Diastereoselective Synthesis of Cycloalkylamines by Samarium Diiodide-Promoted Cyclizations of α-Amino Radicals Derived from α-Benzotriazolylalkenylamines

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Received May 24, 1996[⊗]

The condensation of ω-unsaturated aldehydes with benzotriazole and secondary amines affords α-benzotriazolylalkenylamines that exist in solution as mixtures of the corresponding benzotriazol-1-yl and benzotriazol-2-yl isomers resulting from their rapid dissociation into iminium cations and the benzotriazolyl anion. The reduction of these adducts with samarium diiodide (SmI_2) takes place with formation of the benzotriazolyl anion and α-amino alkenyl radicals that undergo 5- or 6-*exo*-trig cyclizations leading to substituted cycloalkyl- or cycloheteroalkylamines. The presence of an electron-withdrawing substituent in the alkene subunit is required for efficient cyclizations. The formation of cyclopentylamines takes place with unusually high 1,5-*cis* selectivity (hex-5-enyl radical numbering), and the presence of a 2- or 4-Me substituent also imparts high 1,2- or 1,4-*trans* stereoinduction, respectively. The corresponding six-membered rings, however, are formed with low diastereoselectivity. Semiempirical calculations performed on model systems suggest that a stabilizing secondary orbital interaction between the amino group and the electron-deficient alkene might in part account for the enhanced *cis*-selectivity encountered.

Introduction

Samarium diiodide (SmI_2) has emerged in the synthetic field as a versatile one-electron reducing agent capable of promoting a number of useful C−C bond-forming processes with high chemo-, regio-, and stereoselectivity.[1] SmI_2-promoted couplings of carbonyl groups with alkyl-, acyl-, and aryl-halides, or with allylic-, propargylic-, and α-benzoyloxy esters, as well as pinacol-type couplings are all well established procedures that have led to useful synthetic applications.[1] The chemistry of the aza-analogues of the carbonyl group is less developed. In contrast to the high reactivity of aldehydes and ketones toward SmI_2, aliphatic imines are reduced with great difficulty.[2−4] The imine−olefin coupling, unknown with SmI_2, has only recently been reported[5] with Sm/Me_3SiX acting as a Sm(II) equivalent.

In contrast to the behavior shown by imines, other aza-derivatives of carbonyl compounds such as hydrazones[6] and oxime ethers[7] participate in efficient Sm(II)-promoted intramolecular couplings with aldehydes and, in the hydrazone case, also with alkyl halides.[6] However, the nitrogen functionality seems to act in these cases as the acceptor in the addition of a radical generated on the other functional group, as shown by Fallis[6b] for the coupling between alkyl halides and hydrazones. This behavior therefore parallels the well known ability of imines,[8] oxime ethers,[9] and hydrazones[6,8b,10] to trap intramolecularly carbon radicals generated by the tin method.[11]

Iminium ions display a much higher reactivity toward SmI_2, as the electron transfer to the cation produces a stabilized α-amino radical.[12] When this process is carried out in the presence of CSA, the α-amino radicals can be trapped intramolecularly by suitably positioned C−C π-bonds to afford cyclic products.[13,14] From a synthetic perspective, the tactical combination of this kind of reactivity with a convenient method for the convergent

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[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1997.

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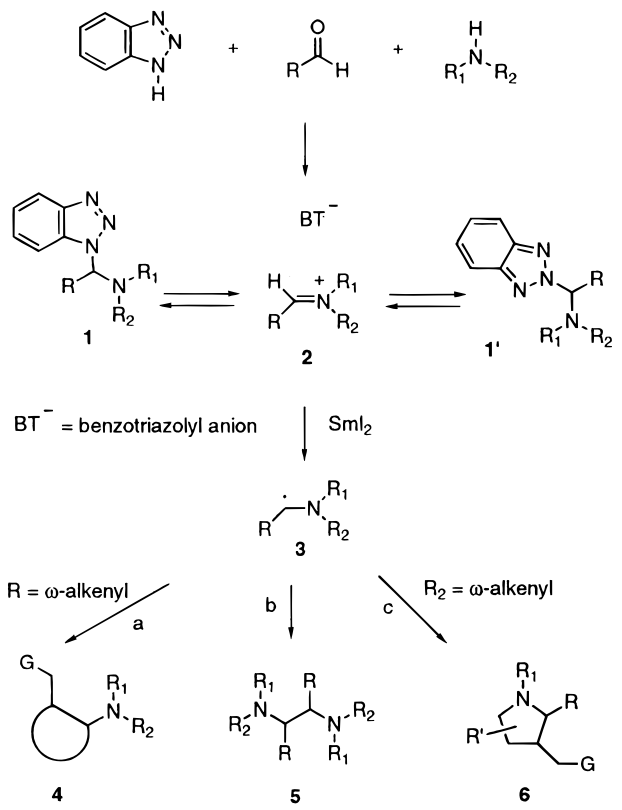
S0022-3263(96)00957-7 CCC: $14.00

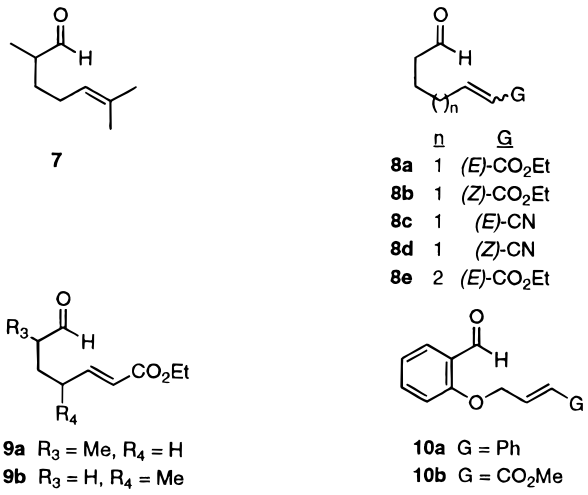
Scheme 1



preparation of iminium cations from simple aldehyde and amine precursors[15] would constitute a very practical entry into both nitrogen-containing heterocycles and amino-substituted carbocycles,[16] as it is generally described in the lower portion of Scheme 1.

The condensation of aldehydes with secondary amines in the presence of benzotriazole provides a very convenient entry into reactive iminium cations **2** as a result of the easy room temperature dissociation and interconversion of the corresponding adducts **1**,**1′** in solution (Scheme 1).[17] This property has led to numerous synthetic applications where the benzotriazole anion is displaced from **1**,**1′** by a variety of nucleophiles under mild reaction conditions.[18] When these adducts are treated in solution with SmI_2, a rapid reduction of the iminium cation takes place to afford a neutral α-amino radical **3**. If suitably located reactive π-bonds are present, an intramolecular radical addition takes place with formation of cycloalkylamines **4** (path a)[19b] or pyrrolidines **6** (path c).[19a] In the absence of such functionality radical dimerization leads to vicinal diamines **5** (path b).[19c]

Chart 1



Following an earlier communication[19b] we now disclose full details of the preparation of cyclic products **4** starting from simple aldehydes and amines using the strategy depicted in Scheme 1. We have also studied the dependence of the stereochemistry of cyclization on the double bond geometry and the effect of Me substituents on different locations around the carbon chain undergoing cyclization. Finally, the extension of this chemistry to the synthesis of six-membered cyclic systems has been briefly explored.

Results and Discussion

Representative aldehydes **8**−**10** (Chart 1) were selected for this study. The choice of enals bearing electron-withdrawing substituents on the alkene portion followed literature precedence on related radical cyclizations[14g−i,19a,20] and some initial experiments performed with aldehyde **7** lacking such groups (*vide infra*).

The route for aldehydes **8**,**9** is shown in Scheme 2. The *E*/*Z* mixtures obtained in the Horner−Wadsworth−Emmons reaction[21] were either separated and each isomer oxidized independently (**8a**,**b**,**e**,**9b**) or carried to the aldehyde stage and separated there (**8c**,**d**). A slightly modified route was followed for aldehyde **9a**. Alkylation of 2-hydroxybenzaldehyde with cinnamyl bromide or methyl 4-bromocrotonate led uneventfully to aldehydes **10**.

Preparation of Benzotriazole Intermediates. The condensation of aldehydes **7**−**10** with a slight excess (5−10%) each of benzotriazole and a secondary aliphatic amine at room temperature, in the presence of 4 Å

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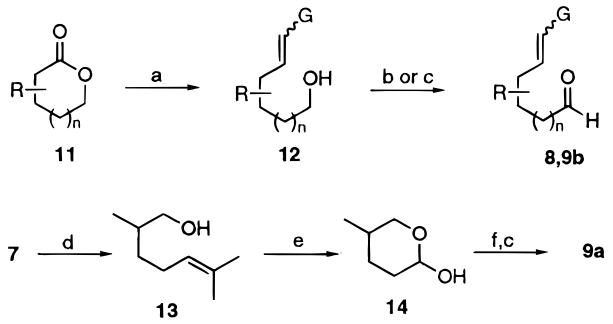
Scheme 2

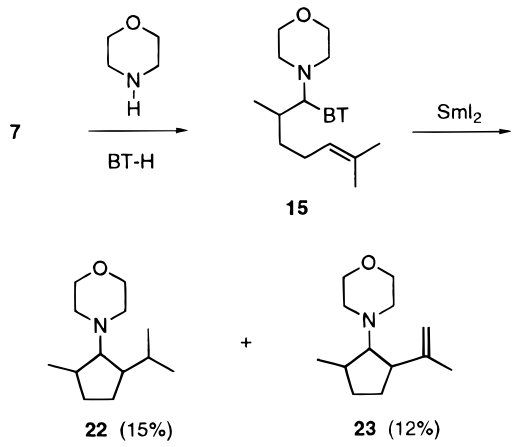


[a] (a) Li[(EtO)$_2$P(O)CHCO$_2$Et] or Li[(EtO)$_2$P(O)CHCN], DIBALH, THF, -78 °C, then 25 °C; (b) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, -60 °C, then 25 °C; (c) PCC, CH$_2$Cl$_2$, 25 °C; (d) NaBH$_4$, EtOH, 25 °C; (e) (i) O$_3$, CH$_2$Cl$_2$, -78 °C, (ii) Zn, HOAc, -78 °C, then 25 °C; (f) Ph$_3$P=CHCO$_2$Et, MeCN, reflux.

