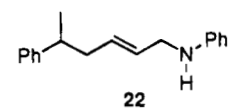
20

and **20** 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 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 **20**), 1.67 (quintet, J = 7.8 Hz, 2 H), 2.05 (q, J = 7.2 Hz, 2 H), 2.57 (t, J = 7.8 Hz, 2 H), 2.87 (s, 3 H, NCH_3 in **20**), 2.89 (s, 3 H), 3.85 (d, J = 5.1 Hz, 2 H), 5.45 (dt, J = 15.3 Hz, J = 5.4 Hz, 1 H), 5.59 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 6.66–6.74 (m, 3 H), 7.12–7.28 (m, 7 H); ^{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 21 and 22. Compounds **21**



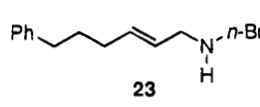
21



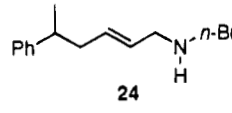
22

and **22** 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 equiv of Na_2CO_3 using procedure B: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **22**), 1.70 (quintet, J = 7.5 Hz, 2 H), 2.07 (q, J = 7.2 Hz, 2 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.70–2.80 (m, 1 H, PhCH in **22**), 3.69 (d, J = 5.7 Hz, 2 H), 5.57 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H), 5.70 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 6.55–6.72 (m, 3 H), 7.14–7.29 (m, 7 H); ^{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, 3052, 3024, 2929, 1602, 1504, 1319, 1251 cm^{-1}; HRMS for $C_{18}H_{21}N$: calcd 251.1674, found 251.1674.

Preparation of Compounds 23 and 24. Compounds **23**



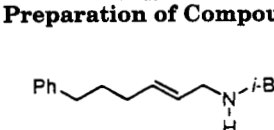
23



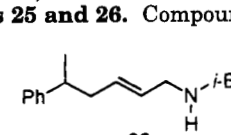
24

and **24** 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_2CH_3 in **24**), 0.91 (t, J = 7.2 Hz, 3 H), 1.24 (d, J = 6.9 Hz, 3 H, P $hCCH_3$ in **24**), 1.34 (sextet, J = 7.2 Hz, 2 H), 1.52 (quintet, J = 7.2 Hz, 2 H), 1.70 (quintet, J = 7.5 Hz, 2 H), 2.07 (q, J = 7.2 Hz, 2 H), 2.53 (t, J = 7.2 Hz, 2 H, NCH_2CH_2 in **24**), 2.61 (t, J = 7.5 Hz, 2 H), 2.62 (t, J = 7.2 Hz, 2 H), 2.89 (br s, 1 H), 3.23 (d, J = 5.4 Hz, 2 H), 5.55 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H), 5.64 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H), 7.15–7.29 (m, 5 H); ^{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 25 and 26. Compounds **25**



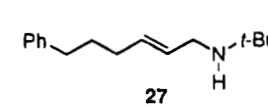
25



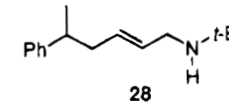
26

and **26** were obtained as an inseparable 92:8 mixture of isomers in 51% combined yield from the coupling of iodobenzene, 5 equiv of 1,5-hexadiene and 5 equiv of isobutylamine using procedure B: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.9 Hz, 6 H), 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **26**), 1.70 (quintet, J = 7.2 Hz, 2 H), 1.85 (nontet, J = 6.9 Hz, 1 H), 2.08 (q, J = 7.2 Hz, 2 H), 2.47 (d, J = 6.9 Hz, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 3.27 (d, J = 5.7 Hz, 2 H), 3.62 (br s, 1 H), 5.57 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H), 5.67 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H), 7.15–7.30 (m, 5 H); ^{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 27 and 28. Compounds **27**



