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Palladium-catalyzed Coupling of Vinylic Halides, Alkenes, and Amines

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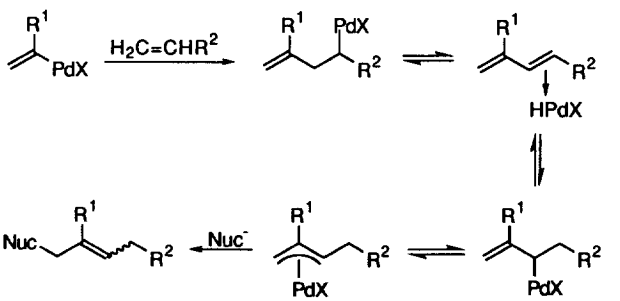
Abstract: The palladium-catalyzed, three component coupling of vinylic halides, alkenes, and amines has been re-examined. The success of the cross-coupling of vinylic halides, alkenes and amines depends heavily on the structures of each of the three substrates, as well as the reaction conditions. The presence of water greatly improves the yield. Secondary amines give much better results than primary amines. Only unhindered, monosubstituted, terminal alkenes react well. Non-conjugated 1,4- and 1,5-dienes afford good yields of a single product, apparently due to chelation during coupling. Relatively unhindered vinylic halides generally, but not always, give the best results. Mixtures of regioisomers arising from vinylic palladium addition to both ends of the alkene double bond are observed when less hindered amines and vinylic halides are employed. Mixtures of stereoisomers are also not uncommon. These reactions proceed via vinylic palladium formation and addition to the alkene, rearrangement to a π-allylpalladium intermediate, and subsequent palladium displacement by the amine.

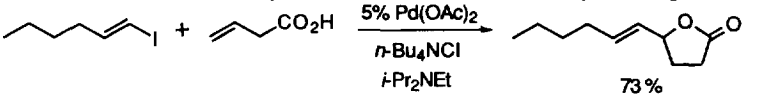
INTRODUCTION

The synthesis and subsequent palladium displacement of π-allylpalladium compounds has proven to be one of the most important advances in organic synthesis in recent years.[1] At present there are a wide variety of methods by which these valuable organometallic intermediates can be generated and utilized in synthesis. One unique approach involves the coupling of a vinylic palladium species with an alkene in which the initial homoallylic species rearranges to a π-allylpalladium intermediate, which subsequently undergoes palladium displacement (Scheme 1).[2]

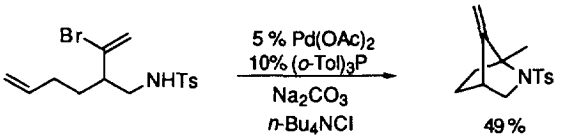
Scheme 1



Recently, two component and strictly intramolecular variations of this chemistry have been effectively employed to prepare unsaturated amines,[3] tosylamides,[4] lactones,[5] and carbocycles[6] (eqs 1 and 2).

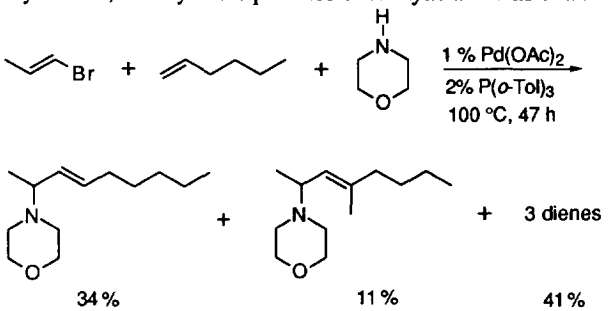


(1)



(2)

Relatively little work has been reported on analogous three component processes. Heck appreciated the synthetic potential of such a process and examined the coupling of several simple vinylic bromides, 1-hexene and primarily two secondary amines, usually in the presence of catalytic amounts of a triarylphosphine (eq 3).[7]

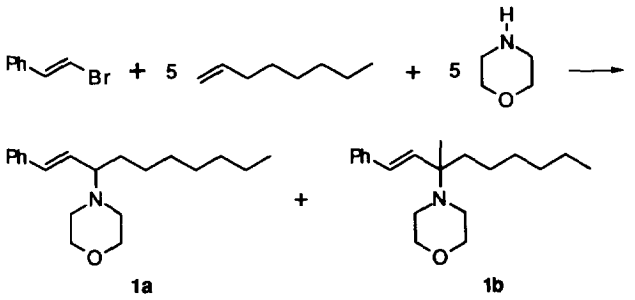


(3)

The reactions were always run neat using an excess of the amine. Unfortunately, that early work utilized only 1-hexene and vinylic bromides, rather than more reactive vinylic iodides, and focused almost exclusively on reactions involving morpholine and piperidine. While some high yields were obtained, the reactions often resulted in only low yields of a mixture of isomeric products, and considerable amounts of dienes were generally observed as by-products. With very effective reaction procedures now available using *n*-Bu_4NCl (TBAC) and our own observations that the presence of triarylphosphines hinders palladium migration and increases the amount of dienes formed,[8] we have elected to re-examine this chemistry in an attempt to overcome some of the earlier problems. We were also interested in examining the effect of varying the structure of the amine and the alkene, not just the vinylic halide as was done previously. In this initial study, we have concentrated on the use of amines as nucleophiles, since they have been the most widely studied of π-allylpalladium nucleophiles and among the most successful.

RESULTS AND DISCUSSION

A variety of reaction conditions similar to those employed previously by us have been examined on the model reaction of β-bromostyrene, 1-octene, and morpholine (eq 4). Our previous work on these types of palladium migration processes has shown that their success is usually strongly dependent on the presence of TBAC and the absence of PPh_3. The latter reagent generally produces large amounts of the analogous Heck reaction product, namely the 1,3-diene. That perhaps accounts for some of the poor results obtained in Heck's prior work on this process (eq 3).[7] The results of our study of reaction conditions are summarized in Table 1.



