Synthesis of Medium-Ring Nitrogen Heterocycles via Palladium-Catalyzed Heteroannulation of 1,2-Dienes

Richard C. Larock,* Chi Tu, and Paola Pace

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received March 18, 1998

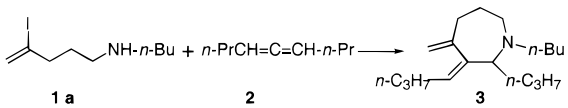
Seven-, eight-, and nine-membered-ring nitrogen heterocycles are readily prepared by the palladium-catalyzed heteroannulation of a variety of 1,2-dienes by a range of tosylamide- and amine-containing aryl and vinylic halides. The ease of ring formation is seven > eight > nine, and better results are obtained using aryl halides, rather than vinylic halides, and tosylamide functionality, rather than amine functionality. The reaction is suggested to proceed by the formation and addition of an aryl or vinylic palladium compound to the allene to generate a π-allylpalladium intermediate, which subsequently undergoes nucleophilic displacement of palladium at the less hindered end of the π-allyl system.

Introduction

Annulation processes are among the most important reactions in organic synthesis.[1] However, few have proven general for the formation of more than one ring size. The palladium-catalyzed hetero- and carboannulation of unsaturated cyclopropanes and cyclobutanes,[2] 1,2-dienes,[3] 1,3-dienes,[4] 1,4-dienes,[5] and alkynes[6] has proven to be a very versatile method for the synthesis of a wide variety of five- and six-membered ring heterocycles and carbocycles, but it has not previously been applied to the synthesis of cyclic products of larger ring sizes. In view of the ease with which large ring carbocyclic and heterocyclic products are formed by intramolecular π-allylpalladium displacement processes[7] and the pronounced biological activity of many such compounds, particularly nitrogen heterocycles, we have chosen to examine the utility of this annulation process for the synthesis of medium-ring compounds. Our initial efforts have focused on the synthesis of nitrogen heterocycles by palladium-catalyzed annulation of allenes, because nitrogen nucleophiles have proven to be among the best nucleophiles for π-allylpalladium displacements[8] and allenes appear to be the most readily annulated of all of the unsaturated substrates we have so far examined.

Results and Discussion

A variety of reaction conditions similar to those employed previously by us for palladium-catalyzed annulation[2−6] have been examined for the model reaction of *N*-*n*-butyl-4-iodo-4-pentenylamine (**1a**) and 4,5-nonadiene (eq 1). This system was chosen because it was the first



1a **2** **3** (1)

example of large ring formation discovered in our group, and it was anticipated from our earlier work that the more difficult annulations were likely to involve more hindered internal allenes and vinylic halides, rather than aryl halides. The results of that study are summarized in Table 1.

The yield has proven to be highly dependent on the palladium catalyst, the solvent, the base, the reaction time and temperature, and the presence or absence of *n*-Bu_4NCl and PPh_3. As indicated in Table 1 (entry 5), the best results were obtained by using 1 equiv of the organic iodide (0.25 mmol), 2 equiv of allene, 5 mol % of $Pd(dba)_2$, 5 mol % of PPh_3, 1 equiv of *n*-Bu_4NCl, and 5 equiv of Na_2CO_3 in 1.0 mL of DMA at 80 °C for 1 day.

(1) (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3. (b) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. (c) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

(2) (a) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529. (b) Larock, R. C.; Yum, E. K. *Tetrahedron* **1996**, *52*, 2743.

(3) (a) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615. (b) Larock, R. C.; He, Y.; Leong, W.; Han, X.; Refvik, M. D.; Zenner, J. M. *J. Org. Chem.* **1998**, *63*, 2154. (c) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482.

(4) (a) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447. (b) Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882. (c) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. G.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807.

(5) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509.

(6) (a) Maitlis, P. M. *J. Organomet. Chem.* **1980**, *200*, 161. (b) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567. (c) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (d) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 2823. (e) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 6981. (f) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (g) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. (h) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 6471. (i) Smith, D. W.; Youcca, F. D.; Yevich, J. P.; Mattson, R. J.; Williams, A.; Ruediger, E. H.; Combrink, K. D., Pearce, B. C. European Patent 0 548 813 A1, 1993. (j) Park, S. S.; Choi, J.-K.; Yum, E. K. *Tetrahedron Lett.* **1998**, *39*, 627.

(7) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (b) Tsuda, T.; Kiyoi, T.; Saegusa, S. *J. Org. Chem.* **1990**, *55*, 3388. (c) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.

(8) (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*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 585. (e) Hegedus, L. S. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, p 401. (f) Pearson, A. J. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 4, p 889. (g) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (h) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

S0022-3263(98)00516-7 CCC: $15.00
Published on Web 09/11/1998

Table 1. Palladium(0)-Catalyzed Reaction of *N*-*n*-Butyl-4-iodo-4-pentenylamine (1A) and 4,5-Nonadiene (2) (eq 1)[a]

entry	Pd catalyst	solvent	time (days)	base (equiv)	% isolated yield of **3**
1	$PdCl_2$	DMA	3	Na_2CO_3 (5)	18
2	$Pd(OAc)_2$	DMA	3	Na_2CO_3 (5)	41
3	$Pd(PPh_3)_4$	DMA	3	Na_2CO_3 (5)	32
4	$Pd(dba)_2$	DMA	3	Na_2CO_3 (5)	42, 49
5	$Pd(dba)_2$	DMA	1	Na_2CO_3 (5)	61
6	$Pd(dba)_2$	DMA	2	Na_2CO_3 (5)	46
7	$Pd(dba)_2$	DMSO	1	Na_2CO_3 (5)	31
8	$Pd(dba)_2$	DMF	1	Na_2CO_3 (5)	35
9	$Pd(dba)_2$	DMA	1	K_2CO_3 (5)	34
10	$Pd(dba)_2$	DMA	1	$NaHCO_3$ (5)	43
11	$Pd(dba)_2$	DMA	1	Li_2CO_3 (5)	0
12	$Pd(dba)_2$	DMA	1	NaOAc (5)	42
13	$Pd(dba)_2$	DMA	1	KOAc (5)	35
14	$Pd(dba)_2$	DMA	1	Na_2CO_3 (2)	37
15	$Pd(dba)_2$	DMA	1	Na_2CO_3 (5)	35[b]
16	$Pd(dba)_2$	DMA	1	Na_2CO_3 (5)	55[c]
17	$Pd(dba)_2$	DMA	1	Na_2CO_3 (5)	48[d]

[a] All reactions were carried out using 1 equiv of **1a** (0.25 mmol), 2 equiv of **2** (0.5 mmol), 5 mol % of Pd catalyst (0.0125 mmol), 5 mol % of PPh_3 (0.0125 mmol), 1 equiv of *n*-Bu_4NCl (0.25 mmol), 2 or 5 equiv of base (0.5 or 1.25 mmol), and 1.0 mL of solvent at 80 °C. [b] Without PPh_3. [c] At 110 °C. [d] With 1 equiv of LiCl and no *n*-Bu_4NCl.

Under these conditions, a 61% yield of a single isomer of compound **3** was obtained. This amine was later established to be the *E*-isomer by ^1H NMR spectroscopy (see the later discussion).

Employing this optimal procedure, we have studied the heteroannulation of four representative allenes using a variety of vinylic and aryl halides bearing either an *n*-butylamino or a tosylamide group. Vinylic and aryl halides were chosen because they have both proven successful previously in the annulation of allenes to form five- and six-membered ring products.[3] Amine functionality was attractive because there is substantial literature precedent for the use of amines as nucleophiles in π-allylpalladium chemistry and they appear to be among the best nucleophiles for such processes.[8] Although tosylamides have been used much less frequently in π-allylpalladium chemistry,[2,3a,4a,5,9] they have proven to be among the most successful nucleophiles in our previous work on palladium-catalyzed annulation. Our results are summarized in Table 2.

A wide variety of seven-membered-ring nitrogen heterocycles have been formed by this process (Table 2, entries 1−14). Amines and tosylamides have proven equally successful. Good results have been obtained from both aryl (entries 12−14) and vinylic iodides, generating both exocyclic and endocyclic double bonds (entries 1−11), although the aryl iodide required a higher reaction temperature of 100 °C. All four of our representative allenes react well, with little evidence for decreasing yields with increasing steric hindrance.