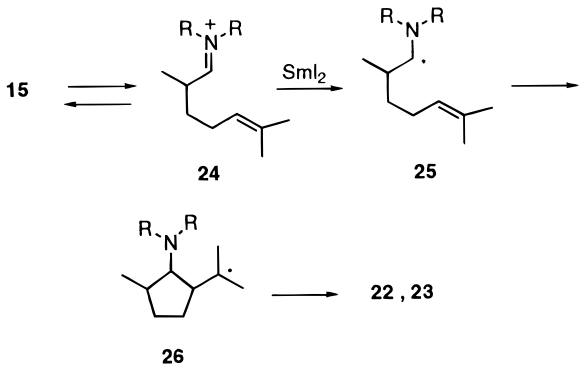
molecular sieves,[22] led to the corresponding α-benzotriazolylalkenylamines **15**−**21** (Schemes 3, 5, 6, 8). Adducts **15**−**21** were usually obtained as thick oils that were difficult to purify[23] and, for preparative purposes, it was decided to use them in a crude form. As a consequence, the cyclization yields reported below are always given for two steps and are referred to the starting aldehyde. Nevertheless, routine inspection of the ^{1}H NMR spectra of the adducts always confirmed their formation and allowed an assessment of their degree of purity to be made. Thus, two sets of resonances were observed in the region δ 5.1−5.9, corresponding to the methine NC*H*N proton indicating that, as expected, adducts **15**−**21** exist in solution as mixtures of 1- and 2-substituted benzotriazoles (*e.g.*, **1**,**1′** in Scheme 1).[24] Also characteristic of these adducts are the signals due to the benzotriazole ring protons. Thus, a doublet at δ 8.0−8.1 is typical of H-4 (benzotriazole numbering) in the benzotriazol-1-yl isomer whereas a multiplet at δ 7.8−8.0 was assigned to H-4 and H-7 of the corresponding 2-substituted isomer.[17] Products other than **15**−**21** and excess benzotriazole and starting amine were either absent or in minor amounts. Furthermore, mass recovery was always in the range 93−100%, after adjusting for the excess starting materials present estimated by ^{1}H NMR integration. Preparation details and full ^{1}H NMR data for **15**−**21** are collected in Tables 4 and 5 (supporting information).[25]

Initial cyclization studies were conducted on adduct **15** (Scheme 3) derived from commercial aldehyde **7**. When a 0.1 M THF solution of SmI_2 was added dropwise to a solution of **15** at 25 °C the reagent was rapidly consumed, as indicated by the disappearance of the SmI_2 characteristic blue color. After the addition of approximately 1.5 equiv the blue color persisted indicating that the starting material had been completely consumed. However, a complex reaction mixture resulted from which

Scheme 3



Scheme 4



cyclized products **22** and **23** were isolated in a ratio of 1.2/1 and a low combined 27% yield. The presence of other uncharacterized products (probably of dimeric structure[19c]) complicated the separation and purification process.[26] Better results were obtained with aldehydes that contained electron-withdrawing substituents, as described below.

The formation of **22** and **23** is readily explained as a result of a 5-*exo*-trig cyclization of radical **25** (Scheme 4) followed by the disproportionation of the resulting cyclized radical **26**. This explanation is also consistent with the consumption of less than 2 equiv of SmI_2 in this reaction. Alternatively, a tertiary organosamarium intermediate derived from **26** could also afford the observed products *via* β-hydride elimination and organometallic disproportionation pathways;[27] however, the reduction of a tertiary alkyl radical by SmI_2 appears to be a difficult process,[28] particularly in the absence of strong donor ligands. In any case, while these results clearly establish the radical nature of the cyclizations, they also evidence that unactivated olefins such as that present in **15** will not be suitable partners for a fast radical cyclization of the α-amino radicals involved here. Similar conclusions have been reached after attempted cyclizations[20c,d] of 2-azahex-5-enyl radicals generated from α-amino sulfides by the tin method. A likely cause for these seemingly slow cyclizations is the interaction between the nitrogen

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(23) Simple α-benzotriazolylalkylamines decompose in contact with water and traces of acid or silica gel chromatography, reverting to the starting aldehyde and amine: Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225.

(24) Adducts **15**−**20** derived from aliphatic aldehydes **7**−**9** exist as 1/1 mixtures of the corresponding benzotriazol-1- and -2-yl isomers whereas in adducts **21**, derived from aromatic aldehydes **10**, the 1-isomer markedly predominates.

(25) Further characterization by ^{13}C NMR and MS for selected cases is also included in the supporting information.

(26) Cyclopentanes **22** and **23** could not be completely separated from each other nor could they be conveniently purified. However, their NMR (^{1}H and ^{13}C) and GC-MS data clearly support the proposed structures.

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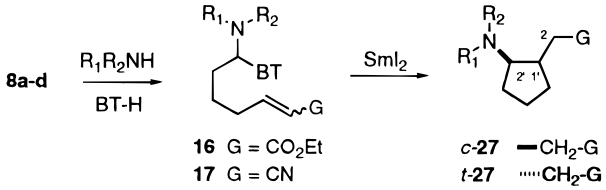
Table 1. Preparation of Disubstituted Cyclopentanes 27 from Aldehydes 8a−d, Benzotriazole, and Amines

entry	aldehyde	R_1	R_2	method[a]	product	yield[b]	ratio *c*/*t*
1	**8a**	$(CH_2)_2O(CH_2)_2$		A	**27a**	50	*c*
2	**8a**	$(CH_2)_2O(CH_2)_2$		B	**27a**	75	*c*
3	**8b**	$(CH_2)_2O(CH_2)_2$		B	**27a**	39	1:1.8
4	**8a**	CH_2Ph	CH_2Ph	A	**27b**	39	4.3:1
5	**8a**	CH_2Ph	CH_2Ph	B	**27b**	69	16:1
6	**8a**	CH_2Ph	CH_2CO_2Et	B	*d*	−	−
7	**8a**	CH_2Ph	$(CH_2)_2Ph$	B	**27d**	63	*c*
8	**8a**	CH_2Ph	Ph	B	**27e**	32	*c*
9	**8a**	CH_2Ph	$(CH_2)_2CN$	B	**27f**	57	*c*
10	**8a**	$(CH_2)_2N(Ph)(CH_2)_2$		B	**27g**	61	*c*
11	**8a**	CH_2Ph	3-butenyl	B	**27h**	53	*c*
12	**8c**, **8d**[e]	CH_2Ph	CH_2Ph	A	**27i**	63	2:1
13	**8c**, **8d**[e]	$(CH_2)_2O(CH_2)_2$		A	**27j**	60	2:1
14	**8c**	$(CH_2)_2O(CH_2)_2$		B	**27j**	67	10:1
15	**8d**	$(CH_2)_2O(CH_2)_2$		B	**27j**	65	6.7:1
16	**8c**, **8d**[e]	allyl	allyl	A	**27k**	65	2.3:1
17	**8c**	allyl	allyl	B	**27k**	71	8.1:1
18	**8d**	allyl	allyl	B	**27k**	62	4.5:1

[a] Method A: SmI_2 added dropwise to benzotriazole adduct at 25 °C. Method B: The adduct added to SmI_2 at $T < -20$ °C and the reaction mixture warmed to 25 °C. [b] Isolated yields are referred to the starting aldehyde (two steps). [c] A single diastereomer to the limit of detection of ^1H and ^{13}C NMR. [d] Complex mixture of products. See text. [e] A 65/35 **8c**/**8d** mixture was used.

Scheme 5



lone pair and the unpaired electron. This confers the radical both a strong stabilization, which is partially lost in the transition state leading to cyclization, and a nucleophilic character which is not matched by the polarity of simple alkyl-substituted olefins. In line with these ideas, both the protonation[13] and the incorporation of electron-withdrawing substituents[29] on the nitrogen atom have resulted in efficient cyclizations since the aforementioned effects are subdued or disappear. Similarly, the use of electron-deficient olefins[20a] has proven useful in the reactions of α-acylamino radicals, as the cyclized radical is also stabilized and the polarity of both reaction partners is better matched. Our results using neutral α-amino radicals and electron-deficient olefins (*vide infra*) support these ideas.

Synthesis of Disubstituted Cyclopentanes. The treatment of benzotriazole adducts **16**, **17** (derived from aldehydes **8a**−**d** containing CO_2Et- or CN-substituted olefins) with SmI_2, under the conditions described above for **15**, produced much cleaner reaction mixtures and resulted in the highly diastereoselective formation of the corresponding cyclopentanes **27** that were isolated in moderate overall yields over two steps starting from aldehydes **8** (Scheme 5, Table 1).[19b] Significantly, these reactions require 2 equiv of SmI_2, indicating that cyclization is followed by fast further reduction to afford a samarium enolate (or a α-cyano organosamarium). While this dropwise addition of SmI_2 to the substrate (method A) conveniently afforded the desired products (as reported in our preliminary communication[19b]), better yields and diastereoselectivities were realized by mixing a dilute (0.1 M) solution of the adducts **16**, **17** with 0.1 M SmI_2 (2.2 equiv) at temperatures below −20 °C and allowing the mixture to slowly reach room temperature (method B). It is likely that the low temperatures ensure a low equilibrium concentration of iminium cations[30] while maintaining a relative high concentration of SmI_2. This is expected to comparatively slow down undesired intermolecular side-reactions and accelerate the reduction of the cyclized radical, thus providing a forward thrust for the overall process. Results using this latter method are collected in Table 1 along with selected examples run with method A for comparison. The two-step sequence works well with aliphatic amines (both cyclic and acyclic) but less efficiently so with the single aniline derivative that was tried (entry 8). Nevertheless, the sequence is tolerant of some useful functionality (entries 9, 11, 16−18) in the amino group. Of particular value is the preparation of mono- and dibenzylated cyclopentylamines since the benzyl group can in principle be easily removed[14a,31] to yield the corresponding secondary and primary amines, respectively. Although less utilized, the allyl group (entries 16−18) can also serve this purpose.[32] As seen in Table 1, both (*E*)-CO_2Et- and (*E*)-CN-groups are effective alkene-activators toward radical cyclization. However, in the (*Z*)-series the presence of a CO_2Et group had a great diminishing impact in the cyclization yield (entry 3) whereas this was largely unaffected by a CN group (entries 15, 18).

