Structure-Selectivity Relationship in Alkyllithium−Aldehyde Condensations Using 3-Aminopyrrolidine Lithium Amides as Chiral Auxiliaries

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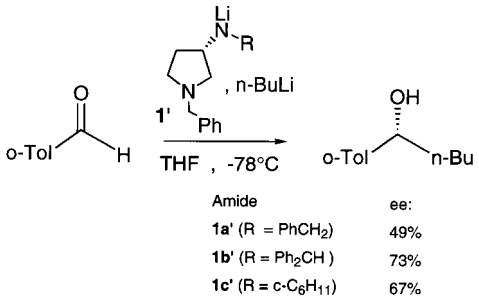
A nonracemizing route to a set of chiral 3-aminopyrrolidines, based on 4-hydroxy-(L)-proline, is described. The induction potential of the lithium amides derived from these diamines has then been investigated in the asymmetric addition of alkyllithium compounds onto various aldehydes. Enantiomeric excesses up to 76% have been obtained in the case of the condensation of *n*-butyllithium onto *o*-tolualdehyde under standard experimental conditions (THF, −78 °C). Interestingly, the presence of a second asymmetric center, such as an α-methylbenzyl group, on the lateral 3-amino group gives access, according to its configuration, to one or the other of the 1-*o*-tolylpentan-1-ol enantiomers.

Introduction

The asymmetric condensation of organometallic compounds onto carbonyl substrates has received a great deal of attention over the years.[1] Many chiral ligands have already been synthesized and tested in this type of reaction; however, because of their high reactivity, the organolithium reagents have proved to be rarely associated with efficient chiral inductions.[2] Only when very strict conditions of temperature and solvent have been employed were good selectivities reported.[2e,g−l] We have recently described our preliminary results in the asymmetric condensation of *n*-butyllithium onto aromatic aldehydes, obtained with 3-aminopyrrolidine (3-AP) lithium amides **1′**, a promising class of chiral auxiliaries.[3] The first set of results, obtained with the amides **1′** derived from commercial (*S*)-1-benzyl-3-aminopyrrolidine, has put into evidence a strong influence of the bulkiness of the 3-amino substituent (Scheme 1).

Scheme 1



A structural study by high-field ^{1}H, ^{13}C, and ^{6}Li NMR spectroscopy showed that amides **1a′** (R = $PhCH_2$) and **1b′** (R = Ph_2CH), which present very different structures in solution,[4] form nevertheless with *n*-BuLi the same type of 1:1 complex, organized around a Li_2 core linking the 3-aminopyrrolidine moiety and the butyl chain. In both complexes, the amide moieties exhibit a rigidified norbornyl-like structure (Scheme 2).

We have proposed[4] that this type of arrangement, which relies on thermodynamic grounds fully confirmed by ab initio calculations,[5] would be probably at the origin of the enantioselectivities observed with this class of chiral inductors in the precedent reaction. The BuLi-**1b′** complex (**1b″**) being somewhat tighter than the BuLi-**1a′** one (**1a″**) could explain the best ee of 1-*o*-tolylpentan-1-ol formed with **1b″** (73% vs 49% with **1a″**; Scheme 1).

We now wish to report the enantioface-differentiating reaction of *n*-butyllithium with *o*-tolualdehyde by using new 3-aminopyrrolidine lithium amides. In this study, we have first varied the substituent borne by the pyrrolidine nitrogen keeping, on the lateral amino function, a cyclohexyl or a diphenylmethyl group, which were shown as the most efficient in the case of 1-benzylamides **1′** (67 and 73%, respectively; Scheme 1). We have then studied

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(2) (a) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, 4097. (b) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R *Tetrahedron* **1971**, *27*, 905. (c) Seebach, D.; Dörr, H.; Bastani, B.; Ehrig, V. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 982. (d) 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*, 302. (e) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455. (f) Whitesell, J. K.; Bao-Rong, J. *J. Org. Chem.* **1981**, *46*, 2798. (g) Mazaleyrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585. (h) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187. (i) Kanoh, S.; Muramoto, H.; Maeda, K.; Kawaguchi, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2244. (j) Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegrass, K.; Hirsh, K. A.; Bollinger, A. M.; Grosz, A. L. *Tetrahedron* **1994**, *50*, 6109. (k) Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937. (l) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.

