JOC Article

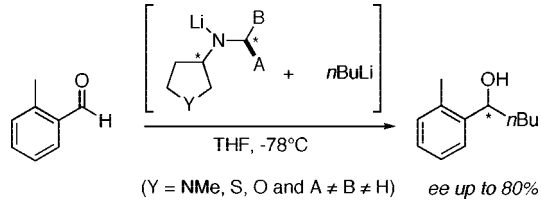
Heterocyclic Lithium Amides as Chiral Ligands for an Enantioselective Hydroxyalkylation with *n*-BuLi

Nicolas Duguet, Sylvain M. Petit, Philippe Marchand, Anne Harrison-Marchand, and Jacques Maddaluno*

Laboratoire des Fonctions Azotées & Oxygénées Complexes de l'IRCOF, UMR CNRS 6014 and FR CNRS 3038, Université de Rouen and INSA de Rouen, 76821 Mont St Aignan Cedex, France

jmaddalu@crihan.fr

Received March 10, 2008



Chiral heterocyclic structures based on 3-aminopyrrolidines (3APs), 3-aminotetrahydrothiophens (3ATTs), and 3-aminotetrahydrofurans (3ATFs) have been synthesized. The corresponding lithium amides have been evaluated as chiral ligands in the condensation of *n*-BuLi on *o*-tolualdehyde. The returned levels of induction were in the 46−80% ee range. The cheap and easily prepared 3ATFLi's turned out to be also the best ligands, giving access to the expected *R* or *S* alcohols in a same 80% level of induction at −78 °C in THF. In all cases, the sense of induction depends on the absolute configuration of C^8 on the 3-amino appendage. A general concept is proposed to rationalize the process of induction in the presence of organolithium species.

Introduction

A nonracemic chiral environment can be introduced into organometallic compounds in two general ways. The first one uses classical complexing agents (Lewis bases) to coordinate the metallic center (chiral ethers, tertiary amines, etc.).[1] Alternatively, advantage can be taken of dipole−dipole interactions between the reactant and a chiral deprotonated entity such as an alcoholate or an amide.[2] This second class of ligands is particularly efficient for organolithium compounds: a tight noncovalent complex results from the association of these polar entities and provides a highly reactive mixed aggregate,[3] which behaves as a good nucleophile toward carbonyl compounds. However, reaching good enantioselectivities in "classical" conditions (use of a single solvent, $T \geq -78$ °C) with such systems still remains a challenge.

Previous studies evidenced that 3-aminopyrrolidine lithium amides **1**Li (Figure 1) can act as satisfying inductors for 1,2- and 1,4-nucleophilic additions of organolithium reactants (76% < ee < 80%).[4]

In an effort to improve the system (easier and cheaper synthesis of the ligand, higher ee's), four structural appendages on **1**Li have been varied (Figure 2). The new set of 3-aminoheterocycle lithium amides has been evaluated as chiral ligands in the addition of *n*-butyllithium onto *o*-tolualdehyde. The results are presented here.

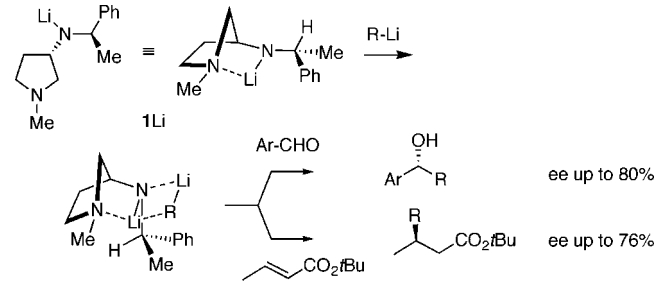


FIGURE 1. 3-Aminopyrrolidine lithium amides as chiral ligands for organolithium reagents.

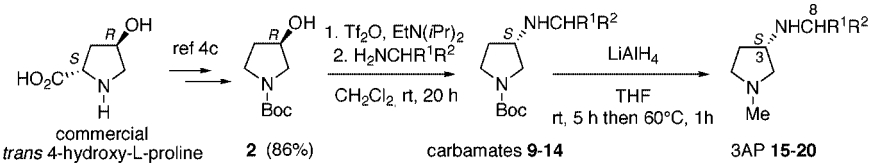
Results and Discussion

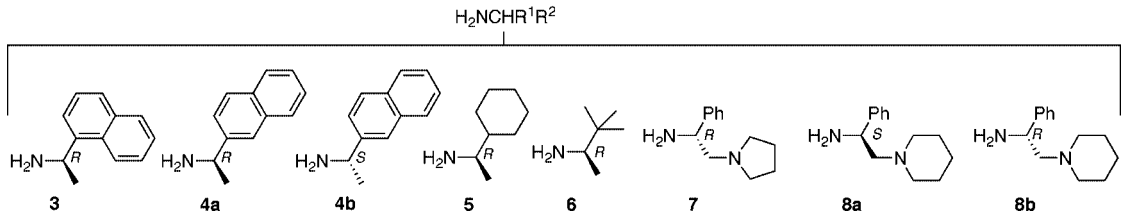
Synthesis of 3-Aminoheterocycles. The access to the new 3-aminoheterocycles was inspired from a strategy based on a 3-hydroxy heterocyclic intermediate.[4c] The case of the pyrrolidines has been considered first.

(a) Modification of the Lateral *N*-Chain of 1. A set of eight new 3-aminopyrrolidines was prepared by varying the substitution of the lateral *N*-chain of **1**. The synthesis relied on a

10.1021/jo8005396 CCC: $40.75 © 2008 American Chemical Society
Published on Web 06/17/2008

SCHEME 1. Synthesis of 3APs 15−20





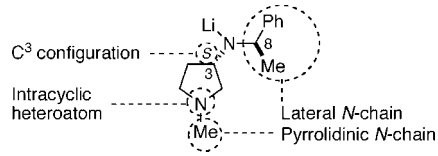


FIGURE 2. Structural parameters modified on **1**Li.

common intermediate (3*R*)-3-hydroxypyrrolidine **2** (Scheme 1), accessible in 86% yield from commercial *trans* 4-hydroxy-L-proline.[4c] A consecutive stereospecific nucleophilic substitution of the triflate of **2** by various chiral amines ($H_2NCHR^1R^2$, **3**−**8**) led to the protected 3-aminopyrrolidines **9**−**14**. Reduction of the Boc by $LiAlH_4$ afforded the 3APs **15**−**20**. Yields, step by step, are summarized in Table 1, and the diastereomeric purities of the final diamines (>92%) were checked by NMR or polarimetry.

Note that (*R*)-1-*tert*-butylethylamine **6** as well as diamines **7** and **8** are not commercially available. Amine **6** was obtained from pinacolone following a route optimized by Moss and colleagues,[5] while diamines **7**, **8a**, and **8b** were synthesized from (*R*)- or (*S*)-phenyloxirane according to the strategy reported by O'Brien.[6]

TABLE 1. Yields Obtained for Syntheses of 3APs 15−20 Depicted in Scheme 1

entries	$H_2NCHR^1R^2$	carbamate:% (from **2**)	3AP:% (from carbamate)
1	**3**	**9**:58	**15** (3*S*,8*R*):80
2	**4a**	**10a**:50	**16a** (3*S*,8*R*):87
3	**4b**	**10b**:51	**16b** (3*S*,8*S*):83
4	**5**	**11**:49	**17** (3*S*,8*R*):81
5	**6**	**12**:44	**18** (3*S*,8*R*):70
6	**7**	**13**:50	**19** (3*S*,8*R*):71
7	**8a**	**14a**:52	**20a** (3*S*,8*S*):92
8	**8b**	**14b**:64	**20b** (3*S*,8*R*):82

(b) Modification of the pyrrolidinic N-chain of 1. Two new triamines **28a** (3*S*,8*R*) and **28b** (3*S*,8*S*) were prepared following two synthetic procedures based, as before, on *trans* 4-hydroxy-L-proline. They vary by the order of introduction of the oxamoyl group and the C^3 amino appendage (Scheme 2).

In route 1, *trans* 4-hydroxy-L-proline was transformed into intermediate **21** following the methodology described previously.[4c] The pyrrolidinic nitrogen was then deprotected by trifluoroacetic acid (TFA), leading to diamines **22a** (3*S*,8*R*) and **22b** (3*S*,8*S*) in 84% and 93% yields, respectively. Each diastereomer of **22** was then reacted with oxamoyl chloride **23**,[7] providing amido dicarbamates **24a** (3*S*,8*R*) and **24b** (3*S*,8*S*) in

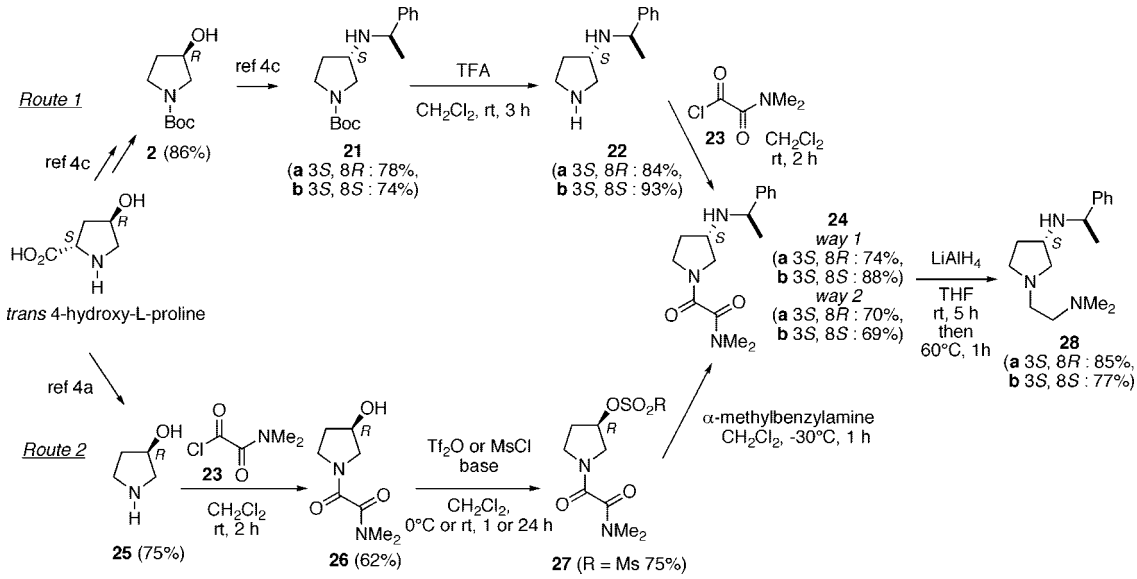
(1) For nucleophilic additions on aldehydes, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. (b) Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301–325. (c) Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695–2698. (d) Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585–4586. (e) Whitesell, J. K.; Jaw, B.-R. *J. Org. Chem.* **1981**, *46*, 2798–2799. (f) Kanoh, S.; Muramoto, H.; Maeda, K.; Kawaguchi, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2244–2246. (g) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 9751–9758. (h) Knollmüller, M.; Ferencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969–3975. (i) Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975–2577. For nucleophilic additions on imines, see: (j) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681–6684. (k) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095–3098. (l) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527–2533. (m) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603–1606. (n) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798. (o) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C.; Faucher, A.-M.; Edwards, J.-P. *J. Org. Chem.* **1995**, *60*, 4884–4892. (p) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878. (q) Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893–8895. (r) Alexakis, A.; Tomassini, A.; Leconte, S. *Tetrahedron* **2004**, *60*, 9479–9484. (s) Kizirian, J.-C.; Cabello, N.; Pinchard, L.; Caille, J.-C.; Alexakis, A. *Tetrahedron* **2005**, *61*, 8939–8946. (t) Cabello, N.; Kizirian, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 4639–4642. (u) Cabello, N.; Kizirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, *483*, 4835–4842. For nucleophilic additions on epoxides, see: (v) Mizuno, M.; Kanai, M.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699–10708. (w) Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett* **1998**, 1165–1167. (x) Oguni, N; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 9023–9026. For nucleophilic additions on nitroolefines and α,β-unsaturated esters, see: (y) Yamashita, M.; Yamada, K.-I.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1954–1955. (z) Yamashita, M.; Yamada, K.-I.; Tomioka, K. *Tetrahedron* **2004**, *60*, 4237–4242.

(2) (a) Goldfus, B. *Synthesis* **2005**, 2271–2280. (b) Mukaiyama, T.; Soai, K.; Kobayashi, S. *Chem. Lett.* **1978**, 219–222. (c) Soai, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 491–492. (d) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455–1460. (e) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron* **1982**, *38*, 2725–2727. (f) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265–7266. (g) Ye, M.; Logaraij, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K. A.; Bolliger, A. M.; Grosz, A. L. *Tetrahedron* **1994**, *50*, 6109–6116. (h) Schön, M.; Naef, R. *Tetrahedron: Asymmetry* **1999**, *10*, 169–176. (i) Sun, X.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039–8046. (j) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590–1594. (k) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187–5190. (l) Hilmersson, G.; Davidsson, Ö. *J. Organomet. Chem.* **1995**, *489*, 175–179. (m) Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* **1995**, *60*, 7660–7669. (n) Hilmersson, G.; Arvidsson, P. I.; Davidsson, Ö.; Håkansson, M. *J. Am. Chem. Soc.* **1998**, *120*, 8143–8149. (o) Arvidsson, P. I.; Davidsson, O.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527–534. (p) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron: Asymmetry* **2003**, *14*, 439–447.

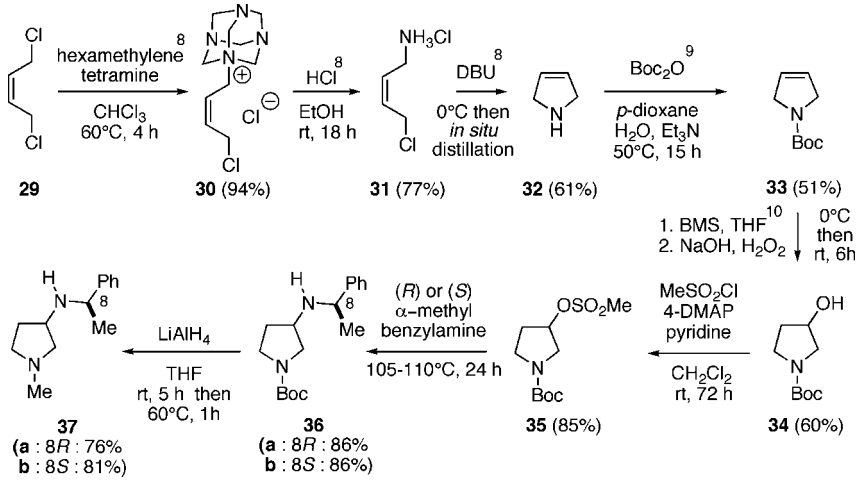
(3) For a physicochemical analysis of the phenomena underlying this association, see for instance: Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Chem. Soc., Perkin Trans. 2* **1999**, *219*, 2197–2201.

(4) For 1,2-additions, see: (a) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266–8275. (b) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Prigent, Y.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042–10048. (c) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267–15279. (d) Flinois, K.; Yuan, Y.; Bastide, C; Harrison-Marchand, A.; Maddaluno, J. *Tetrahedron* **2002**, *58*, 4707–4716. (e) Yuan, Y.; Harrison-Marchand, A.; Maddaluno, J. *Synlett* **2005**, 1555–1558. (f) Duguet, N.; Harrison-Marchand, A.; Maddaluno, J.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5745–5748.