Further synthetic advantage could in principle be gained from the functionalized radical initially obtained in the cyclization step or, alternatively, from the samarium enolate resulting from its reduction by a second equivalent of SmI_2. However, no tandem cyclization[33] product was observed in the reactions involving allylamine derivatives (entries 16−18), indicating that further reduction of the radical formed in the cyclization took place faster than its alternative cyclization onto the

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(30) The presence of Sm(III), a Lewis acid, might facilitate an expectedly slow dissociation at temperatures below 25 °C. See: Katritzky, A. R.; Gordeev, M. F. *J. Org. Chem.* **1993**, *58*, 4049.

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(33) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.

Scheme 6

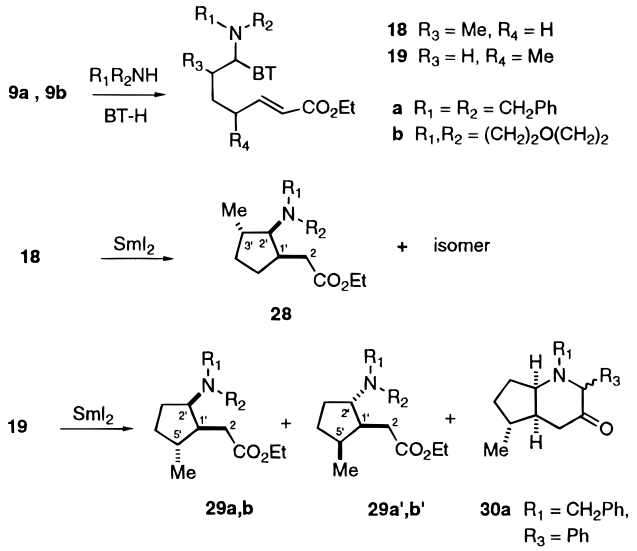


Table 2. Preparation[a] of Trisubstituted Cyclopentanes 28, 29 from Aldehydes 9a,b, Benzotriazole, and Amines

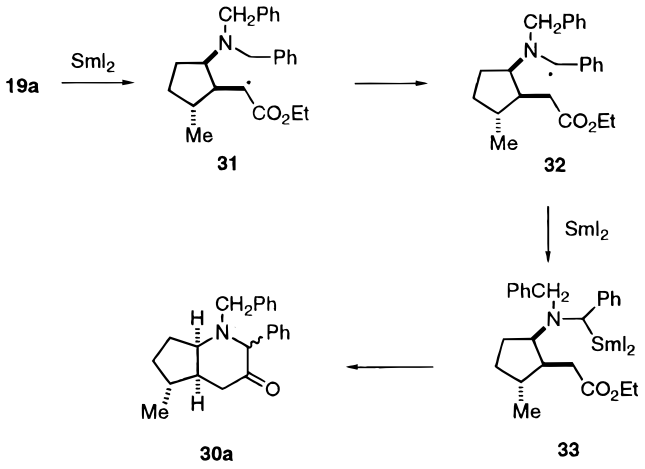
aldehyde	product	yield[b]	diast ratio
9a	**28a**	66	19:1
9a	**28b**	57	*c*
9b	**29a**,**a′**	60[d] (72[e])	6:1
9b	**29b**,**b′**	71	4.5:1

[a] Prepared according to general method B. [b] Isolated yields are referred to the starting aldehyde (two steps). [c] Ratio (approximately 19:1 by ^{1}H NMR) could not be precisely determined. [d] Combined yield of **29** and **30a** (58:1). [e] Yield based on recovered aldehyde **9b**.

allyl group. Furthermore, attempts to trap[34] the presumed samarium enolate precursor of the morpholine derivative obtained in entry 2 were unsuccessful. Thus, cyclopentylamine *c*-**27a** (Scheme 5, Table 1) was still the only product obtained when benzaldehyde was added to the reaction mixture once the total consumption of SmI_2 had been observed. Either the samarium enolate is rather unreactive or it gets protonated before benzaldehyde is introduced. The ethyl ester derivative derived from **8a** and *N*-benzylglycine (entry 6) provided a complex mixture of products.

Synthesis of Trisubstituted Cyclopentanes. The introduction of a 2- or 4-Me[35] substituent on the carbon chain undergoing cyclization resulted in the efficient formation of trisubstituted cyclopentanes **28**, **29** (Scheme 6, Table 2). Overall yields over two steps are satisfactory, and a high stereoselectivity is maintained. Out of four possible diastereomers, one was always very predominantly obtained, amounting to ~95% of the product for cyclopentanes **28** and ~85% for **29** (Table 2). In addition to a somewhat decreased selectivity, the introduction of the 4-Me substituent also caused a significant reduction in reactivity. Thus, decoloration of the SmI_2 reagent,

Scheme 7



readily observed at temperatures between −20 and 25 °C for most substrates, required prolonged stirring at room temperature for the 4-methyl-substituted adducts **19** derived from aldehyde **9b**; in the case of the dibenzylamine adduct **19a** this also led to some degradation. For example, quenching the reaction of **19a** after 20 min at room temperature led to a 58% isolated yield of cyclic products **29a**,**a′**, along with ~20% of recovered starting aldehyde **9b**, but continued stirring at room temperature for 22 h increased the yield of **29a**,**a′** to only 60%. Of some mechanistic significance is the isolation in the reaction of **19a** of small amounts of the bicyclic ketone **30a**. This product originated as the result of a 1,5-translocation[36] of the cyclized radical **31** (Scheme 7) that yields a stabilized benzylic α-amino radical **32**. Reduction to the organosamarium[14a−c] intermediate **33** and intramolecular attack on the ester carbonyl would then lead to the observed product **30a**. While the formation of **30a** confirms the radical nature of these reactions, the small extent to which this occurs indicates that, under the reaction conditions, reduction of the cyclized radical to form a samarium enolate is faster than other alternative radical processes such as translocation or cyclization, as discussed above.

Synthesis of Six-Membered Rings. A brief exploration into the formation of six-membered rings pointed out a severe limitation in the use of this methodology. While yields can still be reasonable in some cases, the diastereoselectivity is significantly eroded (Scheme 8, Table 3). Nevertheless, it is interesting that the impact of chain elongation is less pronounced here than in the related SmI_2/CSA treatment on preformed iminium cations where cyclization on unactivated alkenes is shut off in going from 5-*exo* to the 6-*exo* cases.[13] As noted elsewhere,[19c] the presence of a Ph substituent in place of CO_2-Et in the adducts derived from **10a** led only to the corresponding vicinal diamine showing that the Ph group does not provide in this case enough activation for a fast radical cyclization and evidencing again the need for electron-deficient olefins in these cyclizations.

Interestingly, when the reaction of the adduct **20a** (derived from **8e** and morpholine) was carried out by dropwise addition of the SmI_2 solution to the substrate

(34) Several examples of successful aldol-type processes with samarium enolates formed in SmI_2-mediated reactions have been reported: (a) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317. (b) Enholm, E. J.; Jiang, S. *Tetrahedron Lett.* **1992**, *33*, 313. (c) Enholm, E. J.; Jiang, S. *Heterocycles* **1992**, *34*, 2247. (d) Enholm, E. J.; Jiang, S. *Tetrahedron Lett.* **1992**, *33*, 6069. (e) Enholm, E. J.; Jiang, S. J.; Abboud, K. *J. Org. Chem.* **1993**, *58*, 4061. (f) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1994**, *35*, 1627. (g) Arime, T.; Takahashi, H.; Kobayashi, S.; Yamaguchi, S.; Mori, N. *Synth. Commun.* **1995**, *25*, 389. (h) Enholm, E. J.; Schreier, J. A. *J. Org. Chem.* **1995**, *60*, 1110.

(35) The hex-5-enyl radical numbering will be used throughout the discussion.

(36) Examples of related radical translocations in amine derivatives: (a) Denenmark, D.; Hoffmann, P.; Winkler, T.; Waldner, A.; De Mesmaeker, A. *Synlett* **1991**, 621. (b) Curran, D. P.; Liu, H. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377. (c) Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1801. See also refs 14a−c.