(3) (a) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1519. (b) Corruble, A. Ph.D. Thesis, University of Rouen, 1997.

(4) (a) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042. (b) Prigent, Y.; Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Davoust, D.; Duhamel, P. *J. Chim. Phys.* **1998**, *95*, 401.

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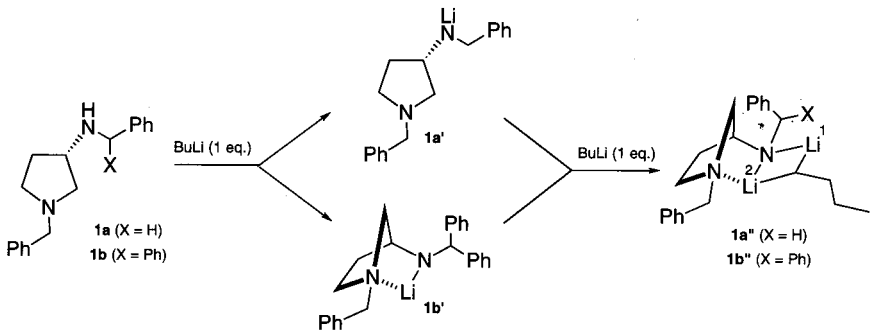
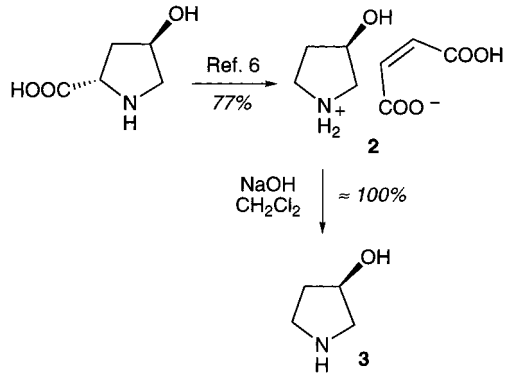
Scheme 2



the influence of a second asymmetric center on this same lateral amino function. Finally, with (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidine lithium amide **1c′** (R = c-C_6H_{11}) remaining as a chiral auxiliary, two sets of experiments have been performed: (i) condensation of a few alkyllithiums onto *o*-tolualdehyde; (ii) condensation of butyllithium onto a few aldehydes.

Syntheses of Chiral 3-Aminopyrrolidines. The synthetic route we have adopted to prepare the new chiral diamines employed in the present study relies on the decarboxylation of 4-hydroxy-(L)-proline described in the literature[6] (Scheme 3). The (*R*)-3-pyrrolidinol thus obtained was stored as the very stable maleate **2** and recovered quantitatively by action of 12 M sodium hydroxide.

Scheme 3



From **3**, three paths were developed to synthesize the final diamines (Schemes 4−6). In the first one (Scheme 4), the (*R*)-3-pyrrolidinol (**3**) was condensed onto an excess of acid chloride (CH_2Cl_2, 0 °C to RT (room temperature)) and the crude mixture of the corresponding amido alcohol/amido ester was reduced ($LiAlH_4$, THF, RT) into (*R*)-1-alkyl-3-pyrrolidinol (**4**) that can be purified by an extraction in acidic medium (yield ∼80−88%). A Mitsunobu reaction[7a,b] between the precedent alcohol and hydrazoic acid[7c] (PPh_3, DEAD, toluene, RT) proceeded with complete inversion[8] to afford the (*S*)-3-azidopyrrolidine **5**, isolated in 74−87% yield after a flash chromatography on silica gel. The reduction of azides **5** was performed cleanly by $LiAlH_4$ in ether, at room temperature, and the resulting compounds **6** (yield ∼93−98%) were transformed, without purification, into diamines **9** (R^2 = c-C_6H_{11}) and **10** (R^2 = $CHPh_2$) in two steps, as already described for (*S*)-1-benzyl-3-aminopyrrolidines **1**.[3] The imines **7** and **8** have been prepared respectively from cyclohexanone (molecular sieves in ether or toluene or Dean−Stark water trapping in toluene) or benzophenone (trans-imination[10a] with diphenylmethylenimine[10b]) and then reduced by LAH. The enantiomeric excesses of **9** and **10**, measured by ^{19}F NMR after derivatization of their lithium amides with AFPA[9a,b] according to the method previously reported,[3,9c] were over 90%.[11]