In all the reactions examined, the annulation is completely regioselective, the sole product being that formed by attack of the nucleophile at the less hindered end of the π-allylpalladium intermediate. The high regioselectivity is a bit surprising, because previous work on the annulation of allenes to form five- and six-membered ring nitrogen heterocycles has not been very regioselective.[3] In fact, 1,2-undecadiene reacted with *N*-tosyl-*2*-iodoaniline to give exclusively the five-membered ring product arising from nucleophilic displacement at the *more* hindered end of the π-allylpalladium intermediate, whereas analogous reactions of this allene with *N*-(*Z*)-(3-iodo-2-methyl-2-propenyl)aniline and *N*-tosyl-2-iodobenzylamine gave mixtures of six-membered-ring regioisomers resulting from attack on both ends of the allylic system.[3a]

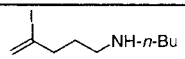
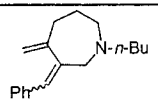
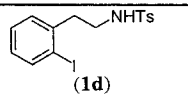
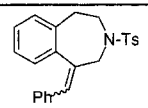
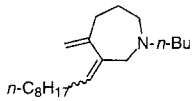
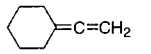
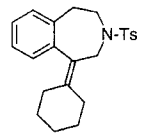
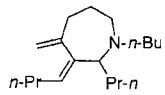
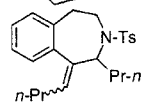
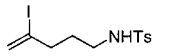
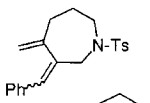
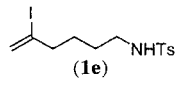
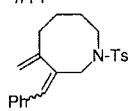
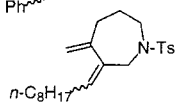
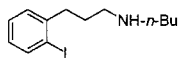
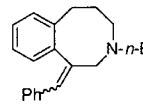
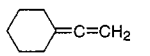
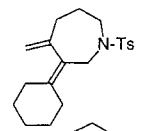
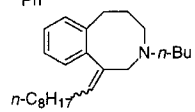
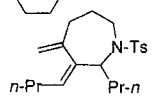
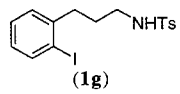
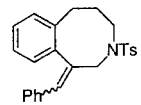
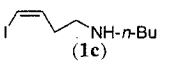
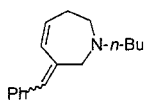
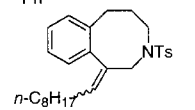
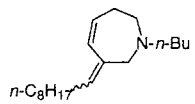
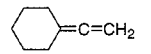
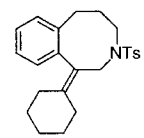
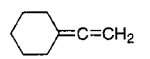
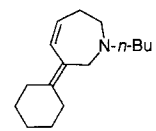
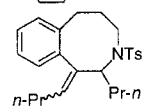
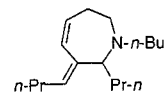
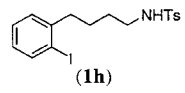
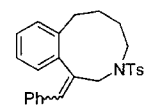
The stereoselectivity of these annulations is generally low and depends primarily on the structures of the allene and the vinylic halide. With the exception of the internal allene 4,5-nonadiene, which has usually produced exclusively or almost exclusively the *E*-isomer (entries 3, 7, 11, and 14), we have usually observed mixtures of stereoisomers. In all but two cases involving 1,2-undecadiene (entries 2 and 5), all the reactions afforded predominantly the *E*-isomer, as can be expected from the thermodynamic preference for *syn*-π-allylpalladium intermediates (see the mechanistic discussion which follows).

The stereochemistry of the products described in Table 2 has been assigned on the basis of 2-D NOESY experiments and chemical shift correlations. In the *E*-isomer of the product described in Table 2, entry 2, the nonylidene vinylic hydrogen and the methylene between the vinylic carbon and the nitrogen generated a clear off-diagonal contour in the NOESY spectrum; furthermore, the allylic CH_2 of the side chain interacted with one of the two terminal methylene protons. In comparing the ^1H NMR spectra of the *Z*- and *E*-isomers in Table 2, entry 2, one notices that the chemical shift of the nonylidene vinylic hydrogen in the *Z*-isomer is further downfield (5.71 ppm) than the corresponding hydrogen in the *E*-isomer (5.36 ppm). In a similar manner, cross-peaks in the NOESY spectrum were observed for the vinylic proton of the butylidene moiety and the methine next to the nitrogen in compound **3** and the allylic hydrogen of the butylidene group and one of the methylene vinylic protons. The stereochemistry of the analogous annulation derivatives described in Table 2, entries 1−11, has been assigned on the basis of these ^1H NMR spectral observations.

The NOESY spectrum of the tetrahydrobenzazepine described in Table 2, entry 14, again exhibited strong interactions between the vinylic hydrogen and the methyne hydrogen in the 2-position of the nitrogen ring and between the allylic CH_2 of the butylidene side chain and the aromatic proton at 7.00 ppm. A similar experiment on the stereoisomeric mixture of the eight-membered rings described in Table 2, entry 19, showed for the major isomer clear cross-peaks between the vinylic proton at 5.73 ppm and the methylene protons adjacent to nitrogen and between the allylic CH_2 of the nonylidene side chain and the aromatic proton at 6.87 ppm, supporting the *E* configuration of the double bond. In contrast, the vinylic proton of the minor isomer showed a cross-peak with the aromatic signal at 6.93 ppm, and the corresponding allylic CH_2 exhibited a cross-peak with the methylene in the 2-position of the nitrogen ring. In both of these latter cases, the chemical shift of the vinylic proton of the *E*-isomer is downfield from that of the corresponding chemical shift of the *Z*-isomer. The stereochemistry of the other products described in entries 12−22 are assigned on the basis of these observations.

Eight-membered-ring nitrogen heterocycles have also been successfully formed by this annulation process, but the process has not proven nearly as general as that involving seven-membered ring formation (entries 15−

Table 2. Synthesis of Medium-Ring Nitrogen Heterocycles[a]

entry	organic iodide	allene	product(s)	% yield[b]	*E*/*Z* ratio[c]	entry	organic iodide	allene	product(s)	% yield[b]	*E*/*Z* ratio[c]
1	 (**1a**)	PhCH=C=CH$_2$		80	55:45	12	 (**1d**)	PhCH=C=CH$_2$		54	78:22
2		*n*-C$_8$H$_{17}$CH=C=CH$_2$		65	21:79	13				31,[d] 95	
3		*n*-PrCH=C=CH-*n*-Pr		61		14		*n*-PrCH=C=CH-*n*-Pr		94	93:7
4	 (**1b**)	PhCH=C=CH$_2$		91	67:33	15	 (**1e**)	PhCH=C=CH$_2$		trace	
5		*n*-C$_8$H$_{17}$CH=C=CH$_2$		51	37:63	16	 (**1f**)	PhCH=C=CH$_2$		66	78:22
6				71		17		*n*-C$_8$H$_{17}$CH=C=CH$_2$		71	78:22
7		*n*-PrCH=C=CH-*n*-Pr		25		18	 (**1g**)	PhCH=C=CH$_2$		94	92:8
8	 (**1c**)	PhCH=C=CH$_2$		83	64:36	19		*n*-C$_8$H$_{17}$CH=C=CH$_2$		73	62:38
9		*n*-C$_8$H$_{17}$CH=C=CH$_2$		85	70:30	20				62	
10				23		21		*n*-PrCH=C=CH-*n*-Pr		68	84:16
11		*n*-PrCH=C=CH-*n*-Pr		81		22	 (**1h**)	PhCH=C=CH$_2$		83[e]	86:14

[a] Reactions were carried out for 24 h at 80 °C (entries 1−11) or at 100 °C (entries 12−22), in DMA as the solvent, using the following molar ratios: organic iodide:allene:Na_2CO_3: *n*−Bu4NCl: Pd(dba)2:PPh_3 = 1:2:5:1:0.05:0.05. [b] Yields are given for isolated products. [c] When the products have been isolated as stereoisomeric mixtures, the *E*/*Z* ratio has been calculated by ^{1}H NMR spectral analysis. [d] At 80 °C. [e] For 3 days.