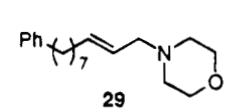
27



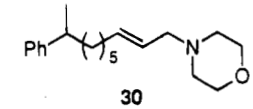
28

and **28** 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: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9 H, $NC(CH_3)_3$ in **28**), 1.14 (s, 9 H), 1.23 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **28**), 1.69 (quintet, J = 7.5 Hz, 2 H), 2.02–2.09 (m, 2 H), 2.15–2.32 (br m, 1 H), 2.60 (t, J = 7.8 Hz, 2 H), 2.75 (sextet, J = 6.9 Hz, 1 H, PhCH in **28**), 3.17 (d, J = 4.8 Hz, 2 H), 5.51–5.67 (m, 2 H), 7.15–7.29 (m, 5 H); ^{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 29 and 30. Compounds **29**



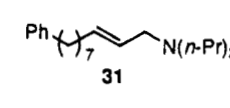
29



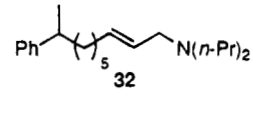
30

and **30** 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: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **30**), 1.26–1.37 (br m, 8 H), 1.55–1.62 (br m, 2 H), 2.01 (q, J = 6.6 Hz, 2 H), 2.42 (br s, 4 H), 2.59 (t, J = 7.5 Hz, 2 H), 2.64 (m, 1 H, PhCH in **30**), 2.92 (d, J = 6.6 Hz, 2 H), 3.70 (t, J = 4.5 Hz, 4 H), 5.45 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 5.58 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 7.14–7.28 (m, 5 H); ^{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 31 and 32. Compounds **31**



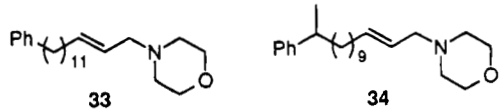
31



32

and **32** 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 dipropylamine using procedure A; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6 H), 1.22 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **32**), 1.30 (br s, 8 H), 1.45 (sextet, J = 7.5 Hz, 4 H), 1.55–1.63 (m, 2 H), 2.01 (q, J = 6.3 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 4 H), 2.59 (t, J = 7.5 Hz, 2 H), 3.02 (d, J = 5.7 Hz, 2 H), 5.45 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 5.53 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 7.15–7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.1, 20.1, 29.1, 29.4 (2 carbon peak), 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.

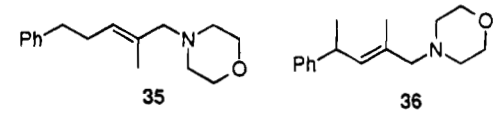
Preparation of Compounds 33 and 34. Compounds **33** and **34** were obtained as an inseparable 80:20 mixture of isomers in 67% combined yield from the coupling of iodobenzene, 5 equiv of 1,13-tetradecadiene and 2 equiv of morpholine



33 34

using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.22–1.30 (br m, 16 H), 1.55–1.64 (br m, 2 H), 2.02 (q, J = 6.6 Hz, 2 H), 2.42 (br s, 4 H), 2.59 (t, J = 7.5 Hz, 2 H), 2.92 (d, J = 6.6 Hz, 2 H), 3.71 (t, J = 4.5 Hz, 4 H), 5.45 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 5.59 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 7.15–7.28 (m, 5 H); ^{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.

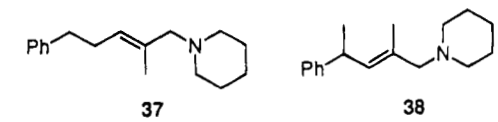
Preparation of Compounds 35 and 36. Compounds **35**



35 36

and **36** 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: ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **36**), 1.57 (s, 3 H), 1.71 (s, 3 H, $=CCH_3$ in **36**), 2.26 (t, J = 4.5 Hz, 4 H), 2.35 (q, J = 7.5 Hz, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.78 (s, 2 H), 3.65 (t, J = 4.5 Hz, 4 H), 5.32 (tq, J = 7.2 Hz, J = 0.9 Hz, 1 H), 5.47 (dq, J = 9.6 Hz, J = 0.9 Hz, 1 H, vinyl in **36**), 7.15–7.28 (m, 5 H); ^{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.