(4)

Table 1. The Palladium(0)-catalyzed Coupling of β-Bromostyrene, 1-Octene and Morpholine.[a]

entry	solvent	temp (°C)	time (day)	water (equiv.)	% isolated yield (**1a+1b**)	ratio (**1a:1b**)
1	DMF	100	2	0	38	70:30
2	DMF	100	2	1	34	75:25
3	DMF	100	2	5	43	73:27
4	DMF	100	2	10	58	77:23
5	DMF	100	2	20	39	75:25
6	DMF	100	2	50	39	70:30
7	DMF	100	1	10	41	76:24
8	DMF	100	3	10	46	79:21
9	DMF	130	2	10	37	70:30
10	DMF	80	2	10	trace	-
11	CH_3CN	100	2	10	46	70:30
12	DMA	100	2	10	98	85:15

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

With regard to the yield and isomeric outcome of the reaction illustrated in eq. 4, the following observations can be made. In general, the reaction produced a mixture of two isomers, **1a** and **1b**, which obviously arise by addition of the vinylic group of the vinylic palladium intermediate to both the terminal carbon, as well as the internal carbon, of the alkene. Similar complications were observed by Heck.[7] Compound **1a** always predominates and the isomeric ratio is little effected by the reaction conditions. In this system, there is no evidence of any product forming from attack of the amine at the other end of the π-allylpalladium intermediate.

The overall yield of product is dramatically affected by the reaction conditions. Water was found to have a significant effect on the yield of this process, although it is not evident mechanistically what role it plays (Table 1, entries 1-6). Using DMF as the solvent, optimal conditions involved 10 equivalents of water reacting for 2 days at a temperature of 100 °C. However, the reactions run in DMF were found to produce significant (30 %) amounts of the corresponding dimethylamino-containing products, which are obviously coming from the solvent, presumably by hydrolysis of the solvent to dimethylamine and subsequent palladium displacement by the liberated amine. To circumvent these difficulties, acetonitrile and *N,N*-dimethylacetamide (DMA) were examined as solvents and found to be superior (entries 11 and 12). Using DMA, the best isomeric ratio yet observed (85:15) and a 98 % overall yield were obtained (entry 12). All subsequent reactions have thus been run using 1 equiv. of vinylic halide (0.25 mmol), 5 equivs. of alkene, 5 equivs. of amine, 1.1 equivs. of TBAC, 5 mol % of $Pd(dba)_2$ in DMA (2 ml) at 100 °C for 2 days.

Table 2 summarizes the reactions of a wide variety of vinylic halides, alkenes and amines employing this optimal procedure. Using β-bromostyrene and 1-octene, we first examined the yield as a function of the amine employed (Table 2, entries 1-6). Secondary amines were found to give much better results than primary amines, with the yield dropping off dramatically as we proceeded from morpholine (98 %) to piperidine (51 %) to the acyclic amine *n*-Bu_2NH (6 %). Under Heck's conditions, piperidine generally gave better results than morpholine.[7] Among the 3 primary amines examined, only *n*-$BuNH_2$ gave any product at all, and that was formed in only 6 % yield. The yields appear to be highly dependent on the basicity and steric hindrance of the amine.

The regioselectivity of the process also varies substantially with the steric hindrance of the amine. The more hindered amines give more of the product of vinylic carbon addition to the terminal carbon of the alkene. Apparently, the more hindered the amine ligands are that are coordinated to the palladium of the vinylic palladium intermediate, the greater the regioselectivity of addition to the alkene.

We next examined the effect of varying the structure of the alkene on the yield, using β-bromostyrene and morpholine as the vinylic halide and amine respectively (entries 7-10). The results were extremely disappointing. The volatile, more hindered terminal alkene 3-methyl-1-butene produced only 20% of the expected product and styrene afforded only a 29 % yield. 3,3-Dimethyl-1-butene and the terminal disubstituted alkene 1,1-diphenylethylene failed to generate any of the anticipated product. Thus, this process appears to be extremely dependent on the structure of the alkene. Only unhindered, mono-substituted, terminal alkenes work.

Non-conjugated dienes produced some very interesting results (entries 11-16). 1,5-Hexadiene afforded good to excellent yields of a *single* product from both morpholine and piperidine (entries 11 and 12). The unexpectedly high regioselectivity of alkene insertion can be explained by a mechanism involving chelated intermediates (Scheme 2).

Table 2. Palladium-catalyzed Coupling of Vinylic Halides, Alkenes and Amines.

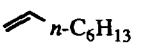
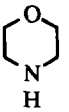
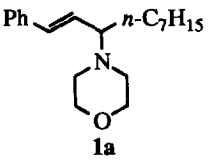
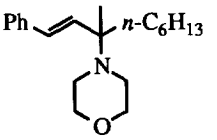
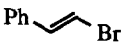
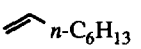
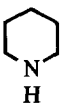
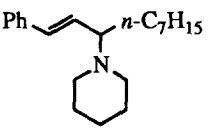
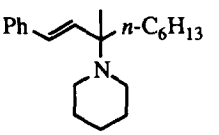
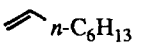
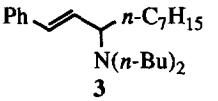
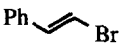
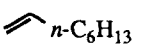
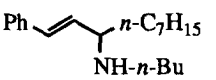
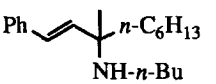
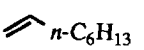
entry	vinylic halide	alkene	amine	product(s)	% isolated yield (ratio)
1				 **1a**	98 (85:15)
				 **1b**	
2				 **2a**	51 (86:14)
				 **2b**	
3			n-Bu_2NH	 **3**	6
4			n-$BuNH_2$	 **4a**	36 (67:33)
				 **4b**	
5			t-$BuNH_2$		0