21). In fact, all attempts to generate eight-membered rings employing vinylic iodides analogous to those used to form the seven-membered rings in entries 1−7 failed completely, except for trace amounts of the product reported in entry 15. Fortunately, aryl halides proved more useful and generally produced good yields of heterocycles, although they again required a reaction temperature of 100 °C. The aryl tosylamide **1g** (entries 18−21) proved clearly superior to the *n*-butylamine derivative **1f** (entries 16 and 17), particularly with the more highly substituted allenes vinylidene cyclohexane and 4,5-nonadiene, which failed to produce any heterocycle when allowed to react with the arylamine **1f**.

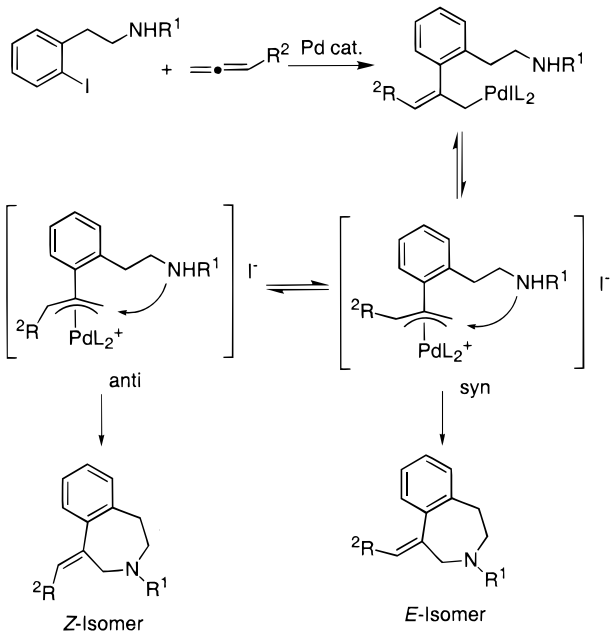
Once again, these reactions forming eight-membered rings have proven to be highly regioselective but only modestly stereoselective. Indeed, nucleophilic attack occurs exclusively on the less hindered end of the π-allylpalladium intermediate, and the stereochemistry of the products changes little from that observed in the formation of seven-membered rings.

Nine-membered ring formation proved very difficult. Since aryl halides had previously proven more successful than vinylic halides and tosyl derivatives more successful than amines, we chose to first prepare *o*-$IC_6H_4(CH_2)_4$-NHTs (**1h**) and examine its utility as an annulating agent. Using our four standard allenes, we were only successful in observing the anticipated nine-membered-ring product in the reaction of phenylallene (Table 2, entry 22). A temperature of 100 °C and 3 days reaction time were required for the reaction to reach completion. All other allenes gave products which appeared to arise by β-elimination of a palladium hydride from the anticipated π-allylpalladium intermediate. This appears to be a common problem when ring closure becomes difficult and explains the generally good results usually obtained in the reactions of phenylallene, where this type of elimination is impossible.

We have only briefly looked at the formation of still larger ring nitrogen heterocycles. We have prepared $H_2C{=}CI(CH_2)_9NH$-*n*-Bu and *o*-$IC_6H_4O(CH_2)_7NHTs$ and examined their reactions with all four of our standard allenes, but we saw no evidence of any 13-membered-ring products in any reaction. It would appear that this methodology is limited to the formation of only the smaller ring nitrogen heterocycles, where the ease of ring formation is seven > eight > nine. Various attempts to form medium-ring lactones, ethers, and carboxamides using this type of annulation process have so far proven unsuccessful.

Our nitrogen heteroannulation process is believed to proceed mechanistically as illustrated in Scheme 1 using an aryl halide as the example. Arylpalladium formation and addition to the allene initially produces a σ-allylpalladium intermediate, which rapidly isomerizes to the corresponding *syn*- and anti-π-allylpalladium intermediates. It is the relative abundance of each of these isomers which appears to determine the stereochemistry of the resulting products. Several factors seem to play a role in the observed distribution of the products. Steric effects in the π-allylpalladium intermediate exerted by substituents originating in the allene and the carbon originally bearing the halide, the number of atoms between the nucleophile and the π-allyl system, and the nature of the nucleophile are all important in determining the *syn*/*anti* ratio of the π-allylpalladium intermediate and ultimately the stereochemistry of the final product. The

Scheme 1



π-allylpalladium intermediate eventually undergoes exclusive intramolecular palladium displacement at the less hindered end of the π-allyl moiety to produce the final observed products.

Conclusions

The palladium-catalyzed heteroannulation of a variety of allenes using both aryl and vinylic iodides bearing tosylamide and amine functionalities provides a useful new route to medium-ring nitrogen heterocycles. Seven-membered-ring products are formed quite readily, while eight-membered rings are a bit more difficult and occasionally require higher temperatures and longer reaction times. Nine-membered-ring products are quite difficult to form. Best results are obtained using aryl halides, rather than vinylic halides, and tosylamides, rather than amines. No success has been achieved in trying to form still larger rings, although only the synthesis of 13-membered rings has been attempted. The exclusive product formed in these annulations is that formed by attack of the nitrogen nucleophile on the less hindered end of the presumed π-allylpalladium intermediate. The nature of the organic halide and the allene appears to determine the stereochemistry of the resulting heterocycle, with the *E*-isomer in all but two cases being the major product.

Experimental Section

Allenes. The following allenes were prepared as indicated. Vinylidene cyclohexane was prepared from (1-chlorocyclohexyl)acetylene using a literature procedure.[10] 1,2-Undecadiene,

(9) (a) Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172. (b) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452. (c) Inoue, Y.; Taguchi, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2721. (d) Byström, S. E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1985**, *26*, 1749. (e) Stolle, A.; Ollivier, J.; Piras, P. P.; Salaun, J.; de Meijere, A. *J. Am. Chem. Soc.* **1992**, *114*, 4051. (f) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826.

(10) Brandsma, L. in *Synthesis of Acetylenes, Allenes, and Cumulenes: a Laboratory Manual*; Elsevier Scientific Publishing Co.: New York, 1981; p 191.

phenylallene, and 4,5-nonadiene were prepared by treating the corresponding 1,1-dibromocyclopropanes with methyllithium according to a literature procedure.[11]

Amines and Tosylamides. *N*-*n*-Butyl-4-iodo-4-pentenylamine (**1a**) was prepared in 76% yield from 5-chloro-2-iodo-1-pentene following the reported procedure:[3b] R_f = 0.17 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H), 1.35 (qt, J = 7.2, 7.2 Hz, 2 H), 1.47 (tt, J = 7.2, 7.2 Hz, 2 H), 1.71 (tt, J = 7.2, 7.2 Hz, 2 H), 2.44 (t, J = 7.2 Hz, 2 H), 2.60 (t, J = 7.2 Hz, 2 H), 2.61 (t, J = 7.2 Hz, 2 H), 5.68 (s, 1 H), 6.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.5, 29.5, 32.3, 43.2, 48.0, 49.6, 111.9, 125.4; IR (neat) 3300, 1610, 891 cm^{-1}. The same procedure was applied to the synthesis of compounds **1c** and **1f**.

N-*n*-Butyl-*(Z)*-4-iodo-3-butenylamine (**1c**) was prepared in 80% yield from *(Z)*-4-iodo-3-butenyl tosylate and *n*-$BuNH_2$: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 6.9 Hz, 3 H), 1.36 (m, 2 H), 1.50 (m, 2 H), 1.88 (br s, 1 H), 2.37 (m, 2 H), 2.65 (t, J = 7.5 Hz, 2 H), 2.76 (t, J = 7.2 Hz, 2 H), 6.27 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.4, 32.0, 35.1, 47.8, 49.4, 83.9, 139.0; IR (neat) 3305, 1610, 891 cm^{-1}.

N-*n*-Butyl-3-(*o*-iodophenyl)propylamine (**1f**) was prepared in 98% yield from 3-(*o*-iodophenyl)propyl chloride and *n*-$BuNH_2$: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H), 1.39 (m, 2 H), 1.50 (m, 2 H), 1.60 (s, 1 H), 1.80 (m, 2 H), 2.72 (m, 6 H), 6.80−7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.5, 30.4, 32.2, 38.5, 49.3, 49.5, 100.5, 127.5, 128.2, 129.2, 139.2, 147.7; IR (neat) 3300, 749 cm^{-1}.