Scheme 8

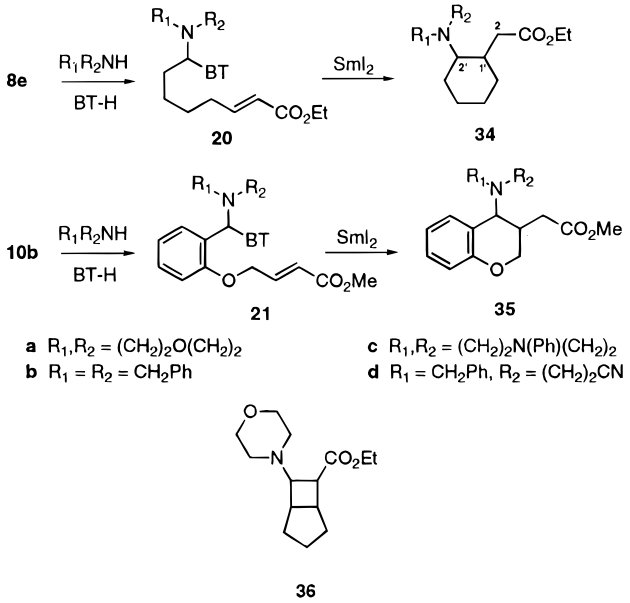


Table 3. Preparation[a] of Six-Membered Cyclic Products 34, 35 from Aldehydes 8e, 10b, Benzotriazole, and Amines

aldehyde	product	yield (%)[b]	diast ratio
8e	**34a**	54	2.3:1
8e	**34b**	34	1:1
10b	**35a**	54	1.5:1[c]
10b	**35c**	53	1:1
10b	**35d**	60	1:1

[a] According to general procedure B. [b] Isolated yields are referred to the starting aldehyde (two steps). [c] The stereochemical identity of the products could not be unambiguously determined.

at 25 °C (method A), only 1.5 equiv of the reducing agent were consumed, and the bicyclic product **36** (8/1 diastereomeric mixture) was obtained along with the expected cyclohexylamine **34a** (5/1 *cis*/*trans*) in a 68% combined yield and 1/1 **34a**/**36** ratio. The bicyclic products **36** were not detected when the reaction was performed under the general optimized conditions (method B). A possible origin of bicycles **36** is an intramolecular cycloaddition[37] of an enamine formed by Sm(III)-promoted β-elimination of benzotriazole from **20a**.[38] The precise mechanism of formation of **36** might actually be more complex since the reaction appears to consume more SmI_2 than expected if the formation of cyclohexylamine **34a** were the only SmI_2-consuming process. Furthermore, the treatment of the same adduct **20a** with SmI_3[39] at room temperature afforded no bicyclic product. The starting material was rapidly consumed, but a complex mixture of uncharacterized products was obtained. In any event, the rapid destruction of the adduct **20a** in the presence of Sm(III) could in part be held responsible for the only modest yields generally obtained in the cyclizations reported here and hints that the advantage of method B over method A might also reside in the higher Sm(II)/Sm(III) ratio maintained in the former case throughout the reaction.[40]

Stereochemistry of Cyclizations. For disubstituted cycloalkanes the use of NOE experiments did not provide conclusive evidence about the stereochemical identity of the cyclic products. Recourse was then made to ^{13}C NMR chemical shift differences between the isomers as stereochemical criteria.[41] The major diastereomers *c*-**27a**,**i**−**k** and *c*-**34a** (see Schemes 5, 8 and Table 1) displayed for carbons C_2, $C_{1'}$, and $C_{2'}$ resonances (Table 6, supporting information) that were significantly upfield from the corresponding signals in the minor isomers *t*-**27** and *t*-**34a′**, thus allowing the assignment of a *cis*-stereochemistry for the former.[41,42] The stereochemistry of the rest of disubstituted products was assigned by analogy with the cases included in Table 6.

In trisubstituted cyclopentanes **28**, **29** the major diastereomers featured again a 1,5-*cis* relationship between the two newly created stereogenic centers whereas the third substituent adopted a *trans*-disposition with respect to the other two. This stereochemical assignment relied on the observation of NOE effects as well as on ^{13}C NMR chemical shift differences between the isomers (Tables 6 and 7, supporting information). The tentative assignment given in this way to the minor dibenzylamine product **29a′** (Scheme 6) was also supported by the observation of proton resonances for $C_{5'}$-Me and H-2′ that were shielded with respect to those found in the major isomer **29a**.

As shown by the results obtained in the formation of disubstituted cyclopentanes (Table 1) the diastereoselectivity of the 5-*exo*-cyclization showed a dependence on reaction conditions, activating group present in the alkene, and double bond geometry. Thus, the comparison between entries 4 and 5 in Table 1 seems to indicate that diastereoselectivity increases with decreasing reaction temperature. This is also apparent in entries 13−18 where the selectivities obtained for the individual geometric isomers at low temperatures would translate into higher than observed selectivities for reactions run at 25 °C with the mixtures of isomers. With a single exception (entry 5), substrates containing an (*E*)-CO_2Et group cyclized, under the improved conditions, with overwhelming *cis*-selectivity as only one diastereoisomer was found. The selectivity dropped somewhat when the (*E*)-CN group was used in place of CO_2Et (entries 14, 17). However, even in these cases the selectivity is remarkably high when compared with the 2.6/1 *cis*/*trans* preference reported for the cyclization of the 1-methylhex-5-enyl radical.[43a] In the (*Z*)-series, we have observed a mixed behavior; thus, while for a (*Z*)-CO_2Et substituent the *cis*−*trans* selectivity was reversed and greatly diminished (entry 3), a (*Z*)-CN group continued to impart high, *albeit* slightly lower, *cis*-selectivity (entries 15, 18). The possible origin of these selectivities will be discussed later (*vide infra*).

The stereochemical preferences observed in these reactions are in agreement with Beckwith's model[43] for the transition structure of radical cyclizations. According to this model the chain undergoing cyclization adopts a chairlike conformation with the substituents occupying

(37) Cook, A. G. In *Enamines. Synthesis, Structure and Reactions*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; p 347.

(38) Although the formation of enamines from *N*-[(*N*′,*N*′-dialkylamino)alkyl]benzotriazoles has been effected only with NaH in refluxing THF,[22b] certain Sm(III)-induced β-eliminations have been reported in reductions with SmI_2. See: Angle, S. R.; Rainier, J. D. *J. Org. Chem.* **1992**, *57*, 6883.

(39) Yu, Y. P.; Lin, R. H.; Zhang, Y. M. *Tetrahedron Lett.* **1993**, *34*, 4547.

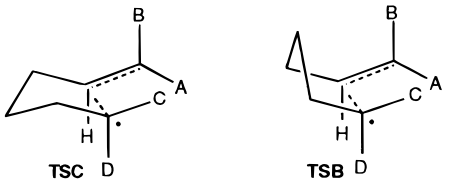
(40) See ref 38 for related observations.

(41) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alycyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987.

(42) Yadav, V.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 779.

(43) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (b) Spellmeyer, D. C.; Houk, K. M. *J. Org. Chem.* **1987**, *52*, 959. (c) Beckwith, A. L. J.; Zimmermann, J. *J. Org. Chem.* **1991**, *56*, 5791. (d) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, *22*, 143.

Chart 2



TSC,B	A	B	C	D
a	H	H	NH_2	H
b	H	H	H	NH_2
c	CN	H	NH_2	H
d	CN	H	H	NH_2
e	H	CN	NH_2	H
f	H	CN	H	NH_2
g	CHO	H	NH_2	H
h	CHO	H	H	NH_2
i	H	CHO	NH_2	H
j	H	CHO	H	NH_2

preferentially pseudoequatorial positions. Detailed studies on the stereoselectivity of cyclization have been carried out for simple 1-, 2-, 3-, or 4-substituted hex-5-enyl radicals, leading to the corresponding disubstituted cyclopentanes. However, the corresponding studies on 1,2-, 1,3-, and 1,4-disubstituted hex-5-enyl radicals are scarce.[44]

While the direction of the stereochemical preference in our cyclizations is conveniently rationalized by Beckwith's model, the extent to which it occurs was not expected. Unconstrained simple alkyl-substituted acyclic radicals display relatively moderate selectivities[43a,45] except for the 4-substituted cases, where allylic strain may contribute decisively to the higher preferences observed.[46] In comparison, the cyclizations of the 1-aminohex-5-enyl radicals reported here afford exclusively *cis*-disubstituted cyclopentanes in almost every case when the alkene moiety is activated by an (*E*)-CO_2Et group. Furthermore, a very high degree of 1,5-*cis* preference is maintained with the introduction of a 2- or 4-Me substituent, while the 4,5-selectivity is comparable to that obtained with the corresponding parent Me-substituted hex-5-enyl radicals, and the 2,5-selectivity is considerably higher than in this latter case. Interestingly, a recent paper also reports on some unusually high stereoselectivities in the cyclizations of related α-amidoyl radicals that yield disubstituted cyclopentanes.[36b]

Although the exact nature of this high selectivity remains to be defined, the origin might reside on the nucleophilic and electrophilic character of the α-amino radical and olefin trap, respectively, in a presumably highly polarized transition state.[43d,47] Attractive interactions between the Me group and the π-bond have been

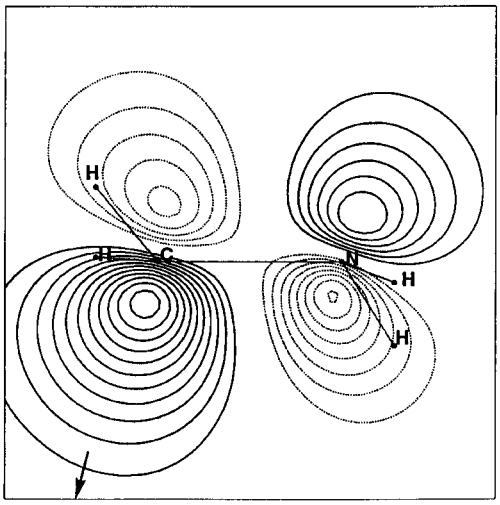


Figure 1. Contour map of the SOMO of the aminomethyl radical, computed at UHF/6-31G* level. Contour values in au range from +0.30 (solid lines) to −0.22 (dotted lines), with a step of −0.025. The black arrow emphasizes the preferencial reactive site of this radical in nucleophilic addition processes.

invoked to explain the preference of the 1-methylhex-5-enyl radical to cyclize preferentially through the more sterically demanding *cis*-transition state.[43b,48] Likewise, a strong donor−acceptor-type interaction between the amino group and the electron-deficient alkene might be responsible for the enhanced *cis*-selectivity in the cyclizations of 1-amino-substituted hex-5-enyl radicals.