Table 2. Continued

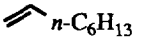
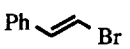
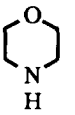
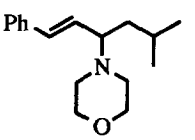
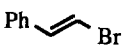
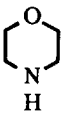
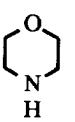
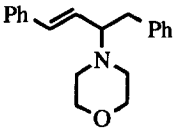
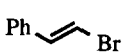
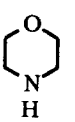
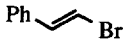
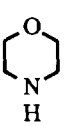
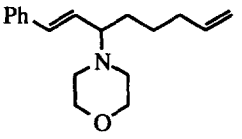
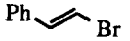
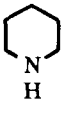
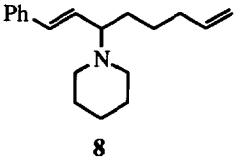
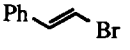
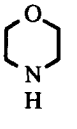
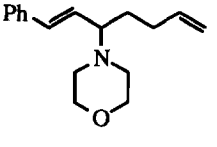
entry	vinylic halide	alkene	amine	product(s)	% isolated yield (ratio)
6			$PhNH_2$		0
7				 **5**	20
8					0
9				 **6**	29
10					0
11				 **7**	95
12				 **8**	50
13				 **9**	45

Table 2. Continued

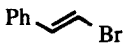
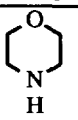
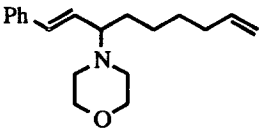
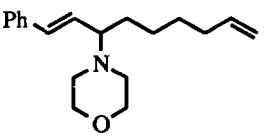
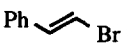
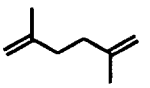
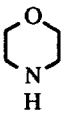
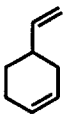
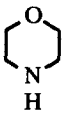
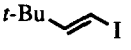
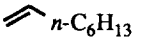
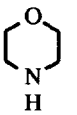
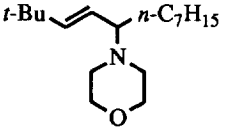
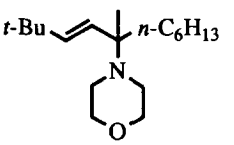
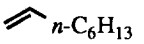
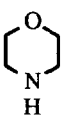
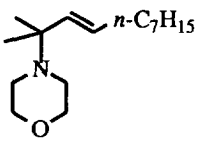
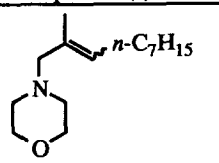
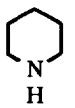
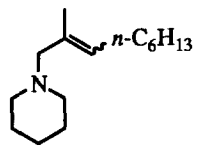
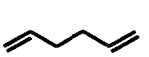
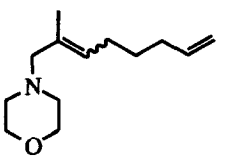
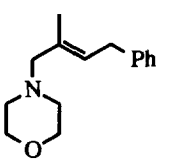
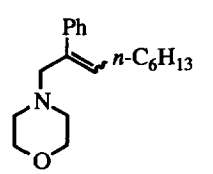
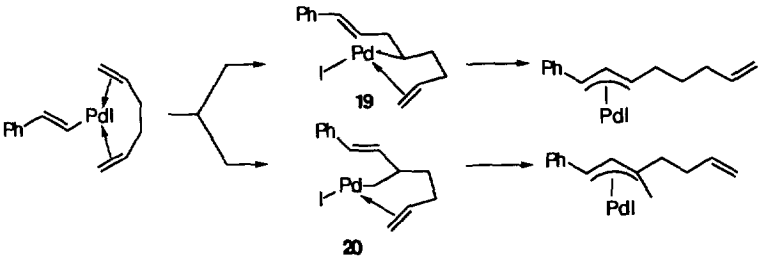
entry	vinylic halide	alkene	amine	product(s)	% isolated yield (ratio)
14				 **10a**  **10b**	68 (75:25)
15					0
16					0
17				 **11a**  **11b**	40 (80:20)
18				 **12**	29

Table 2. Continued

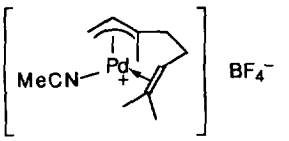
entry	vinylic halide	alkene	amine	product(s)	% isolated yield (ratio)
19				 **13**	73 (89:11)[a]
20				 **14**	57 (89:11)[a]
21				 **15**	98 (83:17)[a]
22				 **16**	35
23					0
24				 **17**	24 (60:40)[a]
25				**17**	11 (60:40)[a]

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

Scheme 2



As illustrated, both double bonds of the diene can coordinate to the vinylic palladium intermediate. Insertion into one of the double bonds results in either of two chelated intermediates, a pseudo-6-membered ring, chair-like intermediate **19** or the corresponding pseudo-7-membered ring intermediate **20**. Apparently the former is more favorable and produces the sole product of the reaction. This intermediate is very similar to the stable, chelated π-allylpalladium species **21**, whose X-ray structure has been reported (Figure 1).[9]



21

Figure 1.

It is particularly noteworthy that no product is observed to arise by palladium migration to the remote double bond, followed by displacement of palladium from the resulting π-allylpalladium intermediate, even though this process occurs readily when aryl halides are employed in place of vinylic halides.[8]

The formation of the postulated, chelated intermediate requires a specific chain length between the two double bonds of the starting diene in order to produce the stable, chair-like, cyclic structure. One more or one less carbon in the side chain might be expected to disrupt chelation and significantly affect the overall reaction. In order to test this hypothesis, we examined the reactions of 1,4-pentadiene and 1,6-heptadiene. 1,4-Pentadiene produced a much lower yield of a single product (entry 13). It would appear that an analogous chelated intermediate may still exist here, but that the interaction between the palladium and the double bond is weakened. 1,6-Heptadiene produced a 75:25 mixture of regioisomers in good yield (entry 14). Judging from the regiochemistry, no chelation is present in this reaction and the results parallel those of 1-octene (entry 1). The more hindered, branched dienes 2,5-dimethyl-1,5-hexadiene and 4-vinylcyclo-hexene failed to produce any products (entries 15 and 16).