N-Tosyl-4-iodo-4-pentenylamine (**1b**) was prepared in 90% yield from 4-iodo-4-pentenylamine following the procedure reported by Hendrickson:[12] TLC (2:1 hexanes/EtOAc) R_f = 0.4; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2 H), 2.36 (t, J = 6.9 Hz, 2 H), 2.43 (s, 3 H), 2.94 (t, J = 6.3 Hz, 2 H), 5.16 (br s, 1 H), 5.66 (s, 1 H), 5.99 (s, 1 H), 7.32 (d, J = 9.3 Hz, 2 H), 7.77 (d, J = 9.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.2, 29.3, 41.1, 41.6, 110.1, 126.0, 126.6, 129.3, 136.4, 142.8; IR (neat) 3300, 1160 cm^{-1}.

N-Tosyl-2-(*o*-iodophenyl)ethylamine (**1d**) was prepared in 91% yield from 2-(*o*-iodophenyl)ethylamine: TLC (2:1 hexanes/EtOAc) R_f = 0.4; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 2.90 (t, J = 7.2 Hz, 2 H), 3.20 (dt, J = 7.2, 7.2 Hz, 2 H), 4.5 (br s, 1 H), 6.9−7.8 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 21.3, 40.4, 42.6, 100.2, 126.9, 128.2, 129.5, 129.9, 139.2, 139.5, 139.5, 140.0, 143.0; IR (neat) 3280, 1598, 1159, 753 cm^{-1}.

N-Tosyl-5-iodo-5-hexenylamine (**1e**) was prepared in 92% yield from 5-iodo-5-hexenylamine: TLC (1:1 hexanes/EtOAc) R_f = 0.67; ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 4 H), 2.31 (t, J = 9.7 Hz, 2 H), 2.43 (s, 3 H), 2.94 (dt, J = 6.6, 6.6 Hz, 2 H), 4.63 (t, J = 6.6 Hz, 1 H), 5.66 (d, J = 1.2 Hz, 1 H), 5.97 (d, J = 1.2 Hz. 1 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.75 (d, J = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3, 25.6, 27.6, 42.5, 44.2, 112.0, 125.4, 126.7, 129.4, 136.5, 143.0; IR (neat) 3520, 1616, 1159, 894 cm^{-1}.

N-Tosyl-3-(*o*-iodophenyl)propylamine (**1g**) was prepared in 91% yield from 3-(*o*-iodophenyl)propylamine: TLC (2:1 hexanes/EtOAc) R_f = 0.45; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 2 H), 2.43 (s, 3 H), 2.69 (t, J = 7.5 Hz, 2 H), 3.02 (m, 2 H), 4.82 (br s, 1 H), 6.86−7.78 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 21.7, 30.1, 37.8, 42.7, 100.6, 127.3, 128.2, 128.6, 129.7, 129.9, 137.0, 139.7, 143.6, 143.7; IR (neat) 3283, 1158, 760 cm^{-1}.

N-Tosyl-4-(*o*-iodophenyl)butylamine (**1h**) was prepared in 94% yield from 4-(*o*-iodophenyl)butylamine: ^{1}H NMR ($CDCl_3$) δ 1.54 (m, 4 H), 2.41 (s, 3 H), 2.62 (m, 2 H), 2.96 (m, 2 H), 4.79 (m, 1 H), 6.8−7.7 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.0, 29.0, 40.0, 42.9, 100.4, 127.0, 127.3, 127.3, 129.3, 129.6, 136.4, 139.4, 143.3, 144.3; IR (neat) 3281, 1157, 751 cm^{-1}.

4-Iodo-4-pentenylamine, 5-iodo-5-hexenylamine, 2-(*o*-iodophenyl)ethylamine, 3-(*o*-iodophenyl)propylamine, and 4-(*o*-iodophenylbutylamine) were prepared by reduction of the corresponding nitrile following the procedure reported by Yoon and Brown.[13]

4-Iodo-4-pentenenitrile, 5-iodo-5-hexenenitrile, 2-iodophenylacetonitrile, and 4-(*o*-iodophenyl)butanenitrile were prepared from the mesylate of the corresponding alcohol by reaction with NaI in acetone at reflux and displacement of the iodide by stirring the mixture in a solution of NaCN in DMSO at 100 °C.

3-Iodo-3-butene-1-ol, 4-iodo-4penten-1-ol, 5-iodo-5-hexen-1-ol, and 5-chloro-2-iodo-1-pentene were prepared by reacting the corresponding alkynes with NaI and chlorotrimethylsilane following a literature procedure.[3b]

(*Z*)-4-Iodo-3-buten-1-ol was prepared from 4-iodo-3-butyn-1-ol following a literature procedure.[14]

3-(2-Iodophenyl)propanol was prepared in 90% yield by reduction of 3-(2-iodophenyl)propanoic acid with borane following a literature procedure:[15] ^{1}H NMR ($CDCl_3$) δ 1.62 (br s, 1 H), 1.90 (m, 2 H), 2.85 (t, J = 9.8 Hz, 2 H), 3.78 (t, J = 9.8 Hz, 2 H), 6.93−7.92 (m, 4 H).

3-(2-Iodophenyl)propanoic acid was prepared in 90% yield from diethyl 2-iodobenzyl malonate following the procedure reported by Cooke and Widene:[16] ^{1}H NMR ($CDCl_3$) δ 2.74 (t, J = 7.9 Hz, 2 H), 3.15 (t, J = 7.9 Hz, 2 H), 6.93−7.92 (m, 4 H), 10.00 (br s, 1 H).

Diethyl 2-iodobenzyl malonate was prepared from 2-iodobenzyl chloride and diethyl malonate following a literature procedure.[17]

3-(2-Iodophenyl)propanenitrile was prepared in 94% yield by decarboxylation of ethyl 2-cyano-3-(2-iodophenyl)propanoate following a procedure reported by Krapcho:[18] ^{1}H NMR ($CDCl_3$) δ 2.56 (t, J = 7.2 Hz, 2 H), 2.97 (t, J = 7.2 Hz, 2 H), 6.93−7.92 (m, 4 H).

Ethyl 2-cyano-3-(2-iodophenyl)propanoate was prepared in 90% yield from the reduction of ethyl 2-cyano-3-(2-iodophenyl)-acrylate following the procedure reported by Nanjo:[19] ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3 H), 3.15 (dd, J = 9.9, 13.8 Hz, 1 H), 3.40 (m, 1 H), 3.85 (dd, J = 9.9, 13.8 Hz, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 6.93−7.82 (m, 4 H).

Ethyl 2-cyano-3-(2-iodophenyl)acrylate was prepared in 96% yield from the condensation of 2-iodobenzaldehyde and ethyl cyanoacetate following the procedure reported by Kasturi:[20] ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 8.7 Hz, 3 H), 4.35 (q, J = 8.7 Hz, 2 H), 7.10−8.00 (m, 4 H), 8.40 (s, 1 H).

General Procedure for the Palladium-Catalyzed Heteroannulation Reactions. Into a 1- or 2-dram screw-capped vial, equipped with a Teflon-lined cap and a magnetic stirring bar, were placed $Pd(dba)_2$ (5 mol %), Ph_3P (5 mol %), *n*-Bu_4-NCl (1 equiv), sodium carbonate (5 equiv), the organic halide (0.25 mmol), the allene (2 equiv), and 1 mL of *N*,*N*-dimethylacetamide (DMA). The vial was then capped and suspended in an oil bath at the desired reaction temperature for the appropriate period of time. The reaction was monitored by TLC. When the reaction was considered complete as measured by disappearance of the organic iodide, the mixture was allowed to cool to room temperature and was directly chromatographed on a silica gel column (230−400 mesh silica gel) with an appropriate eluent, unless otherwise specified. The desired products were collected, and the solvents were removed by rotary evaporation. The products were further purified by flash column chromatography if necessary. The following compounds have been prepared using this general procedure.