SCHEME 2. Synthesis of 3AP 28a and 28b



SCHEME 3. Synthesis of 3APs 37; Both 36 and 37 Obtained as a 1:1 Mixture of Diastereomers



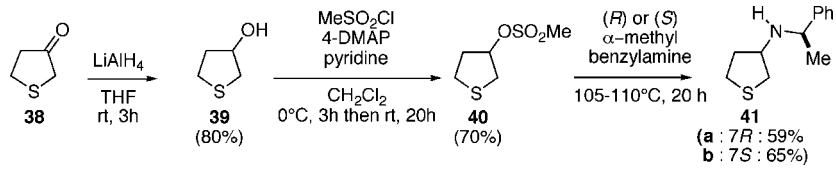
74% and 88% yields, respectively. Intermediates **24** could also be attained following route 2, which introduces the oxamoyl moiety immediately after the decarboxylation of the proline. The amino alcohol **25**, obtained in 75% yield, was reacted with **23**, affording the hydroxy dicarbamate **26** in 62% yield. The α-methylbenzylamino part was introduced next, reproducing the S_N2 sequence reported before. Following this second way, amido dicarbamates **24a** (3*S*,8*R*) and **24b** (3*S*,8*S*) were recovered in 70% and 69% yields from **27**. The final step to attain triamines **28a** and **28b** consisted in the complete reduction of **24** by $LiAlH_4$ (85% for **28a**, 77% for **28b**). Overall, route 1 is twice as efficient as route 2 (40% vs 20% yield).

(c) Modification of the C^3 Configuration of 1. To evaluate the respective contribution of the two stereogenic centers of **1** (C^3 and C^8) to the induction process, a synthesis of the analogue racemic at C^3 (**37**, Scheme 3) has been achieved. The 3-hydroxypyrrolidine **34** (Scheme 3), racemic equivalent of **2**, is not commercially available but could be prepared from *cis*-1,4-dichlorobut-2-ene **29**, transformed in three well-known steps into 3-pyrroline **32** (Scheme 3). Note that this latter is commercially available and inexpensive, but its purity rarely exceeds 85%.

Pure 3-pyrroline **32** was thus prepared from *cis*-1,4-dichlorobut-2-ene **29** as described by Meyers,[8] in an overall yield comparable to that given in literature.[8] An immediate protection of the amino group of **32** into a carbamate (*N*-Boc) was next carried out following Becker's protocol[9] and led to pyrroline **33** in 51% yield. A hydroboration[10] run on **33** with the borane−methyl sulfide complex in THF, followed by an oxidation of the borane intermediate by a mixture of hydrogen peroxide and sodium hydroxide, afforded racemic hydroxy carbamate **34** in 60% yield. Sulfonate **35** was then synthesized in 85% yield and reacted with an excess of α-methylbenzylamine to give amino carbamates **36a** (8*R*) and **36b** (8*S*)

(5) Moss, N.; Gauthier, J.; Ferland, J.-M. *Synlett* **1995**, *2*, 142–144.
(6) (a) O'Brien, P.; Poumellec, P. *Tetrahedron Lett.* **1996**, *37*, 5619–5622. (b) de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans.* **1998**, 1483–1492. (c) Curthbertson, E.; O'Brien, P.; Towers, T. D. *Synthesis* **2001**, 693–695.
(7) Vakemans, J.; Pollers-Wieers, C.; Hoornaet, G. *Heterocycl. Chem.* **1983**, *20*, 919–923.
(8) Warmus, J. S.; Dilley, G. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 270–271.
(9) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139–2145.
(10) Brown, H. C.; Prasad, J. V. N. V.; Zee, S.-H. *J. Org. Chem.* **1985**, *50*, 1582–1589.

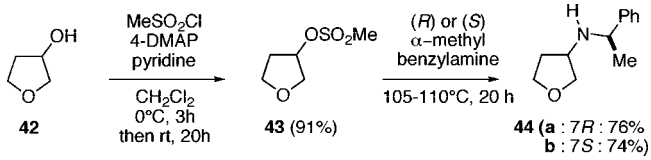
SCHEME 4. Synthesis of 3ATTs 41



in the same 86% yield. A final reduction by $LiAlH_4$ led to diamines **37a** and **37b** in 76% and 81% yields, respectively. Thus, eight steps are necessary to reach **37** in 8% overall yield.

(d) Modification of the Intracyclic Heteroatom of 1. Amines **41** (tetrahydrothiophen, 3ATT, Scheme 4) and **44** (tetrahydrofuran, 3ATF, Scheme 5) are direct analogues of the 3AP **37**, the difference being the nature of the heterocycle. Amines **41a** and **41b** have been prepared following a three-step synthetic scheme (Scheme 4) from commercially available tetrahydrothiophenone **38**. Reduction of this later by $LiAlH_4$ led to the 3-hydroxytetrahydrothiophen **39** in 80% yield, next transformed into mesylate **40** in 70% yield. Substitution of the sulfonyloxy group by the (*R*)- or (*S*)-α-methylbenzylamino appendage afforded 3-aminothiophen **41a** (7*R*) and **41b** (7*S*) in 59% and 65% yields, respectively.

SCHEME 5. Synthesis of 3ATFs 44



The oxygenated heterocyclic analogues **44** were synthesized from commercially available 3-hydroxytetrahydrofuran **42** following a two-step synthetic scheme (Scheme 5). Reacting **42** with methane sulfonyl chloride led to mesylate **43** in 91% yield, which was transformed in amine **44a** (7*R*) and **44b** (7*S*) in 76% and 74% yields, respectively.

In conclusion for this preliminary part, a series of 16 new chiral amines has been synthesized following a single general synthetic scheme based on a 3-hydroxy five-membered ring heterocycle key intermediate.

Inductions in the Presence of 3-Amino Heterocyclic Lithium Amides. Amines **15**−**20**, **28**, **37**, **41**, and **44** (Figure 3) were deprotonated in the presence of a slight excess of *n*-butyllithium to afford the corresponding lithium amides. Those were employed in the model hydroxyalkylation of *o*-tolualdehyde by *n*-butyllithium. Experimental conditions optimized before for reference **1**Li were retained,[11] which consisted of working at −78 °C in THF with a 1.5:2.5:1.0 lithium amide/*n*BuLi/*o*-tolualdehyde ratio. Yields and enantiomeric excesses are gathered in Table 2.

Medium (46%) to satisfying (80%) induction levels were returned in this series of experiments. In all cases, switching from 8*R* to 8*S* on the lithium amide stereochemistry led to an inversion of the configuration of the resulting 1-*o*-tolylpentan-1-ol.

We believe these results can be discussed within the frame of the induction model built from previous results. In preceding papers, we proposed that the induction observed in the test reaction with **1Li** was correlated to the formation in solution of noncovalent aggregates between one **1Li** and one molecule of alkyllithium.[4] The interaction of these complexes with the electrophilic aldehyde was also studied by DFT (Figure 4).[12] According to these results, the enantiodetermining step takes place right after the aldehyde is docked on the Li^2 of the N−Li−C−Li quadrilateral. Thus, modifying the immediate

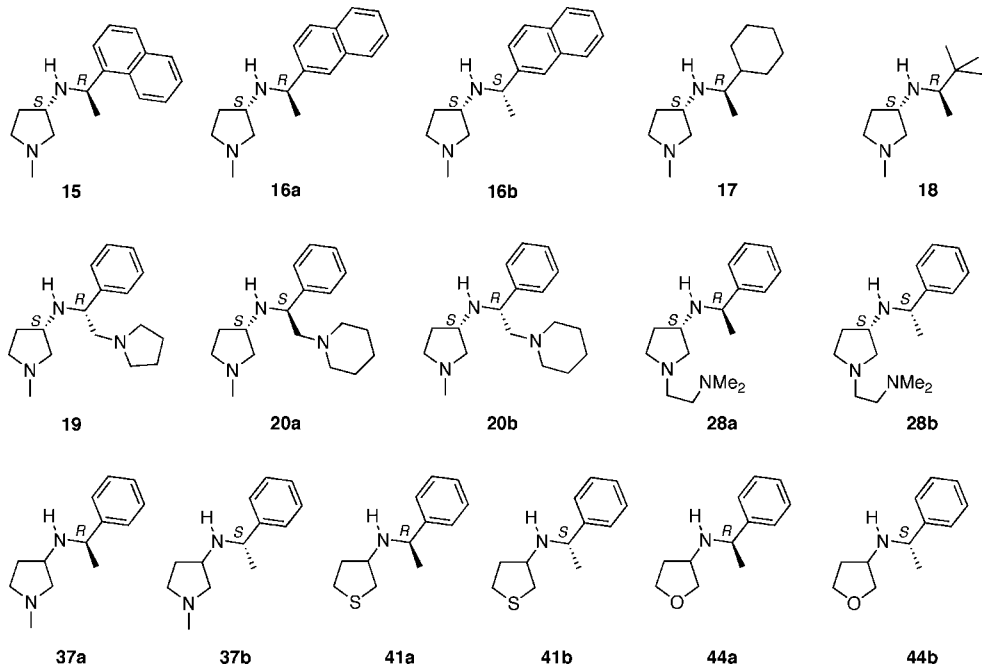
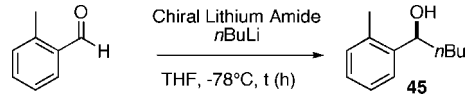


FIGURE 3. Set of the 16 new 3-amino heterocycles synthesized.

TABLE 2. Yields and ee's Obtained for the Model Hydroxyalkylation Reaction; Results Obtained with 1Li[4c] Are Entries 1 and 2



entries	chiral lithium amide	*t* (h)	yield[a] (%)	ee (%)[b]	**45** configuration
1	**1a**Li (3*S*,8*R*)	2	60	80	*R*
2	**1b**Li (3*S*,8*S*)	2	72	71	*S*
3	**15**Li (3*S*,8*R*)	2	74	75	*R*
4	**16a**Li (3*S*,8*R*)	2	72	80	*R*
5	**16b**Li (3*S*,8*S*)	2	68	76	*S*
6	**17**Li (3*S*,8*R*)	2	58	74	*R*
7	**18**Li (3*S*,8*R*)	2	54	66	*R*
8	**19**Li (3*S*,8*R*)	6	69	67	*S*
9	**20a**Li (3*S*,8*S*)	6	56	46	*R*
10	**20b**Li (3*S*,8*R*)	6	63	66	*S*
11	**28a**Li (3*S*,8*R*)	2	58	80	*R*
12	**28b**Li (3*S*,8*S*)	2	54	66	*S*
13	**37a**Li (3rac, 8*R*)	2	62	79	*R*
14	**37b**Li (3rac, 8*S*)	2	56	65	*S*
15	**41a**Li (3rac, 8*R*)	2	68	58	*R*
16	**41b**Li (3rac, 8*S*)	2	70	46	*S*
17	**44a**Li (3rac, 8*R*)	2	66	80	*R*
18	**44b**Li (3rac, 8*S*)	2	71	80	*S*

[a] Isolated yields obtained after purification by column chromatography on silica gel. [b] Enantiomeric excesses determined by HPLC analysis on a Chiralpak OD-H chiral column.

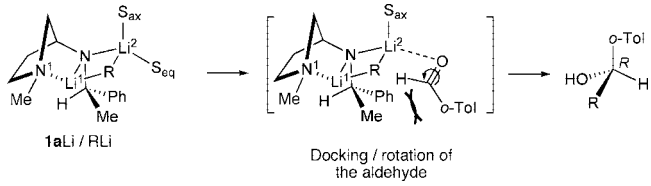


FIGURE 4. Model of the interaction between mixed aggregate **1a**Li/RLi and *o*-tolualdehyde.

surroundings of this substructure seemed a reasonable strategy to increase the induction potential of **1**Li.

One of the most direct ways of influencing the rotation process was to alter the lateral stereogenic appendage (C^8). However, the results of entries 3−7 show that the replacement of the phenyl group by a naphthyl (entries 3−5), cyclohexyl (entry 6), or *tert*-butyl (entry 7) moiety is not beneficial.

Another straightforward modification consisted of changing the coordination pattern around the lithiums, for instance by adding a supplementary nitrogen either on the lateral *N*-chain or on the pyrrolidinic *N*-chain. In the first case (amides **19**Li−**20**Li, entries 8−10), the sense of induction is conserved (the CIP rules impose a formal inversion of the C^8 asymmetric center in these cases), but the ee's tend to drop (by 20%) while the rate of reaction is significantly slowed down (reaction time should be tripled to reach a similar chemical yield: 6 versus 2 h, entries 8−10). Albeit we do not have direct insights on the aggregation state of complexes involving **20**Li or **28**Li, one can assume that an extra N−Li coordination is likely to interfere with the pseudoequatorial docking of the aldehyde (Figure 5 left).[12] In the second case (amide **28**Li, entries 11 and 12), the additional nitrogen exerts no effect, a result that can be understood if this extra nitrogen is inefficient or interacts only with Li[1] (Figure 5 right).

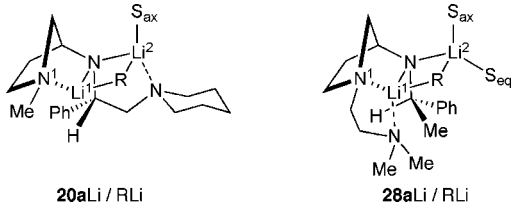


FIGURE 5. Putative structure of complexes derived from triamines **20** and **28** (S = solvent).

Let us now recall that in the absence of a chiral appendage at C^8, the C^3 center (*S*) exerts a medium to good control of the induction in the same model reaction.[4a,11] We thus decided to examine the role played by the stereogenic center at C^3 of **1**Li. The yields and inductions obtained with lithium amides **37a**Li (8*R*) and **37b**Li (8*S*), racemic at C^3, turned out to be similar with the ones determined for **1**Li (compare entries 13 and 1, then 14 and 2). Thus, the stereogenic α-methylbenzylamino group at C^8 would take precedence over C^3, which seem to lose its influence. This phenomenon can be simply understood in light of Figure 6, representing the *exo* topology of amide **1a**Li (3*S*,8*R*), which provides alcohol *R*, and the *endo* topology of amide **1b**Li (3*S*,8*S*), which provides alcohol *S* (left). If we now consider the enantiomer of **1a**Li (that is 3*R*,8*S*), it will necessarily adopt the same *exo* topology (mirror image) and thus will lead to the alcohol *S* this time. The same reasoning applies to *endo* **1b**Li. Therefore, the inversion of the C^3 configuration and, subsequently, that of the topology of the aggregate explains that the sense of the induction finally does not change.

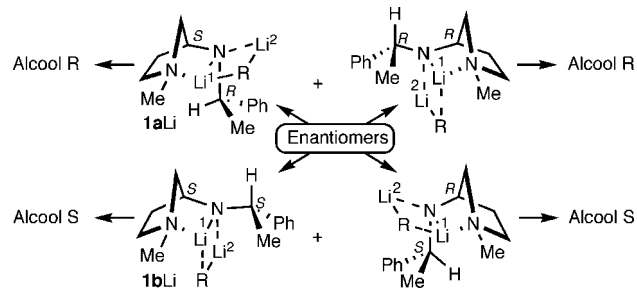


FIGURE 6. Topology of the diastereomeric aggregates involving racemic amide **1**Li.