In the second path (Scheme 5), the (*R*)-3-pyrrolidinol (**3**) was condensed onto 1 equiv of *β*-naphthoyl chloride. After 2 h at 0 °C *p*-tosyl chloride (4 equiv) was added to afford amide **11**, isolated after flash chromatography in 30% yield. The tosyl group in **11** was then substituted by both enantiomers of 1-phenylethylamine (11 equiv, 110 °C) leading to amides **12**, which were finally reduced into diamines **13** in 75% yield and 93−95% ed,[12] as measured by ^1H NMR 500 MHz.

Finally, in the third synthetic route (Scheme 6), the ditosylated compound **14**, prepared by action of a large excess of *p*-tosyl chloride (5 equiv) on (*R*)-3-pyrrolidinol **3**, was substituted by morpholine at 85 °C. The resulting tosylamide **15**, dissolved in THF, was treated with sodium in liquid ammonia in the presence of *tert*-butyl alcohol,[14] to afford (*S*)-3-morpholinopyrrolidine (**16**) in a moderate 43% yield due to the difficulty to isolate this water-soluble diamine. The enantiomeric purity (100%) of this latter compound was checked once again by derivatization with AFPA.[15] During this synthesis, an unexpected N-acetylation of **16** was observed when using

(6) Houghton, P. G.; Humphrey, G. R.; Kennedy, D. J.; Craig Roberts, D.; Wright S. H. B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1421.

(7) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100. (c) *Organic Reactions*; Adams R., Bachmann W. E., Fieser L. F., Johnson J. R., Snyder H. R., Eds; Wiley & Sons, Inc.: New York, 1964; Vol. III, p 327. **WARNING!** *Hydrazoic acid is a highly toxic and volatile compound. These operations must be carried out under a well-ventilated hood.*

(8) The absence of racemization during this step was checked by derivatization, with α-fluorophenylacetic acid (AFPA),[9] of the reduction product **6e** (R^1 = o-$MeOC_6H_4$).

(9) (a) Hamman, S.; Barrelle, M.; Tetaz, F.; Béguin, C. G. *J. Fluorine Chem.* **1987**, *37*, 85. (b) Barrelle, M.; Hamman, S. *J. Chem. Res., Miniprint* **1990**, 701−709. (c) Maddaluno, J.; Corruble, A.; Leroux, V.; Plé, G.; Duhamel, P. *Tetrahedron: Asymmetry* **1992**, *3*, 1239.

(10) (a) Pickard, P. L.; Tolbert, T. L. *Organic Syntheses*; Wiley: New York, **1973**; Collect. Vol. V, p 520. (b) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

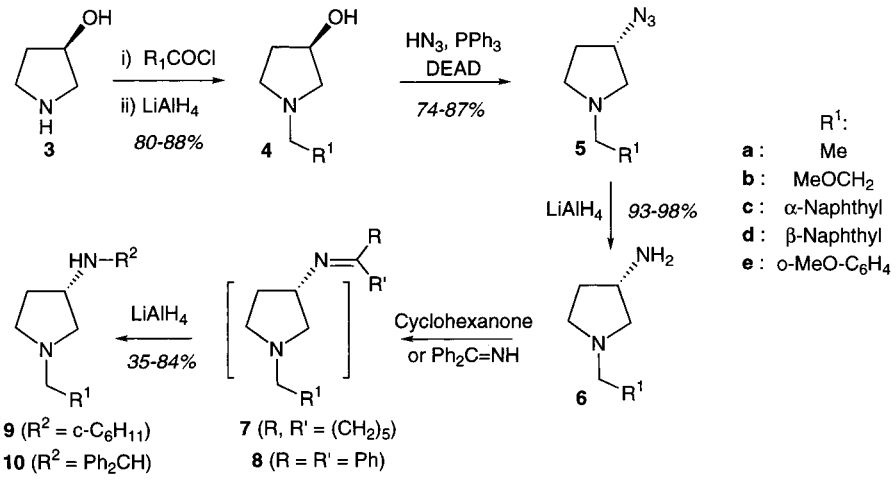
(11) The slight racemization can stem from either the reduction step or from the derivatization one (since this latter relies on basic lithium amides and a racemizable derivatizating agent).