***N*-*n*-Butyl-3-benzylidene-4-methyleneazepane (Table 2, Entry 1).** Obtained as a separable mixture of the *E*- and the *Z*-isomers (*E*/*Z* = 55:45). *E*-isomer: oil; TLC (1:2 hexanes/acetone) R_f = 0.28; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.8 Hz, 3

(11) (a) Landor, P. D. *The Chemistry of Allenes*; Academic Press: New York, 1982; Vol. 3, p 867. (b) Skattebol, L. *Acta Chem. Scand.* 1963, *17*, 1683.

(12) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517.

(13) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927.

(14) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083.

(15) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. *J. Org. Chem.* **1973**, *38*, 2786.

(16) Cooke, M. P.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381.

(17) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171.

(18) Krapcho, A. P. *Synthesis* **1982**, 893.

(19) Nanjo, K.; Suzuki, K.; Sekiya, M. *Chem. Pharm. Bull.* **1977**, *25*, 2396.

(20) Kasturi, T. R.; Abraham, E. M.; Prasad, R. S. *Tetrahedron* **1974**, *30*, 2887.'

H), 1.20−1.40 (m, 2 H), 1.42−1.55 (m, 2 H), 1.70−1.80 (m, 2 H), 2.40−2.60 (m, 4 H), 2.77−2.85 (m, 2 H), 3.44 (s, 2 H), 4.86 (d, J = 1.7 Hz, 1 H), 4.90 (s, 1 H), 6.27 (s, 1 H), 7.05−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 26.9, 29.7, 34.9, 54.4, 55.7, 62.8, 114.8, 126.3, 127.1, 127.5, 128.0, 128.0, 128.1, 128.8 (one peak is not seen due to overlap); IR (neat) 1582, 1451, 751 cm^{-1}; HRMS m/z 255.1998 (calcd 255.1987 for $C_{18}H_{25}N$). *Z*-isomer: oil; TLC (1:2 hexanes/acetone) R_f = 0.63; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 8.4 Hz, 3 H), 1.22−1.33 (m, 4 H), 1.71−1.76 (m, 2 H), 2.42−2.48 (m, 4 H), 2.80 (t, J = 5.6 Hz, 2 H), 3.53 (s, 2 H), 4.81 (s, 1 H), 5.24 (d, J = 1.8 Hz, 1 H), 6.80 (s, 1 H), 7.22−7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 28.8, 29.5, 35.6, 54.7, 55.3, 57.9, 109.8, 126.5, 128.1, 129.1, 138.1, 143.4, 153.2 (one peak is not seen due to overlap); IR (neat) 1657, 890 cm^{-1}; HRMS m/z 255.1991 (calcd 255.1987 for $C_{18}H_{25}N$).

***N*-*n*-Butyl-4-methylene-3-nonylideneazepane (Table 2, Entry 2).** Obtained as a separable mixture of the *E*- and the *Z*-isomers (*E*/*Z* = 21:79). *Z*-isomer: oil; TLC (1:2 hexanes/acetone) R_f = 0.34; ^{1}H NMR ($CDCl_3$) δ 0.85−0.96 (m, 6 H), 1.20−1.50 (m, 16 H), 1.62−1.70 (m, 2 H), 2.06 (q, J = 7.2 Hz, 2 H), 2.33−2.37 (m, 2 H), 2.42−2.47 (m, 2 H), 2.78 (t, J = 5.4 Hz, 2 H), 3.36 (s, 2 H), 4.63 (t, J = 0.9 Hz, 1 H), 5.01 (d, J = 2.4 Hz, 1 H), 5.72 (t, J = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.8, 22.7, 28.0, 28.7, 29.4, 29.5, 29.6, 29.7, 29.7, 29.9, 31.9, 35.7, 53.0, 55.0, 58.5, 108.3, 127.9, 140.2, 153.0; IR (neat) 1463, 884 cm^{-1}; HRMS m/z 291.2921 (calcd 291.2921 for $C_{20}H_{37}N$). *E*-isomer: oil; TLC (1:2 hexanes/acetone) R_f = 0.32; ^{1}H NMR ($CDCl_3$) δ 0.75−0.95 (m, 6 H), 1.15−1.50 (m, 16 H), 1.60−1.70 (m, 2 H), 2.17 (q, J = 7.5 Hz, 2 H), 2.33 (t, J = 5.9 Hz, 2 H), 2.47 (t, J = 7.7 Hz, 2 H), 2.79 (t, J = 5.8 Hz, 2 H), 3.33 (s, 2 H), 4.82 (d, 1 H, J = 2.2 Hz), 5.02 (t, 1 H, J = 2.2 Hz), 5.74 (t, 1 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 22.7, 27.6, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 30.3, 31.9, 36.0, 53.9, 61.3, 105.2, 113.6, 130.3, 148.1; IR (neat) 1688, 1604, 895 cm^{-1}; HRMS m/z 291.2921 (calcd 291.2921 for $C_{20}H_{37}N$).

***N*-*n*-Butyl-3-*(E)*-butylidene-4-methylene-2-propylazepane (Table 2, Entry 3)**: oil; TLC (1:1 hexanes/EtOAc) R_f = 0.48; ^{1}H NMR ($CDCl_3$) δ 0.85−0.95 (m, 9 H), 1.20−1.50 (m, 10 H), 1.52−1.70 (m, 2 H), 2.02−2.15 (m, 2 H), 2.29−2.37 (m, 2 H), 2.42−2.51 (m, 2 H), 2.76−2.80 (m, 2 H), 2.94 (dd, J = 8.3, 5.7 Hz, 1 H), 4.63 (t, J = 1.2 Hz, 1 H), 4.97−4.99 (br s, 1 H), 5.17 (t, J = 6.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 20.2, 21.0, 23.8, 24.6, 29.2, 29.9, 30.4, 34.4, 35.4, 49.9, 52.5, 68.3, 113.8, 126.4, 129.9, 146.9; IR (neat) 1622, 897, 760 cm^{-1}; HRMS m/z 263.2608 (calcd 263.2613 for $C_{18}H_{33}N$).

***N*-Tosyl-3-benzylidene-4-methyleneazepane (Table 2, entry 4).** Obtained as an inseparable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 67:33): oily mixture; ^{1}H NMR ($CDCl_3$) δ 1.64−1.82 (m, 2 H), 2.22−2.35 (m, 2 H), 2.39 (s, 0.99 H), 2.40 (s, 2.01 H), 3.33−3.35 (m, 1.34 H), 3.41 (t, J = 5.7 Hz, 0.66 H), 4.05 (s, 1.34 H), 4.24 (s, 0.66 H), 4.77 (t, J = 0.6 Hz, 0.33 H), 4.85 (d, J = 1.5 Hz, 0.67 H), 4.99 (t, J = 0.6 Hz, 0.67 H), 5.07 (d, J = 1.5 Hz, 0.33 H), 6.28 (s, 0.67 H), 6.68 (s, 0.33 H), 7.18−7.40 (m, 6 H), 7.58 (d, J = 9.8 Hz, 1 H), 7.75 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 29.8, 31.0, 34.6, 34.8, 47.8, 49.2, 51.3, 56.6, 113.0, 115.8, 126.2, 127.0, 127.1, 127.1, 127.5, 128.1, 128.6, 128.8, 129.3, 129.5, 132.3, 136.2, 136.3, 139.0, 140.7, 142.8, 145.8, 150.3; IR (neat) 1623, 1163, 734 cm^{-1}; HRMS m/z 353.1431 (calcd 353.1450 for $C_{20}H_{23}NO_2S$).