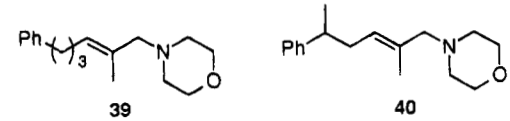
Preparation of Compounds 37 and 38. Compounds **37**



37 38

and **38** 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 **38**), 1.38–1.43 (br m, 2 H), 1.53 (quintet, J = 5.4 Hz, 4 H), 1.58 (s, 3 H), 2.21 (br s, 4 H), 2.35 (q, J = 7.5 Hz, 2 H), 2.65 (t, J = 7.8 Hz, 2 H), 2.76 (s, 2 H), 5.31 (t, J = 7.2 Hz, 1 H), 7.15–7.29 (m, 5 H); ^{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.

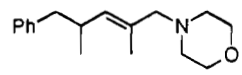
Preparation of Compounds 39 and 40. Compounds **39**



39 40

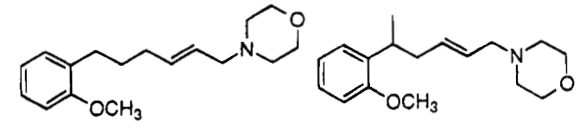
and **40** were obtained as an inseparable 86:14 mixture of isomers in 81% combined yield from the coupling of iodobenzene, 5 equiv of 2-methyl-1,5-hexadiene and 5 equiv of morpholine using procedure C: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3 H, $PhCCH_3$ in **40**), 1.56 (s, 3 H, $=CCH_3$ in **40**), 1.62 (s, 3 H), 1.67 (quintet, J = 7.8 Hz, 2 H), 2.06 (q, J = 7.2 Hz, 2 H), 2.33 (t, J = 4.5 Hz, 4 H), 2.60 (t, J = 7.8 Hz, 2 H), 2.82 (s, 2 H), 3.62 (t, J = 4.5 Hz, 4 H, ring CH_2O in **40**), 3.69 (t, J = 4.5 Hz, 4 H), 5.23 (t, J = 6.9 Hz, 1 H, vinyl in **40**), 5.33 (t, J = 6.9 Hz), 7.15–7.29 (m, 5 H); ^{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 Compound 41. Compound **41** 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), 1.46 (d, J = 1.2 Hz, 3 H), 2.08–2.22 (m, 4 H), 2.48 (dd, J = 13.2 Hz, J = 8.4 Hz, 1 H), 2.62 (dd, J = 13.2 Hz, J = 6.0 Hz, 1 H), 2.65 (d, J = 12.0 Hz, 1 H), 2.69–2.75 (m, 1 H), 2.80 (d, J = 12.0 Hz, 1 H), 3.61 (t, J = 4.5 Hz, 4 H), 5.10 (dq, J = 9.3 Hz, J = 1.2 Hz, 1 H), 7.10–7.25 (m, 5 H); ^{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.



41

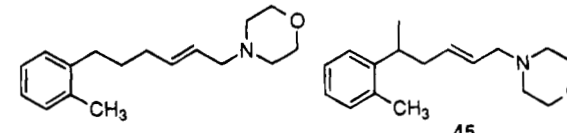
Preparation of Compounds 42 and 43. Compounds **42**



42 43

and **43** 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: ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7.5 Hz, 3 H, $ArCCH_3$ in **43**), 1.66 (quintet, J = 7.5 Hz, 2 H), 2.09 (q, J = 7.2 Hz, 2 H), 2.43 (br s, 4 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.93 (d, J = 6.6 Hz, 2 H), 3.71 (t, J = 4.8 Hz, 4 H), 3.80 (s, 3 H), 5.49 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 5.63 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 6.81–6.89 (m, 2 H), 7.09–7.19 (m, 2 H); ^{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.

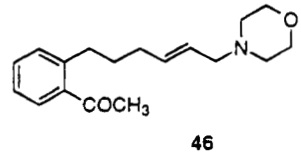
Preparation of Compounds 44 and 45. Compounds **44**



44 45

and **45** 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: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **45**), 1.65 (quintet, J = 7.5 Hz, 2 H), 2.12 (q, J = 6.9 Hz, 2 H), 2.28 (s, 3 H), 2.43 (br s, 4 H), 2.59 (t, J = 7.5 Hz, 2 H), 2.94 (d, J = 6.3 Hz, 2 H), 3.71 (t, J = 4.8 Hz, 4 H), 5.51 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 5.64 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 7.10 (br s, 4 H); ^{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.