(12) The (*R*)-1-ethyl-3-(mesyloxy)pyrrolidine, of which very nucleophilic pyrrolidine nitrogen is not deactivated by an electron-withdrawing group, is likely to undergo an intramolecular substitution leading to an aziridinium ion,[13] as the origin of a partial racemization (ee = 80%) during its reaction with benzylamine.

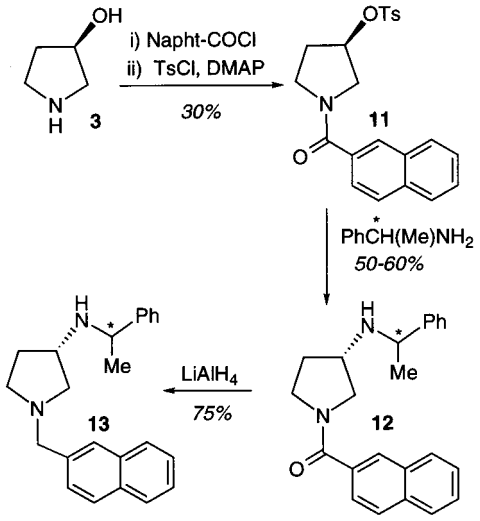
(13) Thottathil, J. K.; Moniot, J. L. *Tetrahedron Lett.* **1986**, *27*, 151.

(14) (a) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417. (b) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron* **1994**, *50*, 5579.

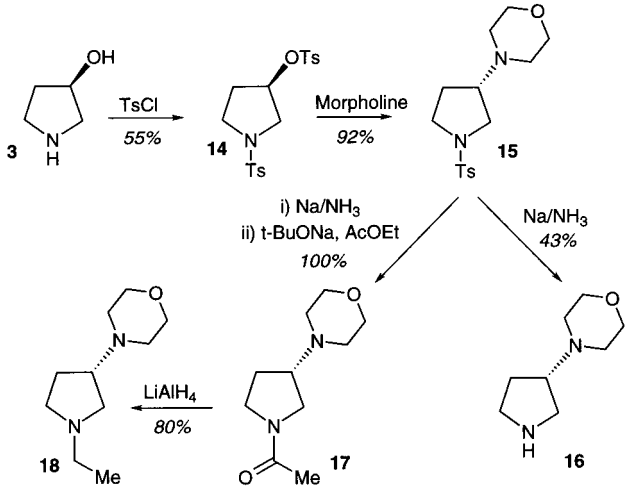
Scheme 4



Scheme 5



Scheme 6



ethyl acetate as workup solvent. This reaction is made possible by the presence of sodium *tert*-butylate since **16** does not react alone with ethyl acetate. The resulting amide **17** was finally reduced ($LiAlH_4$, THF, RT) into diamine **18** (yield ~80%).

(15) For this less bulky amine, the derivatization with AFPA did not require one to preform its lithium amide.[3]

Table 1. Synthesis of 1-*o*-Tolylpentan-1-ol by Asymmetric Addition of *n*-BuLi on *o*-TolCHO in THF at −78 °C Using 3-Aminopyrrolidine Lithium Amides

entry	amine	R^1	R^2	yield[a] (%)	ee[b] (%)
1	**9a**	Me	c-C_6H_{11}	72	63 (*R*)
2	**1c**[d]	Ph	c-C_6H_{11}	72	67 (*R*)
3	**9d**	β-naphthyl	c-C_6H_{11}	67	76[c] (*R*)
4	**9b**	$MeOCH_2$	c-C_6H_{11}	80	51 (*R*)
5	**9e**	*o*-$MeOC_6H_4$	c-C_6H_{11}	71	60 (*R*)
6	**9c**	α-naphthyl	c-C_6H_{11}	65	50 (*R*)
7	**10a**	Me	Ph_2CH	66	64 (*R*)
8	**1b**[d]	Ph	Ph_2CH	77	73 (*R*)
9	**10d**	β-naphthyl	Ph_2CH	98	64 (*R*)
10	**13a**	β-naphthyl	PhCH(Me) (*R*)	95	77[c](*R*)
11	**13b**	β-naphthyl	PhCH(Me) (*S*)	91	51[c](*S*)