We next examined the effect of varying the vinylic halide structure. The terminal vinylic halide *E*-1-iodo-3,3-dimethyl-1-butene afforded only a 40 % yield of an 80:20 mixture of regioisomers arising from addition to both ends of the alkene double bond (entry 17). The amine is observed to attack exclusively the end of the π-allylpalladium system furthest from the *tert*-butyl group, even though that is more highly substituted in the intermediate produced by internal addition of the vinylic group to the alkene.

1-Iodo-2-methylpropene also produced a low yield, but the sole product arises from attack of the amine on the *more* substituted end of the π-allyl system (entry 18). It is known that displacement of palladium at the tertiary center is favored over attack at the secondary carbon in such systems.[7]

2-Bromopropene has given good results with a variety of alkenes (entries 19-22). In all cases, the product results from exclusive addition of the vinylic group to the terminal carbon of the alkene and regioselective attack of the amine at the less substituted end of the π-allyl system, but the alkene generated is usually a mixture of stereoisomers. The stereochemistry of the resulting alkene double bond is presumably determined by the relative stabilities of the *syn* and *anti* π-allylpalladium intermediates. With the presence of the methyl on the central carbon of these intermediates, the two isomers possess similar stabilities.

The more hindered vinylic halide 2-iodo-1-hexene afforded none of the anticipated product (entry 23), while α-iodo- and α-bromostyrene gave only low yields of a 60:40 mixture of stereoisomers in which vinylic addition has occurred exclusively to the terminal carbon of the alkene and attack of the amine occurs exclusively at the less substituted end of the π-allyl system (entries 24 and 25). As anticipated, vinylic iodides are more reactive than the corresponding bromides and generally give higher yields.

As noted, some of these reactions produce mixtures of stereoisomers, presumably reflecting the relative stabilities of the *syn* and *anti* π-allylpalladium intermediates. The ratio of the stereoisomers has usually been determined by integration of the allylic hydrogens adjacent to the nitrogen or in one case by integration of the vinylic hydrogens. Their assignment is based on the ^{13}C chemical shifts of the allylic methyl group. For example, the methyl in the *E*-isomer of compound **13** (entry 19) appears at 15.3 ppm, while the methyl of the *Z*-isomer appears at 22.7 ppm. Other stereoisomers have been assigned in a similar manner.

CONCLUSION

This study provides the first systematic study of the three component coupling of vinylic halides, alkenes and amines. The success of the cross-coupling depends heavily on the reaction conditions and the structures of each of the three substrates. DMA is a much better solvent than DMF for this process. The addition of water to the reaction is observed to significantly improve the yield. Secondary amines give much better results than primary amines. Only unhindered, monosubstituted, terminal alkenes produce products in reasonable yields. Non-conjugated 1,4- and 1,5-dienes afford good yields of a single product, apparently due to chelation during coupling. Relatively unhindered vinylic halides generally, but not always, give the best results. Mixtures of regioisomers arising from vinylic palladium addition to both ends of the alkene double bond are observed when less hindered amines and vinylic halides are employed. Mixtures of stereoisomers are also not uncommon.

A comparison of our results with the earlier results of Heck is in order. We only obtain good yields of products from reactions employing secondary amines and unhindered monosubstituted terminal alkenes, perhaps explaining why Heck only reported examples employing such substrates. Under our conditions, morpholine gives significantly better results than piperidine, just the opposite of Heck's results. We note some unusual effects when 1,4- and 1,5-dienes are employed, suggesting the importance of chelation. We both observe that 1-halo-1-alkenes tend to give mixtures of products in which the vinylic group has added to both ends of the alkene double bond, while 2-halo-1-alkenes react completely regioselectively by attack on the terminal carbon of the alkene and amine displacement at the less substituted end of the π-allylpalladium system, although stereoisomers are now prevalent. Despite a significant difference in the reaction conditions employed in the two studies, similar results have sometimes been obtained. Compare for example our results in Table 2, entries 18 (29 %) and 19 (73 %) with analogous reactions run by Heck involving 1-bromo-2-methylpropene, 1-hexene and

morpholine (31%), and 2-bromopropene, 1-hexene and morpholine (64 %). Between the two major studies of this process, we now have a fairly good understanding of the synthetic potential of this route to allylic amines and also its rather substantial limitations.

EXPERIMENTAL SECTION

Spectral Data and Analysis. All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 at 300 and 75.5 MHz respectively. All infrared spectra were recorded on an IBM IR/98 FT-IR spectrometer or on a Beckmann 4250 spectrometer. High resolution mass spectral analyses were performed on a Kratos or an MS-50 high resolution mass spectrometer. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution (3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL 5% NaOH + 300 mL H_2O).

Reagents. All chemicals were used directly as obtained commercially unless otherwise noted. *N, N*-Dimethylformamide (DMF) and *N, N*-dimethylacetamide were dried over 4 Å molecular sieves. TBAC was purchased from Lancaster Synthesis Inc. $Pd(OAc)_2$ was generously provided by Johnson Matthey Inc. and Kawaken Fine Chemical Co., Inc.

β–Bromostyrene, 1-bromo-2-methylpropene, 2-bromopropene, *E*-1-bromo-propene, 1-octene, 1,5-hexadiene, styrene, 3-methyl-1-butene, 2,5-dimethyl-1,5-hexadiene, 3,3-dimethyl-1-butene, 4-vinylcyclohexene, morpholine, piperidine, *n*-butylamine, di-*n*-butylamine, *t* -butylamine, and aniline were obtained from Aldrich Chemical Company, Inc. 1-Iodo-2-methyl-1-propene[10] and $Pd(dba)_2$[11] were prepared according to literature procedures.

