Pergamon

Tetrahedron 55 (1999) 7345–7362

TETRAHEDRON

Synthesis of 2,3-Disubstituted Pyrrolidines by Intramolecular Addition of α-Aminoalkyl Radicals to Electron Deficient C=C Bonds

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Received 4 February 1999; revised 29 March 1999; accepted 15 April 1999

Abstract: 2,3-Disubstituted pyrrolidines are prepared by SmI_2-promoted cyclization of α-amino radicals generated from *N*-(α-benzotriazolylalkyl)alkenylamines containing a C=C bond activated by an electron withdrawing substituent. The diastereoselectivity of cyclization is moderate and depends on the nature of the substituent at the pyrrolidine 2-position.

Keywords: cyclization, pyrrolidines, radicals, samarium.

Introduction

C-Substituted pyrrolidines represent an important class of heterocyclic compounds frequently encountered as advanced synthetic intermediates in the preparation of complex natural products as well as structural components in a number of biologically active natural products and pharmaceuticals.[1] As a consequence, all major advances in C-C and C-heteroatom bond formation are rapidly applied to the development of new and increasingly efficient and versatile routes for their synthesis.[2] We have focused on intramolecular radical additions as radical reactions often offer advantages over other conventional procedures in terms of high chemo-, regio-, and stereo-selectivity, besides neutral conditions and absence of strongly nucleophilic or electrophilic species.[3] Thus, the synthesis of pyrrolidines has been effected by intramolecular addition of *N*-centered radicals onto suitably positioned C=C bonds,[4] as well as by similar additions of 2-aza-,[5] 3-aza-,[6] 4-aza-[5e,7] or 5-aza-5-hexenyl[8] radicals. While most of these radical cyclizations have proven effective in pyrrolidine synthesis, the use of 1-(α-aminoalkyl)-5-hexenyl radicals[5a] has the added benefit of synthetic convergence as radicals may be generated from iminium ions or their synthetic equivalents and these precursors are formally derived from convenient amine and carbonyl functionalities. However, the cyclizations of these α-amino radicals[9] have not always met with success. Thus, the simple *N*-benzyl-2-aza-5-hexenyl radical **1** failed to give any cyclized product under the standard tin hydride conditions, affording the reduced product **2** exclusively (Scheme 1).[10,11] In a related example, similar problems were overcome by carefully controlled syringe pump tin hydride addition, thus leading to the successful cyclization of radical **3** generated by 1,5-radical translocation (Scheme 1).[5h]

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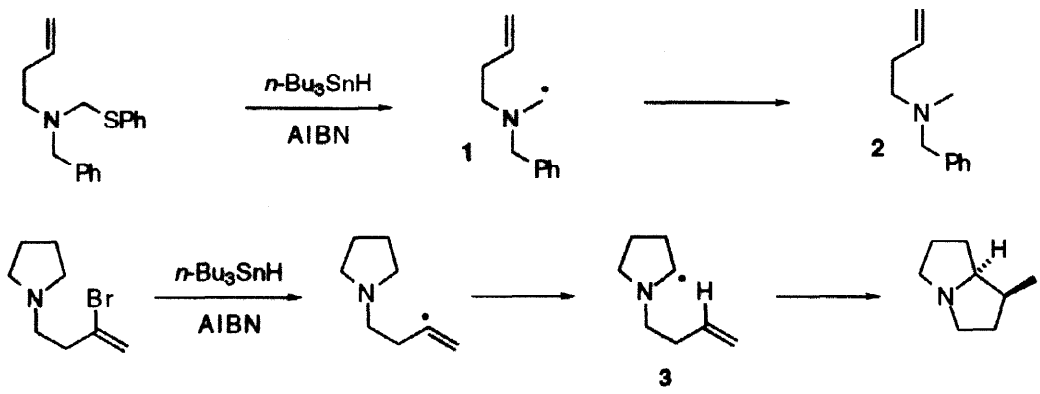
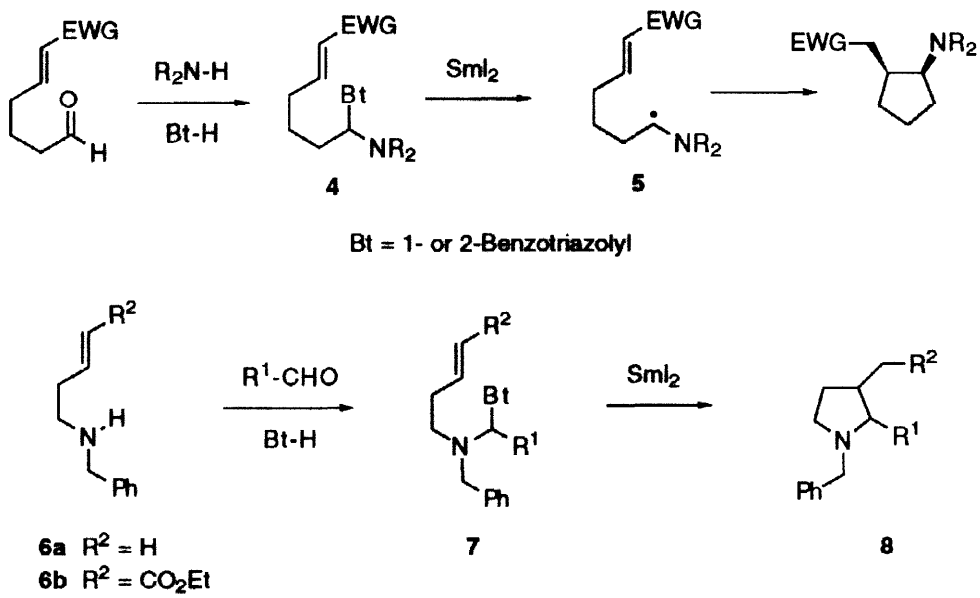
PII: S0040-4020(99)00359-2

Scheme 1



While the tin hydride method probably remains the most frequently employed for radical generation, the use of the one-electron reducing agent samarium diiodide (SmI_2)[12] has seen a truly spectacular growth in recent years and this has also included the generation of α-amino radicals. Thus, the treatment of cyclic iminium ions with SmI_2 in the presence of camphorsulfonic acid (CSA) generates very reactive α-ammonium radicals that are able to participate in 5-*exo-trig* radical ring closures.[13] The alternative use of α-aminoalkenyl benzotriazoles[14] **4** (derived from aldehydes and secondary amines) as *in situ* precursors of iminium ions allows the SmI_2-promoted efficient cyclization of neutral α-amino radicals **5** onto electron deficient double bonds and this has been developed into a general and convergent synthesis of cyclopentylamines starting from convenient and readily available aldehyde and amine fragments (Scheme 2).[14c]

Scheme 2



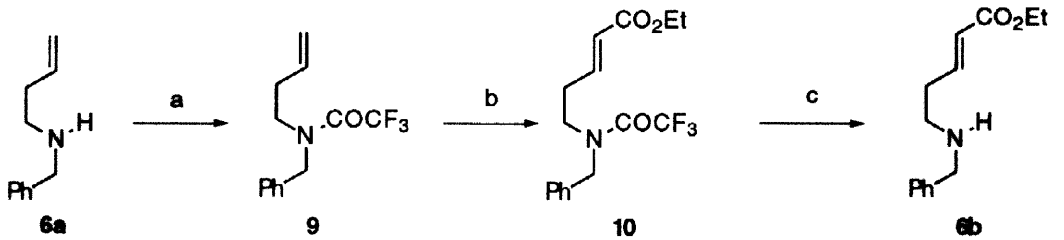
This paper reports full details of the application of this strategy to the stereoselective synthesis of 2,3-disubstituted pyrrolidines **8** from amines **6** and a wide range of aldehydes through intermediate *N*-(α-

benzotriazolylalkyl)alkenylamines **7** (Scheme 2).[14b,15,16] In selected cases, pyrrolidines **8** have been debenzylated, thus extending the potential of this methodology to the synthesis of *N*-unsubstituted pyrrolidines.

Preparation of Disubstituted Pyrrolidines.

Amines **6** were selected as models for this study. Amine **6b**[17] was readily available from **6a**[18] as outlined in Scheme 3. Initially,[14b] the methyl ester **6** (R = CO_2Me)[18] was used but this proved to be somewhat unstable over long periods of storage in a freezer and, furthermore, the acid-promoted deprotection of its BOC-precursor[18] had in our hands a less than desirable efficiency. On the other hand, the use of a trifluoroacetyl protecting group in **10** enabled a very efficient, essentially quantitative, deprotection to give the amine **6b** that could be used synthetically without purification.

Scheme 3



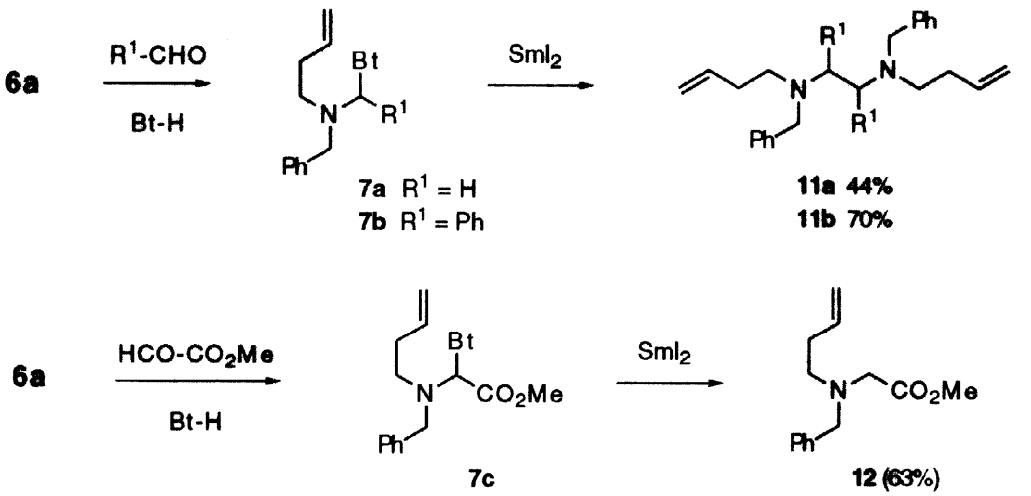
(a) $(CF_3CO)_2O$ / Et_3N / 25 °C. (b) (i) O_3 / -78 °C; (ii) Me_2S; (iii) $Ph_3P{=}CHCO_2Et$ / 25 °C. (c) K_2CO_3 / EtOH

The condensation of amines **6** with aldehydes and benzotriazole[19] in the presence of 4 Å molecular sieves led to the formation of intermediate *N*-(α-benzotriazolylalkyl)alkenylamines **7** (Scheme 4). Due to the lability of these compounds in the presence of water and traces of acids or on silica gel chromatography,[20] they were utilized in a crude form after removal of the sieves by filtration and evaporation of the solvent. Nevertheless, they were routinely checked by ^{1}H NMR to confirm their formation and estimate the percent conversion. Thus, in general, these adducts were characterized by two sets of signals in the region δ 5.2-6.2* for the *N*-CH_n-*N* of 1- and 2-substituted benzotriazoles in equilibrium. Also typical were a doublet at δ 8.0-8.1 corresponding to H-4 (benzotriazole numbering) of the benzotriazol-1-yl isomer and a multiplet at δ 7.8-8.0 assigned to H-4 and H-7 of the 2-substituted isomer. These condensations were generally clean and conversion, as estimated by ^{1}H NMR integration, was generally in the range 90-95%.