***N*-Tosyl-4-methylene-3-nonylideneazepane (Table 2, Entry 5).** Obtained as an inseparable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 37:63): oily mixture; ^{1}H NMR ($CDCl_3$) δ 0.88−0.95 (m, 3 H), 1.15−1.22 (m, 12 H), 1.60−1.80 (m, 2 H), 2.00−2.28 (m, 4 H), 2.41 (s, 3 H), 3.28−3.39 (m, 2 H), 3.90 (s, 0.74 H), 4.00 (s, 1.26 H), 4.59 (s, 0.63 H), 4.68 (s, 0.37 H), 4.87 (s, 0.63 H), 4.97 (s, 0.37 H), 5.39 (t, J = 7.5 Hz, 0.37 H), 5.69 (t, J = 7.2 Hz, 0.63 H), 7.26 (d, J = 7.8 Hz, 2 H), 7.65 (d, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.4, 22.7, 27.9, 29.1, 29.2, 29.3, 29.4, 29.5, 29.8, 30.1, 30.3, 31.9, 34.7, 35.7, 47.9, 48.9, 51.1, 55.4, 110.9, 114.9, 127.0, 127.2, 127.3, 128.6, 129.4, 130.2, 136.8, 137.4, 137.7, 142.8, 145.8, 150.1; IR (neat) 1600, 1160, 734 cm^{-1}; HRMS m/z 389.2386 (calcd 389.2389 for $C_{23}H_{35}NO_2S$).

***N*-Tosyl-3-cyclohexylidene-4-methyleneazepane (Table 2, Entry 6)**: oil; TLC (4:1 hexanes/EtOAc) R_f = 0.48; ^{1}H NMR ($CDCl_3$) δ 1.40−1.60 (m, 6 H), 1.60−1.75 (m, 2 H), 2.05−2.22 (m, 6 H), 2.42 (s, 3 H), 3.22−3.30 (m, 2 H), 3.91 (s, 2 H), 4.61 (s, 1 H), 4.91 (s, 1 H), 7.27 (d, J = 8.1 Hz, 2 H), 7.36 (d, J = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.7, 28.0, 28.5, 28.6, 30.1, 32.1, 36.1, 48.4, 49.5, 113.2, 127.2, 128.2, 129.5, 138.1, 142.8, 148.0 (one peak is not seen due to overlap); IR (neat) 1651, 1162, 893 cm^{-1}; HRMS m/z 345.1756 (calcd 345.1763 for $C_{20}H_{27}NO_2S$).

***N*-Tosyl-3-*(E)*-butylidene-4-methylene-2-propylazepane (Table 2, Entry 7)**: oil; TLC (4:1 hexanes/EtOAc) R_f = 0.51; ^{1}H NMR ($CDCl_3$) δ 0.75−0.98 (m, 6 H), 1.15−1.28 (m, 4 H), 1.45−1.65 (m, 4 H), 1.98 (q, J = 7.9 Hz, 2 H), 2.06−2.12 (m, 1 H), 2.22−2.38 (m, 1 H), 2.40 (s, 3 H), 3.00−3.18 (m, 1 H), 3.62−3.88 (m, 1 H), 4.41 (t, 1 H, J = 7.8 Hz), 4.62 (s, 1 H), 4.98 (s, 1 H), 5.26 (t, J = 7.8 Hz, 1 H), 7.24 (d, 2 H, J = 11.1 Hz), 7.69 (d, 2 H, J = 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.6, 23.1, 27.4, 27.6, 28.4, 29.2, 33.8, 35.2, 43.9, 50.5, 110.0, 127.1, 127.3, 128.6, 129.0, 132.7, 137.6, 143.1; IR (neat) 1627, 1456, 1157, 900 cm^{-1}; HRMS m/z 361.2069 (calcd 361.2076 for $C_{21}H_{31}NO_2S$).

***N*-*n*-Butyl-3-benzylidene-2,3,6,7-tetrahydro-1*H*-azepine (Table 2, Entry 8).** Obtained as a separable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 64:36). *E*-isomer: oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3 H), 1.28−1.35 (m, 2 H), 1.40−1.58 (m, 2 H), 2.40−2.56 (m, 4 H), 2.93 (t, 2 H, J = 5.4 Hz), 3.58 (s, 2 H), 5.89−5.95 (m, 1 H), 6.37 (s, 1 H), 6.43 (d, J = 8.4 Hz, 1 H), 7.20−7.70 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.6, 27.7, 29.9, 54.4, 54.6, 54.7, 126.7, 128.1, 128.1, 128.1, 129.2, 130.9, 132.2, 134.2; IR (neat) 1674, 1102, 760 cm^{-1}; HRMS m/z 241.1831 (calcd 241.1831 for $C_{17}H_{23}N$). *Z*-isomer: oil; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.2 Hz, 3 H), 1.22−1.40 (m, 4 H), 2.38−2.45 (m, 4 H), 3.01 (t, J = 5.4 Hz, 2 H), 3.64 (s, 2 H), 5.73−5.80 (m, 1 H), 6.23 (d, J = 11.1 Hz, 1 H), 6.56 (s, 1 H), 7.20−7.50 (m, 5 H);^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 27.9, 30.1, 54.0, 54.2, 61.3, 126.8, 128.0, 128.6, 129.4, 129.7, 130.1, 132.0, 133.4; IR (neat) 1673, 1167, 760 cm^{-1}; HRMS m/z 241.1828 (calcd 241.1831 for $C_{17}H_{23}N$).

***N*-*n*-Butyl-3-nonylidene-2,3,6,7-tetrahydro-1*H*-azepine (Table 2, Entry 9).** Obtained as a separable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 70:30). *E*-isomer: oil; ^{1}H NMR ($CDCl_3$) δ 0.78−0.99 (m, 6 H), 1.20−1.40 (m, 14 H), 1.41−1.55 (m, 2 H), 2.10 (q, J = 7.9 Hz, 2 H), 2.32−2.36 (m, 2 H), 2.38−2.47 (m, 2 H), 2.87 (t, J = 5.4 Hz, 2 H), 3.41 (s, 2 H), 5.33 (t, J = 7.2 Hz, 1 H), 5.72−5.80 (m, 1 H), 6.32 (d, J = 11.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.8, 22.7, 27.8, 27.9, 29.3, 29.3, 29.3, 29.5, 29.6, 29.9, 31.9, 53.3, 54.3, 61.1, 127.8, 127.8, 130.9, 132.5; IR (neat) 1465, 721 cm^{-1}; HRMS m/z 277.2770 (calcd 277.2770 for $C_{19}H_{35}N$). *Z*-isomer: oil; ^{1}H NMR ($CDCl_3$) δ 0.82−0.98 (m, 6 H), 1.20−1.40 (m, 14 H), 1.41−1.52 (m, 2 H), 2.09 (q, J = 7.9 Hz, 2 H), 2.32−2.40 (m, 2 H), 2.41−2.47 (m, 2 H), 2.89 (t, J = 5.7 Hz, 2 H), 3.54 (s, 2 H), 5.45−5.58 (m, 2 H), 6.02 (d, J = 12.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 22.7, 28.2, 28.4, 29.3, 29.3, 29.4, 29.5, 29.8, 30.2, 31.9, 53.2, 54.2, 54.7, 128.0, 134.1, 134.2, 135.7; IR (neat) 1465, 722 cm^{-1}; HRMS m/z 277.2771 (calcd 277.2770 for $C_{19}H_{35}N$).

***N*-*n*-Butyl-3-cyclohexylidene-2,3,6,7-tetrahydro-1*H*-azepine (Table 2, Entry 10)**: oil; TLC (1:2 hexanes/acetone) R_f = 0.06; ^{1}H NMR ($CDCl_3$) δ 0.80−1.00 (m, 5 H), 1.20−1.40 (m, 4 H), 1.50−1.70 (m, 4 H), 2.25−2.35 (m, 4 H), 2.40−2.60 (m, 4 H), 2.70−2.95 (br s, 2 H), 3.53 (br s, 2 H), 5.69 (dt, J = 11.1, 5.1 Hz, 1 H), 6.42 (d, J = 11.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.9, 26.9, 28.3, 28.8, 31.3, 31.4, 52.4, 53.9, 55.3, 129.8, 130.9, 132.1, 134.3; IR (neat) 1598, 1465 cm^{-1}; HRMS m/z 233.2140 (calcd 233.2143 for $C_{16}H_{27}N$).