General Procedure for the Palladium-Catalyzed Cross-Coupling Reactions. Into a one or two-dram screw-capped vial, equipped with a Teflon-lined cap and a magnetic stirrer, was placed the $Pd(dba)_2$ (5 mol %), *n*-Bu_4NCl (1.1 equivs.), DMA (2 mL), vinylic halide (0.25 mmol), alkene (5 equivs.) and amine (5 equivs.). The vial was then capped and suspended in an oil bath at 100° C for 2 days. The reaction was allowed to cool to room temperature and diluted with ethyl ether (10 mL). The mixture was washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel column (230-400 mesh silica gel) with an appropriate eluent, unless otherwise specified. The desired products were collected and the solvents were removed by rotary evaporation. The products were further purified by chromatography on a silica gel column when necessary. The following compounds have been prepared using this procedure.

(*E*)-3-(*N*-Morpholino)-1-phenyl-1-decene (1a) and (*E*)-3-methyl-3-(*N*-morpholino)-1-phenyl-1-nonene (1b). Obtained in 98 % yield as a separable mixture (**1a**:**1b** = 85:15) from the reaction of β-bromostyrene, morpholine and 1-octene (Table 2, entry 1). Isomer **1a**: TLC (4:1 hexanes/EtOAc) R_f = 0.24; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3 H, *J* = 6.9 Hz), 1.30-1.75 (m, 12 H), 2.53-2.60 (m, 4 H), 2.83 (m, 1 H), 3.72 (m, 4 H), 6.08 (dd, 1 H, *J* = 15.9, 9.0 Hz), 6.43 (d, 1 H, *J* = 15.9 Hz), 7.35 (m, 5 H); IR (neat) 2955, 2926, 1450, 1267, 1119, 970, 748, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 26.2, 29.1, 29.6, 31.7, 31.8, 50.5, 67.1, 68.3, 126.2, 127.3, 128.4, 129.7, 132.7, 136.8; HRMS m/z 301.2408 (Calcd. 301.2414 for $C_{20}H_{31}NO$). Isomer **1b**: TLC (4:1 hexanes/EtOAc) R_f = 0.44; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, *J* = 6.7 Hz),

1.18 (s, 3 H), 1.25-1.55 (m, 10 H), 2.60 (t, 4 H, J = 4.5 Hz), 3.71 (t, 4 H, J = 4.5 Hz), 6.19 (d, 1 H, J = 16.5 Hz), 6.36 (d, 1 H, J = 16.5 Hz), 7.30 (m, 5 H); IR (neat) 2954, 1733, 1452 (C=C), 1118, 963, 747, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.1, 16.8, 22.7, 23.8, 30.0, 31.8, 39.2, 46.6, 60.5, 67.9, 126.2, 127.2, 128.5, 128.9, 136.5, 137.3; HRMS m/z 301.2414 (Calcd. 301.2414 for $C_{20}H_{31}NO$).

(*E*)-1-Phenyl-3-(*N*-piperidino)-1-decene (2a) and (*E*)-3-methyl-1-phenyl-3-(*N*-piperidino)-1-nonene (2b). Obtained in 51 % yield as separable isomers (**2a:2b** = 86:14) from the reaction of β-bromostyrene, piperidine and 1-octene (entry 2). Isomer **2a**: TLC (11:1 hexanes/EtOAc) R_f = 0.21; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 5.8 Hz), 1.30-1.72 (m, 18 H), 2.47-2.60 (m, 4 H), 2.86 (m, 1 H), 6.14 (dd, 1 H, J = 15.9, 9.0 Hz), 6.39 (d, 1 H, J = 15.9 Hz), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.8, 26.4, 26.7, 29.2, 29.7, 31.8, 32.4, 50.9, 68.5, 126.2, 127.1, 128.4, 130.3, 132.0, 137.2; IR (neat) 2926, 2853, 1451, 1099, 968, 747, 692 cm^{-1}; HRMS m/z 200.1439 (Calcd. 200.1439 for $C_{21}H_{33}N$ - C_7H_{15}). Isomer **2b**: TLC (11:1 hexanes/EtOAc) R_f = 0.32; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 5.8 Hz), 1.18 (s, 3 H), 1.28-1.57 (m, 16 H), 2.52 (m, 4 H), 6.25 (d, 1 H, J = 16.5 Hz), 6.33 (d, 1 H, J = 16.5 Hz), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.7, 22.7, 24.0, 25.2, 27.0, 27.0, 30.1, 31.8, 39.8, 47.3, 126.2, 126.9, 128.0, 128.5, 128.5, 138.1; IR (neat) 2927, 1622, 1449 (C=C), 1338, 1185, 1097, 981, 748, 694 cm^{-1}; HRMS m/z 299.2609 (Calcd. 299.2613 for $C_{21}H_{33}N$).

(*E*)-3-(Di-*n*-butylamino)-1-phenyl-1-decene (3). Obtained in 6 % yield from the reaction of β-bromostyrene, di-*n*-butylamine and 1-octene (entry 3). TLC (15:1 hexanes/EtOAc) R_f = 0.61; ^1H NMR ($CDCl_3$) δ 0.90 (m, 9 H), 1.30-1.62 (m, 20 H), 2.38-2.54 (m, 4 H), 3.15 (m, 1 H), 6.12 (dd, 1 H, J = 15.9, 8.7 Hz), 6.38 (d, 1 H, J = 15.9 Hz), 7.30 (m, 5 H). There was not enough material for IR, ^{13}C NMR and HRMS analysis.