To test this hypothesis we have carried out some SCF-MO computations on the transition structures (TSs) depicted in Chart 2, using the semiempirical Hamiltonian PM3,[49] at both UHF and half-electron[50] (HE) levels of theory. The heats of formation of the chair and boat saddle points **TSCa**−**j** and **TSBa**−**j** obtained by both UHF/PM3 and HE/PM3 methods are collected in Table 8 (supporting information). These data predict a preferential formation of *cis*-aminocyclopentanes regardless of the geometry at the double bond present in the starting olefinic moiety, in agreement with the generality of our experimental results (*vide supra*). However, this preference is only modest when the double bond is unsubstituted but markedly increases with the presence of electron-withdrawing group (EWG) substituents on the double bond. The reasons underlying this stereocontrol can be understood upon inspection of the orbitals involved in the addition. Thus, the SOMO of the aminomethyl radical ($H_2NCH_2^{\bullet}$) is a distorted pyramidalized[51] π* orbital between the N and C atoms (Figure 1). A direct consequence of this π-character, as our PM3 calculations show, is the presence of a strong stabilizing in-phase secondary orbital interaction[52] between the SOMO of the aminoalkyl radical and the LUMO of the alkene subunit in the *cis* saddle points (Figure 2). This interaction is favored by the eclipsed conformation between the N, C_1, C_5, and C_α atoms present in the transition states (TS) leading to *cis*-products ($\omega \approx 0$, Figure 2) and does not

(44) (a) Bertrand, M. P.; De Riggi, I.; Lesueur, C.; Gastaldi, S.; Nouguier, R.; Jaime, C.; Virgili, A. *J. Org. Chem.* **1995**, *60*, 6040. (b) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100.

(45) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.

(46) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.

(47) The importance of a favorable polarization in the transition state on the *rates* of radical cyclization and radical hydrogen abstraction processes has been stressed: (a) Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684. (b) Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S.-U. *J. Am. Chem. Soc.* **1995**, *117*, 3674. (c) Horner, J. H.; Martinez, F. N.; Musa, O. M.; Newcomb, M.; Shahin, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 11124.

(48) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986; p 149.

(49) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

(50) (a) Longuett-Higgins, H. C.; Pople, J. A. *Proc. Phys. Soc. A68* **1955**, 591. (b) Dewar, M. J. S.; Trinajstic, N. *J. Chem. Soc. A* **1971**, 1220.

(51) (a) Armstrong, D. A.; Rauk, A.; Yu, D. K. *J. Am. Chem. Soc.* **1993**, *115*, 666. (b) Schubert, S.; Renaud, P.; Carrupt, P. A.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473.

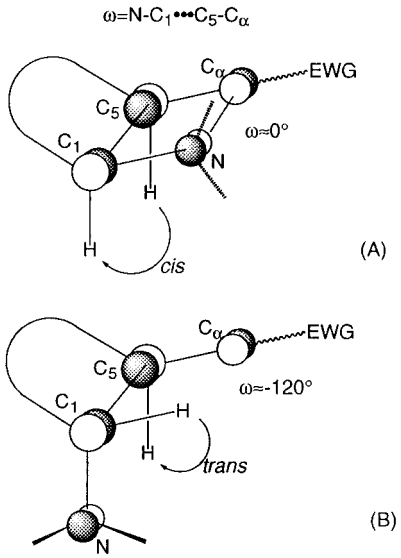


Figure 2. Schematic diagram showing the interaction between the SOMO of an aminomethyl radical and the LUMO of an alkene. (A) Primary and secondary interactions in a TS leading to *cis*-aminocyclopentanes. (B) Primary interaction in a TS leading to *trans*-aminocyclopentanes.

exist in those corresponding to the formation of *trans*-cyclopentanes ($\omega \approx -120$, Figure 2). The lowering of energy provided by the EWG substituents to the alkene LUMO would be expected to further enhance the SOMO−LUMO interactions thus leading to a predicted greater *cis*-selectivity in these cases. It should be noted that the secondary interaction, in principle, depends neither on the geometry of the double bond nor on the conformation of the five-membered ring being formed. Thus, for sterically nondemanding substituents such as a cyano group, the *cis*-product should be the major stereoisomer formed from both (*E*)- and (*Z*)-geometries. The more sterically demanding (and conformationally more mobile) ethoxycarbonyl group might give rise, in the TS associated to a (*Z*)-C=C geometry, to steric congestion with the amino group substituents (not included in the calculations). This could account for the lower selectivity obtained in the cyclization of the morpholine adduct derived from aldehyde **8b** (Table 1, entry 3).

Finally, the higher stereoselectivity observed when the olefin activating group is (*E*)-CO_2Et, rather than (*E*)- or (*Z*)-CN, might indicate that the rate of reduction of the cyclized radical is also important for the stereochemical outcome of the reaction. Thus, a very fast reduction would lead to kinetic products in an essentially irreversible cyclization, and this is expected to be the case for the CO_2Et activating group where the oxophilicity of trivalent samarium would facilitate the formation of the corresponding samarium enolate. A slower reduction of the CN-substituted cyclized radical might allow for some reversibility in the cyclization step therefore leading to a lower stereoselectivity.

Conclusions

We have shown that the reduction with SmI_2 of iminium ions formed *in situ* by dissociation of α-benzotriazolyl amines derived from ω-unsaturated aldehydes affords α-amino radicals that undergo 5- or 6-*exo* cyclizations leading to substituted cycloalkyl- and cycloheteroalkylamines. A simple and convenient synthetic strategy combined with reasonable overall yields and high diastereoselectivities assess to the effectiveness of the overall synthetic scheme for the convergent synthesis of polysubstituted cyclopentylamines. The formation of the corresponding six-membered rings, however, will be severely limited due to lack of diastereoselectivity.

Experimental Section

Unless otherwise stated, reactions were conducted under an atmosphere of dry Ar. THF and benzene were freshly distilled from sodium/benzophenone. THF was deoxygenated prior to use. Dichloromethane, DMSO, and DMF were distilled from CaH_2. Organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Flash column chromatography[53] was performed on silica gel (230−400 mesh). HPLC purifications were carried out with a LiChrosorb Si60 (7 μm, 25 × 2.5 cm) column. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 250 MHz and 62.9 MHz, respectively. Mass spectra were obtained at 70 eV. GC-MS analysis were performed at 70−280 °C (20 °C/min) with a stationary phase of methylphenylsilicone (0.25 μm, 30 m × 0.25 mm).

Computational Methods. All TS calculations were performed using the semiempirical SCF-MO PM3[49] method. TSs were optimized using Bartels[54a] and eigenvector following[54b] methods. All stationary points were refined by minimization of the gradient norm of the energy at least below 0.01 kcal/Å-deg and characterized by harmonic vibrational frequency analysis.[55] The TSs showed only one negative eigenvalue in their diagonalized Hessians, corresponding to motion along the reaction coordinate. The relative preference found with this semiempirical approach was qualitatively reproduced for **TSCa** and **TSCb** using *ab initio* calculations[56,57] at the UHF/6-31G* level.

Preparation of Benzotriazole Intermediates 15−21. General Procedure. A mixture of benzotriazole (0.45 g, 3.54 mmol), a secondary amine (3.54 mmol), the appropriate aldehyde (3.50 mmol), and 4 Å molecular sieves (1 g) in dry benzene (15 mL) was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2 (20 mL) and filtered through Celite. The solvent was eliminated under reduced pressure and the resulting thick oil maintained under vacuum (0.1 mmHg) for 2 h and used without further manipulation. When *N*-benzylaniline was used, molecular sieves were omitted, and the mixture was refluxed in a Dean−Stark until the theoretical amount of water had separated. Evaporation of the solvent afforded the oily product that was processed as described above. Details of the preparation of adducts **15−21** and full ^1H NMR data are collected in Tables 4, 5 (supporting information). ^{13}C NMR and HRMS data for selected cases are also given in the supporting information.

Reactions of Benzotriazole Adducts 15−21 with SmI_2. General Procedure. Method A. A 0.1 M solution of SmI_2[1b] was added dropwise to a stirred solution of the benzotriazole adduct (0.38 mmol) in THF (40 mL) at 25 °C at such a rate as to allow the SmI_2 characteristic blue color to disappear before

(52) See reference 44b for related *unfavorable* secondary orbital interactions between the SOMO of an alkoxy-substituted radical and the HOMO of an electron-rich olefin that have been similarly used to explain a *trans*-preference in radical cyclizations. We thank the Editor for calling this work to our attention.

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(54) (a) Bartels, R. H. Report CNA-44; University of Texas; Center for Numerical Analysis: Austin TX, 1972. (b) Baker, J. *J. Comput. Chem.* **1986**, *7*, 385.
(55) McIver, J. W.; Komornicki, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 2625.
(56) Gaussian 94, Revision B.2, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1995.
(57) Work is now in progress to extend these *ab initio* calculations to the rest of the TSs included in Chart 2 and to related systems.

the next drop was added. Addition continued until the blue color persisted. The mixture was then stirred for 15 min and treated with saturated K_2CO_3 (10 mL), followed by H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL). The crude product was purified as indicated below for the individual cases. **Method B.** A solution of the benzotriazole adduct (0.59 mmol) in THF (6 mL) was added to a THF (15 mL) solution of SmI_2 (1.3 mmol) that had been cooled to below −20 °C. The mixture was stirred for 30 min and then allowed to reach room temperature slowly. It was then proceeded as in method A. Details of method used, yields and stereoselectivities are collected in Tables 1−3. The following compounds were prepared:

1-Isopropyl-3-methyl-2-morpholinocyclopentane (22) and 3-Methyl-1-(1-methylethenyl)-2-morpholinocyclopentane (23). General method A was applied to adduct **15**. Flash chromatography (10% EtOAc in hexanes) afforded in order of elution cyclopentanes **22** (contaminated with some **23**, 15%) and **23** (contaminated with some **22**, 12%), both as yellowish oils. Data for **22**: ^{1}H NMR δ 0.84 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.0−1.8 (m, 6H), 1.9−2.0 (m, 1H), 3.19 (t, J = 6.5 Hz, 1H), 2.4−2.6 (m, 4H), 3.66 (t, J = 4.6 Hz, 4H); ^{13}C NMR δ 18.7, 21.2, 22.1, 25.2, 31.0, 33.1, 34.1, 47.5, 50.6, 67.6, 77.2; GC-MS: t_R = 12.6 min; LRMS (EI) m/z 211 (M^+); HRMS calcd for $C_{13}H_{24}NO$ (M^+ − 1) 210.18579, found 210.18516. Data for **23**: ^{1}H NMR δ 1.03 (d, J = 6.7 Hz, 3H), 1.2−1.8, 1.75 (s, 3H, overlapped with m at 1.2−1.8), 1.99 (m, 1H), 2.38 (t, J = 7.5 Hz, 1H), 2.5−2.7 (m, 4H), 3.66 (t, J = 4.5 Hz, 4H), 4.71 (s, 1H), 4.79 (s, 1H); ^{13}C NMR δ 20.2, 20.8, 30.2, 32.4, 35.6, 49.2, 50.8, 67.5, 76.4, 110.4, 148.8; GC-MS: t_R = 12.7 min; LRMS (EI) m/z 209 (M^+); HRMS calcd for $C_{13}H_{23}NO$ 209.17796, found 209.17671.