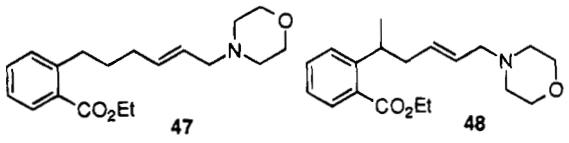
Preparation of Compound 46. Compound **46** was obtained in 70% yield from the coupling of 2-iodoacetophenone, 5 equiv of 1,5-hexadiene and 2 equiv of morpholine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.66 (quintet, J = 7.8 Hz, 2 H), 2.11 (q, J = 7.2 Hz, 2 H), 2.43 (br t, J = 4.2 Hz, 4 H), 2.57



46

(s, 3 H), 2.84 (t, J = 8.1 Hz, 2 H), 2.94 (d, J = 6.3 Hz, 2 H), 3.71 (t, J = 4.5 Hz, 4 H), 5.49 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 5.63 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 7.23–7.28 (m, 2 H), 7.39 (dt, J = 1.2 Hz, J = 7.5 Hz, 1 H), 7.64 (dd, J = 7.8 Hz, J = 1.2 Hz, 1 H); ^{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.

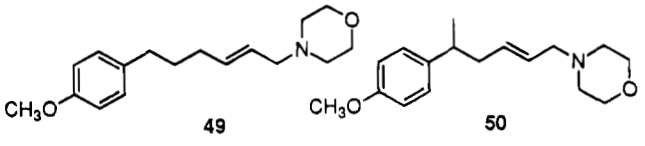
Preparation of Compounds 47 and 48. Compounds **47**



47 48

and **48** 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), 1.69 (quintet, J = 7.5 Hz, 2 H), 2.12 (q, J = 7.2 Hz, 2 H), 2.43 (br s, 4 H), 2.93 (d, J = 6.6 Hz, 2 H), 2.94 (t, J = 7.5 Hz, 2 H), 3.71 (t, J = 4.8 Hz, 4 H), 4.35 (q, J = 7.2 Hz, 2 H), 5.49 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 5.63 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 7.21–7.28 (m, 2 H), 7.40 (dt, J = 1.2 Hz, J = 7.2 Hz, 1 H), 7.85 (dd, J = 7.8 Hz, J = 1.2 Hz, 1 H); ^{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.

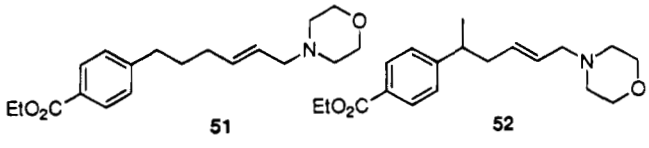
Preparation of Compounds 49 and 50. Compounds **49**



49 50

and **50** 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 **50**), 1.66 (quintet, J = 7.5 Hz, 2 H), 2.06 (q, J = 7.2 Hz, 2 H), 2.43 (br t, J = 4.2 Hz, 4 H), 2.55 (t, J = 7.5 Hz, 2 H), 2.94 (d, J = 6.0 Hz, 2 H), 3.64 (t, J = 4.8 Hz, 4 H, ring CH_2O in **50**), 3.71 (t, J = 4.8 Hz, 4 H), 3.76 (s, 3 H, CH_3O in **50**), 3.77 (s, 3 H), 5.48 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 5.61 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 8.4 Hz, 2 H); ^{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.