(*E*)-3-(*n*-Butylamino)-1-phenyl-1-decene (4a) and (*E*)-3-(*n*-butylamino)-3-methyl-1-phenyl-1-nonene (4b). Obtained in 36 % yield as an inseparable mixture (**4a:4b** = 67:33) from the reaction of β-bromostyrene, *n*-butylamine and 1-octene (entry 4). The isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers: TLC (2:1 hexanes/EtOAc) R_f = 0.06; ^{13}C NMR ($CDCl_3$) δ 14.1, 20.6, 20.6, 22.6, 23.7, 23.8, 26.1, 29.2, 29.7, 29.9, 31.8, 32.5, 33.2, 36.2, 41.1, 42.2, 47.3, 61.6, 126.2, 126.3, 127.0, 127.2, 127.8, 128.5, 130.8, 133.7, 137.9; IR (neat) 2956, 1466, 1449, 980, 692 cm^{-1}; HRMS m/z 287.2610 (Calcd. 287.2613 for $C_{20}H_{33}N$). Isomer **4a**: ^1H NMR ($CDCl_3$) δ 0.90 (m, 6 H), 1.30-1.42 (m, 16 H), 2.51 (m, 2 H), 2.83 (m, 1 H), 5.99 (dd, 1 H, J = 15.8, 8.4 Hz), 6.43 (d, 1 H, J = 15.8 Hz), 7.35 (m, 5 H). Isomer **4b**: ^1H NMR ($CDCl_3$) same as **4a** or not seen, except δ 2.18 (s, 3 H), 3.14 (m, 2 H), 6.11 (d, 1 H, J = 16.3 Hz), 6.36 (d, 1 H, J = 16.3 Hz).

(*E*)-5-Methyl-3-(*N*-morpholino)-1-phenyl-1-hexene (5). Obtained in 20 % yield from the reaction of β-bromostyrene, morpholine and 3-methyl-1-butene (entry 7). TLC (2:1 hexanes/EtOAc) R_f = 0.22; ^1H NMR ($CDCl_3$) δ 0.91 (d, 6 H, J = 5.7 Hz), 1.55 (m, 3 H), 2.55 (m, 2 H), 2.65 (m, 2 H), 2.95 (m, 1 H), 3.70 (m, 4 H), 6.37 (dd, 1 H, J = 15.9, 9.1 Hz), 6.60 (d, 1 H, J = 15.9 Hz), 7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.7, 24.8, 40.9, 50.4, 66.2, 67.3, 126.2, 127.4, 128.6, 129.4, 132.6, 136.0; IR (neat) 2954, 1451, 1285, 1118, 971, 749, 694 cm^{-1}; HRMS m/z 202.1233 (Calcd. 202.1232 for $C_{17}H_{25}NO$ - C_4H_9).

(*E*)-3-(*N*-Morpholino)-1,4-diphenyl-1-butene (6). Obtained in 29 % yield from the reaction of β-bromostyrene, morpholine and styrene (entry 9). ^{1}H NMR ($CDCl_3$) δ 2.68 (m, 6 H), 3.15 (m, 1 H), 3.74 (m, 4 H), 6.08 (dd, 1 H, *J* = 15.9, 8.1 Hz), 6.20 (d, 1 H, *J* = 15.9 Hz), 7.20 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 38.4, 50.5, 67.2, 69.8, 126.0, 126.2, 127.4, 128.1, 128.4, 129.5, 129.5, 133.2, 136.8, 139.1; IR (neat) 2954, 1600, 1494, 1452, 1117, 1030, 921, 746, 695 cm^{-1}; HRMS m/z 293.1780 (Calcd. 293.1773 for $C_{20}H_{23}NO$).

(*E*)-3-(*N*-Morpholino)-1-phenyl-1,7-octadiene (7). Obtained in 95 % yield from the reaction of β-bromostyrene, morpholine and 1,5-hexadiene (entry 11). TLC (6:1 hexanes/EtOAc) R_f = 0.23; ^{1}H NMR ($CDCl_3$) δ 1.47-1.82 (m, 4 H), 2.08 (m, 2 H), 2.55 (m, 2 H), 2.60 (m, 2 H), 2.85 (m, 1 H), 3.71 (m, 4 H), 4.96 (d, 1 H, *J* = 10.2 Hz), 4.99 (d, 1 H, *J* = 18.6 Hz), 5.77 (m, 1 H), 6.10 (dd, 1 H, *J* = 15.9, 9.0 Hz), 6.44 (d, 1 H, *J* = 15.9 Hz), 7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.5, 31.2, 33.7, 50.5, 67.2, 68.1, 114.5, 126.2, 127.3, 128.4, 129.6, 132.7, 136.8, 138.5; IR (neat) 2953, 2854, 1500, 1450, 1190, 970, 912, 750, 694 cm^{-1}; HRMS m/z 271.1939 (Calcd. 271.1936 for $C_{18}H_{25}NO$).

(*E*)-1-Phenyl-3-(*N*-piperidino)-1,7-octadiene (8). Obtained in 50 % yield from the reaction of β-bromostyrene, piperidine and 1,5-hexadiene (entry 12). TLC (2:1 hexanes/EtOAc) R_f = 0.14; ^{1}H NMR ($CDCl_3$) δ 1.41-1.73 (m, 10 H), 2.45-2.58 (m, 4 H), 2.70 (m, 2 H), 2.88 (m, 1 H), 4.93 (d, 1 H, *J* = 11.1 Hz), 5.48 (d, 1 H, *J* = 20.4 Hz), 5.80 (m, 1 H), 6.15 (dd, 1 H, *J* = 17.4, 9.0 Hz), 6.42 (d, 1 H, *J* = 17.4 Hz), 7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.1, 25.4, 31.9, 33.8, 50.9, 68.4, 114.4, 126.2, 127.2, 128.5, 130.1, 132.2, 137.1, 139.8; IR (neat) 2919, 1641 (C=C), 1494, 1443, 992, 969, 910, 748, 693 cm^{-1}; HRMS m/z 200.1445 (Calcd. 200.1439 for $C_{19}H_{25}N$ - C_5H_9).

(*E*)-3-(*N*-Morpholino)-1-phenyl-1,6-heptadiene (9). Obtained in 45 % yield from the reaction of β-bromostyrene, morpholine and 1,4-pentadiene (entry 13) TLC (1:1 hexanes/EtOAc) R_f = 0.31; ^{1}H NMR ($CDCl_3$) 1.70 (m, 2 H), 2.10 (m, 2 H), 2.60 (m, 4 H), 2.90 (m, 1H), 3.78 (m, 4 H), 4.96 (d, 1 H, *J* = 18.9 Hz), 5.01 (d, 1 H, *J* = 9.9 Hz,), 5.80 (m, 1 H), 6.09 (dd, 1 H, *J* = 15.9, 9.0 Hz), 6.45 (d, 1 H, *J* =15.9 Hz), 7.33 (m, 5 H); IR (neat) 2954, 1643 (C=C), 1494, 1452, 1118, 970 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 30.4, 30.9, 50.5, 67.2, 67.6, 114.7, 126.3, 127.5, 128.6, 129.2, 133.1, 136.8, 138.4; HRMS m/z 257.0780 (Calcd. 257.1779 for $C_{17}H_{23}NO$).