Because the access to the racemic 3-hydroxypyrrolidine **34** intermediate is impractical, the synthesis of racemic **37**Li is somewhat tedious, and using this amide does not constitute an attractive alternative to **1**Li. However, when it comes to the synthesis of 3-amino tetrahydrothiophen and tetrahydrofuran, this remark becomes useful: **41** and **44** can be readily prepared from the cheap racemic alcohols **39** and **42**, respectively (Schemes 4 and 5). Thus, **41** and **44** were tested directly under their (3*rac*,8*R* and 3*rac*,8*S*) configurations. The inductions were medium for **41**Li (entries 15 and 16), while similar to those obtained with **1Li** in the case of **44**Li (entries 17 and 18). These observations suggest that an intramolecular S−Li and O−Li coordination could occur with the sulfurated and oxygenated heterocycles, which would trigger a puckering comparable to that observed with the 3-aminopyrrolidine derivatives. NMR and theoretical investigations are currently under progress to substantiate this hypothesis. Note that if Figure 6 suggests that

(11) Harrison-Marchand, A.; Valnot, J.-Y.; Corruble, A.; Duguet, N.; Oulyadi, H.; Desjardins, S.; Fressigné, C.; Maddaluno, J. *Pure Appl. Chem.* **2006**, *78*, 321–331.

(12) Yuan, Y.; Desjardins, S.; Harrison-Marchand, A.; Oulyadi, H.; Fressigné, C.; Giessner-Prettre, C.; Maddaluno, J. *Tetrahedron* **2005**, *31*, 3325–3334.

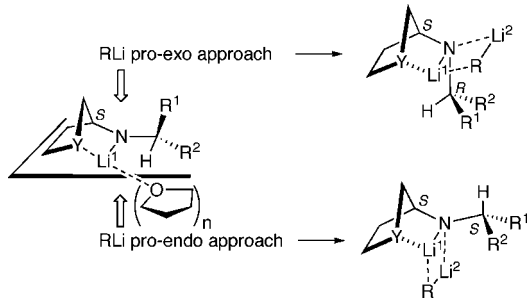


FIGURE 7. Schematic view of the 3-amino heterocycle lithium amides before aggregation.

diastereomers at C^3 should afford the same sense of induction, it does not give any clue on the respective contributions of each epimer (compare for instance entries 1 and 2 or entries 9 and 10 of Table 1). Therefore, a separate testing of the pure diastereomers remains necessary to evaluate properly the induction potential of these new ligands.

Toward an Empirical Model for the Mixed Aggregates of 3-Amino Heterocycle Lithium Amides. If we assume that the new chiral lithium amides we have prepared all form 1:1 mixed aggregates with *n*-butyllithium and adopt arrangements similar to those evidenced before, the above results can be put in a relatively general perspective.

Let us first reason about the formation of the aggregates themselves, and thus the origin of the selectivity in favor of the *endo* or *exo* topology. Two hypotheses can be made:

1. The aggregation is under kinetic control. In this case, the formation of the *endo* or the *exo* forms would depend directly on the accessibility for RLi of the two faces of the lithium amide (Figure 7). Indeed, the nitrogen of the amide is expected to be planar,[13] and the entire structure to be rigidified by a norbornyl-type folding, comparable to that discussed above.[4b] If we now assume that the lithium cation is solvated by at least one molecule of THF, it seems reasonable that the lateral chiral chain CHR^1R^2 adopts a conformation in which the proton lies more or less in the C−N−Li plane. This places R^1 and R^2 on the two sides of the amide average plane, thus orientating the approach of the incoming RLi: the relative bulkiness of R^1 and R^2 is expected to irreversibly control the formation of the *exo* or the *endo* complex. This would explain why for **1**Li, for example, the *exo* topology is obtained for the 3*S*,8*R* (R^1 = Me, R^2 = Ph) derivatives, and similarly, why the 3*S*,8*S* (R^1 = Ph, R^2 = Me) compounds lead to the *endo* arrangement.

2. The aggregation is under thermodynamic control. One must assume in this case that the various species are in rapid equilibrium, and that the *endo* or *exo* arrangement would result from the balance between the steric and electronic interactions, imposed by the lateral chiral chain. Passing from the *exo* to the *endo* topology can indeed be regarded as a simple swap of the coordination of the intracyclic heteroatom Y from one to the other lithium cation (Figure 8, view 2). In these conditions, the Li that is not picked up by Y becomes the Li^2, i.e., the future site for the aldehyde condensation.

Let us now reason on the reactivity of the complexes. Whatever the hypothesis retained for their formation, the two types of mixed aggregates can be looked upon as the assembling of three "independent" layers (Figure 9). Both exhibit a N−Li−C-Li quadrilateral at the heart of the structure, to be

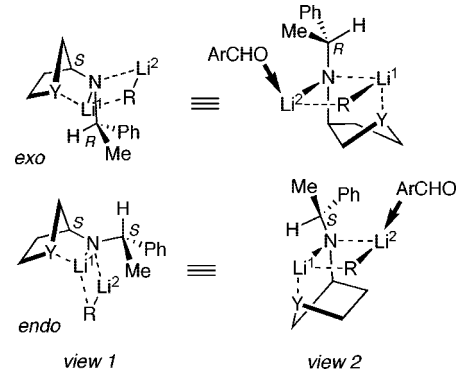


FIGURE 8. Switch from the *exo* to the *endo* arrangements by modulation of the N−Li coordination.

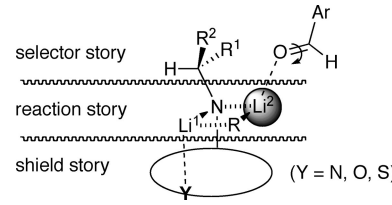


FIGURE 9. Empirical model of mixed aggregates between organolithium and 3-amino heterocycle lithium amides.

considered as the "reaction story". This central layer is surrounded on one side by a "shield story" (the coordinating heterocycle) and on the other by a "selector story" (the chiral amino appendage on C^3). Note that the efficiency of the shielding is secured by the strength of the Y−Li coordination.

Keeping in mind the Curtin−Hammett principle, it is reasonable to assume that the aggregates are directly involved in the global enantioselective process. For the reaction to proceed, the aldehyde has to approach the complex and to dock on one of the two lithiums.[14] As pointed out before, only lithium Li^2 seems to be accessible.[12] On the basis of the empirical model, this cation should be preferentially approached along the less hindered face of the quadrilateral to which it belongs and that bears the chiral selector. This preliminary phase ends up with the rotation of the aldehyde around the O−Li direction to expose its π-face to the nucleophilic alkyl R. The sense of this rotation, probably determined by the Ar/R^1+R^2 interactions, corresponds to the enantiodetermining event. Thus, the final success of the induction would rely on the ability for the chiral lateral appendage to discriminate between the opposite rotations.

Conclusion

This paper presents a general synthetic pathway to synthesize easily new chiral structures based on 3-aminopyrrolidines, 3-aminotetrahydrothiophens, and 3-aminotetrahydrofurans scaffolds. Their lithium amides have been evaluated as chiral ligands in the condensation of *n*-butyllithium on *o*-tolualdehyde. The 1-*o*-tolylpentan-1-ol was isolated in good yields and ee's up to 80% in favor of the *R* or *S* enantiomer, depending on the absolute configuration of the lateral chiral amino appendage. These attractive values were obtained using the very simple, cheap and easy to prepare lithium amide 3-(*R* or *S*-α-methylbenzylamido)-tetrahydrofuran **44Li**. This later now constitutes our favorite chiral ligand for organolithium derivatives and

(13) Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C.; Silvi, B. *J. Org. Chem.* **2001**, *66*, 6476–6479.

(14) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; Chapter V, pp 255−297.

further works testing its inductive potential on a large set of enantioselective reactions, as well as spectroscopic investigations to characterize their respective complexes, are under way. The modifications made on the ligands were correlated to previous structural data concerning 3APLi/*n*BuLi mixed aggregates (the **1**Li/*n*BuLi *exo* and *endo* complexes). This led us to propose a three-layer model, organized around a N−Li−C−Li quadrilateral, to schematize the complexes. The docking of the aldehyde on the under-coordinated lithium of this "reaction story" would occur along its only accessible face that also bears the C^8 chiral appendage. Thus, the role of this selector is to influence the sense of rotation of the aldehyde just before the C−C bond forming reaction reaches its transition state.

Experimental Section

General Procedure for Stereospecific S_N2 Reaction in the Presence of Chiral Primary Amines (via a Triflate). A solution of *N*,*N*-di-isopropylethylamine (1.83 mL, 10.5 mmol, 2.1 equiv) in CH_2Cl_2 (2 mL) was added to a cooled (−30 °C) solution of *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). Trifluoromethanesulfonic anhydride (0.88 mL, 5.25 mmol, 1.05 equiv) was added dropwise over a 10-min period and the mixture was stirred at −30 °C for 45 min. A solution of chiral amine **3**−**8** (7.50 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL) was introduced over a 5-min period and the reaction mixture was stirred at room temperature for 24 h. The solution was washed with saturated $NaHCO_3$ (2 × 20 mL) and brine (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure.

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*R*)-α-naphthylethyl)-aminopyrrolidine 9.** Carbamate **9** was obtained reacting *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol) with (*R*)-(+)-1-(α-naphthyl)ethylamine **3** (1.28 g, 7.50 mmol), and following the above general procedure for the S_N2. Purification of the residue by flash chromatography (EtOAc/cyclohexane 40:60) gave **9** (0.99 g, 58%) as a viscous orange oil: ^{1}H NMR δ 1.43−1.44 (9H, m), 1.50 (3H, d, J = 6.4), 1.58−1.80 (2H, m), 1.87−2.10 (1H, m), 2.94−3.29 (3H, m), 3.33−3.66 (2H, m), 4.73 (1H, q, J = 6.7), 7.37−7.58 (3H, m), 7.59−7.71 (1H, m), 7.75 (1H, d, J = 8.3), 7.87 (1H, d, J = 8.4), 8.01−8.29 (1H, m); ^{13}C NMR (293 K, two rotamers observed) δ 23.9 and 24.3 (CH_3), 28.6 (3 × CH_3), 31.4 and 32.2 (CH_2), 44.1 and 44.5 (CH_2), 51.6 (CH), 52.2 (CH_2), 54.7 and 55.6 (CH), 79.1 (C), 122.8 (CH), 123.0 and 123.1 (CH), 125.4 and 125.5 (CH), 125.7, 125.9, 127.4, 129.1 (4 × CH), 131.2 (C), 134.0 (C), 140.9 and 141.0 (C), 154.6 and 154.7 (C); IR (neat) ν 3316 (NH), 2973, 2928, 2873, 1681 (C═O), 1595, 1510, 1477, 1453, 1411, 1365, 1255, 1215, 1168, 1123; $[\alpha]^{20}_D$ +6.0 (*c* 1.43, $CHCl_3$).

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*R*)-β-naphthylethyl)aminopyrrolidine 10a.** Carbamate **10a** was obtained reacting *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol) with (*R*)-(+)-1-(β-naphthyl)ethylamine **4a** (1.28 g, 7.50 mmol), and following the above general procedure for the S_N2. Purification of the residue by flash chromatography (EtOAc/cyclohexane 40:60) gave **10a** (0.85 g, 50%) as a pale yellow oil: ^{1}H NMR δ 1.28−1.53 (13H, m), 1.53−1.95 (1H, 2m), 1.96−2.12 (1H, m), 2.83−3.65 (5H, 3m), 4.02 (1H, q, J = 6.5), 7.38−7.55 (3H, m), 7.73 (1H, s), 7.77−7.89 (3H, m); ^{13}C NMR (293 K, two rotamers observed) δ 24.5 and 24.6 (CH_3), 28.3 and 28.4 (3 × CH_3), 30.9 and 31.6 (CH_2), 43.9 and 44.3 (CH_2), 51.8 and 52.1 (CH_2), 54.4 and 55.3 (CH), 56.3 and 56.7 (CH), 78.8 (C), 124.5 (CH), 125.0 and 125.1 (CH), 125.4, 125.9, 127.5, 127.6, 128.2 (5 × CH), 132.8, 133.3, 142.7 (3 × C), 154.4 and 154.5 (C); IR (neat) ν 3447 (NH), 3053, 2973, 2875, 2360, 2244, 1685 (C═O), 1600, 1507, 1476, 1451, 1410, 1364, 1252, 1168, 1125; $[\alpha]^{20}_D$ +24.9 (*c* 0.41, $CHCl_3$); EIMS (70 eV) *m*/*z* 340 (M^+, 21), 325 (M^+ − Me, 3), 283 (M^+ − *t*-Bu, 19), 269 (M^+ − O*t*-Bu, 51), 239 (M^+ − CO_2*t*-Bu, 3), 185 (M^+ − $C_{12}H_{11}$, 2), 170 ($C_{12}H_{12}N$ and $C_9H_{16}NO_2$, 85), 155 ($C_{12}H_{11}$, 100), 141 (M^+ − $C_{10}H_7$ − O*t*-Bu, 10), 129 (M^+ − $C_{10}H_7$, 21), 113 (M^+ − $C_{10}H_7$ − CO_2*t*-Bu, 7), 85 (M^+ − $C_{12}H_{11}$ − CO_2*t*-Bu, 10), 57 (*t*-Bu, 28).

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*S*)-β-naphthylethyl)aminopyrrolidine 10b.** Carbamate **10b** was obtained reacting *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol) with (*S*)-(+)-1-(β-naphthyl)ethylamine **4b** (1.28 g, 7.50 mmol), and following the above general procedure for the S_N2. Purification of the residue by flash chromatography (EtOAc/cyclohexane 40:60) gave **10b** (0.87 g, 51%) as a pale yellow oil: ^{1}H NMR δ 1.30−1.53 (13H, m), 1.53−1.79 (1H, m), 1.79−2.12 (1H, m), 2.85−3.28 (3H, m), 3.29−3.69 (2H, m), 3.97 (1H, q, J = 6.7), 7.38−7.54 (3H, m), 7.74 (1H, s), 7.77−7.92 (3H, m); ^{13}C NMR (293 K, two rotamers observed) δ 24.8 (CH_3), 28.6 (3 × CH_3), 32.0 and 32.7 (CH_2), 44.1 and 44.4 (CH_2), 51.4 and 52.0 (CH_2), 54.6 and 55.5 (CH), 56.9 (CH), 79.0 and 79.1 (C), 124.7, 125.2, 125.4, 125.6, 126.1, 127.7, 128.4 (7 × CH), 132.9, 133.4 (2 × C), 142.7 and 142.9 (C), 154.6 (C); IR (neat) ν 3479 (NH), 3308, 3053, 2973, 2929, 2875, 2244, 1686 (C═O), 1600, 1506, 1477, 1452, 1408, 1365, 1253, 1169, 1125; $[\alpha]^{20}_D$ −90.5 (*c* 0.50, $CHCl_3$); EIMS (70 eV) *m*/*z* 340 (M^+, 19), 325 (M^+ − Me, 2), 283 (M^+ − *t*-Bu, 18), 269 (M^+ − O*t*-Bu, 40), 239 (M^+ − CO_2*t*-Bu, 3), 185 (M^+ − $C_{12}H_{11}$, 2), 170 ($C_{12}H_{12}N$ and $C_9H_{16}NO_2$, 100), 155 ($C_{12}H_{11}$, 90), 141 (M^+ − $C_{10}H_7$ − O*t*-Bu, 10), 129 (M^+ − $C_{10}H_7$, 27), 113 (M^+ − $C_{10}H_7$ − CO_2*t*-Bu, 10), 85 (M^+ − $C_{12}H_{11}$ − CO_2*t*-Bu, 16), 57 (*t*-Bu, 36).