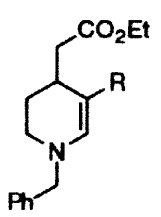
The treatment of benzotriazoles **7a,b** (R = H) derived from amine **6a** with two equivalents of SmI_2 afforded none of the desired cyclic products. Instead, vicinal diamines **11a,b** were obtained in 44 and 70% yield, respectively (Scheme 4). Interestingly, no dimerization took place in a similar reaction with adduct **7c** (R = H; R^1 = CO_2Me) derived from methyl glyoxylate and **6a** (Scheme 4), the β-aminoester **12** being the only isolated product (63% yield).

* R^1 = Alkyl. For benzotriazoles **7** derived from aromatic aldehydes the signal appeared in the aromatic region.

Scheme 4



In sharp contrast, the analogous reaction of adducts **7d-r** derived from amine **6b**, containing an electron-deficient double bond, led to the efficient formation of pyrrolidines **8** (Table 1). Due to the lability of adducts **7** to hydrolysis, yields are referred to a two-step procedure starting from amine **6b**. Initial cyclization conditions[14b] involved mixing the reactants, SmI_2 and **7**, at low temperatures (-78 °C or -10 °C) in THF and allowing the mixture to reach room temperature. This procedure worked well for reactions run on a 0.24 mmol scale but was not consistently reproducible on a 10-fold scale-up. Alternatively, the slow addition of **7** to excess SmI_2 at 25 °C gave consistent and reproducible results but generally yields were only moderate (Table 1, entries 1,3,5,7). Subsequently, we have found that using the former conditions in the presence of 2 equivalents of *t*-BuOH[21] led to the best results, as exemplified by comparison of entries 1 and 3 with entries 2 and 4, respectively (Table 1). Pyrrolidines derived from aliphatic aldehydes were usually accompanied by small amounts (4-12%) of tetrahydropyridines **13**, that probably originate in the Sm(III)-promoted β-elimination of benzotriazole from adducts **7**.[22] These compounds were relatively unstable and their formation was almost suppressed when *t*-BuOH was used as an additive (compare, for example, entries 5 and 6).



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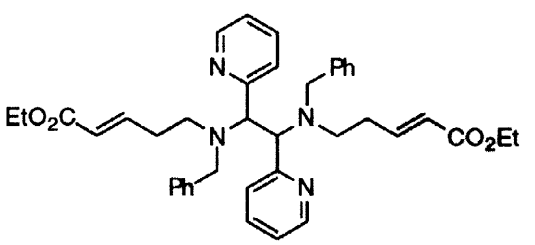

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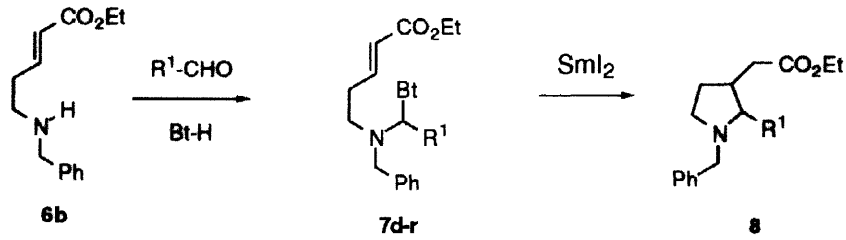
Table 1. Preparation of Disubstituted Pyrrolidines 8 from Amine 6b and Aldehydes



Entry	R^1	Cyclization Conditions[a]	8 (% yield)[b]	*Cis/Trans* Ratio[c]
1	*n*-C_5H_{11}	A	**8a** (44)	83:17
2	*n*-$C_{10}H_{21}$	B	**8b** (78)[d]	86:14
3	*i*-Pr	A	**8c** (45)	76:24
4	*i*-Pr	B	**8c** (74)	73:27
5	$Ph(CH_2)_2$	A	**8d** (49)[e]	71:29
6	3,4-$(MeO)_2C_6H_3(CH_2)_2$	B	**8e** (72)[f]	88:12
7	*trans*-Non-3-enyl	A	**8f** (44)	73:27
8	Pent-4-ynyl	B	**8g** (68)	87:13
9	$(CH_2)_4CO_2Et$	B	**8h** (65)	91:9
10	CH_2OCH_2Ph	B	**8i** (29)	g
11	Ph	B	**8j** (56)	10:90
12	3-ClC_6H_5	B	**8k** (60)	16:84
13	2-Naphthyl	B	**8l** (53)	9:91
14	3-Pyridyl	B	**8m** (65)	83:17
15	2-Pyridyl	B	**8n** (33)[h]	78:22

[a] A: Adduct **7** added to SmI_2 at 25 °C. B: Adduct **7** and *t*-BuOH added to SmI_2 at -78 °C. [b] Yields refer to two steps starting from amine **6b**. [c] Determined by integration of appropriate resonances in the NMR spectra of the purified products. [d] A 96:4 mixture of pyrrolidine **8b** and tetrahydropyridine **13b** (R = *n*-C_9H_{19}). [e] Tetrahydropyridine **13d** (R = CH_2Ph) was also obtained in 12% yield. [f] Tetrahydropyridine **13e** [R = $CH_2C_6H_3(OMe)_2$] was also obtained in 4% yield. [g] Not determined due to severe losses of the minor product upon purification. [h] Diamine **14** was also obtained in 10% yield.

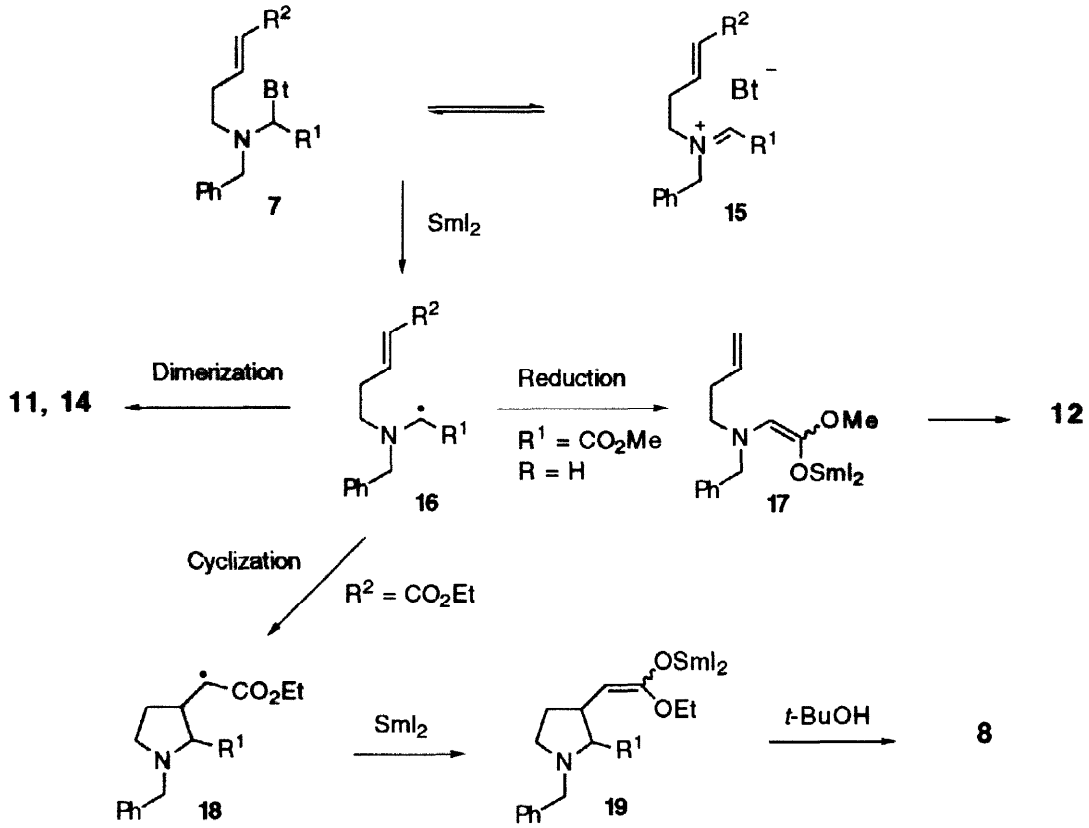
Inspection of Table 1 reveals that the formation of disubstituted pyrrolidines with this procedure is general for a wide range of aldehydes. With optimized conditions yields for a two-step procedure starting from amine **6** are good for both aliphatic and aromatic aldehydes. A number of useful functional groups are incorporated in the aldehyde partner without deleterious effects on yields (entries 7-9). Several limitations of this methodology were also found. For example, attempts to prepare adducts **7** derived from α,β-unsaturated aldehydes, such as *trans*-cinnamaldehyde and *trans*-2-nonenal, were unsuccessful probably due to competing conjugate addition of benzotriazole.[19] On the other hand, the use of adducts **7** derived from furfural, benzyloxyacetaldehyde (entry 10) and phenylacetaldehyde led upon treatment with SmI_2 to complex mixtures and low yields and/or unidentified materials. In contrast to the pyridin-3-yl pyrrolidine **8m**, that was obtained in good yield, the pyridin-2-yl analog

8n was formed in much lower yield and comparatively large amounts of diamine **14** were also isolated from this reaction.

Discussion.

α-Aminoalkenyl benzotriazoles of general structure **7** (Scheme 5) react readily with the one-electron reducing agent SmI_2 to generate α-amino radicals **16**. This reaction takes place by one-electron transfer from SmI_2 to iminium ions **15** derived from the *in situ* dissociation of the α-aminoalkenyl benzotriazoles **7**.[23] The α-amino substituent confers the carbon radical both a strong stabilization and a pronounced nucleophilic character. For unactivated alkenes the combination of these two features renders the cyclization a slow process. In this scenario, other competing processes may prevail to the exclusion of cyclization.[24] For example, radicals derived from **7a,b** (R^2 = H) either dimerize[14a] to yield vicinal diamines **11** or undergo reduction to a samarium enolate **17** (R^1 = CO_2Me, R^2 = H, Scheme 5). Alternatively, diamine **11a** (R^1 = R^2 = H) may arise by addition to **15** of an organosamarium formed by reduction of the α-amino radical.[14d] On the other hand, electron-deficient alkenes are able to trap neutral α-aminoalkyl radicals intramolecularly[14c] to afford a cyclized radical **18**. The success of this latter case is ascribed to (i) the lower energy of the olefin LUMO, much closer to the radical SOMO, (ii) the enhanced stability of the product radical **18**, and (iii) the presumably rapid reduction of **18** to a samarium enolate **19** that provides a termination step for the radical reaction. In the presence of *t*-BuOH rapid *in situ* protonation of **19** leads to the final product **8** preventing the enolate from participating in unwanted side-reactions.