(*E*)-3-(*N*-Morpholino)-1-phenyl-1,8-nonadiene (10a) and (*E*)-3-methyl-3-(*N*-morpholino)-1-phenyl-1,7-octadiene (10b). Obtained in 68 % yield as a separable mixture (**10a**:**10b** = 75:25) from the reaction of β-bromostyrene, morpholine and 1,6-heptadiene (entry 14). Isomer **10a**: TLC (2:1 hexanes/EtOAc) R_f = 0.35; ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 2 H), 1.38 (m, 4 H), 1.72 (m, 2 H), 2.58 (m, 4 H), 2.85 (m, 1 H), 3.62 (m, 4 H), 4.92 (d, 1 H, *J* = 10.8 Hz), 4.97 (d, 1 H, *J* = 20.1 Hz), 5.78 (m, 1 H), 6.09 (dd, 1 H, *J* = 15.9, 9.0 Hz), 6.44 (d, 1 H, *J* = 15.9 Hz), 7.38 (m, 5 H); IR (neat) 2932, 1495, 1450, 1267, 1119, 993, 970, 750, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 25.5, 29.0, 31.2, 33.7, 50.5, 67.2, 68.1, 114.5, 126.2, 127.3, 128.4, 129.6, 132.7, 136.8, 138.5; HRMS m/z 285.2091 (Calcd. 285.2093 for $C_{19}H_{27}NO$). Isomer **10b**: TLC (2:1 hexanes/EtOAc) R_f = 0.51; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.40 (m, 2 H), 1.59 (m, 2 H), 2.01 (m, 2 H), 2.57 (m, 4 H), 3.70 (m, 4 H), 4.94 (d, 1 H, *J* = 10.8 Hz), 4.99 (d, 1 H, *J* = 17.7 Hz), 5.78 (m, 1 H), 6.19 (d, 1 H, *J* = 16.2 Hz), 6.37 (d, 1 H, *J* = 16.2 Hz), 7.35 (m, 5 H); IR (neat) 2921, 1640 (C=C), 1494, 1446,

1118, 911, 694 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 16.9, 23.2, 34.3, 38.5, 46.6, 52.0, 67.8, 114.7, 126.2, 126.9, 128.0, 128.6, 129.1, 136.3, 138.7; HRMS m/z 285.2093 (Calcd. 285.2093 for $C_{19}H_{27}NO$).

(*E*)-2,2-Dimethyl-5-(*N*-morpholino)-3-dodecene (11a) and (*E*)-2,2,5-trimethyl-5-(*N*-morpholino)-3-undecene (11b). Obtained in 40 % yield as separable isomers (**11a:11b** = 80:20) from the reaction of *E*-1-iodo-3,3-dimethyl-1-butene, morpholine and 1-octene (entry 17). Isomer **11a**: TLC (11:1 hexanes/EtOAc) R_f = 0.40; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 4.7 Hz), 1.02 (s, 9 H), 1.28 (m, 10 H), 1.60 (m, 2 H), 2.42 (m, 2 H), 2.75 (m, 3 H), 3.72 (m, 4 H), 5.15 (dd, 1 H, *J* = 15.6, 9.1 Hz), 5.58 (d, 1 H, *J* = 15.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 26.3, 29.2, 29.6, 29.7, 31.8, 31.9, 33.1, 50.9, 67.3, 68.2, 128.6, 146.8; IR (neat) 2955, 2927, 1452, 1362, 1119, 977 cm^{-1}; HRMS m/z 182.1548 (Calcd. 182.1545 for $C_{18}H_{25}NO$ - C_8H_{17}). Isomer **11b**: TLC (11:1 hexanes/EtOAc) Rf = 0.45; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 4.7 Hz), 1.02 (s, 9 H), 1.28 (m, 9 H), 1.42 (m, 2 H), 1.62 (m, 2 H), 2.51 (m, 4 H), 3.69 (m, 4 H), 5.24 (d, 1 H, *J* = 16.3 Hz), 5.48 (d, 1 H, *J* = 16.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.0, 22.6, 23.8, 29.3, 29.9, 30.0, 31.8, 33.1, 39.0, 46.4, 67.8, 140.9, 143.3; IR (neat) 2955, 1672 (C=C), 1614, 1454, 1120, 985, 963, 697 cm^{-1}; HRMS m/z 281.2717 (Calcd. 281.2719 for $C_{18}H_{35}NO$).

(*E*)-2-Methyl-2-(*N*-morpholino)-3-undecene (12). Obtained in 29 % yield from the reaction of 1-iodo-2-methylpropene, morpholine and 1-octene (entry 18). TLC (2:1 hexanes/EtOAc) R_f = 0.31; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 6.7 Hz), 1.12 (s, 6 H), 1.28 (m, 10 H), 2.03 (m, 2 H), 2.53 (t, 4 H, *J* = 4.8 Hz), 3.72 (t, 4 H, *J* = 4.8 Hz), 5.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.0, 23.6, 25.9, 28.5, 32.9, 34.1, 44.4, 51.8, 52.2, 52.3, 52.4, 64.7, 124.2, 133.6; IR (neat) 2957, 2814, 1466, 1452, 1381, 1275, 1177, 1130, 978, 959, 862 cm^{-1}; HRMS m/z 253.4320 (Calcd. 253.4316 for $C_{16}H_{31}NO$).