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*R*)-cyclohexylethyl)aminopyrrolidine 11.** Carbamate **11** was obtained reacting *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol) with (*R*)-(−)-1-cyclohexylethylamine **5** (1.11 mL, 7.50 mmol), and following the above general procedure for the S_N2. Purification of the residue by flash chromatography (EtOAc/cyclohexane 40:60) gave **11** (0.73 g, 49%) as an orange oil: ^{1}H NMR δ 0.82−1.02 (5H, m), 1.02−1.30 (5H, m), 1.41 (9H, s), 1.50−1.78 (6H, m), 1.87−2.12 (1H, m), 2.30−2.50 (1H, m), 2.86−3.03 (1H, m), 3.12−3.61 (4H, m); ^{13}C NMR (293 K, two rotamers observed) δ 17.3 and 17.4 (CH_3), 26.5, 26.6, 26.8, 28.2, 28.6 (5 × CH_2), 29.8 (3 × CH_3), 32.2 and 33.0 (CH_2), 43.3 (CH), 44.1 and 44.5 (CH_2), 51.7 and 52.1 (CH_2), 54.4 and 55.2 (CH), 55.9 and 56.0 (CH), 79.1 (C), 154.7 and 154.8 (C); IR (neat) ν 3315 (NH), 2971, 2924, 2851, 1693 (C═O), 1540, 1477, 1449, 1407, 1364, 1254, 1168, 1120; $[\alpha]^{20}_D$ −22.5 (*c* 1.06, $CHCl_3$); EIMS (70 eV) *m*/*z* 296 (M^+, <1), 213 (M^+ − C_6H_{11}, 19), 157 (M^+ − C_6H_{11} − *t*-Bu, 100), 139 (M^+ − C_6H_{11} − O*t*-Bu, 16), 110 (M^+ − C_6H_{11}Et, 22), 70 (40), 58 (95).

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(2-(*R*)-(3,3-dimethylbutyl))aminopyrrolidine 12.** Carbamate **12** was obtained reacting *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol) with 3,3-dimethyl-2-(*R*)-butylamine **6** (0.76 g, 7.50 mmol), and following the above general procedure for the S_N2. Purification of the residue by column chromatography (EtOAc/cyclohexane 20:80) gave **12** (0.60 g, 44%) as a pale yellow oil: ^{1}H NMR δ 0.85 (9H, s), 0.99 (3H, d, J = 6.8), 1.45 (9H, s), 1.54−1.72 (1H, m), 1.96−2.11 (1H, m), 2.12−2.29 (1H, m), 2.96−3.12 (1H, m), 3.20−3.58 (4H, m); ^{13}C NMR (293 K, two rotamers observed) δ 15.2 and 15.4 (CH_3), 26.3 (3 × CH_3), 28.5 (3 × CH_3), 32.6 and 33.3 (CH_2), 34.2 and 34.3 (C), 44.2 and 44.6 (CH_2), 51.4 and 51.8 (CH_2), 54.9 and 55.9 (CH), 60.0 and 60.1 (CH), 78.9 (C), 154.7 and 154.8 (C); IR (neat) ν 3320 (NH), 2968, 2870, 1697 (C═O), 1478, 1454, 1404, 1364, 1253, 1169, 1120; $[\alpha]^{20}_D$ −47.0 (*c* 0.98, $CHCl_3$).

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*R*)-phenyl-2-*N*'-pyrrolidinylethyl)aminopyrrolidine 13.** Carbamate **13** was obtained reacting *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol, 1.0 equiv) with (*R*)-1-phenyl-2-(pyrrolidin-1-yl)ethanamine **7** (1.42 g, 7.50 mmol, 1.5 equiv), and following the above general procedure. Purification of the residue by column chromatography (EtOAc/acetone 95:5) gave **13** (0.90 g, 50%) as a pale yellow oil: ^{1}H NMR δ 1.20−1.50 (9H, m), 1.50−2.10 (6H, m), 2.15−2.42 (1H, m), 2.42−3.21 (9H, m), 3.22−3.53 (2H, m), 3.63−3.84 (1H,

m), 7.12−7.40 (5H, m); ^{13}C NMR (293 K, two rotamers observed) δ 23.7 (2 × CH_2), 28.6 (3 × CH_3), 32.2 and 32.8 (CH_2), 44.1 and 44.4 (CH_2), 51.1 and 51.5 (CH_2), 53.9 and 54.0 (2 × CH_2), 54.4 and 55.6 (CH), 60.2 and 60.4 (CH), 63.5 and 63.8 (CH_2), 79.2 (C), 127.5, 128.5 (5 × CH), 142.6 and 142.9 (C), 154.8 (C); IR (neat) ν 3293 (NH), 3063, 2974, 2876, 2802, 2246, 1682 (C═O), 1602, 1477, 1454, 1413, 1366, 1255, 1167, 1125; $[\alpha]^{20}_D$ −67.5 (*c* 0.54, $CHCl_3$); CIMS (200 eV, *t*-BuH) *m*/*z* 360 (MH^+, 100), 323 (13), 302 (MH^+ − *t*-Bu, 7), 286 (MH^+ − O*t*-Bu, 7), 275 (MH^+ − $C_5H_{10}N$, 15), 219 (MH^+ − $C_5H_{10}N$ − *t*-Bu, 12), 174 ($C_{12}H_{16}N$, 6), 154 (12), 84 ($C_5H_{10}N$, 39); HRMS (*m*/*z*) [MH^+] $C_{21}H_{34}N_3O_2$ requires 360.2659, found 360.2659.

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*S*)-phenyl-2-*N*′-piperidinylethyl)aminopyrrolidine 14a.** Carbamate **14a** was obtained using *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol, 1.0 equiv) with (*S*)-1-phenyl-2-(piperidin-1-yl)ethanamine **8a** (1.53 g, 7.50 mmol, 1.5 equiv), and following the above general procedure. Purification of the residue by column chromatography (EtOAc/acetone 95:5) gave **14a** (0.98 g, 52%) as a pale yellow oil: ^{1}H NMR δ 1.24−1.70 (17H, 2m), 1.71−2.09 (1H, m), 2.10−2.74 (6H, 3m), 2.80−3.65 (5H, 3m), 3.67−3.88 (1H, m), 7.03−7.42 (5H, m); ^{13}C NMR (293 K, two rotamers observed) δ 24.5 (CH_2), 26.2 (2 × CH_2), 28.6 (3 × CH_3), 30.9 and 31.6 (CH_2), 44.2 and 44.5 (CH_2), 51.9 and 52.5 (CH_2), 54.4 and 54.6 (2 × CH_2), 55.2 and 55.4 (CH), 57.9 and 58.2 (CH), 66.3 (CH_2), 79.1 and 79.2 (C), 127.4, 127.5, 128.5 (5 × CH), 142.9 (C), 154.7 and 154.8 (C); IR (neat) ν 3291 (NH), 3062, 3010, 2976, 2937, 2805, 2399, 1681 (C═O), 1602, 1476, 1453, 1414, 1365; $[\alpha]^{20}_D$ +57.1 (*c* 0.64, $CHCl_3$); HRMS (*m*/*z*) [MH^+] $C_{22}H_{36}N_3O_2$ requires 374.2816, found 374.2826.

***N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*R*)-phenyl-2-*N*′-piperidinylethyl)aminopyrrolidine 14b.** Carbamate **14b** was obtained using *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **2** (0.94 g, 5.00 mmol, 1.0 equiv) with (*R*)-1-phenyl-2-(piperidin-1-yl)ethanamine **8b** (1.53 g, 7.50 mmol, 1.5 equiv), and following the above general procedure. Purification of the residue by column chromatography (EtOAc/acetone 95:5) gave **14b** (1.20 g, 64%) as a pale yellow oil: ^{1}H NMR δ 1.00−1.68 (17H, 2m), 1.70−1.95 (1H, m), 1.96−2.60 (6H, 2m), 2.81−3.21 (3H, m), 3.22−3.52 (2H, 2m), 3.53−3.85 (1H, m), 6.99−7.42 (5H, m); ^{13}C NMR (293 K, two rotamers observed) δ 24.6 (CH_2), 26.3 (2 × CH_2), 28.6 (3 × CH_3), 32.3 and 33.0 (CH_2), 44.1 and 44.5 (CH_2), 51.2 and 51.6 (CH_2), 54.5 (2 × CH_2), 55.8 (CH), 58.4 (CH), 66.4 (CH_2), 79.2 (C), 127.4, 127.5, 127.6, 128.5 (5 × CH), 142.9 and 143.2 (C), 154.8 (C); IR (neat) ν 3290 (NH), 3061, 2975, 2935, 2854, 2805, 2244, 1686 (C═O), 1602, 1477, 1453, 1408, 1365, 1255, 1166, 1138, 1117; $[\alpha]^{20}_D$ −74.2 (*c* 0.78, $CHCl_3$); CIMS (200 eV, *t*-BuH) *m*/*z* 374 (MH^+, 100), 360 (4), 318 (3), 275 (MH^+ − $C_6H_{12}N$, 4), 219 (MH^+ − *t*-Bu − $C_6H_{12}N$, 5), 188 (5), 154 (2), 98 ($C_6H_{12}N$, 35), 86 ($C_5H_{12}N$, 4); HRMS (*m*/*z*) [MH^+] $C_{22}H_{36}N_3O_2$ requires 374.2816, found 374.2826.

General Procedure for Reduction of the Boc Group. A solution of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-aminopyrrolidine **9**-**14** (2.00 mmol, 1.0 equiv) in dry THF (60 mL) was added over a 30-min period to a suspension of lithium aluminum hydride ($LiAlH_4$, 0.42 g, 11.0 mmol, 5.5 equiv) in freshly distilled THF (20 mL), placed under an argon atmosphere at 0 °C. The solution was stirred at room temperature for 5 h then heated at 60 °C for 1 h. After cooling at 0 °C, the excess of $LiAlH_4$ was hydrolyzed by successive addition of cold water (1.2 mL), 4 M aqueous sodium hydroxide (1.2 mL), and cold water (1.6 mL). The white precipitate was filtered on celite and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated, and the residue was dissolved in Et_2O (20 mL). Aqueous hydrochloric acid (1 M, 20 mL) was added and the solution was stirred at room temperature for 15 min. The acidic aqueous layer was extracted and $NaHCO_3$ was slowly added until pH 9. The medium was then extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure.

***N*-Methyl-3-(*S*)-(1-(*R*)-α-naphthylethyl)aminopyrrolidine 15.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*R*)-α-naphthylethyl)aminopyrrolidine **9** (0.68 g, 2.00 mmol) following the above general procedure gave **15** (0.41 g, 80%) as an orange oil: ^{1}H NMR δ 1.48 (3H, d, *J* = 6.8), 1.64−1.77 (1H, m), 1.97−2.19 (1H, m), 2.19−2.48 (2H, m), 2.29 (3H, s), 2.48−2.74 (2H, m), 3.17−3.33 (1H, m), 4.68 (1H, q, *J* = 6.8), 7.37−7.57 (3H, m), 7.67 (1H, d, *J* = 6.8), 7.74 (1H, d, *J* = 8.3), 7.81−7.93 (1H, m), 8.07−8.30 (1H, m); ^{13}C NMR δ 24.1 (CH_3), 33.1 (CH_2), 42.4 (CH_3), 51.5 (CH), 55.5 (CH_2), 55.6 (CH), 63.6 (CH_2), 123.0, 123.3, 125.3 (3 × CH), 125.8 (2 × CH), 127.2, 129.1 (2 × CH), 131.4, 134.0, 141.3 (3 × C) (diastereomer 3*R*,8*R*, visible peaks 24.2, 33.5, 51.8, 55.3, 55.4, 122.9, 123.0); IR (neat) ν 3304 (NH), 3047, 2960, 2863, 2833, 2775, 1594, 1509, 1477, 1447, 1393, 1367, 1232, 1174, 1136; $[\alpha]_D^{21}$ +38.4 (*c* 0.87, $CHCl_3$); EIMS (70 eV) *m*/*z* 254 (M^+, <1), 170 ($C_{12}H_{12}N$, 13), 155 ($C_{12}H_{11}$, 25), 141 (3), 127 ($C_{10}H_7$ and $C_7H_{15}N_2$, 8), 113 (5), 96 (14), 83 (M^+ − $C_{12}H_{12}N$, 28), 58 (100).

***N*-Methyl-3-(*S*)-(1-(*R*)-β-naphthylethyl)aminopyrrolidine 16a.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*R*)-β-naphthylethyl)-aminopyrrolidine **10a** (0.68 g, 2.00 mmol) following the above general procedure gave **16a** (0.44 g, 87%) as a pale yellow oil: ^{1}H NMR δ 1.42 (3H, d, *J* = 6.4), 1.46−1.95 (2H, m), 1.95−2.14 (1H, m), 2.14−2.43 (2H, m), 2.27 (3H, s), 2.43−2.52 (1H, m), 2.52−2.71 (1H, m), 3.08−3.26 (1H, m), 3.96 (1H, q, *J* = 6.4), 7.35−7.60 (3H, m), 7.73 (1H, s), 7.74−7.90 (3H, m); ^{13}C NMR δ 24.5 (CH_3), 32.7 (CH_2), 42.2 (CH_3), 55.2 (CH_2), 55.4 (CH), 56.3 (CH), 63.5 (CH_2), 125.0, 125.3, 125.4, 125.9, 127.6, 127.7, 128.1 (7 × CH), 132.8, 133.4, 143.0 (3 × C) (diastereomer 3*R*,8*R*, visible peaks 24.6, 33.4, 42.3, 55.19, 55.22, 56.7, 62.4, 124.9, 125.3, 125.4, 125.9, 127.6, 127.7, 128.2, 132.8, 133.4, 142.9); IR (neat) ν 3307 (NH), 3054, 2962, 2838, 2783, 2359, 2189, 1600, 1506, 1477, 1448; $[\alpha]^{20}_D$ +58.4 (*c* 1.02, $CHCl_3$); EIMS (70 eV) *m*/*z* 254 (M^+, 22), 170 ($C_{12}H_{12}N$, 100), 155 ($C_{12}H_{11}$, 46), 127 ($C_{10}H_7$ and $C_7H_{15}N_2$, 9), 99 (M^+ − $C_{12}H_{11}$, 56), 85 (M^+ − $C_{12}H_{12}N$, 38), 57 (71).