Scheme 5



The pyridin-2-yl case in entry 15 (Table 1) is interesting since both cyclization and dimerization are observed. Delocalization of the unpaired electron onto both the alkylamino and the heterocyclic nitrogens gives the radical a capto-dative character with an increased tendency towards dimerization.[26]

The formation of pyrrolidines **8** takes place with moderate stereoselectivity the sense of which depends on the structure of the starting aldehydes and to a lesser degree on reaction temperature. Stereochemical assignments were made on the basis of the upfield shifts generally experienced by carbons C-2 and C-3 of the *cis*-isomers relative to the *trans*-isomers (Table 2), due to the occurrence of eclipsing interactions in the former.[27] Also supportive of the assignments were the corresponding downfield shifts observed for H-2 (Table 2) in the ^{1}H NMR spectra of the *cis*-isomers when compared to the same resonance in the *trans*-products.[27a]

Table 2. Selected ^{1}H- and ^{13}C-NMR Resonances of Pyrrolidines 8,20-22

Pyrrolidine	H-2[a,b]	C-2[c]	C-3[c]	Pyrrolidine	H-2[a,b]	C-2[c]	C-3[c]
cis-**8a**	2.93	66.1	36.9	*trans*-**8a**	2.85	69.5	39.1
cis-**8b**	2.93	66.2	36.8	*trans*-**8b**	2.86	69.5	39.1
cis-**8c**	2.97	70.2	d	*trans*-**8c**	2.84	74.8	d
cis-**8d**	2.97	65.6	37.1	*trans*-**8d**	2.90	69.2	39.1
cis-**8e**	2.97	65.4	36.9	*trans*-**8e**	2.89	69.1	38.9
cis-**8f**	2.93	65.5	36.9	*trans*-**8f**	2.83	69.0	39.2
cis-**8g**	2.93	65.4	36.9	*trans*-**8g**	2.83	68.9	38.7
cis-**8h**	2.91	65.7	36.8	*trans*-**8h**	2.83	69.1	38.8
cis-**8i**	e	63.5	36.9	*trans*-**8i**	2.88	68.7	38.3
cis-**8j**	3.75	71.3	39.2	*trans*-**8j**	3.00	75.5	44.3
cis-**8k**	3.73	70.4	38.9	*trans*-**8k**	3.00	74.7	44.3
cis-**8l**	d	71.1	39.0	*trans*-**8l**	d	75.4	43.9
cis-**8m**	3.79	68.6	39.1	*trans*-**8m**	3.79	72.7	44.4
cis-**8n**	d	71.9	38.5	*trans*-**8n**	d	76.2	43.4
cis-**20**	d	69.1	36.6	*trans*-**20**	d	70.1	38.3
cis-**21**	d	60.3	38.0	*trans*-**21**	d	63.8	41.4
cis-**22**	d	60.7	37.9	*trans*-**22**	d	64.1	41.5

[a] For multiplets, only the center of the signal is indicated. [b] Assigned by decoupling experiments. [c] Generally determined from a combination of DEPT experiments and inspection of signal intensity on the diastereomeric mixtures. [d] Could not be unambiguously assigned. [e] Included in a multiplet at 2.90-3.05.

The stereochemical preferences observed in the cyclized products **8** derived from aliphatic aldehydes are readily rationalized with Beckwith's model for radical ring-closures.[28] Thus, *cis*-products are formed predominantly in an early 5-*exo*-*trig* TS that accommodates all substituents in pseudoequatorial positions, as the stereoelectronic benefits of this arrangement usually outweigh the steric repulsions associated with the *cis*-relationship of two adjacent substituents. Increasing the steric bulk of R^1 in going from primary to secondary alkyl (entries 2,6,8,9 *vs* entry 4 in Table 1) results in a slightly diminished *cis*-preference as the above-mentioned steric repulsions disfavor the *cis*-TS relative to other alternative TSs that lead to *trans*-products. A broad comparison between conditions A and B in Table 1 appears to indicate that lowering the reaction temperature brings about a modest increase in diastereoselectivity. One noticeable aspect of these cyclizations is that

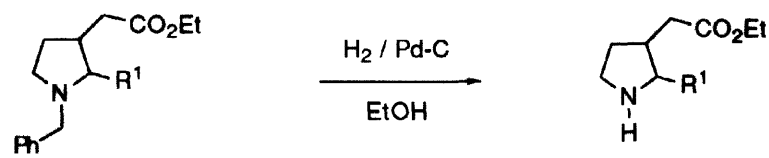
stereoselectivities are lower than those obtained in related α-amino radical cyclizations leading to cyclopentylamines.[14c] In this latter case the *cis*-TS benefits additionally from a secondary stabilizing orbital interaction between SOMO and LUMO π-type orbitals. This interaction cannot take place during formation of pyrrolidines due to the endocyclic nature of the N-C• bond throughout cyclization.

In contrast, products derived from aromatic aldehydes in entries 11-13 are formed with *trans*-stereoselectivity. One possible explanation for this divergent behaviour is that a further increase in the steric demand of R^1 could outweigh the usual stereoelectronic effects favoring *cis*-products. Additionally, the enhanced stability of radical **16** when R^1 = Ar (Scheme 5) could render the cyclization step reversible in these cases. The predominant formation of *trans*-products would then also be a reflection of their greater thermodynamic stability. The apparently anomalous *cis*-preference in the formation of the pyridyl-substituted pyrrolidines **8m,n** (entries 14, 15, Table 1) remains unexplained at this point.

Deprotection of N-Benzyl-2,3-Disubstituted Pyrrolidines.

One important synthetic aspect of this pyrrolidine synthesis is the possibility of debenzylating the cyclized products to arrive at *N*-unsubstituted pyrrolidines ready to be incorporated into more complex targets through the N-H functionality. Removal of the *N*-benzyl group of **8** was effected in selected cases on the diastereomeric mixtures, under typical hydrogenolysis conditions, to afford very satisfying yields of the corresponding secondary amines **20-22** (Scheme 6).

Scheme 6



8c R^1 = *i*-Pr
8f R^1 = $(CH_2)_2C_6H_3(OMe)_2$
8j R^1 = $(CH_2)_4CO_2Et$

20 88%
21 79%
22 87%

Conclusions.

This work demonstrates the feasibility of a convergent synthesis of disubstituted pyrrolidines from suitably functionalized amines and carbonyl compounds through a two-step procedure that involves condensation of the amine and aldehyde components in the presence of benzotriazole, and SmI_2-promoted reductive cyclization of the resulting α-aminoalkenyl benzotriazoles. From a strategic point of view, this sequence offers advantages over existing methodology in terms of functional group compatibility and the possibility of introducing a large variety of substituents at the pyrrolidine 2-position.

Experimental.

General. All reactions involving air- and moisture-sensitive materials were performed under an atmosphere of dry Ar. THF was freshly distilled from sodium/benzophenone and, for reactions with SmI_2, it was deoxygenated prior to use. Other solvents were routinely purified using literature procedures.[29] SmI_2 (*ca* 0.1 M in THF) was prepared from diiodomethane.[12b] Flash chromatography[30] was performed on silica gel (230-400 mesh). HPLC purifications were carried out with a μ-Bondapak NH_2 column. ^1H and ^{13}C-NMR spectra were

obtained in $CDCl_3$ at 250 MHz and 62.9 MHz, respectively. IR data include only characteristic absorptions. GC-MS analysis were performed at 70-280 °C (20 °C/min) with a stationary phase of methylphenylsilicone (0.25 μm, 30 m x 0.25 mm). Mass spectra were obtained at 70 eV.

Synthesis of ***Amine 6b.***

N-Benzyl-N-(but-3-enyl)-2,2,2-trifluoroacetamide (**9**). Trifluoroacetic anhydride (89 mL, 0.62 mol) was added dropwise to a solution of *N*-benzyl-*N*-(but-3-enyl)amine[18] (33.53 g, 0.21 mol) and dry triethylamine (175 mL) in dry CH_2Cl_2 (300 mL) at 0 °C. The solution was stirred for 1 h, allowed to warm to room temperature and evaporated. 1 M HCl (300 mL) was added to the resulting residue and the aqueous layer was extracted with CH_2Cl_2 (3 x 400 mL). The residue after evaporation was purified by flash chromatography (4:96 EtOAc/hexanes) to afford **9** (44.15 g, 81%, mixture of rotamers): ^{1}H NMR δ 2.25-2.41 (m, 2H, H-2'), 3.36-3.44 (m, 2H, H-1'), 4.63 and 4.68 (s, total 2H, PhCH_2), 5.02-5.14 (m, 2H, H-4'), 5.62-5.80 (m, 1H, H-3'), 7.15-7.54 (m, 5H); ^{13}C NMR δ 30.9, 32.6, 45.6, 45.9, 49.2, 50.9, 116.6 (q, J = 287.8 Hz, CF_3), 117.4, 117.9, 127.2, 127.9, 128.2 , 128.9, 133.3, 134.2, 134.8, 135.3 , 157.0 (q, J = 35.9 Hz, C=O), 157.6 (q, J = 35.9 Hz, C=O); IR (neat) ν 1710, 1695, 1680, 1645, 1170, 1000, 920 cm^{-1}. Anal. Calcd for $C_{13}H_{14}F_3NO$: C, 60.68; H, 5.49; N, 5.45. Found: C, 60.58; H, 5.23; N, 5.44.