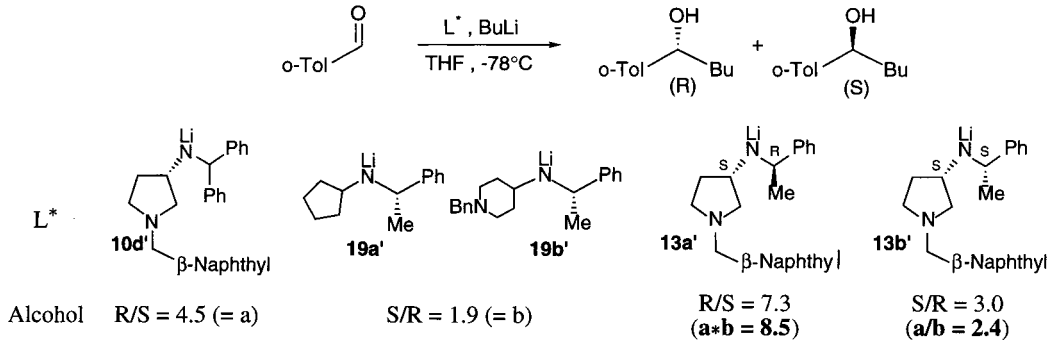
[a] Calculated by integration of C*H*O and C*H*(OH) of aldehyde and alcohol on the crude products ^1H NMR spectra. [b] Determined by direct $Eu(hfc)_3$ chiral-shift experiments. Configurations have been determined by chemical correlation from *o*-methylmandelic acid.[16] [c] Ee confirmed by HPLC using a CHIRALCEL OD column. [d] Amines prepared from commercial (*S*)-1-benzyl-3-aminopyrrolidine.[3]

Results and Discussion

In the first place, we have tested the amides derived from the precedent diamines in the condensation of *n*-BuLi onto *o*-tolualdehyde, in THF at −78 °C, with a ratio Li amide/*n*-BuLi/TolCHO of 1.5/2.5/1.0. These conditions were found optimal in our preliminary results using (*S*)-1-benzyl-3-(benzylamino)pyrrolidine **(1a)**.[3] The values are reported in Table 1.

Comparison of entries 1−3 and 7−9 of Table 1 shows that there is no simple rule for the variation of enantioselectivity with R^1: With a cyclohexyl group on the lateral nitrogen, the ee slightly increases when R^1 goes from an alkyl substituent (Me) to an aromatic one (Ph) and reaches a maximum (76%) when the aromatic shield is more important (β-naphthyl). With a 3-((diphenylmethyl)amino) group, the selectivity is the same for R^1 being Me or β-naphthyl and becomes a little superior (73%) for R^1 = Ph. Entries 1, 2 and 4, 5 illustrate the negative effect of a supplementary coordinating substituent such as a methoxy. This same observation has already been made for the group borne by the lateral nitrogen in the condensation of *n*-BuLi onto benzaldehyde.[3] Finally, replacing the β-naphthyl group by its α isomer decreases the selectivity (entries 3, 6). In conclusion, substituting the phenyl of the original benzyl group

Table 2

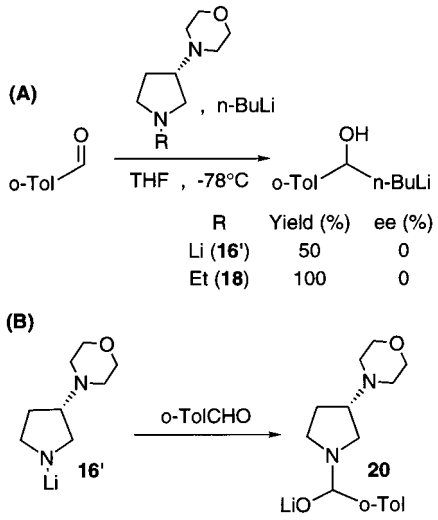


borne by the pyrrolidinic nitrogen by various R^1 groups does not improve significantly the selectivities.[3]