***N*-Methyl-3-(*S*)-(1-(*S*)-β-naphthylethyl)aminopyrrolidine 16b.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*S*)-β-naphthylethyl)-aminopyrrolidine **10b** (0.68 g, 2.00 mmol) following the above general procedure gave **16b** (0.42 g, 83%) as a pale yellow oil: ^{1}H NMR δ 1.41 (3H, d, *J* = 6.8), 1.42−1.59 (1H, m), 1.60−1.93 (1H, m), 1.95−2.12 (1H, m), 2.12−2.40 (1H, m), 2.32 (3H, s), 2.40−2.52 (1H, m), 2.52−2.72 (2H, m), 3.07−3.26 (1H, m), 3.94 (1H, q, *J* = 6.8), 7.35−7.58 (3H, m), 7.73 (1H, s), 7.76−7.92 (3H, m); ^{13}C NMR δ 24.6 (CH_3), 33.4 (CH_2), 42.3 (CH_3), 55.1 (CH_2), 55.2 (CH), 56.7 (CH), 62.4 (CH_2), 124.9, 125.3, 125.4, 125.9, 127.6, 127.7, 128.2 (7 × CH), 132.8, 133.4, 142.9 (3 × C) (diastereomer 3*R*,8*S*, visible peaks 24.5, 32.7, 42.2, 55.3, 55.4, 56.3, 63.5, 125.0, 125.3, 125.4, 125.9, 127.6, 127.7, 128.1, 132.8, 133.4, 143.0); IR (neat) ν 3307 (NH), 3054, 2963, 2839, 2783, 2189, 1600, 1506, 1477, 1448; $[\alpha]^{20}_D$ −72.1 (*c* 1.16, $CHCl_3$); EIMS (70 eV) *m*/*z* 254 (M^+, 14), 170 ($C_{12}H_{12}N$, 100), 155 ($C_{12}H_{11}$, 35), 127 ($C_{10}H_7$ and $C_7H_{15}N_2$, 10), 99 (M^+ − $C_{12}H_{11}$, 65), 85 (M^+ − $C_{12}H_{12}N$, 31), 57 (73).

***N*-Methyl-3-(*S*)-(1-(*R*)-cyclohexylethyl)aminopyrrolidine 17.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*R*)-cyclohexylethyl)-aminopyrrolidine **11** (0.59 g, 2.00 mmol) following the above general procedure gave **17** (0.34 g, 81%) as a yellow-orange oil: ^{1}H NMR δ 0.77−1.37 (7H, m), 0.95 (3H, d, *J* = 6.4), 1.42−1.57 (1H, m), 1.57−1.80 (5H, m), 2.00−2.23 (1H, m), 2.23−2.35 (1H, m), 2.30 (3H, s), 2.35−2.48 (2H, m), 2.48−2.77 (2H, 2m), 3.26−3.47 (1H, m); ^{13}C NMR δ 16.8 (CH_3), 26.4, 26.6, 26.7, 27.9, 29.9 (5 × CH_2), 33.5 (CH_2), 42.3 (CH_3), 43.2 (CH), 55.0 (CH), 55.3 (CH_2), 55.9 (CH), 63.1 (CH_2) (diastereomer 3*R*,8*R*, visible peaks 16.9, 28.0, 29.8, 32.9, 43.0, 55.1, 55.6, 63.7); IR (neat) ν 3304 (NH), 2922, 2850, 2772, 1476, 1447, 1373, 1344, 1232, 1155; $[\alpha]^{20}_D$ −24.0 (*c* 0.80, $CHCl_3$); EIMS (70 eV) *m*/*z* 210 (M^+, 6), 166 (5), 127 (M^+ − C_6H_{11}, 56), 126 ($C_8H_{16}N$, 46), 93 (23), 82 (60), 70 (22), 58 (100).

***N*-Methyl-3-(*S*)-(2-(*R*)-(3,3-dimethylbutyl))aminopyrrolidine 18.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(2-(*R*)-(3,3-dimethylbutyl))aminopyrrolidine **12** (0.54 g, 2.00 mmol) following

the above general procedure gave **18** (0.26 g, 70%) as a colorless liquid: ^{1}H NMR δ 0.84 (9H, s), 0.94 (3H, d, J = 6.4), 1.35−1.55 (1H, m), 2.06−2.33 (3H, m), 2.30 (3H, s), 2.34−2.46 (1H, m), 2.50−2.62 (2H, m), 3.25−3.42 (1H, m); ^{13}C NMR δ 15.0 (CH_3), 26.5 (3 × CH_3), 33.9 (CH_2), 34.2 (C), 42.5 (CH_3), 55.5 (CH_2), 55.9 (CH), 60.6 (CH), 63.1 (CH_2) (diastereomer 3*R*,8*R*, visible peaks 32.7, 45.7, 56.2, 60.0, 64.1); IR (neat) ν 2956, 2867, 2833, 2772, 1478, 1446, 1391, 1372, 1362, 1232, 1126; $[\alpha]^{21}_D$ −64.0 (*c* 1.00, $CHCl_3$); EIMS (70 eV) *m*/*z* 184 (M^+, <1), 143 (2), 127 (M^+ − *t*Bu, 11), 93 (8), 82 (14), 70 (11), 58 (70), 44 (C_2H_6N, 100).

***N*-Methyl-3-(*S*)-(1-(*R*)-phenyl-2-*N*'-pyrrolidinylethyl)aminopyrrolidine 19.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*R*)-phenyl-2-*N*'-pyrrolidinylethyl)amino pyrrolidine **13** (0.72 g, 2.00 mmol) following the above general procedure gave **19** (0.39 g, 71%) as a pale yellow oil: ^{1}H NMR δ 1.30−1.53 (1H, m), 1.54−1.80 (4H, m), 1.83−2.04 (1H, m), 2.04−2.30 (2H, m), 2.24 (3H, s), 2.30−2.63 (8H, 2m), 2.75 (1H, t, J = 10.5), 2.90−3.16 (1H, m), 3.65 (1H, dd, J = 10.5, 3.4), 7.00−7.39 (5H, m); ^{13}C NMR δ 23.7 (2 × CH_2), 33.6 (CH_2), 42.6 (CH_3), 54.2 (2 × CH_2), 55.2 (CH_2), 55.3 (CH), 60.7 (CH), 62.4 (CH_2), 64.1 (CH_2), 127.3, 127.6, 128.4 (5 × CH), 143.1 (C); IR (neat) ν 3296 (NH), 3062, 2966, 2874, 2789, 1602, 1491, 1478, 1451, 1381, 1349, 1216, 1149, 1117; $[\alpha]^{22}_D$ −98.8 (*c* 0.82, $CHCl_3$).

***N*-Methyl-3-(*S*)-(1-(*S*)-phenyl-2-*N*'-piperidinylethyl)aminopyrrolidine 20a.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*S*)-phenyl-2-*N*'-piperidinylethyl)aminopyrrolidine **14a** (0.75 g, 2.00 mmol) following the above general procedure gave **20a** (0.53 g, 92%) as a pale yellow oil: ^{1}H NMR δ 1.20−1.63 (7H, m), 1.75−2.90 (14H, m), 2.94−3.13 (1H, m), 3.69 (1H, dd, J = 11.3, 3.4), 7.03−7.45 (5H, m); ^{13}C NMR δ 24.6 (CH_2), 26.2 (2 × CH_2), 32.9 (CH_2), 42.5 (CH_3), 54.7, 55.4 (3 × CH_2), 55.8 (CH), 58.4 (CH), 63.7 (CH_2), 66.5 (CH_2), 127.2, 127.7, 128.3 (5 × CH), 143.2 (C); IR (neat) ν 3284 (NH), 3062, 3017, 2939, 2852, 2788, 1491, 1467, 1452; $[\alpha]^{20}_D$ +97.6 (*c* 1.09, $CHCl_3$); EIMS (70 eV) *m*/*z* 287 (M^+, <1), 189 (M^+ − $C_6H_{12}N$, 29), 98 ($C_6H_{12}N$, 100), 82 (22).

***N*-Methyl-3-(*S*)-(1-(*R*)-phenyl-2-*N*'-piperidinylethyl)aminopyrrolidine 20b.** Reduction of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*R*)-phenyl-2-*N*'-piperidinylethyl)aminopyrrolidine **14b** (0.75 g, 2.00 mmol) following the above general procedure gave **20b** (0.47 g, 82%) as a pale yellow oil: ^{1}H NMR δ 1.18−1.61 (7H, 2m), 1.79−2.01 (1H, m), 2.02−2.60 (14H, m), 2.89−3.15 (1H, m), 3.66 (1H, dd, J = 10.9, 3.4), 6.93−7.37 (5H, m); ^{13}C NMR δ 24.6 (CH_2), 26.2 (2 × CH_2), 33.7 (CH_2), 42.6 (CH_3), 54.8, 55.2 (3 × CH_2), 55.5 (CH), 58.8 (CH), 62.7 (CH_2), 66.7 (CH_2), 127.2, 127.7, 128.4 (5 × CH), 143.2 (C); IR (neat) ν 3392 (NH), 3060, 3024, 2934, 2771, 1490, 1466, 1452; $[\alpha]_D^{21}$: −107.4 (*c* 0.91, $CHCl_3$); CIMS (200 eV, *t*-BuH) *m*/*z* 288 (MH^+, 100), 205 (10), 189 (MH^+ − $C_6H_{12}N$, 31), 166 (6), 154 (14), 132 (7), 98 ($C_6H_{12}N$, 39), 82 (23); HRMS (*m*/*z*) [MH^+] $C_{18}H_{30}N_3$ requires 288.2440, found 288.2439.

General Procedure for Deprotection of the Boc Group of 21a and 21b. Trifluoroacetic acid (TFA, 3.06 mL, 40.0 mmol, 8 equiv) was added dropwise to a stirred solution of amine **21a** or **21b** (1.45 g, 5.00 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 7 h and then the excess of TFA and the solvent were removed in vacuo. CH_2Cl_2 (30 mL) was added and evaporated. This operation was performed twice. The residue was diluted in CH_2Cl_2 (30 mL) and 1 M aqueous hydrochloric acid solution (30 mL) was added. The resulting mixture was stirred at room temperature for 15 min. The acidic aqueous layer was extracted and 4 M aqueous sodium hydroxide solution was slowly added until pH 9. The medium was then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure.

3-(*S*)-(1-(*R*)-Phenylethyl)aminopyrrolidine 22a. Deprotection of the Boc group of *N*-(*tert*-butoxy-carbonyl)-3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine **21a** (1.45 g, 5.00 mmol) by TFA following the above general procedure gave **22a** (0.80 g, 84%) as a pale orange oil: ^{1}H NMR δ 1.27 (3H, d, J = 6.8), 1.42−1.60 (1H, m), 1.76−1.95 (1H, m), 1.98−2.35 (2H, br), 2.48 (1H, dd, J = 11.3, 4.9), 2.64−2.88 (2H, m), 2.91−3.14 (2H, m), 3.72 (1H, q, J = 6.8), 7.08−7.40 (5H, m); IR (neat) ν 3271 (NH), 3027, 2964, 2868, 1492, 1451, 1265; EIMS (70 eV) *m*/*z* 191 (M^+, <1), 160 (9), 146 (3), 132 (4), 120 ($C_8H_{10}N$, 42), 105 (PhEt, 100), 85 (M^+ − PhEt, 26), 77 (C_6H_5, 31).

3-(*S*)-(1-(*S*)-Phenylethyl)aminopyrrolidine 22b. Deprotection of the Boc group of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*S*)-phenylethyl)aminopyrrolidine **21b** (1.45 g, 5.00 mmol) by TFA following the above general procedure gave **22b** (0.88 g, 93%) as a pale orange oil: ^{1}H NMR δ 1.22 (3H, d, J = 6.8), 1.15−1.35 (1H, m), 1.65−2.23 (3H, 2m), 2.59−2.75 (2H, m), 2.78 (1H, dd, J = 10.9, 5.6), 2.84−3.07 (2H, m), 3.65 (1H, q, J = 6.8), 7.00−7.30 (5H, m); ^{13}C NMR δ 24.7 (CH_3), 33.9 (CH_2), 45.8 (CH_2), 53.1 (CH_2), 56.3 (CH), 56.7 (CH), 126.6, 127.0, 128.5 (5 × CH), 145.6 (C); IR (neat) ν 3276 (NH), 3024, 2964, 2867, 1492, 1450; $[\alpha]^{20}_D$ −91.9 (*c* 0.98, $CHCl_3$); EIMS (70 eV) *m*/*z* 191 (M^+, <1), 160 (7), 146 (5), 132 (4), 120 ($C_8H_{10}N$, 34), 105 (PhEt, 100), 85 (M^+ − PhEt, 25), 77 (C_6H_5, 32).

***N*,*N*-Dimethyloxamoyl chloride 23.** Oxalyl chloride (0.52 mL, 6.00 mmol, 3.0 equiv) was added dropwise to a suspension of dimethylamine hydrochloride (0.16 g, 2.00 mmol, 1.0 equiv) in CCl_4 (80 mL) at 0 °C and the reaction mixture was stirred at 65 °C for 18 h (until the liberation of HCl had stopped). After cooling to room temperature, the excess of oxalyl chloride and the solvent were removed under reduce pressure and CCl_4 (30 mL) was added and evaporated. This operation was performed twice to give **23** as a colorless oil. The crude product was used in the next step without any purification. The *N*,*N*-dimethyloxamoyl chloride **23** can be characterized after hydrolysis of the crude product by MeOH. The residue was purified by column chromatography (EtOAc) to give the corresponding amidoester (0.13 g, 50%) as a pale yellow oil: ^{1}H NMR δ 2.98 (3H, s), 3.01 (3H, s), 3.86 (3H, s); ^{13}C NMR (293 K, two rotamers observed) δ 34.2 and 34.3 (CH_3), 37.2 and 37.3 (CH_3), 52.6 and 52.7 (CH_3), 161.4 and 161.5 (C), 163.3 and 163.4 (C); IR (neat) ν 3511, 3011, 2957, 1743 (C═O), 1665 (C═O), 1508, 1436, 1414, 1280, 1249; EIMS (70 eV) *m*/*z* 131 (M^+, 19), 72 (M^+ − CO_2Me, 100).

General Procedure for Introduction of the Oxamoyl Group $(CO)_2NMe_2$ on Diamines 22a and 22b. A solution of diamine **22a** or **22b** (0.38 g, 2.00 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added at 0 °C to a solution of **23** (0.27 g, 2.00 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) and the mixture was stirred at room temperature for 2 h. The precipitate formed was filtered through a celite pad and the filtrate was concentrated under reduce pressure.