(*E*)-and (*Z*)-2-Methyl-1-(*N*-morpholino)-2-decene (13). Obtained in 73 % yield from the reaction of 2-bromopropene, morpholine and 1-octene as an inseparable mixture of isomers (*E*/*Z* = 89:11) (entry 19). The isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens adjacent to the nitrogen atom. The following data were taken from a mixture of the isomers: TLC (4:1 hexanes/EtOAc) R_f = 0.29; ^{13}C NMR ($CDCl_3$) δ 14.1, 15.3, 22.7, 27.8, 29.2, 29.8, 31.9, 53.6, 66.9, 67.1, 67.9, 128.8, 131.7; IR (neat) 2922, 1453, 1289, 1119, 1007, 908, 869 cm^{-1}; HRMS m/z 239.2249 (Calcd. 239.2245 for $C_{18}H_{25}NO$). The *E*-isomer: ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 8.5 Hz), 1.26 (m, 10 H), 1.66 (s, 3 H), 2.03 (m, 2 H), 2.35 (m, 4 H), 2.83 (s, 2 H), 3.70 (m, 4 H,), 5.32 (t, 1 H, *J* = 8.6 Hz). The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 2.91 (s, 2 H).

(*E*)-and (*Z*)-2-Methyl-1-(*N*-piperidino)-2-nonene (14). Obtained in 57 % yield from the reaction of 2-bromopropene, piperidine and 1-heptene as an inseparable mixture of isomers (*E*/*Z* = 89:11) (entry 20). The isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens adjacent to the nitrogen atom. The following data were taken from a mixture of the isomers: ^{13}C NMR ($CDCl_3$) δ 14.1, 15.2, 22.6, 24.4, 25.8, 27.8, 29.0, 29.6, 31.7, 54.4, 68.2, 118.5, 128.6; IR (neat) 2930, 1466, 1338, 1119, 1104, 863, 808 cm^{-1}; HRMS m/z 223.2296 (Calcd. 223.2300 for $C_{15}H_{29}N$). The *E*-isomer: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.9 Hz), 1.27-1.57 (m, 14 H), 1.64 (s, 3 H), 2.01 (m, 2 H),

2.30 (4 H), 2.83 (s, 2 H), 5.29 (t, 1 H, J = 7.2 Hz). The Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer or not seen, except δ 2.94 (s, 2 H).

(*E*)-and (*Z*)-2-Methyl-1-(*N*-morpholino)-2,7-octadiene (15). Obtained in 98 % yield from the reaction of 2-bromopropene, morpholine and 1,5-hexadiene as an inseparable mixture of isomers (E/Z = 83:17) (entry 21). The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens adjacent to the nitrogen atom. The following data were taken from a mixture of the isomers: IR (neat) 2927, 1640 (C=C), 1453, 1290, 1119 cm^{-1}; HRMS m/z 209.1785 (Calcd. 209.1780 for $C_{13}H_{23}NO$). The E-isomer: TLC (2:1 hexanes/EtOAc) R_f = 0.34; ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 2 H), 1.64 (s, 3 H), 2.05 (m, 4 H), 2.35 (m, 4 H), 2.83 (s, 2 H), 3.70 (m, 4 H), 4.94 (d, 1 H, J = 9.0 Hz), 4.99 (d, 1 H, J = 18.0 Hz,), 5.30 (t, 1 H, J = 6.0 Hz), 5.81 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.0, 27.2, 28.8, 33.4, 53.5, 67.0, 67.8, 114.4, 128.5, 131.8, 138.8. The Z-isomer: TLC (2:1 hexanes/EtOAc) R_f = 0.42; ^{1}H NMR ($CDCl_3$) same as the E-isomer or not seen, except δ 1.70 (s, 3 H), 2.90 (d, 2 H, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen, except δ 22.3, 29.2, 33.3, 34.4, 59.0, 61.4, 128.3, 129.3, 132.0.

(*E*)-2-Methyl-1-(*N*-morpholino)-4-phenyl-2-butene (16). Obtained in 35 % yield from the reaction of 2-bromopropene, morpholine and styrene (entry 22). TLC (2:1 hexanes/EtOAc) R_f = 0.27; ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3 H), 2.36 (t, 4 H, J = 4.5 Hz), 2.88 (s, 2 H), 3.39 (d, 2 H, J = 7.2 Hz), 3.70 (t, 4 H, J = 4.5 Hz), 5.52 (t, 1 H, J = 7.2 Hz), 7.22 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.1, 34.1, 53.6, 67.1, 67.7, 125.8, 126.8, 128.3, 128.4, 133.0, 141.2; IR (neat) 2957, 2805, 1602, 1452, 1117, 1005, 866, 743 cm^{-1}; HRMS m/z 231.1622 (Calcd. 231.1623 for $C_{15}H_{21}NO$).

(*E*)-and (*Z*)-1-(*N*-Morpholino)-2-phenyl-2-nonene (17). Obtained in 24 % yield as an inseparable mixture (E/Z = 60:40) from the reaction of α-iodostyrene, morpholine and 1-heptene (entry 24). The isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogens. The following data were taken from a mixture of the isomers: TLC (4:1 hexanes/EtOAc) R_f = 0.63; ^{13}C NMR ($CDCl_3$) δ 16.1, 16.8, 24.5, 28.2, 31.7, 31.7, 31.9, 33.0, 44.6, 51.7, 52.1, 114.5, 127.0, 127.2, 127.8, 128.5, 128.7, 128.9, 129.8, 132.9, 133.8, 134.4; HRMS m/z 287.2249 (Calcd. 287.2247 for $C_{19}H_{29}NO$). There was not enough material for IR data. The E-isomer: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.0 Hz), 1.33 (m, 8 H), 2.25 (m, 2 H), 2.52 (m, 4 H), 3.36 (s, 2 H), 3.64 (m, 4 H), 5.92 (t, 1 H, J = 7.5 Hz), 7.24 (m, 5 H). The Z-isomer: ^{1}H NMR ($CDCl_3$) same as that of the E-isomer or not seen, except δ 3.20 (s, 2 H), 5.61 (t, 1 H, J = 6.9 Hz).

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