We then decided to get a closer look to R^2 influence testing, in the same reaction, the diamines **13** possessing a second asymmetric center at the α-position of the 3-nitrogen (entries 10, 11). While the diastereoisomer (*S*,*R*)-**13a** leads to 1-*o*-tolylpentan-1-ol with 77% ee in favor of the usual *R* enantiomer, its (*S*,*S*) counterpart **13b** decreases the selectivity to 51% providing the *S* alcohol this time. These results could be examined in light of the "matched/mismatched" concept introduced, for aldolization reactions between two chiral substrates, by Masamune *et al.*[17a−c] and later extended to intramolecular situations (such as in **13**) as the "internal cooperativity of chirality" by Togni and colleagues.[17d−f] Inductions brought about by each single asymmetric center have been estimated resorting to amines **10d** ratio on one hand and **19a**,**b** on the other. Monoamines **19**, derived from 1-phenylethylamine,[18] are structurally related to **13** through the cyclopentyl and *N*-benzylpiperidinyl groups which "mimic" the pyrrolidinic nucleus. The addition of *n*-BuLi to *o*-tolualdehyde, in the presence of amides **10d′** and **19′**, afforded the two enantiomers of the corresponding alcohol in 4.5/1.0 (=*a*) and 1.0/1.9 (=*b*) ratios, respectively (Table 2). The good agreement between the *ab* product (=8.5) and the *a*/*b* ratio (=2.4) and the selectivities obtained with the diastereoisomers **13′** (7.3 for **13a′** and 3.0 for **13b′**) indicate that such intramolecular systems nicely fits within the frame of the Masamune/Togni theory.

Finally, the diamines **16** and **18** were also tested in the reaction of *n*-BuLi with *o*-tolualdehyde (Scheme 7A). With lithium amide **16′**, the condensation yield remains moderate. This is probably due to the direct addition of the very nucleophilic amide onto the aldehyde, leading to the lithium α-amino alcoholate **20** (Scheme 7B). Such a reaction is well-known in the literature[19] and has even been put into evidence for the amide derived from (*S*)-1-benzyl-3-(benzylamino)pyrrolidine (**1a**).[3] With the ditertiary diamine **18**, this reaction becomes impossible and

Scheme 7



the conversion into 1-*o*-tolylpentan-1-ol is thus quantitative. In both cases, there was no induction and this seems to underline the importance of a secondary lateral amino group in the 3-aminopyrrolidinic system.

In a next step, the asymmetric addition of various alkyllithium compounds to aldehydes was carried out in the presence of (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidine lithium amide **1c′**, one of the best auxiliaries among the different 3-aminopyrrolidines tested until now and easily prepared from commercial (*S*)-1-benzyl-3-aminopyrrolidine. The results are summarized in Table 3.

A special emphasis has then been put on the condensation of *n*-butyllithium onto various aldehydes. A clear dependence between the enantioselectivity and the bulkiness of the aromatic aldehyde's ortho substituent is observed comparing entries 1, 2, and 3. The presence of a meta substituent, such as in β-naphthaldehyde, leads to the corresponding alcohol in only 33% ee (entry 4) while pivalaldehyde affords a poor selectivity (entry 5). Interestingly, the selectivity increases using methyl-

(16) (a) Colon, D. F.; Pickard, S. T.; Smith, H. E. *J. Org. Chem.* **1991**, *56*, 2322. (b) Valnot, J. Y. Unpublished results.

(17) (a) Masamune, S.; Asrof Ali, Sk.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (b) Masamune, S.; Choy, W. *Aldrichim. Acta* **1982**, *15*, 47. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (d) Pastor, S. D.; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333. (e) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649. (f) Pastor, S. D.; Togni, A. *Helv. Chim. Acta* **1991**, *74*, 905.

(18) Diamines **19** were prepared by condensation of 1-phenylethylamine onto cyclopentanone and *N*-benzylpiperidinone, respectively, and then reduction ($LiAlH_4$) of the resulting imines.