Ethyl (E)-5-(N-benzyltrifluoroacetamido)pent-2-enoate (**10**).[17] Ozone (0.7 A, 100 L/min) was bubbled through a solution of **9** (44.15 g, 0.17 mol) and absolute MeOH (43 mL) in dry CH_2Cl_2 (460 mL) at -78 °C until a blue solution was obtained. Argon was bubbled until decoloration and then Me_2S (29 mL, 0.4 mol) was added. The solution was allowed to warm to room temperature, stirred for 12 h and evaporated. The residue was dissolved on EtOAc (700 mL), extracted with water (2 x 150 mL) and evaporated. The new residue was dissolved on CH_2Cl_2 (430 mL) and ethoxycarbonylmethylentriphenylphosphorane (63.00 g, 0.17 mol) was added in portions to the cooled (0 °C) solution. After warming to room temperature, the solution was stirred for 2 h and evaporated. The residue was purified by filtration through silica gel and dry column flash chromatography[31] (hexanes to 90:10 hexanes/EtOAc gradient) to afford **10** (35.0 g, 63% for two steps, mixture of rotamers): ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3H, CH_3), 2.35-2.53 (m, 2H, H-4), 3.38-3.48 (m, 2H, H-5), 4.12-4.22 (m, 2H, OCH_2), 4.61 and 4.67 (s, total 2H, PhCH_2), 5.79 and 5.83 (dt, J = 15.7, 1.5 Hz, total 1H, H-2), 6.77 (dt, J = 15.6, 7.2 Hz, 1H, H-3), 7.18-7.41 (m, 5H). These data coincide with those reported in the literature.[17]

Ethyl (E)-5-(N-benzylamino)pent-2-enoate (**6b**).[17] To a solution of **10** (2.53 g, 7.7 mmol) in EtOH (68 mL) was added 5 % K_2CO_3 (40 mL). The solution was stirred until total conversion of substrate (TLC, 15 h) and evaporated. The residue was dissolved in CH_2Cl_2 (150 mL) and the solution was washed with a 1:2 mixture of brine and water (150 mL). The aqueous layer was back-extracted with CH_2Cl_2 (2 x 150 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated to afford **6b** (1.71g, 95%) which was used without purification: ^{1}H NMR δ 1.28 (t, J = 7.1 Hz, 3H, CH_3), 1.45 (s, 1H, NH), 2.38-2.46 (m, 2H, H-4), 2.78 (t, J = 6.9 Hz, 2H, H-5), 3.80 (s, 2H, PhCH_2), 4.18 (q, J = 7.1 Hz, 2H, OCH_2), 5.87 (d, J = 15.7 Hz, 1H, H-2), 6.94 (dt, J = 15.7, 7.0 Hz, 1H, H-3), 7.24-7.33 (m, 5H). These data coincide with those reported in the literature.[17]

Preparation of Pyrrolidines.

General Procedure for preparation of Benzotriazole Intermediates **7**. A mixture of benzotriazole (1.1 equiv), amine **6**, the appropriate aldehyde (1.0 equiv) and 4 Å molecular sieves (2.3 g/mmol of amine) in dry benzene (13 mL/mmol of amine) was stirred at room temperature for 14 h. The mixture was diluted with CH_2Cl_2 (7

mL/mmol of amine) and filtered through Celite. The solvent was eliminated under reduced pressure and the resulting oil maintained under vacuum (0.1 mmHg) for 2 h and used without purification.

Reactions of **7** *with* SmI_2. *Representative procedures.* Conditions A: A solution of crude **7** (*ca* 3.18 mmol) in THF (132 mL) was added (syringe pump, 20 mL/h) at room temperature to a solution of SmI_2 (*ca* 0.1 M in THF, 9.6 mmol). The resulting mixture was stirred for 30 min and poured over a 1:1 mixture of saturated K_2CO_3 and water (250 mL), and the aqueous layer was extracted with EtOAc (3 x 250 mL). The combined organic extracts were washed with a 1:1 mixture of brine and water (250 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product after evaporation was purified by flash chromatography as specified for the individual cases. Conditions B: A solution of crude **7** (*ca* 1.7 mmol) and dry *t*-BuOH (3.5 mmol) in THF (36 mL) was added dropwise to a solution of SmI_2 (*ca* 0.1 M in THF, 5.0 mmol) at -78 °C. The resulting mixture was stirred for 30 min, allowed to reach room temperature and stirred for an additional hour. Work-up proceeded as indicated above.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-pentylpyrrolidine (**8a**). Initial purification by flash chromatography with 99:1 hexanes/triethylamine yielded **8a** contaminated with a presumed tetrahydropyridine byproduct. This was removed by flash chromatography eluting with 94:6 hexanes/EtOAc. Further elution with 80:20 hexanes/triethylamine afforded pure **8a.** Data for the diastereomeric mixture: ^{1}H NMR δ 0.91 (t, *J* = 6.5 Hz, 3H, C*H*$_3$), 1.20-1.57 (m, 13H, that includes t at 1.26, *J* = 7.1 Hz), 1.84-1.97 (m, 1H), 2.10-2.63 (m, 4H), 2.81-2.97 (m, 1H), 3.18 (d, *J* = 12.9 Hz, PhC*H trans*-isomer) and 3.22 (d, *J* = 13.2 Hz, PhC*H cis*-isomer) (total 1H), 4.00 (d, *J* = 12.9 Hz, PhC*H trans*-isomer) and 4.03 (d, *J* = 13.2 Hz, PhC*H cis*-isomer) (total 1H), 4.14 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 7.18-7.34 (m, 5H); ^{13}C NMR δ 14.0, 14.2, 22.6, 24.7, 26.3, 29.0, 29.2, 29.6, 32.2, 32.3, 32.4, 35.2, 36.9 (*C-3 cis*-isomer), 39.1 (*C-3 trans*-isomer), 39.9, 52.1, 52.5, 58.6, 59.0, 60.1, 66.1 (*C-2 cis*-isomer), 69.5 (*C-2 trans*-isomer), 126.6, 126.7, 128.0, 128.1, 128.5, 128.7, 139.6, 140.1, 172.7, 173.6; IR (neat) ν 1740, 1250 cm^{-1}; HRMS calcd for $C_{20}H_{31}NO_2$ 317.2355, found 317.2348. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.65; H, 9.85; N, 4.41. Found: C, 75.33; H, 9.93; N, 4.38.

N-Benzyl-2-decyl-3-(ethoxycarbonylmethyl)pyrrolidine (**8b**). Eluting with 2:98 triethylamine/hexanes, afforded a mixture of pyrrolidine **8b** and tetrahydropyridine **13b** (R = *n*-C_9H_{19}), which were separated using 4:96 EtOAc/hexanes and then 10:90 triethylamine/hexanes as eluent. Data for **13b** (further purified by HPLC, 1:99 EtOAc/hexanes, 8 mL/min): t_R = 11.7 min; ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H) 1.10-1.53 (br, 18H), 1.61-1.65 (m, 1H), 1.75-2.11 (m, 3H), 2.05 (dd, *J* =15.7, 11.3 Hz, C*H*CO$_2$Et, included in m at 1.75-2.11), 2.51-2.78 (m, 4H), 3.91 (s, 2H, PhC*H*$_2$), 4.11 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 5.79 (s, 1H, H-2), 7.24-7.34 (m, 5H); ^{13}C NMR 14.1, 14.2, 22.6, 27.4, 28.5, 29.2, 29.4, 29.5, 30.2, 31.8, 32.7, 39.6, 43.3, 59.5, 60.1, 111.1, 127.0, 128.2, 128.3, 132.4, 138.5, 173.2; IR (neat) ν 1740, 1680, 1030 cm^{-1}. Data for **8b** (diastereomeric mixture): ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.22-1.40 (m, 21H), 1.41-1.48 (m, 2H), 1.87-1.90 (m, 1H), 2.13 (dd, *J* = 17.0, 8.0 Hz, 1H, C*H*CO$_2$Et), 2.21-2.53 (m, 3H), 2.86-2.95 (m, 1H, H-2), 3.20 (d, *J* = 13 Hz, 1H, PhC*H*$_2$N), 4.02 (d, *J* = 8 Hz, 1H, C*H*CO$_2$Et), 4.13 (q, *J* = 7 Hz, 2H, OC*H*$_2$), 7.21-7.31 (m, 5H); ^{13}C NMR δ 14.1, 14.2, 22.6, 25.0, 26.5, 28.9, 29.1, 29.3, 30.1, 31.8, 32.2, 35.2, 36.7 (*C-3 cis*-isomer), 39.0 (*C-3 trans*-isomer), 39.9, 52.1, 52.6, 58.6, 58.9, 60.1, 66.0 (*C-2 cis*-isomer), 69.5 (*C-2 trans*-isomer), 126.5, 126.7, 128.0, 128.1, 128.5, 128.7, 139.5, 140.0, 172.8, 173.7; IR (neat) ν 1745, 1150, 1030 cm^{-1}. Anal. Calcd for $C_{25}H_{41}NO_2$: C, 77.46; H, 10.67; N, 3.50. Found: C, 77.01; H, 10.79; N, 3.62.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-isopropylpyrrolidine (**8c**). Eluent 98:2 hexanes/triethylamine. Data for the diastereomeric mixture: ^{1}H NMR δ 0.91-1.09 (m, 6H, C*H*$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.39-