***N*-*n*-Butyl-3-*(E)*-butylidene-2-propyl-2,3,6,7-tetrahydro-1*H*-azepine (Table 2, Entry 11)**: oil; TLC (1:2 hexanes/acetone) R_f = 0.05; ^{1}H NMR ($CDCl_3$) δ 0.80−1.00 (m, 9 H), 1.05−1.85 (m, 8 H), 2.03 (q, J = 7.9 Hz, 2 H), 2.08−2.18 (m, 2 H), 2.40−2.68 (m, 1 H and t, J = 7.8 Hz, 2 H), 2.70−2.80 (m, 1 H), 2.98−3.05 (m, 2 H), 3.07−3.15 (m, 1 H), 5.30 (t, J = 7.2 Hz, 1 H), 5.66 (dt, J = 11.7, 6.3 Hz, 1 H), 6.09 (d, J = 11.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.0, 14.1, 20.4, 20.8, 22.8, 28.5,

29.7, 29.9, 36.3, 47.8, 52.9, 69.6, 125.9, 129.9, 131.7, 137.1; IR (neat) 1463 cm^{-1}; HRMS *m/z* 249.2457 (calcd 249.2460 for $C_{17}H_{31}N$).

***N*-Tosyl-1-benzylidene-2,3,4,5-tetrahydro-1*H*-3-benzazepine (Table 2, Entry 12).** Obtained as an inseparable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 78:22): oily mixture; TLC (4:1 hexanes/EtOAc) R_f = 0.31;^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3 H), 2.90 (t, *J* = 6.0 Hz, 0.44 H), 2.98−3.02 (m, 1.56 H), 3.42−3.45 (m, 1.56 H), 3.51 (t, *J* = 12.0 Hz, 0.44 H), 3.98 (s, 1.56 H), 4.29 (s, 0.44 H), 6.72 (s, 0.22 H), 6.79 (s, 0.78 H), 6.80−7.50 (m, 11 H), 7.68 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 36.1, 47.4, 55.8, 127.2, 127.3, 127.7, 127.9, 128.5, 129.3, 129.4, 129.5, 129.6, 131.8, 132.0, 136.2, 137.3, 138.3, 140.0, 143.2; IR (neat) 1598, 1163, 920 cm^{-1}; HRMS *m/z* 389.1449 (calcd 389.1450 for $C_{24}H_{23}NO_2S$).

***N*-Tosyl-1-cyclohexylidene-2,3,4,5-tetrahydro-1*H*-3-benzazepine (Table 2, Entry 13)**: mp 128−130 °C; TLC (4:1 hexanes/EtOAc) R_f = 0.48; ^{1}H NMR ($CDCl_3$) δ 1.40−1.65 (m, 4 H), 1.68−1.70 (m, 2 H), 2.01−2.10 (m, 2 H), 2.37 (s, 3 H), 2.40−2.60 (m, 3 H), 2.61−2.81 (m, 2 H), 3.00−3.10 (m, 1 H), 3.87−3.93 (m, 1 H), 4.78 (dd, *J* = 12.9, 0.9 Hz, 1 H), 6.90−7.00 (m, 1 H), 7.02−7.18 (m, 2 H), 7.42−7.55 (m, 3 H), 7.60 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.6, 28.3, 28.6, 30.4, 32.4, 35.5, 48.1, 49.2, 126.2, 126.3, 126.6, 127.3, 128.8, 128.9, 129.5, 134.4, 138.2, 142.5, 142.8, 143.2; IR (neat) 1598, 1164, 714 cm^{-1}; HRMS *m/z* 381.1762 (calcd 381.1763 for $C_{23}H_{27}NO_2S$).

***N*-Tosyl-1-*(E)*-butylidene-2-propyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (Table 2, Entry 14).** The mixture of the *E*- and *Z*-isomers (*E*/*Z* = 93:7) first isolated was further purified by flash column chromatography to afford a pure sample of the *E*-isomer (85% yield): oil; TLC (4:1 hexanes/EtOAc) R_f = 0.47; ^{1}H NMR ($CDCl_3$) δ 0.70−0.80 (m, 6 H), 1.15−1.40 (m, 6 H), 1.70−1.85 (m, 1 H), 1.80−2.00 (m, 1 H), 2.40 (s, 3 H), 2.55 (dd, *J* = 14.9, 5.7 Hz, 1 H), 2.80 (t, *J* = 13.5 Hz, 1 H), 3.15 (dd, *J* = 14.7, 10.8 Hz, 1 H), 3.93 (dd, *J* = 14.7, 6.0 Hz, 1 H), 4.63−4.65 (m, 1 H), 5.69 (dd, *J* = 8.1, 6.6 Hz, 1 H), 6.92−7.00 (m, 1 H), 7.00−7.10 (m, 1 H), 7.10−7.18 (m, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.75 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 19.3, 21.7, 22.9, 31.0, 33.0, 36.7, 41.5, 62.3, 126.3, 127.4, 127.6, 129.2, 129.7, 130.9, 133.4, 137.6, 138.8, 139.1, 140.3, 143.0; IR (neat) 1597, 1161, 754 cm^{-1}; HRMS *m/z* 397.5855 (calcd 397.5852 for $C_{24}H_{31}NO_2S$). The following ^{1}H NMR data for the *Z* isomer were taken from the mixture: δ 4.93−5.05 (m, 1 H), 5.12−5.20 (m, 1 H), 5.57 (t, *J* = 6.3 Hz, 1 H).

***N*-*n*-Butyl-1-benzylidene-1,2,3,4,5,6-hexahydro-3-benzazocine (Table 2, Entry 16).** Obtained as a separable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 78:22). *E*-isomer: oil; TLC (4:1 hexanes/EtOAc) R_f = 0.41; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, *J* = 7.2 Hz, 3 H), 0.80−1.00 (m, 1 H), 1.10−1.20 (m, 2 H), 1.20−1.40 (m, 3 H), 1.60−1.80 (m, 1 H), 2.48 (t, *J* = 7.5 Hz, 2 H), 2.60−2.75 (m, 3 H), 3.47 (s, 2 H), 6.52 (s, 1 H), 6.80−6.95 (m, 2 H), 7.00−7.30 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.2, 30.0, 32.2, 33.0, 53.3, 55.8, 68.1, 126.5, 126.6, 126.7, 127.1, 127.4, 128.0, 128.6, 128.9, 136.8, 140.6, 141.5, 142.5; IR (neat) 1599, 751 cm^{-1}; HRMS *m/z* 305.2139 (calcd 305.2144 for $C_{22}H_{27}N$). *Z*-isomer: oil; TLC (4:1 hexanes/EtOAc) R_f = 0.51; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, *J* = 7.2 Hz, 3 H), 1.10−1.40 (m, 6 H), 1.60−1.75 (m, 2 H), 2.39−2.49 (m, 3 H), 2.80−2.86 (m, 1 H), 3.46 (s, 2 H), 6.46 (s, 1 H), 7.00−7.45 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.2, 30.2, 31.8, 32.4, 54.8, 58.0, 59.9, 125.6, 126.6, 127.0, 127.5, 127.9, 128.0, 128.0, 128.1, 128.4, 128.6, 129.2, 129.3, 129.5; IR (neat) 1599, 751 cm^{-1}; HRMS *m/z* 305.2139 (calcd 305.2144 for $C_{22}H_{27}N$).

***N*-*n*-Butyl-1,2,3,4,5,6-hexahydro-1-nonylidene-3-benzazocine (Table 2, Entry 17).** The mixture of the *E*- and *Z*-isomers (*E*/*Z* = 78:22) first isolated was further purified by flash column chromatography to obtain a pure sample of the *E*-isomer (56% yield): oil; ^{1}H NMR ($CDCl_3$) δ 0.80−0.95 (m, 6 H), 1.05−1.40 (m, 18 H), 1.60−1.80 (m, 3 H), 2.44 (t, *J* = 7.5 Hz, 2 H), 2.48−2.64 (m, 3 H), 3.28 (s, 2 H), 5.58 (t, *J* = 6.9 Hz, 1 H), 6.90−6.93 (m, 1 H), 7.10−7.20 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 20.3, 22.7, 28.8, 29.2, 29.3, 29.3, 29.4, 29.9, 31.9, 32.4, 32.7, 52.7, 52.1, 66.3, 125.7, 126.7, 127.5, 128.4, 129.5, 129.5, 129.6, 140.5; IR (neat) 1457, 748 cm^{-1}; HRMS *m/z* 341.3073 (calcd 341.3083 for $C_{23}H_{39}N$). The following ^{1}H NMR data for the *Z* isomer were taken from the mixture: δ 3.35 (s, 2 H), 5.33 (t, *J* = 6.9 Hz, 1 H).