Ethyl *cis*- and *trans*-(2-Morpholinocyclopentyl)ethanoate (27a). Flash chromatography (20% EtOAc in hexanes, then EtOAc) afforded in order of elution (where appropriate; see Table 1) *c*-**27a** and *t*-**27a** as yellowish oils. Data for *c*-**27a**: ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 1.3−1.8 (m, 6H), 1.97 (dd, J = 16.2, 11.4 Hz, 1H), 2.3−2.6 (m, 7H), 3.67 (t, J = 4.7 Hz, 4H), 4.10 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.3, 20.1, 26.7, 28.8, 32.9, 37.0, 53.0, 60.1, 67.0, 69.4, 174.2. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.30; H, 9.56; N, 5.60. Data for *t*-**27a**: ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 1.2−1.3 (m, 2H, overlapped with t at 1.25), 1.5−2.5 (m, 12H), 3.68 (t, J = 4.0 Hz, 4H), 4.12 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.2, 22.9, 25.8, 30.8, 37.5, 39.9, 50.7, 60.2, 67.3, 72.2, 174.2; HRMS calcd for $C_{13}H_{23}NO_3$ 241.167793, found 241.167007.

Ethyl *cis*- and *trans*-[2-(*N*,*N*-Dibenzylamino)cyclopentyl]ethanoate (27b). Colorless oil after flash chromatography (15% EtOAc in hexanes). Data for the diastereomeric mixture: ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3H), 1.4−1.8 (m, 6H), 2.20 (dd, J = 15.5, 10.7 Hz, 1H), 2.6−2.7 (m, 1H), 2.88 (dd, J = 15.5, 3.8 Hz, 1H), 3.1 (m, 1H), 3.38 (d, J = 13.7 Hz, 2H, *trans*-isomer), 3.56 and 3.71 (AB q J = 14.4 Hz, 4H, *cis*-isomer), 3.84 (d, J = 13.7 Hz, 2H, *trans*-isomer), 4.10 (q, J = 7.1 Hz, 2H), 7.2−7.4 (m, 10H); ^{13}C NMR δ 14.2, 21.3, 21.6, 22.1, 27.4, 29.4, 30.0, 33.7, 38.4, 54.7, 56.1, 60.1, 65.5, 126.6, 128.1, 128.6, 128.7, 139.5, 140.3, 174.2. Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.98. Found: C, 78.74; H, 8.30; N, 4.28.

Ethyl *cis*-[2-[*N*-Benzyl-*N*-(2-phenylethyl)amino]cyclopentyl]ethanoate (*c*-27d). Flash chromatography (6% EtOAc in hexanes) afforded the titled compound as a yellowish oil that crystallized on standing (microcrystals): mp 38−40 °C; ^{1}H NMR δ 1.29 (t, J = 7.1 Hz, 3H), 1.3−1.9 (m, 6H), 2.12 (dd, J = 15.0, 10.8 Hz, 1H), 2.5−2.8 (m, 6H), 3.0−3.2 (m, 1H), 3.73 and 3.85 (AB q, J = 14.1 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 7.0−7.4 (m, 10H); ^{13}C NMR δ 14.3, 20.8, 27.7, 29.1, 30.7, 33.2, 38.3, 53.4, 56.1, 60.1, 65.3, 125.7, 126.7, 128.2, 128.3, 128.5, 128.6, 140.0, 140.7, 174.3. Anal. Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55; N, 3.83. Found: C, 79.05; H, 8.41; N, 3.81.

Ethyl *cis*-[2-(*N*-Benzyl-*N*-phenylamino)cyclopentyl]-ethanoate (*c*-27e). Flash chromatography (6% EtOAc in hexanes) afforded the titled compound as a colorless oil that crystallized on standing (microcrystals). The analytical sample was obtained after HPLC purification (12 mL/min, 6% EtOAc in hexanes, t_R = 19 min): mp 56−58°C; ^{1}H NMR δ 1.17 (t, J = 6.9 Hz, 3H), 1.4−1.8 (m, 4H), 1.9−2.2 (m, 3H), 2.15 (dd, J = 15.4, 10.5 Hz, 1H, overlapped with m at 1.9−2.2), 2.9−3.0 (m, 1H), 3.9−4.0 (m, 2H), 4.36 (q, J = 8.3 Hz, 1H), 4.51 and 4.60 (AB q, J = 17.9 Hz, 2H), 6.7 (m, 2H), 7.1−7.3 (m, 8H); ^{13}C NMR δ 14.1, 22.8, 30.0, 31.5, 35.9, 37.9, 51.8, 60.2, 61.1, 113.2, 116.8, 126.1, 126.5, 128.4, 129.0, 139.8, 149.3, 173.1. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.30; H, 8.04; N, 4.15.

Ethyl *cis*-[2-[*N*-Benzyl-*N*-(2-cyanoethyl)amino]cyclopentyl]ethanoate (*c*-27f). Flash chromatography (14% EtOAc in hexanes) afforded the titled compound as a colorless oil. The analytical sample was obtained after HPLC purification (10 mL/min, 14% EtOAc in hexanes, t_R = 26 min): ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, 3H), 1.5−1.9 (m, 6H), 2.12 (dd, J = 15.5, 10.2 Hz, 1H), 2.30 (t, J = 7.1 Hz, 2H), 2.5−2.6 (m, 1H), 2.72 (dd, J = 15.5, 3.8 Hz, 1H), 2.8−2.9 (m, 2H), 2.9−3.1 (m, 1H), 3.59 and 3.75 (AB q, J = 14.2 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 7.2−7.4 (m, 5H); ^{13}C NMR δ 14.1, 14.2, 20.7, 27.5, 29.2, 33.1, 38.2, 47.4, 56.3, 60.2, 65.2, 119.0, 127.3, 128.4, 128.5, 138.5, 173.9. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.50; H, 8.40; N, 8.94.

Ethyl *cis*-[2-(4-Phenylpiperazin-1-yl)cyclopentyl]ethanoate (*c*-27g). Flash chromatography (10% EtOAc in hexanes) afforded the titled compound as microcrystals: mp 39−41°C; ^{1}H NMR δ 1.26 (t, J = 7.3 Hz, 3H), 1.4−1.9 (m, 6H), 2.01 (dd, J = 16.2, 11.3 Hz, 1H), 2.4−2.7 (m, 7H), 3.17 (t, J = 5.0 Hz, 4H), 4.13 (q, J = 7.3 Hz, 2H), 6.8−6.9 (m, 3H), 7.2−7.3 (m, 2H); ^{13}C NMR δ 14.2, 20.2, 27.0, 28.9, 33.0, 37.2, 49.0, 52.5, 60.1, 69.1, 115.8, 119.5, 129.0, 151.3, 174.2. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.01; H, 8.89; N, 9.08.

Ethyl *cis*-[2-[*N*-Benzyl-*N*-(3-butenyl)amino]cyclopentyl]ethanoate (*c*-27h). Flash chromatography (5% EtOAc in hexanes) afforded the titled compound as a colorless oil. The analytical sample was obtained after HPLC purification (10 mL/min, 4% EtOAc in hexanes, t_R = 18 min); ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 1.5−1.8 (m, 6H), 2.08 (dd, J = 15.6, 10.8 Hz, 1H), 2.1−2.2 (m, 2H), 2.5−2.7 (m, 3H), 2.75 (dd, J = 15.6, 3.5 Hz, 1H), 2.9−3.1 (m, 1H), 3.61 and 3.72 (AB q, J = 14.3 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.9−5.1 (m, 2H), 5.6−5.7 (m, 1H), 7.2−7.4 (m, 5H); ^{13}C NMR δ 14.2, 20.8, 27.6, 28.9, 29.1, 33.2, 38.2, 50.8, 55.9, 60.1, 65.3, 115.4, 126.6, 128.1, 128.4, 136.9, 140.2, 174.3. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.98; H, 9.27; N, 4.67.

***cis*- and *trans*-[2-(*N*,*N*-Dibenzylamino)cyclopentyl]ethanenitrile (*c*-27i, *t*-27i).** Colorless oil after flash chromatography (20% EtOAc in hexanes). Data for the mixture of isomers: ^{1}H NMR δ 1.4−2.1 (m, 6H), 2.22 (dd, J = 16.8, 10.8 Hz, 1H), 2.4−2.6 (m, 1H), 2.74 (dd, J = 16.8, 3.9 Hz, 1H), 3.0−3.1 (m, 1H, *cis*-isomer), 3.40 (d, J = 13.7 Hz, 2H, *trans*-isomer), 3.60 and 3.70 (AB q, J = 14.3 Hz, 4H, *cis*-isomer), 3.80 (d, J = 13.7 Hz, 2H, *trans*-isomer), 7.25−7.35 (m, 10H); ^{13}C NMR δ 17.1, 20.6, 20.9, 21.7, 22.0, 27.3, 28.8, 29.2, 38.5, 38.9, 54.8, 56.4, 65.3, 65.7, 119.2, 120.5, 127.0, 128.3, 128.5, 128.6, 138.9, 139.7. Anal. Calcd for $C_{21}H_{24}N$: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.50; H, 7.90; N, 9.42.