1.61 (m, 1H), 1.72-1.90 (m, 2H), 2.13-2.75 (m, 5H), 2.81-2.87 (m, H-2 *trans*-isomer) and 2.93-3.01 (m, H-2 *cis*-isomer) (total 1H), 3.27 (d, J = 13.1 Hz, C*H*Ph *trans*-isomer) and 3.45 (d, J = 13.6 Hz, C*H*Ph *cis*-isomer) (total 1H), 3.98-4.21 (m, 3H, OCH_2 and C*H*Ph), 7.18-7.40 (m, 5H); ^{13}C NMR δ 14.2, 16.9, 18.9, 19.6, 21.3, 29.8, 30.1, 30.3, 30.6, 35.1, 35.3, 38.4 (*C-3 cis*-isomer), 41.0, 52.2, 53.2, 59.6, 60.1, 62.0, 70.2 (*C-2 cis*-isomer), 74.8 (*C-2 trans*-isomer), 126.5, 128.0, 128.1, 128.4, 140.3, 140.7, 172.7, 173.3; IR (neat) ν 1750, 1260, 1220 cm^{-1}. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.69; H, 9.41; N, 4.84. Found: C, 74.46; H, 9.47; N, 4.66.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-(2-phenylethyl)pyrrolidine (**8d**). Eluting with 84:16 to 80:20 hexanes/EtOAc gradient afforded tetrahydropyridine **13d** (R = CH_2Ph) and pyrrolidine **8d** that were further purified by elution with 98:2 hexanes/triethylamine. Data for **13d**: ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.66-1.76 (m, 1H, H-5), 1.82-1.96 (m, 1H, H-5), 2.13 (dd, J = 16.2, 11.6 Hz, 1H, C*H*CO), 2.47-2.60 (m, 2H, C*H*CO and H-4), 2.75-2.88 (m, 2H, H-6), 3.28 and 3.33 (AB q, J = 15.2 Hz, 2H, 3-CH_2), 4.00 (s, 2H, NCH_2Ph), 4.12 (q, J = 7.1 Hz, 2H, OCH_2), 5.92 (s, 1H, H-2), 7.18-7.44 (m, 10H); ^{13}C NMR δ 14.2, 27.2, 30.2, 39.4, 39.6, 42.9, 59.5, 60.1, 109.6, 125.8, 127.1, 128.1, 128.1, 128.3, 128.6, 134.4, 138.3, 141.2 , 172.9; IR (neat) ν 1740, 1660, 1450 cm^{-1}; HRMS calcd for $C_{23}H_{27}NO_2$ 349.2042, found 349.2030. Data for **8d** (diastereomeric mixture): ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, CH_3 *cis*-isomer) and 1.28 (t, J = 7.1 Hz, CH_3 *trans*-isomer) (total 3H), 1.45-1.78 (m, 2H), 1.80-2.12 (m, 2H), 2.18-3.01 (m, 8H), 3.26 (d, J = 12.7 Hz, C*H*Ph *trans*-isomer) and 3.31 (d, J = 13.2 Hz, C*H*Ph *cis*-isomer) (total 1H), 4.03 (d, J = 13.2 Hz, 1H, C*H*Ph), 4.16 (q, J = 7.1 Hz, 2H, OCH_2), 7.12-7.40 (m, 10H); ^{13}C NMR δ 14.2, 29.4, 31.2, 31.7, 32.9, 34.0, 35.3, 37.1 (*C-3 cis*-isomer), 39.1 (*C-3 trans*-isomer), 39.8, 52.2, 52.5, 58.6, 59.3, 60.2, 65.6 (*C-2 cis*-isomer), 69.2 (*C-2 trans*-isomer), 125.6, 125.8, 126.7, 126.8, 128.1, 128.3, 128.6, 128.7, 139.7, 140.0, 142.4, 142.8, 172.6, 173.4; IR (neat) ν 1740, 1250 cm^{-1}. Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.32; N, 3.99. Found: C, 78.29; H, 8.42; N, 3.99.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine (**8e**). Obtained from amine **6b** and 3-(3,4-dimethoxyphenyl)propanal.[32] Eluting with 88:10:2 hexanes/EtOAc/triethylamine afforded a mixture of **13** [R = 3,4-$(MeO)_2C_6H_3CH_2$] and **8e** which was separated using 70:30 hexanes/EtOAc and then 70:30 hexanes/triethylamine. Data for **13** [R = 3,4-$(MeO)_2C_6H_3CH_2$]: ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 3H, CH_3), 1.62-1.69 (m, 1H), 1.77-1.91 (m, 1H), 2.00-2.12 (m, 1H), 2.43-2.54 (m, 2H), 2.70-2.84 (m, 2H), 3.18 and 3.23 (AB q, J = 15.4 Hz, 2H, C-3-CH_2), 3.86 (s, 6H, *OCH$_3$*), 3.97 (s, 2H, PhCH_2N), 4.07 (q, J = 7.1 Hz, 2H, OCH_2), 5.87 (s, 1H, H-2), 6.72-6.81 (m, 3H), 7.23-7.35 (m, 5H); ^{13}C NMR δ 14.2, 27.3, 30.3, 39.1, 39.6, 42.9, 55.7, 55.8, 59.4, 60.1, 109.7, 111.0, 111.9, 120.5, 127.1, 128.1, 128.3, 133.8, 134.1, 138.3, 147.1, 148.7, 172.9; IR (neat) ν 1730, 1660, 1260, 1230 cm^{-1}; HRMS calcd for $C_{25}H_{31}NO_4$ 409.2253, found 409.2244. Data for **8e** (mixture of diastereomers): ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, CH_3 *cis*-isomer) and 1.27 (t, J = 7.1 Hz, CH_3 *trans*-isomer) (total 3H), 1.44-1.67 (m, 2H), 1.74-2.04 (m, 2H), 2.17-2.70 (m, 7H), 2.92-3.01 (m, 1H), 3.26 (d, J = 11.6 Hz, PhC*H* *trans*-isomer) and 3.31 (d, J = 13.2 Hz, PhC*H* *cis*-isomer) (total 1H), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.01 (d, J = 13.2 Hz, 1H, PhC*H*), 4.14 (q, J = 7.1 Hz, 2H, OCH_2), 6.71-6.81 (m, 3H), 7.20-7.34 (m, 5H); ^{13}C NMR δ 14.2, 29.2, 30.6, 31.8, 32.3, 34.1, 35.2, 36.9 (*C-3 cis*-isomer), 38.9 (*C-3 trans*-isomer), 39.8, 52.1, 52.5, 55.7, 55.8, 58.6, 59.2, 60.2, 65.4 (*C-2 cis*-isomer), 69.1 (*C-2 trans*-isomer), 111.2, 111.6, 119.9, 126.6, 126.7, 128.0, 128.1, 128.5, 128.6, 135.0, 135.3, 139.6, 139.9, 147.0 , 147.1, 148.8, 172.6, 173.4; IR (neat) ν 1735, 1260, 1240 cm^{-1}; HRMS calcd for $C_{25}H_{33}NO_4$ 411.2410, found 411.2407.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-[(E)-non-3-enyl]pyrrolidine (**8f**). Eluent 99:1

hexanes/triethylamine. Data for the diastereomeric mixture: ^{1}H NMR δ 0.89 (t, J = 6.7 Hz, 3H, CH_3), 1.19-1.66 (m, 12H), 1.84-2.62 (m, 10H), 2.83 (m, H-2, *trans*-isomer) and 2.88-2.97 (m, H-2, *cis*-isomer) (total 1H), 3.19 (d, J = 13.0 Hz, PhC*H trans*-isomer) and 3.24 (d, J = 13.2 Hz, PhC*H cis*-isomer) (total 1H), 3.99 (d, J = 13.0 Hz, PhC*H trans*-isomer) and 4.02 (d, J = 13.2 Hz, PhC*H cis*-isomer) (total 1H), 4.14 (q, J = 7.1 Hz, 2H, OCH_2), 5.33-5.50 (m, 2H, H-3' and H-4'), 7.19-7.34 (m, 5H); ^{13}C NMR δ 14.1, 14.3, 22.5, 28.2, 29.1, 29.2, 29.6, 29.7, 31.4, 32.3, 32.5, 35.3, 36.9 (*C-3 cis*-isomer), 39.2 (*C-3 trans*-isomer), 39.9, 52.1, 52.5, 58.6, 59.1, 60.2, 65.5 (*C-2 cis*-isomer), 69.0 (*C-2 trans*-isomer), 126.7, 126.8, 128.1, 128.6, 128.8, 129.8, 130.1, 130.6, 130.8, 139.6, 140.0, 172.8, 173.6; IR (neat) ν 1740, 1650, 1250 cm^{-1}; HRMS calcd for $C_{24}H_{37}NO_2$ 371.2824, found 371.2829.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-(pent-4-ynyl)pyrrolidine (**8g**). From amine **6b** and 5-hexynal.[33] Initial purification by flash chromatography with 99:1 hexanes/triethylamine yielded **8g** contaminated with a presumed tetrahydropyridine byproduct. This was removed by flash chromatography eluting with 94:6 hexanes/EtOAc. Further elution with 90:10 hexanes/triethylamine afforded pure **8g**. Data for the diastereomeric mixture: ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, 3H, CH_3), 1.35-1.78 (m, 5H), 1.84-1.95 (m, 1H), 1.97 (t, J = 2.6 Hz, 1H, H-5'), 2.07-2.62 (m, 7H), 2.80-2.87 (m, H-2 *trans*-isomer) and 2.88-2.97 (m, H-2 *cis*-isomer) (total 1H), 3.17 (d, J = 12.9 Hz, PhC*H trans*-isomer) and 3.25 (d, J = 13.1 Hz, PhC*H cis*-isomer) (total 1H), 4.00 (d, J = 12.9 Hz, PhC*H trans*-isomer) and 4.01 (d, J = 13.1 Hz, PhC*H cis*-isomer) (total 1H), 4.13 (q, J = 7.1 Hz, 2H, OCH_2), 7.18-7.34 (m, 5H); ^{13}C NMR δ 14.2, 18.7, 18.8, 23.6, 25.4, 28.8, 29.0, 29.1, 30.8, 35.1, 36.9 (*C-3 cis*-isomer), 38.7 (*C-3 trans*-isomer), 39.7, 52.0, 52.4, 58.5, 59.1, 60.2, 65.4 (*C-2 cis*-isomer), 68.5, 68.9 (*C-2 trans*-isomer), 84.2, 84.4, 126.6, 126.7, 128.0, 128.1, 128.5, 128.6, 139.5, 139.9, 172.6, 173.4 ; IR (neat) ν 3290, 2110, 1735, 1150 cm^{-1}; HRMS calcd for $C_{20}H_{27}NO_2$ 313.2042, found 313.2039.

N-Benzyl-2-(4-ethoxycarbonylbutyl)-3-(ethoxycarbonylmethyl)pyrrolidine (**8h**). From amine **6b** and ethyl 6-oxohexanoate.[34] Initial purification by flash chromatography with 98:2 hexanes/triethylamine yielded **8h** contaminated with a presumed tetrahydropyridine byproduct. This was removed by flash chromatography eluting with 90:10 hexanes/EtOAc. Further elution with 90:10 hexanes/triethylamine afforded pure **8h**. Data for the diastereomeric mixture: ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 6H, CH_3), 1.30-1.71 (m, 7H), 1.83-1.95 (m, 1H), 2.15 (dd, J = 17.6, 8.5 Hz, 1H, C-3-C*H*CO$_2$Et), 2.22-2.42 (m, 4H), 2.45-2.62 (m, 2H), 2.80-2.83 (m, H-2, *trans*-isomer) and 2.87-2.95 (m, H-2, *cis*-isomer) (total 1H), 3.16 (d, J = 12.9 Hz, PhC*H trans*-isomer) and 3.22 (d, J = 13.1 Hz, PhC*H cis*-isomer) (total 1H), 3.96 (d, J = 12.9 Hz, PhC*H trans*-isomer) and 3.99 (d, J = 13.1 Hz, PhC*H cis*-isomer) (total 1H), 4.12 (q, J = 7.1 Hz, OCH_2) and 4.13 (q, J = 7.1 Hz, OCH_2) (total 4H), 7.18-7.37 (m, 5H); ^{13}C NMR δ 14.1, 24.3, 25.3, 25.9, 28.9, 29.3, 31.6, 34.1, 35.0, 36.8 (*C-3 cis*-isomer), 38.8 (*C-3 trans*-isomer), 39.7, 52.0, 52.5, 58.5, 59.0, 60.1, 65.7 (*C-2 cis*-isomer), 69.1 (*C-2 trans*-isomer), 126.5, 126.7, 128.0, 128.0, 128.4, 128.6, 139.4, 139.9, 172.6, 173.4, 173.5; IR (neat) ν 1735, 1150 cm^{-1}. Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.36; H, 8.86; N, 3.73. Found: C, 70.36; H, 9.15; N, 3.72.