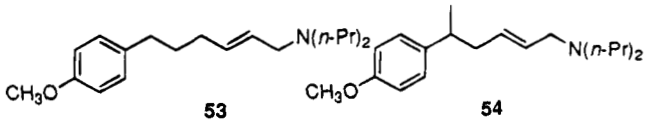
Preparation of Compounds 51 and 52. Compounds **51**



51 52

and **52** were obtained as an inseparable 86:14 mixture of isomers in 85% combined yield from the coupling of ethyl 4-iodobenzoate, 5 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 **52**), 1.38 (t, J = 7.2 Hz, 3 H), 1.72 (quintet, J = 7.5 Hz, 2 H), 2.08 (q, J = 7.2 Hz, 2 H), 2.43 (br s, 4 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.94 (d, J = 6.6 Hz, 2 H), 3.63 (t, J = 4.8 Hz, 4 H, ring CH_2O in **52**), 3.71 (t, J = 4.8 Hz, 4 H), 4.36 (q, J = 7.2 Hz, 2 H), 5.49 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 5.61 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 7.22 (d, J = 8.1 Hz, 2 H), 7.95 (d, J = 8.1 Hz, 2 H); ^{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.

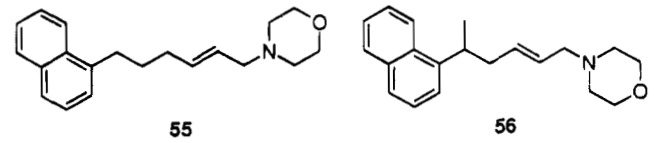
Preparation of Compounds 53 and 54. Compounds **53**



53 54

and **54** 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), 1.21 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **54**), 1.46 (sextet, J = 7.5 Hz, 4 H), 1.66 (quintet, J = 7.5 Hz, 2 H), 2.05 (q, J = 6.9 Hz, 2 H), 2.37 (t, J = 7.5 Hz, 4 H), 2.55 (t, J = 7.5 Hz, 2 H), 2.75 (m, 1 H, ArCH in **54**), 3.04 (d, J = 5.7 Hz, 2 H), 3.77 (s, 3 H), 5.49 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H), 5.57 (dt, J = 15.3 Hz, J = 6.0 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 2 H), 7.08 (d, J = 8.7 Hz, 2 H); ^{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.

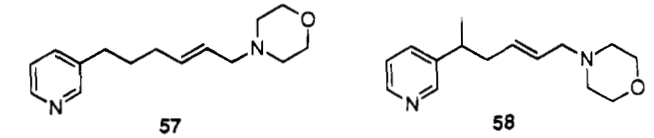
Preparation of Compounds 55 and 56. Compounds **55**



55 56

and **56** 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: ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **56**), 1.83 (quintet, J = 7.5 Hz, 2 H), 2.16 (q, J = 7.2 Hz, 2 H), 2.41 (br s, 4 H), 2.93 (d, J = 6.6 Hz, 2 H), 3.05 (t, J = 7.8 Hz, 2 H), 3.61 (t, J = 4.8 Hz, 4 H, ring CH_2O in **56**), 3.69 (t, J = 4.5 Hz, 4 H), 5.51 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 5.64 (dt, J = 15.3 Hz, J = 6.6 Hz, 1 H), 7.27–8.01 (m, 7 H); ^{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.

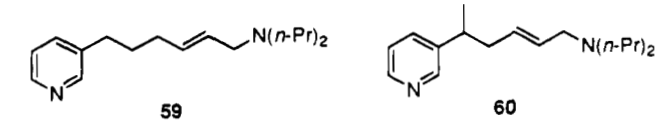
Preparation of Compounds 57 and 58. Compounds **57**



57 58

and **58** 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: ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 3 H, $PyCCH_3$ in **58**), 1.71 (quintet, J = 7.8 Hz, 2 H), 2.09 (q, J = 6.9 Hz, 2 H), 2.43 (br s, 4 H), 2.61 (t, J = 7.8 Hz, 2 H), 2.95 (d, J = 6.3 Hz, 2 H), 3.66 (t, J = 4.5 Hz, 4 H, ring CH_2O in **58**), 3.72 (t, J = 4.5 Hz, 4 H), 5.50 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 5.62 (dt, J = 15.3 Hz, J = 6.3 Hz, 1 H), 7.20 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 8.43 (br m, 2 H); ^{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 59 and 60. Compounds **59**