***cis*- and *trans*-(2-Morpholinocyclopentyl)ethanenitrile (*c*-27j, *t*-27j).** Flash chromatography (40% EtOAc in hexanes) afforded in order of elution *c*-**27j** and *t*-**27j** as yellowish oils. Data for *c*-**27j**: ^{1}H NMR δ 1.2−1.5 (m, 1H), 1.6−1.9 (m, 5H), 2.04 (dd, J = 16.4, 9.3 Hz, 1H), 2.4−2.5 (m, 7H), 3.68 (t, J = 4.6 Hz, 4H); ^{13}C NMR δ 16.5, 19.9, 26.3, 28.5, 37.4, 53.0, 66.8, 68.9, 120.5; HRMS calcd for $C_{11}H_{18}N_2O$ 194.1419, found 194.1422. Data for *t*-**27j**: ^{1}H NMR δ 1.4−1.8 (m, 5H), 1.8−2.0 (m, 1H), 2.0−2.2 (m, 1H), 2.3−2.5 (m, 7H), 3.67 (s, 4H); ^{13}C NMR δ 21.6, 22.4, 25.0, 29.9, 37.2, 50.4, 67.1, 71.3, 119.1. Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found (mixture of isomers): C, 67.85; H, 9.01; N, 14.17.

***cis*- and *trans*-[2-(*N*,*N*-Diallylamino)cyclopentyl]ethanenitrile (*c*-27k, *t*-27k).** Flash chromatography (20% EtOAc in hexanes) afforded in order of elution *c*-**27k** and *t*-**27k** as yellowish oils. Data for *c*-**27k**: ^{1}H NMR δ 1.4−1.6 (m, 1H), 1.6−1.9 (m, 5H,), 2.05 (dd, J = 16.9, 10.6 Hz, 1H), 2.3−2.4 (m, 1H), 2.56 (dd, J = 16.9, 3.9 Hz, 1H), 2.9−3.0 (m, 1H), 3.14 (d, J = 6.3 Hz, 4H), 5.1−5.2 (m, 4H), 5.7−5.9 (m, 2H); ^{13}C NMR δ 16.7, 20.5, 27.1, 28.5, 38.5, 54.0, 64.5, 117.5, 120.7, 134.5.

Data for *t*-**27k**: ^{1}H NMR δ 1.2−1.3 (m, 7H), 2.32 (dd, J = 16.8, 9.1 Hz, 1H), 2.58 (dd, J = 16.8, 4.1 Hz, 1H), 2.8−3.0 (m, 3H), 3.1−3.2 (m, 2H), 5.1−5.2 (m, 4H), 5.7−5.9 (m, 2H); ^{13}C NMR δ 20.7, 21.9, 22.9, 29.0, 38.5, 53.5, 66.4, 116.7, 119.4, 136.8. Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found (mixture of isomers): C, 76.05; H, 9.71; N, 13.39.

Ethyl [(1*R,2*R**,3*S**)-2-(*N*,*N*-Dibenzylamino)-3-methylcyclopentyl]ethanoate (28a).** Flash chromatography (4% EtOAc in hexanes) afforded the titled compound (95/5 diastereomeric mixture) as a colorless oil. Data for the major (1*R**,2*R**,3*S**)-isomer: ^{1}H NMR δ 1.11 (d, J = 6.6 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H, overlapped with m at 1.1−1.5), 1.1−1.5 (m, 7H), 1.8−2.0 (m, 2H), 2.3−2.7 (m, 3H), 2.8−2.9 (m, 2H), 3.6 (d, J = 14.0 Hz, 2H), 4.0−4.2 (m, 2H), 7.2−7.4 (m, 10H); ^{13}C NMR δ 14.2, 22.2, 31.3, 32.5, 32.9, 35.6, 39.1, 55.7, 60.0, 67.8, 126.7, 128.1, 128.3, 140.0, 173.7; HRMS calcd for $C_{24}H_{31}NO_2$ 365.23548, found 365.23541.

Ethyl [(1*R,2*R**,3*S**)-3-Methyl-2-morpholinocyclopentyl]ethanoate (28b).** The crude product was purified by flash chromatography (35% EtOAc in hexanes) and HPLC (12 mL/min, 30% EtOAc in hexanes, t_R = 26 min) to yield the titled compound (∼95/5 diastereomeric mixture) as a colorless oil: ^{1}H NMR δ 1.01 (d, J = 6.0 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H, overlapped with m at 1.1−1.2), 1.1−1.2 (m, 1H), 1.3−1.4 (m, 1H), 1.6−1.8 (m, 1H), 1.9−2.1 (m, 3H), 2.23 (t, J = 6.5 Hz, 1H), 2.3−2.6 (m, 6H), 3.60 (t, J = 4.5 Hz, 4H), 4.07 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.2, 23.0, 29.1, 32.2, 32.7, 33.8, 39.4, 52.7, 59.9, 67.1, 75.5, 174.0; HRMS calcd for $C_{14}H_{25}NO_3$ 255.18344, found 255.18335.

Ethyl [(1*S,2*R**,5*R**)-2-(*N*,*N*-Dibenzylamino)-5-methylcyclopentyl]ethanoate (29a) and Its (1*S**,2*R**,5*S**)-isomer (29a′).** Following General method B, after the reaction mixture reached room temperature it was stirred at that temperature further 22 h. The normal workup afforded, after flash chromatography (1% EtOAc in hexanes), the mixture of **29a**, **29a′**, and **30a** in a ratio (^{1}H NMR) of 84.3:14.0:1.7. The mixture was separated by HPLC (8 mL/min, 5% EtOAc in hexanes) to yield in order of elution **29a′**, **29a**, and **30a** as colorless oils. Data for **29a′**: t_R 26 min; ^{1}H NMR δ 0.93 (d, J = 6.9 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.3−1.4 (m, 2H), 1.7−1.8 (m, 1H), 2.10 (dd, J = 16.8, 9.8 Hz, 1H, overlapped with m at 2.0−2.2), 2.0−2.2 (m, 1H), 2.7−2.8 (m, 1H), 2.94 (dd, J = 16.8, 2.2 Hz, 1H), 2.9−3.0 (m, 1H), 3.52 and 3.76 (AB q, J = 14.4 Hz, 4H), 4.1 (m, 2H), 7.2−7.3 (m, 10H); ^{13}C NMR δ 14.2, 16.0, 27.9, 28.4, 29.0, 35.3, 42.0, 55.4, 60.2, 66.7, 126.6, 128.0, 128.9, 139.2, 174.7; HRMS calcd for $C_{24}H_{31}NO_2$ 365.23548, found 365.23563. Data for **29a**: t_R 28 min; ^{1}H NMR δ 0.99 (d, J = 6.2 Hz, 3H), 1.0−1.2 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.5−2.0 (m, 4H), 2.1−2.3 (m, 2H), 2.84 (dd, J = 14.6, 4.8 Hz, 1H), 3.26 (dt, J = 8.1, 7.6 Hz, 1H), 3.53 and 3.61 (AB q, J = 14.3 Hz, 4H), 4.0−4.2 (m, 2H), 7.2−7.5 (m, 10H); ^{13}C NMR δ 14.2, 21.6, 26.4, 32.1, 34.2, 38.5, 46.2, 56.2, 60.1, 63.2, 126.7, 128.1, 128.6, 139.7, 174.0; HRMS calcd for $C_{24}H_{31}NO_2$ 365.23548, found 365.23513. Data for **30a**: t_R 33 min; ^{1}H NMR δ 0.97 (d, J = 6.5 Hz, 3H), 1.1−1.2 (m, 1H), 1.4−1.6 (m, 2H), 1.7−1.8 (m, 2H), 2.19 (dd, J = 12.6, 2.5 Hz, 1H, overlapped with m at 2.0−2.2), 2.0−2.2 (m, 1H), 3.08 (dd, J = 12.6, 7.7 Hz, 1H), 3.23 (d, J = 13.7 Hz, 1H), 3.4−3.6 (m, 1H), 3.67 (d, J = 13.7 Hz, 1H), 4.20 (s, 1H), 7.2−7.4 (m, 8H), 7.53 (dd, J = 8.1, 1.4 Hz, 2H); ^{13}C NMR δ 19.8, 24.3, 32.6, 39.5, 40.5, 43.2, 54.2, 57.5, 72.9, 127.0, 128.1, 128.3, 128.4, 128.4, 128.8, 137.5, 138.9, 211.3; HRMS calcd for $C_{22}H_{25}NO$ 319.19361, found 319.19324.

Ethyl [(1*S,2*R**,5*R**)-5-Methyl-2-morpholinocyclopentyl]ethanoate (29b).** Following General method B, after the reaction mixture reached room temperature it was stirred at that temperature further 17 h. The normal workup afforded, after flash chromatography (30% EtOAc in hexanes), the diastereomeric mixture of **29b** and **29b′** as a colorless oil from where the major isomer **29b** could be separated by HPLC (12 mL/min, 30% EtOAc in hexanes, t_R = 23 min): ^{1}H NMR δ 0.98 (d, J = 6.9 Hz, 3H), 1.1−1.3 (m, 1H, overlapped with t at 1.23), 1.23 (t, J = 7.1 Hz, 3H), 1.3−1.4 (m, 1H), 1.4−2.0 (m, 4H), 2.0−2.2 (m, 1H), 2.3−2.7 (m, 6H), 3.64 (t, J = 4.7 Hz, 4H), 4.10 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.2, 22.9, 27.2, 30.3, 34.3, 37.5, 44.2, 52.8, 60.0, 66.9, 67.2, 174.1. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 65.85; H, 9.87; N, 5.48. Found: C, 65.47; H, 9.83; N, 5.61.