N-Benzyl-2-(benzyloxymethyl)-3-(ethoxycarbonylmethyl)pyrrolidine (**8i**). Flash chromatography 99:1 hexanes/triethylamine afforded, in order of elution *cis*-**8i** and *trans*-**8i**. Data for *cis*-**8i**: ^{1}H NMR δ 1.23 (t, J = 7.1 Hz, 3H, CH_3), 1.50-1.59 (m, 1H), 1.88-1.97 (m, 1H), 2.28-2.42 (m, 2H), 2.62-2.76 (m, 2H), 2.90-3.05 (m, 2H), 3.36-3.48 (m, 2H), 3.55 (d, J = 13.1 Hz, 1H, PhC*H*N), 4.01 (d, J = 13.1 Hz, 1H, PhC*H*N), 4.00-4.14 (m, 2H, OCH_2CH$_3$), 4.47 (s, 2H, PhCH_2O), 7.22-7.39 (m, 10H); ^{13}C NMR δ 14.1, 30.4, 35.0, 36.9 (*C-3*), 52.8, 59.5, 60.1, 63.5 (*C-2*), 70.6, 73.2, 126.7, 127.4, 127.6, 128.1, 128.2, 128.7, 138.2, 139.6 , 173.2; IR (neat) ν 1735, 1500, 1100 cm^{-1}; HRMS calcd for $C_{23}H_{29}NO_3$ 367.2147, found 367.2143. Data for *trans*-**8i**

(further purified by HPLC, 96:4 hexanes/EtOAc, 8 mL/min): t_R = 22 min; ^{1}H NMR δ 1.24 (t, *J* = 7.1 Hz, 3H, C*H*$_3$), 1.39-1.49 (m, 1H), 1.93-2.08 (m, 1H), 2.23-2.56 (m, 5H), 2.85-2.92 (m, 1H), 3.36 (d, *J* = 13.1 Hz, 1H, PhC*H*N), 3.51 (dd, *J* = 9.6, 4.7 Hz, 1H, C-2-C*H*), 3.59 (dd, *J* = 9.6, 4.7 Hz, 1H, C-2-C*H*), 4.11 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.14 (d, *J* = 13.1 Hz, 1H, PhC*H*N), 4.54 (s, 2H, PhC*H*$_2$O), 7.21-7.34 (m, 10H); ^{13}C NMR δ 14.2, 29.2, 38.3 (*C-3*), 39.5, 52.6, 59.4, 60.2, 68.7 (*C-2*), 72.9, 73.3, 126.8, 127.5, 127.5, 128.1, 128.3, 128.8, 138.3, 139.3, 172.6; IR (neat) ν 1735, 1500 cm^{-1}; HRMS calcd for $C_{23}H_{29}NO_3$ 367.2147, found 367.2131.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-phenylpyrrolidine (**8j**). Eluent 92:8 hexanes/EtOAc. Data for the mixture of diastereomers: ^{1}H NMR δ 1.08-1.30 (m, 3H, C*H*$_3$), 1.50-1.63 (m, 1H), 1.88-2.50 (m, 5H), 2.84-3.17 (m, 3H), 3.73-4.08 (m, 3H), 7.19-7.51 (m, 10H); ^{13}C NMR δ 14.1, 29.0, 30.4, 37.8, 37.9, 39.2 (*C-3 cis*-isomer), 44.3 (*C-3 trans*-isomer), 51.9, 52.3, 58.0, 58.4, 59.9, 60.1, 71.3 (*C-2 cis*-isomer), 75.5 (*C-2 trans*-isomer), 126.7, 127.1, 127.5, 128.0, 128.1, 128.5, 128.6, 128.7, 139.5, 139.6, 140.2, 141.8, 172.3, 173.0; IR (neat) ν 1740, 1250 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.97; H, 7.80; N, 4.33. Found: C, 77.70; H, 8.07; N, 4.33.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-(3-chlorophenyl)pyrrolidine (**8k**). Eluent 98:2 hexanes/triethylamine. Data for the diastereomeric mixture: ^{1}H NMR δ 1.14-1.23 (m, 3H, C*H*$_3$), 1.49-1.64 (m, 1H, H-4), 1.91 (dd, *J* = 16.0, 6.6 Hz, C*H*CO$_2$Et *cis*-isomer), 2.06 (dd, *J* = 16.0, 8.9 Hz, C*H*CO$_2$Et *cis*-isomer), 2.04-2.51 (m, C*H*$_2$CO$_2$Et *trans*-isomer; H-3 *trans*-isomer; H-4 and H-5) and 2.79-2.94 (m, H-3 *cis*-isomer) (total 5H), 3.00 (d, *J* = 9.0 Hz, H-2 *trans*-isomer) and 3.73 (d, *J* = 9.9 Hz, H-2 *cis*-isomer) (total 1H), 3.05 (d, *J* = 13.3 Hz, C*H*Ph *trans*-isomer) and 3.16 (d, *J* = 13.4 Hz, C*H*Ph *cis*-isomer) (total 1H), 3.06-3.16 (m, 1H, H-5), 3.78 (d, *J* = 13.2 Hz, C*H*Ph *trans*-isomer) and 3.88 (d, *J* = 13.2 Hz, C*H*Ph *cis*-isomer) (total 1H), 3.93-4.12 (m, 2H, OC*H*$_2$), 7.20-7.38 (m, 8H), 7.42 (s, H-2' *cis*-isomer) and 7.49 (s, H-2' *trans*-isomer) (total 1H); ^{13}C NMR δ 14.1, 28.9, 30.3, 37.6, 37.7, 38.9 (*C-3 cis*-isomer), 44.3 (*C-3 trans*-isomer), 51.7, 52.1, 58.0, 58.3, 60.1, 60.2, 70.4 (*C-2 cis*-isomer), 74.7 (*C-2 trans*-isomer), 126.2, 126.8, 126.9, 127.2, 127.6, 128.0, 128.1, 128.5, 128.7, 129.4, 129.7, 134.1, 134.3, 139.0, 139.1, 142.7, 144.1, 172.1, 172.8; IR (neat) ν 1740, 1250 cm^{-1}. Anal. Calcd for $C_{21}H_{24}NO_2Cl$: C, 70.56; H, 6.77; N, 3.92. Found: C, 70.28; H, 6.66; N, 3.77.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-(2-naphthyl)pyrrolidine (**8l**). Eluent 93:7 hexanes/EtOAc. Data for the diastereomeric mixture: ^{1}H NMR δ 1.02 (t, *J* = 7.1 Hz, C*H*$_3$ *cis*-isomer) and 1.17 (t, *J* = 7.1 Hz, C*H*$_3$ *trans*-isomer) (total 3H), 1.59-1.73 (m, 1H), 1.95-2.66 (m, 5H), 2.98-3.22 (m, 3H), 3.82-4.07 (m, 3H), 7.23-7.42 (m, 5H), 7.47-7.57 (m, 2H), 7.64-7.96 (m, 5H); ^{13}C NMR δ 13.8, 14.0, 29.0, 30.4, 37.8, 39.0 (*C-3 cis*-isomer), 43.9 (*C-3 trans*-isomer), 51.9, 52.2, 58.0, 58.3, 59.9, 60.1, 71.1 (*C-2 cis*-isomer), 75.4 (*C-2 trans*-isomer), 125.5, 125.6, 125.9, 126.7, 126.9, 127.4, 127.6, 127.7, 128.0, 128.4, 128.6, 132.9, 133.2, 133.3, 137.8, 139.1, 139.2, 139.4, 172.3, 173.0; IR (neat) ν 1730, 1240 cm^{-1}; HRMS calcd for $C_{25}H_{27}NO_2$ 373.2042, found 373.2052. Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 79.90; H, 7.36; N, 3.72.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-(3-pyridyl)pyrrolidine (**8m**). Eluent 72:26:2 hexanes/EtOAc/triethylemine. Data for the diastereomeric mixture: ^{1}H NMR δ 1.12 (t, *J* = 7.1 Hz, C*H*$_3$ *cis*-isomer) and 1.16 (t, *J* = 7.1 Hz, C*H*$_3$ *trans*-isomer) (total 3H), 1.51-1.66 (m, 1H), 1.89 (dd, *J* = 16.0, 6.9 Hz, C*H*CO$_2$Et *cis*-isomer) and 2.02-2.43 (m) (total 4H), 2.83-2.93 (m, *cis*-isomer), 3.05-3.16 (m) and 3.20 (d, *J* = 13.2 Hz, C*H*Ph *cis*-isomer) (total 3H), 3.72 (d, *J* = 13.1 Hz, C*H*Ph *trans*-isomer) and 3.81 (d, *J* = 13.2 Hz,

C*H*Ph *cis*-isomer) (total 1H), 3.79 (d, J = 8.6 Hz, H-2), 3.89-4.05 (m, 2H, OCH_2), 7.26-7.33 (m, 6H), 7.71 (dt, J = 7.7, 1.9 Hz, *cis*-isomer) and 7.81 (dt, J = 7.9, 2.0 Hz, *trans*-isomer) (total 1H), 8.49 (dd, J = 4.8, 1.6 Hz, *cis*-isomer) and 8.52 (dd, J = 4.8, 1.7 Hz, *trans*-isomer) (total 1H), 8.59 (d, J = 2.0 Hz, *cis*-isomer) and 8.62 (d, J = 2.0 Hz, *trans*-isomer) (total 1H); ^{13}C NMR δ 14.0, 29.1, 30.5, 37.6, 39.1 (*C-3 cis*-isomer), 44.4 (*C-3 trans*-isomer), 51.9, 52.3, 58.0, 58.3, 60.1, 60.2, 68.6 (*C-2 cis*-isomer), 72.7 (*C-2 trans*-isomer), 123.0, 123.6, 126.9, 128.1, 128.5, 135.4, 135.9, 136.3, 137.2, 138.9, 148.6, 149.2, 150.0, 150.6, 171.9, 172.4; IR (neat) ν 1740, 1250 cm^{-1}; HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1839.