***N*-(*N*',*N*'-Dimethyloxamoyl)-3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine 24a.** The amine **24a** was prepared using 3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine **22a** (0.38 g, 2.00 mmol) and *N*,*N*-dimethyloxamoyl chloride **23** (0.27 g, 2.00 mmol) following the above general procedure. The residue was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to give **24a** (0.43 g, 74%) as a yellow oil: ^{1}H NMR (293 K, two rotamers observed) δ 1.18−1.37 (1H, m), 1.25 (3H, d, J = 6.4), 1.51−1.80 (1H, m), 1.90−2.12 (1H, m), 2.83 and 2.84 (3H, 2 × s), 2.88 and 2.90 (3H, 2 × s), 2.78−2.98 and 3.00−3.10 (1H, 2 × m), 3.10−3.24 (1H, m), 3.24−3.42 and 3.42−3.68 (3H, 2 × m), 3.68−3.82 (1H, 2 × q, J = 6.4), 7.09−7.32 (5H, m); ^{13}C NMR (293 K, two rotamers observed) δ 24.5 and 24.6 (CH_3), 30.4 and 31.6 (CH_2), 33.5 and 33.6 (CH_3), 36.9 and 37.0 (CH_3), 43.2 and 44.9 (CH_2), 51.0 and 52.6 (CH_2), 53.8 and 55.5 (CH), 56.2 and 56.6 (CH), 126.4 and 126.5, 127.1, 128.4 and 128.5 (5 × CH), 145.1 and 145.2 (C), 163.2 (C), 164.9 and 165.0 (C); IR (neat) ν 3491 (NH_{bonded}), 3305 (NH_{free}), 3053, 3025, 2996, 2883, 1631 (2 × C═O), 1466, 1451, 1434, 1391, 1265, 1146; $[\alpha]^{20}_D$ +26.6 (*c* 0.61, $CHCl_3$); EIMS (70 eV) *m*/*z* 289 (M^+, <1), 274 (M^+ − CH_3, 7), 189 (M^+ − $(CO)_2NMe_2$, 9), 120 ($C_8H_{10}N$, 100), 105 (PhEt, 86), 85 (M^+ − PhEt − $(CO)_2NMe_2$, 16), 72 ($CONMe_2$, 72).

***N*-(*N*',*N*'-Dimethyloxamoyl)-3-(*S*)-(1-(*S*)-phenylethyl)aminopyrrolidine 24b.** The amine **24b** was prepared using 3-(*S*)-(1-(*S*)-phenylethyl)aminopyrrolidine **22b** (0.38 g, 2.00 mmol) and *N*,*N*-

dimethyloxamoyl chloride **23** (0.27 g, 2.00 mmol) following the above general procedure. The residue was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to give **24b** (0.51 g, 88%) as a yellow oil: ^{1}H NMR (293 K, two rotamers observed) δ 1.23 and 1.25 (3H, d, J = 6.4), 1.46−1.69 (1H, m), 1.70−2.13 (2H, m), 2.87 and 2.90 (6H, 2s), 3.05−3.21 and 3.21−3.38 (3H, 2m), 3.39−3.61 (2H, m), 3.61−3.78 (1H, m), 7.04−7.33 (5H, m); ^{13}C NMR (293 K, two rotamers observed) δ 25.1 (CH_3), 31.4 and 32.8 (CH_2), 33.9 and 34.0 (CH_3), 37.3 (CH_3), 43.6 and 45.2 (CH_2), 50.8 and 52.5 (CH_2), 54.1 and 55.4 (CH), 56.8 and 56.9 (CH), 126.6 and 126.7, 126.8 and 127.4, 127.4 and 128.8 (5 × CH), 145.3 (C), 163.5 and 163.7 (C), 165.3 and 165.4 (C); IR (neat) ν 3450 (NH), 3052, 2966, 2885, 1636 (2 × C═O), 1466, 1451, 1435, 1393, 1265; $[\alpha]^{20}_D$ −91.9 (*c* 0.57, $CHCl_3$); EIMS (70 eV) *m*/*z* 289 (M^+, 4), 274 ($M^+ - CH_3$, 22), 189 ($M^+ - (CO)_2NMe_2$, 22), 120 ($C_8H_{10}N$, 100), 105 (PhEt, 86), 85 (M^+ − PhEt − $(CO)_2NMe_2$, 16), 72 ($CONMe_2$, 72).

***N*-(*N'*,*N'*-Dimethyloxamoyl)-3-(*R*)-hydroxypyrrolidine 26.** A solution of 3-(*R*)-hydroxypyrrolidine **25** (0.15 mL, 1.81 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **23** (0.25 g, 1.81 mmol, 1.0 equiv) in CH_2Cl_2 (55 mL) at 0 °C and the mixture was stirred at room temperature for 1 h. The precipitate formed was filtered through a celite pad and the filtrate was concentrated under reduce pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH 99:1 → 95:5) to give **26** (0.21 g, 62%) as a pale brown oil: ^{1}H NMR δ 1.90−2.10 (2H, m), 2.94−2.96 (3H, m), 2.98−3.00 (3H, m), 3.30−3.80 (5H, m), 4.35−4.57 (1H, m); ^{13}C NMR (293 K, two rotamers observed) δ 32.7 and 34.0 (CH_2), 33.8 and 33.9 (CH_3), 37.2 (CH_3), 43.1 and 44.6 (CH_2), 53.6 and 54.9 (CH_2), 69.2 and 70.3 (CH), 163.6 and 163.7 (C), 165.3 (C); IR (neat) ν 3407 (OH), 3053, 2945, 2358, 1635 (2 × C═O), 1521, 1471, 1437, 1394; $[\alpha]^{19}_D$ −32.4 (*c* 1.21, $CHCl_3$); EIMS (70 eV) *m*/*z* 186 (M^+, 3), 168 ($M^+ - H_2O$, 5), 149 (7), 114 ($M^+ - CONMe_2$, 29), 86 ($M^+ - (CO)_2NMe_2$, 67), 72 ($CONMe_2$, 100).

***N*-(*N'*,*N'*-Dimethyloxamoyl)-3-(*R*)-methylsulfonyloxypyrrolidine 27.** Pyridine (0.33 mL, 4.14 mmol), methanesulfonyl chloride (0.33 mL, 4.27 mmol), and a catalytic amount of 4-dimethylaminopyridine (4-DMAP, 15 mg) were added to a solution of *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*R*)-hydroxypyrrolidine **26** (0.51 g, 2.74 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred for 72 h at room temperature, the solution was concentrated and EtOAc (10 mL) was added to the residue. The insoluble salt was filtered through celite and the remaining solution was concentrated. The residue was purified by column chromatography (CH_2Cl_2/MeOH 96:4) to give **27** (0.54 g, 75%) as a pale yellow oil: ^{1}H NMR (293 K, two rotamers observed) δ 2.00−2.44 (2H, m), 2.92 and 2.93 (3H, 2 × s), 2.97 and 2.98 (3H, 2 × s), 2.99 and 3.00 (3H, 2 × s), 3.49−3.91 (4H, m), 5.19−5.33 (1H, m); ^{13}C NMR (293 K, two rotamers observed) δ 30.8 and 32.7 (CH_2), 33.9 and 34.0 (CH_3), 37.2 and 37.3 (CH_3), 38.8 (CH_3), 42.8 and 44.2 (CH_2), 51.4 and 53.0 (CH_2), 78.3 and 79.4 (CH), 163.1 and 163.2 (C), 164.5 (C); IR (neat) ν 3489, 3014, 2936, 1636 (2 × C═O), 1517, 1469, 1436, 1395, 1354 (RSO_2OR), 1263, 1233, 1172 (RSO_2OR), 1150, 1082, 1059; $[\alpha]^{20}_D$ −31.4 (*c* 1.02, $CHCl_3$); EIMS (70 eV) *m*/*z* 264 (M^+, 4), 192 ($M^+ - CONMe_2$, 15), 164 ($M^+ - (CO)_2NMe_2$, 15), 114 ($M^+ - CONMe_2 - SO_2Me$, 4), 96 (CH_3SO_3H, 17), 72 ($CONMe_2$, 100).

General Procedure for Introduction of the (*R*)- or (*S*)-α-Methylbenzylamine Group from Pyrrolidinol 26 (via a Triflate). A solution of *N*,*N*-di-isopropylethylamine (0.73 mL, 4.20 mmol, 2.1 equiv) in CH_2Cl_2 (1.0 mL) was added to a cooled (−30 °C) solution of *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*R*)-hydroxypyrrolidine **26** (0.37 g, 2.00 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL). Trifluoromethanesulfonic anhydride (0.35 mL, 2.10 mmol, 1.05 equiv) was added dropwise under a 10-min period and the mixture was stirred at −30 °C for 45 min. A solution of (*R*)- or (*S*)-α-methylbenzylamine (0.39 mL, 3.00 mmol 1.5 equiv) in CH_2Cl_2 (5 mL) was introduced over a 5-min period and the reaction mixture was stirred at room temperature for 24 h. The solution was washed with saturated $NaHCO_3$ (2 × 2 mL) and brine (2 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure.

***N*-(*N'*,*N'*-Dimethyloxamoyl)-3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine 24a.** The amine **24a** was prepared from *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*R*)-hydroxypyrrolidine **26** (0.37 g, 2.00 mmol) and (*R*)-α-methylbenzylamine (0.39 mL, 3.00 mmol) following the above general procedure. Purification of the residue by column chromatography (CH_2Cl_2/MeOH 95:5) gave **24a** (0.20 g, 54%) as a yellow oil.

***N*-(*N'*,*N'*-Dimethyloxamoyl)-3-(*S*)-(1-(*S*)-phenylethyl)aminopyrrolidine 24b.** The amine **24b** was prepared from *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*R*)-hydroxypyrrolidine **26** (0.37 g, 2.00 mmol) and (*S*)-α-methylbenzylamine (0.39 mL, 3.00 mmol) following the above general procedure. Purification of the residue by column chromatography (CH_2Cl_2/MeOH 95:5) gave **24b** (0.19 g, 51%) as a yellow oil.

General Procedure for Introduction of the (*R*)- or (*S*)-α-Methylbenzylamine Group from 27 (via a Mesylate). A mixture of *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*R*)-methylsulfonyloxypyrrolidine **27** (0.53 g, 2.00 mmol, 1.0 equiv) and (*R*)- or (*S*)-α-methylbenzylamine (2.06 mL, 16.0 mmol, 8 equiv) was heated at 105−110 °C for 24 h. After cooling to room temperature, EtOAc (10 mL) and 4 M aqueous NaOH solution (5 mL) were added and the mixture was stirred vigorously. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the organic layers were combined, washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

***N*-(*N'*,*N'*-Dimethyloxamoyl)-3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine 24a.** The amine **24a** was thus prepared from *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*R*)-methylsulfonyloxypyrrolidine **27** (0.53 g, 2.00 mmol) and (*R*)-α-methylbenzylamine (2.06 mL, 16.0 mmol) following the above general procedure. Purification of the residue by column chromatography (CH_2Cl_2/MeOH 95:5) gave **24b** (0.42 g, 70%) as a yellow oil.

***N*-(*N'*,*N'*-Dimethyloxamoyl)-3-(*S*)-(1-(*S*)-phenylethyl)aminopyrrolidine 24b.** The amine **24b** was thus prepared from *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*R*)-methylsulfonyloxypyrrolidine **27** (0.53 g, 2.00 mmol) and (*S*)-α-methylbenzylamine (2.06 mL, 16.0 mmol) following the above general procedure. Purification of the residue by column chromatography (CH_2Cl_2/MeOH 95:5) gave **24b** (0.40 g, 69%) as a yellow oil.

General Procedure for Reduction of the Diamido Group of 24. A solution of amine **24a** or **24b** (0.29 g, 1.00 mmol, 1.0 equiv) in dry THF (30 mL) was added over 30 min to a suspension of lithium aluminum hydride ($LiAlH_4$, 0.38 g, 10.0 mmol, 10.0 equiv) in freshly distilled THF (10 mL), placed under argon atmosphere at 0 °C. The solution was stirred at room temperature for 5 h then heated at 60 °C for 1 h. After cooling at 0 °C, the excess of $LiAlH_4$ was hydrolyzed by successive addition of cold water (0.9 mL), 4 M aqueous sodium hydroxide (0.9 mL) and cold water (1.3 mL). The white precipitate was filtered on celite and washed with CH_2Cl_2 (15 mL). The filtrate was concentrated and the residue was dissolved in Et_2O (15 mL). 1 M aqueous hydrochloric acid (15 mL) was added and the solution was stirred at room temperature for 15 min. The acidic aqueous layer was extracted and $NaHCO_3$ was slowly added until pH 9. The medium was then extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure.

***N*-(*N'*,*N'*-Dimethylaminoethyl)-3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine 28a.** Reduction of *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine **24a** (0.29 g, 1.00 mmol) by $LiAlH_4$ (0.38 g, 10.0 mmol) following the above general procedure gave **28a** (0.222 g, 85%) as pale orange oil: ^{1}H NMR δ 1.26 (3H, d, J = 6.4), 1.45−1.59 (1H, m), 1.59−1.88 (1H, br), 1.89−2.05 (1H, m), 2.06−2.22 (1H, m), 2.14 (6H, s), 2.25−2.62 (7H, m), 2.97−3.16 (1H, m), 3.71 (1H, q, J = 6.4), 7.06−7.33 (5H, m); ^{13}C NMR δ 24.4 (CH_3), 31.6 (CH_2), 45.8 (CH_3), 45.9 (CH_3), 53.6 (CH_2), 54.2 (CH_2), 54.7 (CH), 56.3 (CH), 58.2 (CH_2),

61.5 (CH_2), 126.8, 127.1, 128.5 (5 × CH), 145.2 (C) (diastereomer 3*R*,8*R* visible peaks 24.5, 32.5, 53.4, 54.4, 54.5, 56.7, 60.8); IR (neat) ν 3304 (NH), 3026, 2959, 2860, 2814, 1492, 1451, 1265; $[\alpha]^{20}_D$ +26.1 (*c* 0.52, $CHCl_3$); EIMS (70 eV) *m*/*z* 261 (M^+, 3), 260 ($M^+ - H$, 19), 203 ($M^+ - CH_2NMe_2$, 24), 160 ($M^+ - C_6H_5 - NMe_2$, 38), 140 ($M^+ - C_8H_{10}N$, 17), 120 ($C_8H_{10}N$, 8), 105 (Ph(CH)Me, 63), 101 (100), 58 (CH_2NMe_2, 67).

***N*-(*N'*,*N'*-Dimethylaminoethyl)-3-(*S*)-(1-(*S*)-phenylethyl)aminopyrrolidine 28b.** Reduction of *N*-(*N'*,*N'*-dimethyloxamoyl)-3-(*S*)-(1-(*S*)-phenylethyl)aminopyrrolidine **24b** (0.29 g, 1.00 mmol) by $LiAlH_4$ (0.38 g, 10.0 mmol) following the above general procedure gave **28b** (0.20 g, 77%) as a pale yellow oil: ^{1}H NMR δ 1.29 (3H, d, J = 6.8), 1.35−1.50 (1H, m), 1.50−1.89 (1H, br), 1.89−2.06 (1H, m), 2.20 (6H, s), 2.28−2.66 (8H, m), 3.02−3.18 (1H, m), 3.73 (1H, q, J = 6.8), 7.12−7.33 (5H, m); ^{13}C NMR δ 24.6 (CH_3), 32.7 (CH_2), 46.1 (2 × CH_3), 53.6 (CH_2), 54.6 (CH), 54.8 (CH_2), 56.7 (CH), 58.5 (CH_2), 61.1 (CH_2), 126.8, 127.1, 128.5 (5 × CH), 145.6 (C); IR (neat) ν 3373 (NH), 3052, 2964, 2817, 1451, 1264; $[\alpha]^{20}_D$ −81.9 (*c* 0.80, $CHCl_3$); EIMS (70 eV) *m*/*z* 261 (M^+, 1), 260 ($M^+ - H$, 2), 203 ($M^+ - CH_2NMe_2$, 23), 160 ($M^+ - C_6H_5 - NMe_2$, 8), 140 ($M^+ - C_8H_{10}N$, 26), 120 ($C_8H_{10}N$, 5), 105 (Ph(CH)Me, 67), 58 (CH_2NMe_2, 100).