***N*-Tosyl-1-benzylidene-1,2,3,4,5,6-hexahydro-3-benzazocine (Table 2, Entry 18).** Obtained as an inseparable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 92:8): oily mixture; TLC (4:1 hexanes/EtOAc) R_f = 0.31; ^{1}H NMR ($CDCl_3$) δ 1.60−1.80 (m, 1 H), 1.80−1.90 (m, 1 H), 2.36 (s, 0.24 H), 2.39 (s, 2.76 H), 2.50−2.70 (m, 2 H), 3.00−3.20 (m, 1 H), 3.20−3.50 (m, 1 H), 3.80−4.00 (br s, 0.92 H), 4.00−4.18 (br s, 0.92 H), 4.20 (s, 0.16 H), 6.59 (s, 0.08 H), 6.62 (s, 0.92 H), 6.88−7.40 (m, 11 H), 7.45 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 32.1, 32.2, 48.7, 60.9, 127.1, 127.1, 127.2, 127.4, 127.9, 128.2, 128.7, 129.5, 129.6, 130.2, 135.5, 135.8, 137.9, 139.1, 140.1, 142.8; IR (neat) 1598, 1162, 754 cm^{-1}; HRMS *m/z* 403.1604 (calcd 403.1606 for $C_{25}H_{25}NO_2S$).

***N*-Tosyl-1,2,3,4,5,6-hexahydro-1-nonylidene-3-benzazocine (Table 2, Entry 19).** Obtained as an inseparable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 62:38): oily mixture; TLC (4:1 hexanes/EtOAc) R_f = 0.41; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.18−1.30 (m, 14 H), 1.73 (q, *J* = 7.2 Hz, 1.24 H), 2.35 (q, *J* = 7.2 Hz, 0.76 H), 2.38 (s, 3 H), 2.50−2.70 (m, 1.24 H), 2.68−2.80 (m, 0.76 H), 2.99−3.05 (m, 0.76 H), 3.00−3.15 (m, 1.24 H), 3.80 (br s, 1.24 H), 3.90 (s, 0.76 H), 5.48 (t, *J* = 6.9 Hz, 0.38 H), 5.73 (t, *J* = 7.9 Hz, 0.62 H), 6.87 (dd, *J* = 7.2, 0.9 Hz, 0.62 H), 6.94 (dd, *J* = 7.2, 0.9 Hz, 0.38 H), 7.11−7.20 (m, 5 H), 7.48 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.3, 22.5, 27.8, 28.7, 28.9, 29.0, 29.1, 29.2, 31.6, 31.7, 32.2, 48.1, 48.3, 51.9, 59.0, 126.2, 126.9, 127.0, 127.4, 127.7, 128.6, 128.8, 129.3, 132.7, 133.8, 136.5, 139.0, 139.9, 142.6; IR (neat) 1588, 1162 cm^{-1}; HRMS *m/z* 439.2545 (calcd 439.2545 for $C_{27}H_{37}NO_2S$).

***N*-Tosyl-1-cyclohexylidene-1,2,3,4,5,6-hexahydro-3-benzazocine (Table 2, Entry 20)**: mp 90−92 °C; TLC (4:1 hexanes/EtOAc) R_f = 0.37; ^{1}H NMR ($CDCl_3$) δ 1.38−1.49 (m, 2 H), 1.50−1.70 (m, 6 H), 1.81 (t, *J* = 6.3 Hz, 2 H), 1.88−2.00 (m, 1 H), 2.38 (s, 3 H), 2.40−2.50 (m, 1 H), 2.57 (td, *J* = 13.5, 3.9 Hz, 1 H), 2.80 (dt, *J* = 3.6, 13.2 Hz, 1 H), 2.90−3.10 (m, 2 H), 3.35 (d, *J* = 13.3 Hz, 1 H), 4.48 (d, *J* = 13.5 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 7.08−7.19 (m, 5 H), 7.48 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.6, 27.8, 28.1, 29.9, 31.5, 32.3, 32.5, 48.5, 52.5, 126.3, 127.0, 127.0, 127.9, 128.7, 129.4, 136.4, 140.3, 141.0, 141.6, 142.6, 142.6; IR (neat) 1598, 1159, 748 cm^{-1}; HRMS *m/z* 395.1917 (calcd 395.1919 for $C_{24}H_{29}NO_2S$).

***N*-Tosyl-1-butylidene-1,2,3,4,5,6-hexahydro-2-propyl-3-benzazocine (Table 2, Entry 21).** Obtained as an inseparable mixture of *E*- and *Z*-isomers (*E*/*Z* = 84:16): oily mixture; TLC (4:1 hexanes/EtOAc) R_f = 0.50; ^{1}H NMR ($CDCl_3$) δ 0.70−0.85 (m, 6 H), 0.85−1.05 (m, 1 H), 1.10−1.70 (m, 7 H), 2.20−2.50 (m, 4 H), 2.41 (s, 2.52 H), 2.42 (s, 0.48 H), 2.57 (dt, *J* = 4.5, 13.2 Hz, 0.84 H), 2.83 (dt, *J* = 4.2, 13.2 Hz, 0.16 H), 3.33 (dd, *J* = 14.7, 3.9 Hz, 0.16 H), 3.41 (dd, *J* = 4.2, 14.7 Hz, 0.84), 4.54 (dd, *J* = 8.4, 5.9 Hz, 0.84 H), 5.04 (dd, *J* = 9.6, 4.4 Hz, 0.16 H), 5.34 (t, *J* = 7.2 Hz, 0.16 H), 5.67 (t, *J* = 7.2 Hz, 0.84 H), 6.82 (d, *J* = 7.5 Hz, 0.84 H), 6.84−7.00 (m, 0.48 H), 7.00−7.24 (m, 2.68 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.8, 21.4, 22.2, 29.1, 30.5, 32.6, 32.7, 33.0, 39.7, 64.8, 125.6, 127.1, 127.6, 128.8, 129.3, 130.0, 133.3, 134.2, 137.4, 139.3, 139.7, 142.7; IR (neat) 1598, 1157, 760 cm^{-1}; HRMS *m/z* 411.2250 (calcd 411.2232 for $C_{25}H_{33}NO_2S$).

***N*-Tosyl-1-benzylidene-1,2,3,4,5,6,7-heptahydro-1*H*-benzazonine (Table 2, Entry 22).** Obtained as an inseparable mixture of the *E*- and *Z*-isomers (*E*/*Z* = 86:14): oily mixture; TLC (4:1 hexanes/EtOAc) R_f = 0.40; ^{1}H NMR ($CDCl_3$) δ 1.20−1.70 (m, 2 H), 1.80−2.00 (m, 1 H), 2.39 (s, 0.42 H), 2.43 (s, 2.58 H), 2.50−2.65 (m, 1 H), 2.80−3.00 (m, 2H + 0.86 H), 3.78 (ddd, *J* = 3.9, 7.2, 12.5 Hz, 0.86 H), 3.95 (d, *J* = 12.7 Hz, 0.86 H), 4.05 (d, *J* = 12.7 Hz, 0.86 H), 4.18−4.28 (m, 0.28 H), 4.30−4.33 (m, 0.28 H), 6.58 (s, 0.14 H), 6.80 (s, 0.86 H), 6.80−7.40 (m, 11 H), 7.60 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 22.9, 25.6, 27.4, 27.5, 27.7, 31.0, 31.9, 48.2, 51.3, 58.3, 60.8, 126.7, 127.1, 127.4, 127.8, 127.9, 128.3, 128.8, 129.3, 129.4, 129.5, 130.8, 132.6, 136.2, 137.7, 139.4, 140.7, 143.1; IR (neat)

1598, 1157, 760 cm^{-1}; HRMS *m*/*z* 418.1802 (calcd 418.1841 for $C_{26}H_{28}NO_2S$).

Acknowledgment. We gratefully acknowledge Johnson Matthey, Inc. and Kawaken Fine Chemical Co., Ltd., for the palladium acetate. Dr. Pace acknowledges the NATO-CNR Advanced Fellowships Program, sponsored by the Consiglio Nazionale delle Ricerche, for support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all products described in Table 2 (55 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.

JO980516P