N-Benzyl-3-(ethoxycarbonylmethyl)-2-(2-pyridyl)pyrrolidine (**8n**). Eluting with 74:24:2 hexanes/EtOAc/triethylamine afforded a mixture of diamine **14** and pyrrolidine **8n** that were separated by another flash chromatography (70:30 hexanes/EtOAc, then 73:30 hexanes/triethylamine). Data for diamine **14**: ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 6H, CH_3), 1.97-2.26 (m, 4H), 2.27-2.46 (m, 2H), 2.51-2.68 (m, 2H), 3.11 (d, J = 14.2 Hz, 2H, C*H*Ph), 4.01 (d, J = 14.2 Hz, 2H, C*H*Ph), 4.14 (q, J = 7.1 Hz, 4H, OCH_2), 4.83 (s, 2H, H-1, H-2), 5.58 (dt, J = 15.7, 1.2 Hz, 2H), 6.59 (dt, J = 15.7, 7.0 Hz, 2H), 6.70-6.74 (m, 4H), 7.08-7.15 (m, 8H), 7.25-7.30 (m, 2H), 7.69 (td, J = 7.6, 1.8 Hz, 2H), 8.71-8.73 (m, 2H); ^{13}C NMR δ 14.3, 30.9, 49.4, 54.7, 59.9, 65.2, 121.7, 121.9, 124.8, 126.5, 127.8, 128.5, 135.2 , 139.9, 147.7, 149.1, 157.6, 166.4; IR (neat) ν 1720, 1270 cm^{-1}. Anal. Calcd for $C_{40}H_{46}N_4O_4$: C, 74.26; H, 7.17; N, 8.67. Found: C, 73.97; H, 7.36; N, 8.59. Data for pyrrolidine **8n** (mixture of diastereomers): ^{1}H NMR δ 1.09-1.17 (m, 3H, CH_3), 1.50-1.65 (m, 1H, H-4), 1.90 (d, J = 7.8 Hz) and 2.04-2.60 (m) (total 4H), 2.94-3.03 (m, H-3 *cis*-isomer), 3.07-3.17 (m), 3.25 (d, J = 8.3 Hz) and 3.27 (d, J = 13.4 Hz) (total 3H), 3.75 (d, J = 13.2 Hz, C*H*Ph *trans*-isomer) and 3.85 (d, J = 13.3 Hz, C*H*Ph *cis*-isomer) (total 1H), 3.91-4.03 (m, 3H), 7.09-7.28 (m, 6H), 7.55-7.67 (m, 2H), 8.51-8.55 (m, 1H); ^{13}C NMR δ 14.0, 29.2, 30.4, 37.2, 37.9, 38.5 (*C-3 cis*-isomer), 43.4 (*C-3 trans*-isomer), 51.8, 52.3, 58.2, 58.5, 59.9, 60.0, 71.9 (*C-2 cis*-isomer), 76.2 (*C-2 trans*-isomer), 121.4, 121.8, 122.2, 122.5, 126.6, 128.0, 128.4, 128.5, 136.1, 136.7, 138.8, 139.0, 148.8, 149.0, 161.1, 162.1, 172.4, 172.5; IR (neat) ν 1730, 1250 cm^{-1}; HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1840.

1,2-Bis[N-benzyl-N-(but-3-enyl)amino]ethane (**11a**). Procedure A was followed. Eluent 90/10 hexanes/EtOAc: ^{1}H NMR δ 2.19 (q, J = 7.0 Hz, 4H, H-2'), 2.50 (t, J = 7.4 Hz, 4H, H-1'), 2.57 (s, 4H, H-1), 3.56 (s, 4H, CH_2-Ph), 5.0 (m, 4H, H-4'), 5.7-5.8 (m, 2H, H-3'), 7.2-7.4 (m, 10H); ^{13}C NMR δ 31.6, 51.6, 53.8, 58.9, 115.3, 126.7, 128.1, 128.8, 136.9, 139.8; IR (neat) ν 2940, 2800, 1645 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.47; H, 9.21; N, 8.22.

1,2-Bis[N-benzyl-N-(but-3-enyl)amino]-1,2-diphenylethane (**11b**). A 0.1 M SmI_2 solution in THF was added dropwise to a stirred solution of the corresponding benzotriazole adduct at -40 °C at such a rate as to allow the SmI_2 characteristic blue color to disappear before the next drop was added. Addition was continued until the blue color persisted (*ca* 1 equiv of SmI_2).[35] Work-up as above afforded a crude product that was purified by flash chromatography (90:10 hexanes/EtOAc) to afford **11b** as a diastereomeric mixture (67:33): ^{1}H NMR δ 1.7-2.0 (m, 2H), 2.1-2.6 (m, 6H), 2.9-3.1 (m, 2H, C*H*-Ph), 3.80 (d, J = 13.4 Hz, C*H*-Ph, minor isomer) and 3.86 (d, J = 13.8 Hz, C*H*-Ph, major isomer) (total 2H), 4.34 (s, H-1, major isomer) and 4.39 (s, H-1, minor isomer) (total 2H), 4.8-5.0 (m, H-4', minor isomer) and 5.0-5.2 (m, H-4', major isomer) (total 4H), 5.4-5.6 (m, H-3', minor isomer) and 5.8-6.1 (m, H-3', major isomer) (total 2H), 6.6-7.5 (m, 20H); ^{13}C NMR δ 32.7, 33.6, 48.9, 49.9, 54.2, 54.3, 64.2, 115.0, 115.4, 126.5, 126.7, 126.8, 127.4, 127.8, 128.0, 128.9, 129.1, 129.6, 130.0, 136.6, 136.7, 137.0, 139.9, 140.4; IR (neat) ν 1640, 1600 cm^{-1}.

Methyl [N-benzyl-N-(but-3-enyl)amino]ethanoate (**12**). Procedure A was followed performing the addition at -10 °C and then stirring the mixture at room temperature for 12 h. Work-up as above afforded a crude product that was purified by flash chromatography (90:10 hexanes/EtOAc): ^{1}H NMR δ 2.27 (q, *J* = 7.2 Hz, 2H, H-2'), 2.75 (t, *J* = 7.2 Hz, 2H, H-1'), 3.34 (s, 2H, H-2), 3.69 (s, 3H, C*H*$_3$), 3.81 (s, 2H, C*H*$_2$-Ph), 5.0-5.1 (m, 2H, H-4'), 5.8-5.83 (m, 1H, H-3'), 7.2-7.4 (m, 5H); ^{13}C NMR δ 32.1, 51.2, 53.3, 53.9, 58.0, 115.6, 127.0, 128.2, 128.8, 136.5, 138.9, 171.8; IR (neat) ν 1745, 1645. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.33; H, 8.35; N, 5.96.

Debenzylation Reactions.

General procedure. A deoxygenated mixture of pyrrolidine **8** (3.4 mmol), 10 % Pd/C (0.1-0.2 mg/mg of substrate) and absolute ethanol (10 mL/mmol of substrate) was hydrogenated (60 psi) at room temperature until total conversion of substrate (TLC, 20-108 h). The resulting mixture was filtered througth Celite and evaporated under reduced pressure. The crude product after evaporation was purified by flash chromatography as specified for the individual cases.

3-(Ethoxycarbonylmethyl)-2-isopropylpyrrolidine (**20**). From **8c** (76:27 *cis/trans*). Eluent 70:28:2 EtOAc/hexanes/Et$_2$NH. Data for the diastereomeric mixture (78:22 *cis/trans*): ^{1}H NMR δ 0.92 (d, *J* = 6.5 Hz, CHC*H*$_3$), 0.96 (d, *J* = 6.8 Hz, CHC*H*$_3$) and 0.99 (d, *J* = 6.5 Hz, CHC*H*$_3$) (total 6H), 1.25 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.44-1.53 (m, 1H), 1.60-1.69 (m, 1H), 1.75 (br s, 1H), 1.90-2.01 (m, 1H), 2.11 (dd, *J* = 15.0, 11.5 Hz, *cis*-isomer) and 2.18-2.27 (m, *trans*-isomer) (total 1H), 2.36-2.42 (m, 1H), 2.44-2.53 (m) and 2.59 (dd, J=9.7, 5.2 Hz, *cis*-isomer) (total 2H), 2.82-2.98 (m) and 3.02-3.08 (m, *cis*-isomer) (total 2H), 4.13 (q, *J* = 7.1 Hz, OC*H*$_2$ *trans*-isomer) and 4.13 (q, *J* = 7.1 Hz, OC*H*$_2$ *cis*-isomer) (total 2H); ^{13}C NMR δ 14.2, 18.4, 20.3, 20.4, 21.3, 29.3, 31.1, 32.0, 33.0, 33.3, 36.6 (*C-3 cis*-isomer), 38.3 (*C-3 trans*-isomer), 39.9, 44.0, 45.7, 60.3, 69.1 (*C-2 cis*-isomer), 70.1 (*C-2 trans*-isomer), 172.8, 173.6; IR (neat) ν 3440, 1735 cm^{-1}; HRMS calcd for $C_{11}H_{20}NO_2$ (M^+-1) 198.1494, found 198.1490.

3-(Ethoxycarbonyl)-2-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine (**21**). From **8e** (88:12 *cis/trans*). Eluent 98:2 EtOAc/Et$_2$NH. Data for the diastereomeric mixture (88:12 *cis/trans*): ^{1}H NMR δ 1.20 (t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$ *cis*-isomer) and 1.21 (t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$ *trans*-isomer) (total 3H), 1.42-1.70 (m, 3H), 1.83 (br s, 1H), 1.90-2.05 (m, 1H), 2.16 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.33-2.75 (m, 4H), 2.81-2.93 (m, 1H), 2.96-3.10 (m, 2H), 3.82 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 4.08 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 6.69-6.77 (m, 3H); ^{13}C NMR δ 14.1, 31.2, 32.3, 32.8, 33.2, 33.3, 34.6, 37.2, 38.0 (*C-3 cis*-isomer), 38.5, 41.4 (*C-3 trans*-isomer), 44.4, 45.3, 55.7, 55.8, 60.2, 60.3 (*C-2 cis*-isomer), 63.8 (*C-2 trans*-isomer), 111.0, 111.4, 111.5, 119.9, 119.9, 134.6, 146.9, 147.0, 148.6, 172.7, 173.2; IR (neat) ν 3320, 1735, 1520 cm^{-1}; HRMS calcd for $C_{18}H_{27}NO_4$ 321.1940, found 321.1941.

3-(Ethoxycarbonylmethyl)-2-(4-ethoxycarbonylbutyl)pyrrolidine (**22**). From **8h** (91:9 *cis/trans*). Eluent 98:2 EtOAc/Et$_2$NH. Data for the diastereomeric mixture (88:12 *cis/trans*): ^{1}H NMR δ 1.14-1.59 (m, 13H), 1.86-2.44 (m, 7H), 2.74-2.85 (m, 1H), 2.90-3.01 (m, 2H), 4.00-4.10 (m, 4H); ^{13}C NMR δ 14.2, 25.0, 26.9, 27.0, 30.4, 31.3, 32.4, 34.2, 34.5, 34.8, 37.9 (*C-3 cis*-isomer), 38.5, 41.5 (*C-3 trans*-isomer), 44.4, 45.2, 60.2, 60.3, 60.4, 60.6, 60.7(*C-2 cis*-isomer), 64.1 (*C-2 trans*-isomer), 172.8, 173.3, 173.6; IR (neat) ν 3420, 1735, 1640 cm^{-1}; HRMS calcd for $C_{15}H_{27}NO_4$ 285.1940, found 285.1925.