(±)-*N*-(*tert*-Butoxycarbonyl)-3-hydroxypyrrolidine 34. [10] BMS (0.45 mL, 5 mmol, 1.0 equiv) was added to a solution of *N*-(*tert*-butoxycarbonyl)-3-pyrroline **33** (2.5 g, 15 mmol, 3 equiv) in freshly distilled THF (15 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h then cooled to 0 °C to be oxidized by using 3 M sodium hydroxide (5 mL) and 30% hydrogen peroxide (5 mL). The reaction mixture was stirred at room temperature for 12 h and the aqueous phase was saturated with anhydrous potassium carbonate (8 g). The organic layer was extracted, dried ($MgSO_4$), filtered and concentrated to yield **34** (1.7 g, 60%) as a pale yellow oil: ^{1}H NMR δ 1.37 (9H, s), 1.70−2.00 (2H, m), 3.03−3.51 (4H, m), 3.65−3.99 (1H, m), 4.15−4.43 (1H, m); ^{13}C NMR (293 K, two rotamers observed) δ 28.5 (3 × CH_3), 33.4 and 33.9 (CH_2), 43.6 and 44.0 (CH_2), 54.0 and 54.2 (CH_2), 69.8 and 70.6 (CH), 79.4 (C), 154.9 (C); IR (neat) ν 3410 (OH), 2975, 2932, 2890, 1673 (C═O), 1478, 1419, 1365, 1165, 1121; EIMS (70 eV) *m*/*z* 187 (M^+, 25), 114 (M^+ − O*t*-Bu, 100), 87 ($M^+ - CO_2t$-Bu, 47); HRMS (*m*/*z*) [M^+] $C_9H_{17}NO_3$ requires 187.1208, found 187.1207.

(±)-*N*-(*tert*-Butoxycarbonyl)-3-methylsulfonyloxypyrrolidine 35. Pyridine (0.13 mL, 1.59 mmol, 1.5 equiv), freshly distilled methanesulfonylchloride (0.13 mL, 1.68 mmol, 1.6 equiv) and 4-dimethylaminopyridine (4-DMAP, 15 mg) were successively added to a solution of (±)-*N*-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine **34** (0.20 g, 1.07 mmol, 1.0 equiv) in dry dichloromethane (4 mL). After stirring 70 h at room temperature, dichloromethane and pyridine were evaporated and the residue was dissolved in EtOAc (4 mL). The salts were filtered and the filtrate was concentrated under reduce pressure. The residue was purified by column chromatography (EtOAc/cyclohexane 30:70) to give **35** (0.241 g, 85%) as a pale yellow oil: ^{1}H NMR δ 1.40 (9H, s), 1.93−2.33 (2H, m), 3.00 (3H, s), 3.29−3.72 (4H, m), 5.20 (1H, br); ^{13}C NMR (293 K, two rotamers observed) δ 28.4 (3 × CH_3), 31.7 and 32.6 (CH_2), 38.7 (CH_3), 43.2 and 43.6 (CH_2), 51.7 and 52.2 (CH_2), 79.6 and 80.1 (CH), 79.8 (C), 154.1 and 154.2 (C); IR (neat) ν 3470, 2977, 2936, 2888, 1693 (C═O), 1478, 1410, 1357; CIMS (NH_3) *m*/*z* 266 (MH^+, 7), 250 ($MH^+ - CH_3$, 3), 210 ($MH^+ - t$-Bu, 100), 166 ($MH^+ - CO_2t$-Bu, 23), 114 ($MH^+ - SO_2CH_3$ − O*t*-Bu, 7), 86 ($MH^+ - SO_2CH_3 - CO_2t$-Bu, 2); HRMS (*m*/*z*) [MH^+] $C_{10}H_{20}NO_5S$ requires 266.1062, found 266.1063.

General Procedure for Introduction of the (*R*)- or (*S*)-α-Methylbenzylamine Group on 35. A mixture of (±)-*N*-(*tert*-butoxycarbonyl)-3-methylsulfonyloxypyrrolidine **35** (0.53 g, 2.00 mmol, 1.0 equiv) and (*R*)- or (*S*)-α-methylbenzylamine (2.06 mL, 16.0 mmol, 8.0 equiv) was heated at 105−110 °C for 24 h. After cooling to room temperature, EtOAc (10 mL) and 4 M aqueous NaOH solution (5 mL) were added and the mixture was stirred vigorously. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the organic layers were combined, washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

(3*R*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-(1-(*R*)-phenylethyl)-aminopyrrolidine 36a. Carbamate **36a** was prepared reacting (±)-*N*-(*tert*-butoxycarbonyl)-3-methylsulfonyloxypyrrolidine **35** (0.53 g, 2.00 mmol) with (*R*)-α-methylbenzylamine (2.06 mL, 16.0 mmol), and following the above general procedure. Purification of the residue by column chromatography (EtOAc/cyclohexane 60:40) gave **36a** (0.50 g, 86%) as a pale orange oil: ^{1}H NMR (1:1 mixture of diastereomers) δ 1.20−1.30 (2 × 3H, d, J = 6.8), 1.30−1.43 (2 × 9H, s), 1.43−1.70 (2 × 1H, m), 1.71−2.02 (2 × 2H, 2m), 2.74−2.82 (1H, m), 2.82−3.55 (4H + 5H, 2m), 3.65−3.83 (2 × 1H, q, J = 6.8), 7.08−7.36 (2 × 5H, m); ^{13}C NMR (293 K, 1:1 mixture of diastereomers, two rotamers observed for each) δ 25.2 and 25.3 (CH_3), 25.4 and 25.5 (CH_3), 29.1 (3 × CH_3), 29.2 (3 × CH_3), 31.7 and 32.5 (CH_2), 32.6 and 33.4 (CH_2), 44.6 and 45.1 (CH_2), 44.7 and 45.0 (CH_2), 52.0 and 52.6 (CH_2), 52.5 and 52.9 (CH_2), 55.1 and 56.0 (CH), 55.2 and 56.0 (CH), 57.0 (CH), 57.3 (CH), 79.7 and 79.9 (C), 79.8 (C), 127.2, 127.8, 129.2 (2 × 5 × CH), 146.0 (2 × C), 155.2 (C), 155.3 (C); IR (neat) ν 3436 (NH), 3052, 3026, 2975, 2876, 1681 (C═O), 1492, 1477, 1451, 1408, 1365, 1265, 1169, 1120; $[\alpha]^{20}_D$ +58.8 (*c* 0.78, $CHCl_3$); EIMS (70 eV) *m*/*z* 290 (M^+, <1), 232 ($M^+ - t$-Bu, 10), 219 (M^+ − O*t*-Bu, 28), 129 ($M^+ - t$-Bu − PhEt, 40), 118 (72), 101 (CO_2t-Bu, 100), 83 ($M^+ - CO_2t$-Bu − PhEt, 43), 57 (*t*-Bu, 96).

(3*R*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-(1-(*S*)-phenylethyl)-aminopyrrolidine 36b. Carbamate **36b** was prepared reacting (±)-*N*-(*tert*-butoxycarbonyl)-3-methylsulfonyloxypyrrolidine **35** (0.53 g, 2.00 mmol) with (*S*)-α-methylbenzylamine (2.06 mL, 16.0 mmol), and following the above general procedure. Purification of the residue by column chromatography (EtOAc/cyclohexane 60:40) gave **36b** (0.50 g, 86%) as a pale orange oil: ^{1}H NMR (1:1 mixture of diastereomers) δ 1.20−1.30 (2 × 3H, d, J = 6.8), 1.30−1.43 (2 × 9H, s), 1.43−1.70 (2 × 1H, m), 1.71−2.02 (2 × 2H, 2m), 2.74−2.82 (1H, m), 2.92−3.55 (4H + 5H, 2m), 3.69−3.81 (2 × 1H, q, J = 6.8), 7.08−7.36 (2 × 5H, m); ^{13}C NMR (293 K, 1:1 mixture of diastereomers, two rotamers observed for each) δ 25.2 and 25.3 (CH_3), 25.4 and 25.5 (CH_3), 29.1 (3 × CH_3), 29.2 (3 × CH_3), 31.7 and 32.5 (CH_2), 32.6 and 33.4 (CH_2), 44.6 and 45.1 (CH_2), 44.7 and 45.0 (CH_2), 52.0 and 52.6 (CH_2), 52.5 and 52.9 (CH_2), 55.1 and 56.0 (CH), 55.2 and 56.0 (CH), 57.0 (CH), 57.3 (CH), 79.7 and 79.9 (C), 79.8 (C), 127.2, 127.8, 129.2 (2 × 5 × CH), 146.0 (2 × C), 155.2 (C), 155.3 (C); IR (neat) ν 3436 (NH), 3052, 3026, 2975, 2876, 1681 (C═O), 1492, 1477, 1451, 1408, 1365, 1265, 1169, 1120; $[\alpha]^{20}_D$ −59.0 (*c* 1.15, $CHCl_3$); EIMS (70 eV) *m*/*z* 290 (M^+, <1), 232 ($M^+ - t$-Bu, 10), 219 (M^+ − O*t*-Bu, 28), 129 ($M^+ - t$-Bu − PhEt, 40), 118 (72), 101 (CO_2t-Bu, 100), 83 ($M^+ - CO_2t$-Bu − PhEt, 43), 57 (*t*-Bu, 96).

General Procedure for Reduction of the Boc Group of 36. A solution of **36a** or **36b** (3.00 mmol, 1.0 equiv) in dry THF (90 mL) was added over a 30-min period to a suspension of lithium aluminum hydride ($LiAlH_4$, 0.63 g, 16.5 mmol, 5.5 equiv) in freshly distilled THF (30 mL), placed under an argon atmosphere at 0 °C. The solution was stirred at room temperature for 5 h then heated at 60 °C for 1 h. After cooling at 0 °C, the excess of $LiAlH_4$ was hydrolyzed by successive addition of cold water (1.8 mL), 4 M aqueous sodium hydroxide (1.8 mL) and cold water (2.4 mL). The white precipitate was filtered on celite and washed with CH_2Cl_2 (45 mL). The filtrate was concentrated and the residue was dissolved in Et_2O (30 mL). Aqueous hydrochloric acid (1M, 30 mL) was added and the solution was stirred at room temperature for 15 min. The acidic aqueous layer was extracted and $NaHCO_3$ was slowly added until pH 9. The medium was then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure.

(3*R*,3*S*)-*N*-Methyl-3-(1-(*R*)-phenylethyl)-aminopyrrolidine 37a. Reduction of (3*R*,3*S*)-*N*-(*tert*-butoxycarbonyl)-3-(1-(*R*)-phenylethyl)-aminopyrrolidine **36a** (0.87 g, 3.00 mmol) following the above

general procedure gave **37a** (0.47 g, 76%) as a yellow oil: ^{1}H NMR (1:1 mixture of diastereomers) δ 1.20 (2 × 3H, d, J = 6.8), 1.38−1.41 (1H, m), 1.41−1.56 (1H, m), 1.82−2.02 (2 × 1H, m), 2.04−2.55 (2 × 4H, m), 2.15 (3H, s), 2.18 (3H, m), 2.92−3.10 (2 × 1H, m), 3.55−3.72 (2 × 1H, q, J = 6.8), 7.02−7.26 (2 × 5H, m); ^{13}C NMR (293 K, 1:1 mixture of diastereomers) δ 24.4 and 24.6 (2 × CH_3), 32.7 and 33.4 (2 × CH_2), 42.2 and 42.3 (2 × CH_3), 55.1 and 55.3 (2 × CH), 55.2 and 55.4 (2 × CH_2), 56.2 and 56.5 (2 × CH), 62.6 and 63.5 (2 × CH_2), 126.7 (4 × CH), 126.9 (2 × CH), 128.4 (4 × CH), 145.5 and 145.6 (2 × C); IR (neat) ν 3060, 3023, 2960, 2936, 2862, 2833, 2773, 1602, 1491, 1477, 1449; $[\alpha]^{20}_D$ +71.1 (c 1.75, $CHCl_3$).

(3*R*,3*S*)-*N*-Methyl-3-(1-(*S*)-phenylethyl)-aminopyrrolidine 37b. Reduction of (3*R*,3*S*)-*N*-(*tert*-butoxycarbonyl)-3-(1-(*S*)-phenylethyl)-aminopyrrolidine **36b** (0.87 g, 3.00 mmol) following the above general procedure gave **37b** (0.50 g, 81%) as a yellow oil: ^{1}H NMR (1:1 mixture of diastereomers) δ 1.28 (2 × 3H, d, J = 6.8), 1.35−1.76 (2 × 2H, m), 1.90−2.11 (2 × 1H, m), 2.12−2.49 (2 × 3H, m), 2.19 (3H, s), 2.23 (3H, s), 2.49−2.62 (2 × 1H, m), 3.00−3.16 (2 × 1H, m), 3.62−3.80 (2 × 1H, q, J = 6.8), 7.07−7.35 (2 × 5H, m); ^{13}C NMR (293 K, 1:1 mixture of diastereomers) δ 24.4 and 24.6 (2 × CH_3), 32.7 and 33.4 (2 × CH_2), 42.2 and 42.3 (2 × CH_3), 55.1 and 55.3 (2 × CH), 55.2 and 55.4 (2 × CH_2), 56.2 and 56.5 (2 × CH), 62.5 and 63.5 (2 × CH_2), 126.7 (4 × CH), 126.9 (2 × CH), 128.35 and 128.4 (4 × CH), 145.5 (2 × C); IR (neat) ν 3060, 3023, 2960, 2936, 2862, 2833, 2773, 1602, 1491, 1477, 1449, 1367, 1348, 1306, 1233, 1198, 1152, 1131; $[\alpha]^{20}_D$ −72.2 (c 1.21, $CHCl_3$).

(±)-3-Hydroxytetrahydrothiophen 39. A solution of tetrahydrothiophen-3-one **38** (0.42 mL, 4.9 mmol) in THF (25 mL) was added dropwise to a suspension of lithium aluminum hydride ($LiAlH_4$, 0.93 g, 24.5 mmol) in THF (25 mL) at 0 °C under argon atmosphere. After stirring 3 h at room temperature, the excess of $LiAlH_4$ was hydrolyzed by addition of cold water (1 mL) at 0 °C. The white precipitate was filtered through a celite pad and washed with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give **39** (0.41 g, 80%) as an orange oil without any purification: ^{1}H NMR δ 1.60−1.85 (1H, m), 1.85−2.12 (1H, m), 2.48−3.01 (4H, m), 3.22−3.82 (1H, br), 4.35−4.58 (1H, m); ^{13}C NMR δ 28.1 (CH_2), 37.8 (CH_2), 39.2 (CH_2), 74.1 (CH); IR (neat) ν 3473 (OH), 2932, 1425.