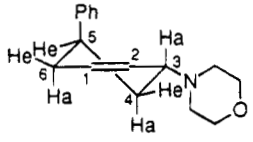


59 60

and **60** were obtained as an inseparable 91:9 mixture of

isomers in 56% combined yield from the coupling of 3-iodopyridine, 5 equiv of 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), 1.27 (d, J = 6.9 Hz, 3 H, $ArCCH_3$ in **60**), 1.47 (sextet, J = 7.5 Hz, 4 H), 1.71 (quintet, J = 7.5 Hz, 2 H), 2.09 (m, 2 H), 2.38 (t, J = 7.5 Hz, 4 H), 2.61 (t, J = 7.5 Hz, 2 H), 3.06 (d, J = 5.7 Hz, 2 H), 5.51 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H), 5.58 (dt, J = 15.3 Hz, J = 5.7 Hz, 1 H), 7.20 (dd, J = 7.8 Hz, J = 4.8 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 8.42–8.45 (m, 2 H); ^{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.

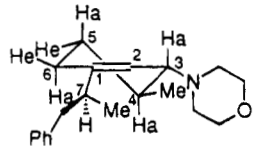
Preparation of *trans*-3-Morpholino-5-phenylcyclohexene (61). Compound **61** was obtained in 70% yield from the



61

coupling of iodobenzene, 5 equiv of 1,4-cyclohexadiene and 2 equiv of morpholine using procedure A: ^{1}H NMR ($CDCl_3$) δ 1.73 (ddd, J = 13.8 Hz, J = 11.4 Hz, J = 5.7 Hz, 1 H), 2.09–2.18 (m, 2 H), 2.37 (dt, J = 18.0 Hz, J = 4.5 Hz, 1 H), 2.50–2.69 (m, 4 H), 2.95–3.08 (m, 2 H), 3.70 (br s, 4 H), 5.79 (d, J = 9.9 Hz, 1 H), 6.01 (ddd, J = 9.9 Hz, J = 4.5 Hz, J = 2.4 Hz, 1 H), 7.18–7.33 (m, 5 H); ^{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.

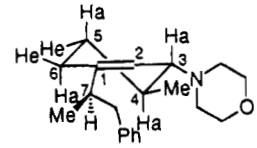
Preparation of Compound 62. Compound **62** was ob-



62

tained 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), 1.05 (d, J = 6.6 Hz, 3 H), 1.22–1.34 (m, 1 H), 1.54 (ddt, J = 16.8 Hz, J = 3.0 Hz, J = 6.9 Hz, 1 H), 1.65 (ddd, J = 12.6 Hz, J = 8.1 Hz, J = 4.8 Hz, 1 H), 1.89–1.94 (br m, 2 H), 2.16 (dt, J = 11.4 Hz, J = 4.5 Hz, 2 H), 2.34 (dt, J = 11.7 Hz, J = 4.5 Hz, 2 H), 2.44 (dd, J = 15.0 Hz, J = 6.6 Hz, 1 H), 2.55 (m, 1 H), 2.58 (dd, J = 13.2 Hz, J = 6.6 Hz, 2 H), 2.63 (dd, J = 13.2 Hz, J = 8.7 Hz, 2 H), 3.56 (t, J = 4.5 Hz, 4 H), 5.26 (br s, 1 H), 7.09–7.25 (m, 5 H); ^{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 63. Compound **63** was ob-



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tained in 15% yield from the coupling of iodobenzene, 5 equiv of (1*R*)-(+)-*trans*-isolimonene and 5 equiv of morpholine using procedure C: $[\alpha]^{26}_D$ −10.0° (c 0.10, CH_3COCH_3); ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H), 1.24–1.37 (m, 1 H), 1.60–1.67 (m, 1 H), 1.71 (ddd, J = 12.6 Hz, J = 8.4 Hz, J = 4.8 Hz, 1 H), 1.92–1.99 (br m, 2 H), 2.33–2.43 (m, 3 H), 2.51–2.60 (m, 4 H), 2.74 (dd, J = 13.2 Hz, J = 6.6 Hz, 1 H), 3.64 (t, J = 4.5 Hz, 4 H), 5.35 (br s, 1 H), 7.10–7.27 (m, 5 H).

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Supplementary Material Available: Copies of ^{1}H NMR spectra of all compounds in the Experimental Section (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.