Acknowledgments. Financial support was provided by Dirección General de Investigación Científica y Técnica (DGICYT PB92-0449 and PB95-0344), Universidad del País Vasco (UPV 170.310-EC021/92 and UPV

170.310-EC216/97) and Janssen-Cilag. Fellowships to A.F. and J.M.G. (from Gobierno Vasco and Janssen-Cilag, respectively) are also gratefully acknowledged.

References and Notes

1. Some recent references: (a) Ganem, B. *Acc. Chem. Res.* **1996,** *29*, 340-347. (b) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997,** *62*, 1896-1898. (c) O'Hagan, D. *Nat. Prod. Rep.* **1997,** *14*, 637-651. (d) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275-276. (e) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron Lett.* **1997,** *38*, 3931-3934. (f) Lee, R. E.; Smith, M. D.; Nash, R. J.; Griffiths, R. C.; Mcneil, M.; Grewal, R. K.; Yan, W. X.; Besra, G. S.; Brennan, P. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1997,** *38*, 6733-6736. (g) Bols, M. *Acc. Chem. Res.* **1998,** *31*, 1-8. (h) Carretero, J. C.; Arrayas, R. G. *J. Org. Chem.* **1998,** *63*, 2993-3005. (i) Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998,** *63*, 3607-3617. (j) Mukai, C.; Sugimoto, Y.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998,** *63*, 6281-6287.
2. A recent review: Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996,** *96*, 1825-1872.
3. General reviews: (a) Curran, D. P. *Synthesis* **1988**, 417-439. (b) Curran, D. P. *Synthesis* **1988**, 489-513. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991,** *91*, 1237-1286. (d) Koert, U. *Angew. Chem. Int. Ed. Engl.* **1996,** *35*, 405-407. (e) Giese, B.; Kopping, B.; Göbel, T.; Dickhant, J.; Thoma, G.; Kulicke, K. J.; Trach, F. in *Organic Reactions;* Paquette, L. A. Ed.; John Wiley & Sons: New York, 1996; Vol. 48; pp 301-856. (f) Aldabbagh, F.; Bowman, W. R. *Contemp. Org. Synth.* **1997,** *4*, 261-280.
4. A recent review: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997,** *53*, 17543-17594.
5. A review: (a) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913-926. Recent references: (b) Clive, D. L. J.; Yang, W. *Chem. Commun.* **1996**, 1605-1606. (c) Della, E. W.; Knill, A. M.; Smith, P. A. *Chem. Commun.* **1996**, 1637-1638. (d) Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 219-224. (e) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 465-473. (f) Ikeda, M.; Kugo, Y.; Sato, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1819-1824. (g) Rios, L. A.; Dolbier, W. R.; Paredes, R.; Lusztyk, J.; Ingold, K. U.; Jonsson, M. *J. Am. Chem. Soc.* **1996,** *118*, 11313-11314. (h) Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996,** *37*, 5825-5828. (i) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179-180. (j) Ref 1b.
6. Recent references: (a) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996,** *61*, 5418-5424. (b) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996,** *61*, 7529-7533. (c) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996,** *52*, 1069-1084. (d) Goodall, K.; Parsons, A. F. *Tetrahedron* **1996,** *52*, 6739-6758. (e) Andrés, C.; Duque-Soladana, J. P.; Iglesias, J. M.; Pedrosa, R. *Tetrahedron Lett.* **1996,** *37*, 9085-9086. (f) Ref 1d. (g) Bertrand, M. P.; Gastaldi, S.; Nouguier, R. *Synlett* **1997**, 1420-1422. (h) Parsons, A. F.; Pettifer, R. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 651-660. (i) Ikeda, M.; Teranishi, H.; Nozaki, K.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1691-1687. (j) Giovannini, R.; Petrini, M. *Synlett* **1998**, 90-92. (k) El Kaim, L.; Gacon, A.; Perroux, A. *Tetrahedron Lett.* **1998,** *39*, 371-374. (l) Gupta, V.; Besev, M.; Engman, L. *Tetrahedron Lett.* **1998,** *39*, 2429-2432. (m) Baker, S. R.; Parsons, A. F.; Pons, J. F.; Wilson, M. *Tetrahedron Lett.* **1998,** *39*, 7197-7200.
7. Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 793-802.
8. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998,** *120*, 5838-5839.

9. Generation of α-aminoalkyl radicals: (a) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992,** *57,* 793-794. (b) Collin, J.; Namy, J. L.; Jones, G.; Kagan, H. B. *Tetrahedron Lett.* **1992,** *33,* 2973-2976. (c) Schubert, S.; Renaud, P.; Carrupt, P. A.; Schenk, K. *Helv. Chim. Acta* **1993,** *76,* 2473-2489. (d) Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994,** *50,* 13697-13708. (e) Santamaria, J. *Pure Appl. Chem.* **1995,** *67,* 141-147. (f) Das, S.; Kumar, J. S. D.; Shivaramayya, K.; George, M. V. *J. Chem. Soc., Perkin Trans. 1* **1995,** 1797-1799. (g) Booth, S. E.; Benneche, T.; Undheim, K. *Tetrahedron* **1995,** *51,* 3665-3674. (h) Khim, S. K.; Cederstrom, E.; Ferri, D. C.; Mariano, P. S. *Tetrahedron* **1996,** *52,* 3195-3222. (i) Su, Z.; Falvey, D. E.; Yoon, U. C.; Mariano, P. S. *J. Am. Chem. Soc.* **1997,** *119,* 5261-5262. (j) Ref 5h,i.
10. Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985,** *50,* 5620-5627.
11. Padwa, A.; Dent, W.; Nimmesgern, H.; Venkatramanan, M. K.; Wong, G. S. K. *Chem. Ber.* **1986,** *119,* 813-828.
12. Recent reviews: (a) Molander, G. A. *Chem. Rev.* **1992,** *92,* 29-68. (b) Molander, G. A. in *Organic Reactions;* Paquette, L. A. Ed.; John Wiley & Sons: New York, 1994; Vol. 46; pp 211-367. (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996,** *96,* 307-338. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998,** *54,* 3321-3354.
13. Martin, S. F.; Yang, C. P.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988,** *29,* 6685-6688.
14. (a) Aurrecoechea, J. M.; Fernández-Acebes, A. *Tetrahedron Lett.* **1992,** *33,* 4763-4766. (b) Preliminary communication: Aurrecoechea, J. M.; Fernandez-Acebes, A. *Synlett* **1996,** 39-42. (c) Aurrecoechea, J. M.; López, B.; Fernández, A.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1997,** *62,* 1125-1135. (d) Katritzky, A. R.; Qi, M.; Feng, D. M.; Nichols, D. A. *J. Org. Chem.* **1997,** *62,* 4121-4124. (e) Katritzky, A. R.; Qi, M.; Feng, D. *J. Org. Chem.* **1998,** *63,* 6712-6714.
15. For alternative syntheses of pyrrolidines using SmI_2-mediated ring-closures see: (a) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992,** *114,* 8729-8730. (b) Shiue, J. S.; Fang, J. M. *J. Chem. Soc., Chem. Commun.* **1993,** 1277-1278. (c) Baldwin, J. E.; Mackenzieturner, S. C.; Moloney, M. G. *Tetrahedron* **1994,** *50,* 9411-9424. (d) Baldwin, J. E.; Mackenzieturner, S. C.; Moloney, M. G. *Tetrahedron* **1994,** *50,* 9425-9438. (e) Ha, D. C.; Yun, C. S.; Yu, E. *Tetrahedron Lett.* **1996,** *37,* 2577-2580.
16. For a recent synthesis of 2,5-substituted pyrrolidines using benzotriazole methodology see: Katritzky, A. R.; Cui, X. L.; Yang, B. Z.; Steel, P. J. *Tetrahedron Lett.* **1998,** *39,* 1697-1700.
17. Hirai, Y.; Terada, T.; Hagiwara, A.; Yamazaki, T. *Chem. Pharm. Bull.* **1988,** *36,* 1343-1350.
18. Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991,** *47,* 2005-2026.
19. A recent review on benzotriazole synthetic applications: Katritzky, A. R.; Lan, X. F.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998,** *98,* 409-548.
20. Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989,** 225-233.
21. The beneficial effect of *t*-BuOH in SmI_2-promoted conjugate-additions has been recently illustrated: Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997,** *62,* 7418-7429.
22. For a related example, see Ref 14c.
23. Katritzky, A. R.; Yannakapoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M.; Skarjune, R. *J. Chem. Soc., Perkin Trans. 1* **1987,** 2673-2679.

24. Alternatively, it has been recently found that, in the presence of HMPA, secondary α-aminoalkenyl radicals cyclize efficiently onto unactivated C=C double bonds. In these reactions HMPA appears to facilitate[25] the rapid and irreversible reduction of the radical produced in a reversible α-amino radical cyclization: Katritzky, A. R.; Feng, D.; Qi, M.; Aurrecoechea, J. M.; Suero, R.; Aurrekoetxea, N. *J. Org. Chem.* **1999**, submitted.
25. (a) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992,** *114*, 6050-6058. (b) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993,** *34*, 1717-1720.
26. (a) Viehe, H. G.; Janousek, Z.; Merényi, R. *Acc. Chem. Res.* **1985,** *18*, 148-154. (b) Sustmann, R.; Korth, H. G. *Adv. Phys. Org. Chem.* **1990,** *26*, 131-178.
27. (a) Yadav, V.; Fallis, A. G. *Can. J. Chem.* **1991,** *69*, 779-789. (b) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987.
28. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985,** *41*, 3925-3941. (b) Spellmeyer, D. C.; Houk, K. M. *J. Org. Chem.* **1987,** *52*, 959-974. (c) Beckwith, A. L. J.; Zimmermann, J. *J. Org. Chem.* **1991,** *56*, 5791-5796. (d) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993,** *22*, 143-151.
29. Perrin, D. D.; Armarego, W. F. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.
30. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43*, 2923-2925.
31. Harwood, L. M. *Aldrichimica Acta* **1985,** *18*, 25.
32. Padwa, A.; Brodney, M. A.; Marino, J., J. P.; Sheehan, S. M. *J. Org. Chem.* **1997,** *62*, 78-87.
33. Ma, D.; Lu, X. *Tetrahedron* **1990,** *46*, 6319-6330.
34. Bosone, E.; Farina, P.; Guazzi, G.; Innocenti, S.; Marotta, V. *Synthesis* **1983**, 942-944.
35. Optimized conditions for diamine **11b**. Other attempts, under different conditions, led to lower yields of **11b** and no cyclization.