(±)-3-Methylsulfonyloxytetrahydrothiophen 40. Pyridine (3.2 mL, 39.5 mmol), methanesulfonylchloride (2.3 mL, 29.6 mmol) and a catalytic amount of 4-dimethylaminopyridine (4-DMAP, 15 mg) were added to a solution of (±)-3-hydroxytetrahydrothiophen **39** (2.05 g, 19.7 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After being stirred 3 h at 0 °C and 20 h at room temperature, the mixture was concentrated and EtOAc (30 mL) was added to the residue. The resulting salt was filtered through a celite pad and the filtrate was concentrated under reduce pressure. The residue was purified by column chromatography (EtOAc/cyclohexane 30:70) to give **40** (2.52 g, 70%) as a pale yellow oil: ^{1}H NMR δ 1.98−2.14 (1H, m), 2.39−2.53 (1H, m), 2.85−3.23 (4H, m), 3.04 (3H, s), 5.37−5.50 (1H, m); ^{13}C NMR δ 28.3 (CH_2), 37.0, 37.1 (2 × CH_2), 38.9 (CH_3), 83.0 (CH); IR (neat) ν 3546, 3024, 2938, 2868, 1428; EIMS (70 eV) m/z 182 (M^+, 20), 149 (11), 102 ($M^+ - CH_3SO_2$, 10), 86 ($M^+ - CH_3SO_3$, 100), 85 (66), 79 (8). Anal. Calcd for $C_5H_{10}O_3S_2$: C 32.95, H 5.53, S 35.19. Found: C 33.04, H 5.86, S 35.37.

General Procedure for Introduction of the (*R*)- or (*S*)-α-Methylbenzylamine Group on 40. A mixture of (±)-3-methylsulfonyloxytetrahydrothiophen **40** (0.89 g, 4.88 mmol, 1.0 equiv) and (*R*)- or (*S*)-α-methylbenzylamine (5.1 mL, 39.2 mmol, 8 equiv) was heated at 105−110 °C for 24 h. After cooling to room temperature, EtOAc (15 mL) and 4 M aqueous NaOH solution (7.5 mL) were added and the mixture was stirred vigorously. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the organic layers were combined, washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

(3*R*,3*S*)-(1-(*R*)-Phenylethyl)tetrahydrothiophen 41a. The amine **41a** was prepared using (±)-3-methylsulfonyloxytetrahydrothiophen **40** (0.89 g, 4.88 mmol) and (*R*)-α-methylbenzylamine (5.1 mL, 39.2 mmol) and following the above general procedure. Purification of the residue by column chromatography (EtOAc/cyclohexane 30:70) gave **41a** (0.60 g, 59%) as a yellow oil: ^{1}H NMR (1:1 mixture of diastereomers) δ 1.26−1.29 (2 × 3H, d, J = 6.4), 1.45−1.55 (2 × 1H, br), 1.70−2.00 (2 × 2H, m), 2.46 (1H, dd, J = 10.6, 5.7), 2.63 (1H, dd, J = 10.6, 5.3), 2.68−2.87 (2 × 3H, m), 3.13−3.27 (2 × 1H, m), 3.78 (2 × 1H, q, J = 6.4), 7.12−7.35 (2 × 5H, m); ^{13}C NMR (1:1 mixture of diastereomers) δ 24.8 and 25.2 (2 × CH_3), 28.5 and 28.6 (2 × CH_2), 35.3 and 36.2 (2 × CH_2), 36.8 and 37.3 (2 × CH_2), 56.5 (2 × CH), 59.9 and 60.1 (2 × CH), 126.7 and 126.8 (4 × CH), 127.2 (2 × CH), 128.6 (4 × CH), 145.5 and 145.7 (2 × C); IR (neat) ν 3305 (NH), 3060, 3023, 2961, 1492, 1450; $[\alpha]^{20}_D$ +70.0 (c 1.00, $CHCl_3$); EIMS (70 eV) m/z 207 (M^+, 11), 192 ($M^+ - CH_3$, 11), 179 (18), 160 (24), 146 (29), 120 ($C_8H_{10}N$, 48), 105 (Ph(CH)Me, 100), 87 ($M^+ - C_8H_{10}N$, 16), 71 (9).

(3*R*,3*S*)-(1-(*S*)-Phenylethyl)tetrahydrothiophen 41b. The amine **41b** was prepared using (±)-3-methylsulfonyloxytetrahydrothiophen **40** (0.89 g, 4.88 mmol) and (*S*)-α-methylbenzylamine (5.1 mL, 39.2 mmol) and following the above general procedure. Purification of the residue by column chromatography (EtOAc/cyclohexane 30:70) gave **41b** (0.66 g, 65%) as a yellow oil: ^{1}H NMR (1:1 mixture of diastereomers) δ 1.26 (3H, d, J = 6.8), 1.27 (3H, d, J = 6.8), 1.35−1.55 (2 × 1H, br), 1.55−2.00 (2 × 2H, m), 2.37−2.51 (1H, dd, J = 10.5, 5.6), 2.55−2.88 (7H, m), 3.04−3.32 (2 × 1H, m), 3.76 (1H, q, J = 6.8), 3.78 (1H, q, J = 6.8), 7.02−7.35 (2 × 5H, m); ^{13}C NMR (1:1 mixture of diastereomers) δ 24.8 and 25.2 (2 × CH_3), 28.4 and 28.5 (2 × CH_2), 35.2 and 36.2 (2 × CH_2), 36.7 and 37.3 (2 × CH_2), 56.4 (2 × CH), 59.9 and 60.0 (2 × CH), 126.6 and 126.7 (4 × CH), 127.1 (2 × CH), 128.6 (4 × CH), 145.5 and 145.7 (2 × C); IR (neat) ν 3305 (NH), 3060, 3023, 2959, 2926, 2853, 2359, 1601, 1492, 1450; $[\alpha]^{20}_D$ −69.8 (c 1.00, $CHCl_3$); EIMS (70 eV) m/z 207 (M^+, 39), 130 ($M^+ - C_6H_5$, 7), 120 ($C_8H_{10}N$, 54), 105 (Ph(CH)Me, 100), 83 (46), 70 (32).

(±)-3-Methylsulfonyloxytetrahydrofuran 43. Pyridine (1.28 mL, 15.9 mmol), methanesulfonylchloride (1.31 mL, 17.0 mmol) and a catalytic amount of 4-dimethylaminopyridine (4-DMAP, 15 mg) were added to a solution of (±)-3-hydroxytetrahydrofuran **42** (0.92 mL, 11.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After being stirred 3 h at 0 °C and 20 h at room temperature, the mixture was concentrated and EtOAc (10 mL) was added to the residue. The resulting salt was filtered through a celite pad and the filtrate was concentrated under reduce pressure. The residue was purified by column chromatography (EtOAc) to give **43** (1.72 g, 91%) as a pale yellow oil: ^{1}H NMR δ 2.15−2.21 (2H, m), 2.98 (3H, s), 3.77−3.97 (4H, m), 5.23−5.24 (1H, m); ^{13}C NMR δ 33.4 (CH_2), 38.6 (CH_3), 66.8 (CH_2), 73.0 (CH_2), 80.8 (CH); IR (neat) ν 3022, 2939, 2875, 1439, 1416, 1350; EIMS (70 eV) m/z 167 (M^+, 40), 149 ($M^+ - H_2O$, 100), 113 (14), 86 ($M^+ - CH_3SO_2$, 47), 71 ($M^+ - CH_3SO_3$, 28). Anal. Calcd for $C_5H_{10}O_4S$: C 36.13, H 6.06, S 19.29. Found: C 35.96, H 6.14, S 19.02.

General Procedure for Introduction of the (*R*)- or (*S*)-α-Methylbenzylamine Group on 43. A mixture of (±)-3-methylsulfonyloxytetrahydrofuran **43** (0.50 g, 3 mmol, 1.0 equiv) and (*R*)- or (*S*)-α-methylbenzylamine (3.1 mL, 24.0 mmol, 8 equiv) was heated at 105−110 °C for 24 h. After cooling to room temperature, EtOAc (15 mL) and 4 M aqueous NaOH solution (7.5 mL) were added and the mixture was stirred vigorously. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the organic layers were combined, washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

(3*R*,3*S*)-(1-(*R*)-Phenylethyl)tetrahydrofuran 44a. The amine **44a** was prepared using (±)-3-methylsulfonyloxytetrahydrofuran **43** (0.50 g, 3 mmol) and (*R*)-α-methylbenzylamine (3.1 mL, 24.0 mmol) and following the above general procedure. Purification of the residue by column chromatography (CH_2Cl_2/MeOH 90:10) gave **44a** (0.44 g, 76%) as a pale yellow oil: ^{1}H NMR (1:1 mixture of

diastereomers) δ 1.29 (3H, d, J = 6.4), 1.30 (3H, d, J = 6.4), 1.34−1.50 (2 × 1H, br), 1.50−1.64 (1H, m), 1.54−1.78 (1H, m), 1.85−2.05 (2 × 1H, m), 3.11 −3.23 (2 × 1H, m), 3.29−3.39 (1H, dd, J = 9.0, 4.9), 3.55−3.79 (7H, m), 3.79−3.90 (2 × 1H, m), 7.13−7.37 (2 × 5H, m); ^{13}C NMR (1:1 mixture of diastereomers) δ 24.5 (2 × CH_3), 32.7 and 33.5 (2 × CH_2), 56.0 and 56.1 (2 × CH), 56.5 and 56.7 (2 × CH), 66.9 and 67.1 (2 × CH_2), 72.9 and 73.7 (2 × CH_2), 126.5 and 126.6 (4 × CH), 126.9 and 127.0 (2 × CH), 128.4 (4 × CH), 145.3 (2 × C); IR (neat) ν 3308 (NH), 3082, 3060, 3024, 2965, 2862, 1602, 1492, 1451; $[\alpha]^{20}_D$ +73.0 (*c* 1.43, $CHCl_3$); EIMS (70 eV) *m*/*z* 191 (M^+, 8), 176 ($M^+ - CH_3$, 79), 160 (28), 146 (23), 132 (6), 120 ($C_8H_{10}N$, 9), 105 (Ph(CH)Me, 100), 91 (Ph(CH), 36), 77 (C_6H_5, 76).

(3*R*,3*S*)-(1-(*S*)-Phenylethyl)tetrahydrofuran 44b. The amine **44b** was prepared using (±)-3-methylsulfonyloxytetrahydrofuran **43** (0.50 g, 3 mmol) and (*S*)-α-methylbenzylamine (3.1 mL, 24.0 mmol) and following the above general procedure. Purification of the residue by column chromatography (CH_2Cl_2/MeOH 90:10) gave **44b** (0.42 g, 74%) as a pale yellow oil: ^{1}H NMR (1:1 mixture of diastereomers) δ 1.27 (3H, d, J = 6.4), 1.28 (3H, d, J = 6.4), 1.18−1.42 (2 × 1H, br), 1.45−1.61 (1H, m), 1.61−1.75 (1H, m), 1.81−2.04 (2 × 1H, m), 3.07 −3.21 (2 × 1H, m), 3.26−3.36 (1H, dd, J = 8.7, 4.5), 3.52−3.76 (7H, m), 3.76−3.88 (2 × 1H, m), 7.10−7.35 (2 × 5H, m); ^{13}C NMR (1:1 mixture of diastereomers) δ 24.5 (2 × CH_3), 32.7 and 33.5 (2 × CH_2), 55.9 and 56.1 (2 × CH), 56.5 and 56.7 (2 × CH), 66.9 and 67.0 (2 × CH_2), 72.9 and 73.6 (2 × CH_2), 126.5 and 126.6 (4 × CH), 126.9 and 127.0 (2 × CH), 128.4 (4 × CH), 145.3 (2 × C); IR (neat) ν 3308 (NH), 3082, 3060, 3024, 2965, 2862, 1951, 1602, 1492, 1451; $[\alpha]^{20}_D$ −75.2 (*c* 1.00, $CHCl_3$); EIMS (70 eV) *m*/*z* 191 (M^+, 8), 176 ($M^+ - CH_3$, 79), 160 (28), 146 (23), 132 (6), 120 ($C_8H_{10}N$, 9), 105 (Ph(CH)Me, 100), 91 (Ph(CH), 36), 77 (C_6H_5, 76).

General Procedure for Enantioselective Nucleophilic Alkylations of *n*-Butyllithium onto *o*-Tolualdehyde in the Presence of Chiral 3APLi, 3ATFLi, or 3ATTLi. Under an argon atmosphere, *n*-BuLi (0.75 mmol, 2.5 M solution in hexanes) was added to a solution of 3AP or 3ATF or 3ATT (0.75 mmol) in THF (15 mL) at −20 °C. After stirring 20 min, a second aliquot of *n*-BuLi (1.25 mmol, 2.5 M solution in hexanes) was added dropwise to the preformed solution of lithium amide (3APLi or 3ATFLi or 3ATTLi) and the resulting mixture was stirred for 30 min at −20 °C. Then, the mixture was cooled to −78 °C and aged 30 min at this temperature. A solution of *o*-tolualdehyde (0.5 mmol) in THF (2 mL) was added at −78 °C over a 5-min period and the mixture was stirred at −78 °C for the indicated time. The medium was quenched at −78 °C with 3 M aqueous HCl solution (3 mL) and was extracted with Et_2O (3 × 10 mL) after reaching room temperature. The combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduce pressure. The residue was purified by column chromatography to give the corresponding alcohol.

The chiral ligand engaged in the reaction can be recovered: $NaHCO_3$ was added to the acidic aqueous layer followed by several drops of 4 M aqueous NaOH solution and the amine was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduce pressure.

1-*o*-Tolylpentan-1-ol 45. Purification of the residue by column chromatography (EtOAc/cyclohexane 30:70) gave 1-*o*-tolylpentan-1-ol **45** as a colorless oil: ^{1}H NMR δ 0.83 (3H, t, J = 6.8), 1.10−1.50 (4H, m), 1.50−1.70 (2H, m), 1.74 (1H, s), 2.25 (3H, s), 4.85 (1H, t, J = 6.8), 6.95−7.20 (3H, m), 7.39 (1H, d, J = 7.2); ^{13}C NMR δ 14.0 (CH_3), 19.0 (CH_3), 22.6 (CH_2), 28.1 (CH_2), 37.8 (CH_2), 70.5 (CH), 125.1, 128.2, 128.9, 130.2 (4 × CH), 134.4, 143.1 (2 × C); IR (neat) ν 3344 (OH), 2957, 2856, 1465; $[\alpha]^{20}_D$ +54.1 (*c* 0.37, $CHCl_3$) for *R*-isomer, 81% e.e. and −50.1 (*c* 0.75, $CHCl_3$) for *S*-isomer, 76% e.e. (HPLC Daicel Chiralpak OD-H, hexane/*i*-PrOH 99:1, 1.0 mL/min, 218 nm, *S*-isomer 19.5 min and *R*-isomer 21.5 min); EIMS (70 eV) *m*/*z* 178 (M^+, 11), 160 ($M^+ - H_2O$, 3), 121 ($M^+ - C_4H_9$, 100), 93 (31), 91 (C_7H_7, 14).

Acknowledgment. N.D. acknowledges the Ministère de la Recherche et de la Technologie for a Ph.D. grant.

Supporting Information Available: Copies of the ^{1}H NMR and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8005396