Ethyl *cis*- and *trans*-(2-Morpholinocyclohexyl)ethanoate (*c*-34a, *t*-34a). Flash chromatography (15% EtOAc in hexanes) afforded in order of elution *t*-**34a** (16%) and *c*-**34a** (38%) as yellowish oils. Data for *t*-**34a**: ^{1}H NMR δ 1.0−1.3 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H, overlapped with m at 1.0−1.3), 1.6−2.0 (m, 8H), 2.3−2.4 (m, 2H), 2.6−2.7 (m, 3H), 3.6−3.7 (m, 4H), 4.1 (m, 2H); ^{13}C NMR δ 14.2, 23.9, 25.9, 33.1, 36.7, 39.6, 48.9, 59.9, 67.5, 68.8, 173.9; HRMS calcd for $C_{14}H_{25}NO_3$ 255.18344, found 255.18383. Data for *c*-**34a**: ^{1}H NMR δ 1.0−1.4 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H, overlapped with m at 1.0−1.4), 1.6−1.8 (m, 4H), 2.0−2.7 (m, 8H), 3.67 (t, J = 4.7 Hz, 4H), 4.11 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.2, 20.0, 24.1, 25.4, 29.0, 31.3, 31.7, 50.6, 60.1, 65.0, 67.3, 174.2; HRMS calcd for $C_{14}H_{25}NO_3$ 255.18344, found 255.18347.

6-(Ethoxycarbonyl)-7-morpholinobicyclo[3.2.0]heptane (36). General procedure A was used. Flash chromatography (15% EtOAc in hexanes) afforded in order of elution *t*-**34a** (6%), **36a** (4%), *c*-**34a** (29%), and **36a′** (30%) as thick colorless oils. Data for the less polar isomer of **36**: ^{1}H NMR δ 1.23 (t, J = 7.1 Hz, 3H), 1.4−1.9 (m, 6H), 2.2 (m, 4H), 2.37 (t, J = 7.1 Hz, 1H), 2.6−2.9 (m, 2H), 2.90 (t, J = 8.0 Hz, 1H), 3.66 (t, J = 4.7 Hz, 4H), 4.10 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.2, 25.3, 26.3, 32.1, 37.9, 38.3, 45.4, 50.3, 59.9, 60.3, 66.7, 174.7; HRMS calcd for $C_{14}H_{23}NO_3$ 253.16779, found 253.16829. Data for the more polar isomer of **36**: ^{1}H NMR δ 1.24 (t, J = 7.1 Hz, 3H), 1.3−1.7 (m, 6H), 2.2−2.4 (m, 4H), 2.5 (m, 1H), 2.6 (m, 1H), 2.9−3.0 (m, 2H), 3.68 (t, J = 4.6 Hz, 4H), 4.0−4.2 (m, 2H); ^{13}C NMR δ 14.4, 26.2, 28.1, 32.0, 35.8, 40.5, 42.7, 50.2, 60.2, 64.4, 66.6, 172.5; HRMS calcd for $C_{14}H_{23}NO_3$ 253.16779, found 253.16814. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.74; H, 8.88; N, 5.40.

Ethyl *cis*- and *trans*-[2-(*N*,*N*-Dibenzylamino)cyclohexyl]ethanoate (34b). Flash chromatography (15% EtOAc in hexanes) afforded the titled compound as a colorless oil. Data for the diastereomeric mixture: ^{1}H NMR δ 0.8−2.2 (m, 13H), 2.40 (dd, J = 14.8, 10.7 Hz, 1H, one isomer), 2.69 (d, J = 8.6 Hz, 2H, one isomer), 2.87 (d, J = 14.8 Hz, 1H, one isomer), 3.35 (d, J = 13.7 Hz, 2H, one isomer), 3.63 (d, J = 14.6 Hz, 2H), 3.83 (d, J = 14.6 Hz, 2H), 7.2−7.4 (m, 10H); ^{13}C NMR δ 14.3, 20.1, 23.3, 25.8, 25.9, 26.0, 28.9, 31.8, 32.6, 34.1, 37.3, 38.5, 53.4, 55.1, 60.0, 60.2, 60.7, 62.3, 126.5, 126.7, 128.1, 128.1, 128.4, 128.8, 129.1, 140.3, 140.7, 174.3; HRMS calcd for $C_{24}H_{31}NO_2$ 365.23548, found 365.23595.

***cis*- and *trans*-3-[(Methoxycarbonyl)methyl]-4-morpholinochroman (35a).** Flash chromatography (25% EtOAc in hexanes) afforded the separated isomers as yellowish oils. Data for the less polar isomer: mp 62−64°C; ^{1}H NMR δ 2.1−2.7 (m, 7H), 3.20 (bs, 1H), 3.5−3.7 (m, 4H), 3.67 (s, 3H), 3.9−4.2 (m, 1H), 4.35 (dd, J = 10.9, 2.4 Hz, 1H), 6.8−6.9 (m, 2H), 7.1−7.2 (m, 2H); ^{13}C NMR δ 31.2, 34.2, 51.2, 51.6, 62.7, 66.2, 67.5, 116.8, 118.9, 119.9, 129.0, 132.5, 154.7, 172.8. Data for the more polar isomer: ^{1}H NMR δ 2.3−2.7 (m, 6H), 2.76 (q, J = 7.9 Hz, 1H), 3.6−3.7 (m, 5H), 3.71 (s, 3H), 3.94 (t, J = 11.0 Hz, 1H), 4.1−4.2 (m, 1H), 6.7−7.2 (m, 4H); ^{13}C NMR δ 32.4, 35.6, 51.7, 54.2, 60.1, 66.1, 67.6, 116.8, 119.8, 119.9, 129.1, 130.9, 154.5, 172.8. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found (diastereomeric mixture): C, 65.60; H, 7.12; N, 5.03.

***cis*- and *trans*-4-(4-Phenylpiperazin-1-yl)-3-[(methoxycarbonyl)methyl]chroman (35c).** Flash chromatography (20% EtOAc in hexanes) afforded the diastereomeric mixture of **35c** as an oil. The isomers were separated by HPLC (12 mL/min, 27% EtOAc in hexanes). Data for the less polar isomer: t_R 11.8 min; ^{1}H NMR δ 2.2−2.5 (m, 2H), 2.5−2.7 (m, 3H), 2.8−2.9 (m, 2H), 3.15 (t, J = 4.9 Hz, 4H), 3.30 (bs, 1H), 3.69 (s, 3H), 4.06 (dd, J = 11.0, 2.0 Hz, 1H), 4.37 (dd, J = 11.0, 1.5 Hz, 1H), 6.8−7.0 (m, 5H), 7.1−7.3 (m, 4H). Data for the more polar isomer: t_R 13.2 min; ^{1}H NMR δ 2.37 (dd, J = 15.7, 5.5 Hz, 1H), 2.5−2.8 (m, 6H), 3.13 (t, J = 4.8 Hz, 4H), 3.71 (s, 3H), 3.83 (d, J = 3.6 Hz, 1H), 3.99 (t, J = 11.1 Hz, 1H), 4.15 (dd, J = 11.1, 3.9 Hz, 1H), 6.8−7.0 (m, 5H), 7.1−7.3 (m, 4H); ^{13}C NMR (diastereomeric mixture) δ 31.5, 32.4, 34.4, 35.6, 49.8, 50.6, 51.6, 53.6, 59.5, 62.4, 66.0, 66.4, 116.0, 116.7, 116.8, 119.4, 119.6, 119.7, 120.0, 120.1, 129.0, 130.8, 132.4,

151.3, 154.4, 154.7, 172.8. Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found (diastereomeric mixture): C, 71.63; H, 7.23; N, 7.64.

***cis*- and *trans*-4-[*N*-Benzyl-*N*-(2-cyanoethyl)amino]-3-[(methoxycarbonyl)methyl]chroman (35d).** Flash chromatography (32% EtOAc in hexanes) afforded the diastereomeric mixture of **35d** as an oil: ^{1}H NMR δ 2.2−2.3 (m, 7H), 3.67 and 3.68 (s, 3H), 3.6−4.3 (m, 5H), 6.9−7.5 (m, 9H); ^{13}C NMR δ 17.5, 18.3, 32.0, 32.6, 34.7, 34.9, 47.2, 49.5, 51.7, 56.2, 56.9, 58.5, 59.1, 66.1, 67.3, 117.1, 118.8, 120.2, 120.6, 121.0, 127.5, 127.6, 128.5, 128.6, 128.8, 129.0, 129.2, 129.6, 130.8, 138.6, 139.1, 154.8, 155.4, 172.7; GC-MS, t_R = 15.4, 16.1 min; HRMS calcd for $C_{22}H_{24}N_2O_3$ 364.17869, found 364.17883.

Acknowledgment. Financial support by the Dirección General de Investigación Científica y Técnica (DGICYT PB89-0412 and PB92-0449) and by the Universidad del País Vasco (UPV 170.310-EC201/94) is gratefully acknowledged. We also thank the Departamento de Educación, Universidades e Investigación (Gobierno Vasco, Spain) for a Fellowship (to A.F-A.).

Supporting Information Available: Preparation and characterization data for **8**−**10**; ^{13}C NMR and HRMS data for **15**, **16b**, and **17b**; Tables 4, 5, 6−8; copies of ^{1}H and ^{13}C NMR spectra of compounds **8b**−**d**, **9**, **22**, **23**, *t*-**27a**, **28a**, **28b**, **29a**, **29a′**, **30a**, *c*-**34a**, *t*-**34a**, **34b**, **35d** (44 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960957D