(19) (a) Kowalsky, C.; Creary, X.; Rollin, A. J.; Carmel Burke, M. *J. Org. Chem.* **1978**, *43*, 2601. (b) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213. (c) Seebach, D.; Schiess, M. *Helv. Chim. Acta* **1982**, *65*, 2598. (d) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (e) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1983**, *24*, 5465. (f) Seebach, D.; Weber, T. *Tetrahedron Lett.* **1983**, *24*, 3315. (g) Seebach, D.; Beck, A. K.; Schiess, M.; Widler, L.; Wonnacott, A. *Pure Appl. Chem.* **1983**, *55*, 1807. (h) Seebach, D.; Betschart, C.; Schiess, M. *Helv. Chim. Acta* **1984**, *67*, 1593. (i) Seebach, D.; Weber, T. *Helv. Chim. Acta* **1984**, *67*, 1650. (j) Seebach, D.; Schiess, M.; Schweizer, W. B. *Chimia* **1985**, *39*, 272. (k) Comins, D. L. *Synlett* **1992**, 615.

Table 3. Asymmetric Addition of Alkyllithium Compounds to Aldehydes Using (*S*)-1-Benzyl-3-aminopyrrolidine Lithium Amide 1c′

entry	R^3Li	R^4CHO	yield[a] (%)	ee[b] (%)
1	*n*-BuLi	PhCHO	80	42 (*R*)
2	*n*-BuLi	α-naphthyl-CHO	65	55[c]
3	*n*-BuLi	o-MeC_6H_4CHO	72 (63)	67 (*R*)
4	*n*-BuLi	*β*-naphthyl-CHO	69	33 (*R*)
5	*n*-BuLi	*t*-BuCHO	(32)	17[c]
6	MeLi	PhCHO	76	57 (*R*)
7	PhLi	*n*-PrCHO	(32)	28 (*S*)
8	PhLi	*n*-BuCHO	(60)	18 (*S*)

[a] Calculated by integration of C*H*O and C*H*(OH) of aldehyde and alcohol on the crude products of ^{1}H NMR spectra (between parentheses isolated yields after flash chromatography). [b] Determined by direct Eu(hfc)$_3$ chiral-shift experiments and/or HPLC. [c] Configuration to be determined.

lithium instead of *n*-butyllithium (compare entries 1 and 6). As expected, the condensation of phenyllithium onto pentanal inverses the sense of induction with respect to the *n*-BuLi/PhCHO couple (entries 1 and 8); nevertheless, the ee is lower, probably because of the floppy character of the butyl chain in pentanal, less organized than the aromatic group of benzaldehyde. For the PhLi/butanal system, the selectivity is slightly better but remains weak (entry 7), but it is worth underlining that even enolizable aldehydes provide fair to good condensation yields in these conditions.

In conclusion, we have shown that chiral 3-aminopyrrolidine lithium amides bearing bulky substituents on the 3-amino position induce good selectivities (up to 77%) in the condensation of *n*-butyllithium onto *o*-tolualdehyde, under standard conditions (THF, −78 °C). Within the framework of the complexes evidenced previously (Scheme 2),[20] the nitrogen substituents should play a key role in the control of the enantioface differenciation during the transition state. From the experimental results reported here, it is clear that the substituents on the lateral amino group are more important than those borne by the pyrrolidinic one. This could suggest that the aldehyde−lithium preliminary docking step[1j] is likely to take place rather on Li^1, which stands in close proximity to the lateral group, than on Li^2 (Scheme 2). This hypothesis leads to the same conclusions than that previously drawn from purely steric arguments.[4] The dramatic influence of an eventual asymmetric center on this lateral substituent makes also full sense in this context. NMR spectroscopic studies are currently under way on amides **13′** to elucidate the role of this second chiral center.

Experimental Section

^{1}H NMR spectra were generally recorded at 200 or 500 MHz; chemical shifts (*δ*) are given in parts per million (ppm), and the coupling constants (*J*), in hertz. ^{13}C NMR spectra were recorded at 50 MHz. The solvent was $CDCl_3$, unless otherwise indicated. IR spectra were realized by transmission. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane (CH_4), isobutane (*t*-BuH), or ammonia (NH_3) were used for chemical ionization (CI). Optical rotations, [α], were measured in quartz cells (d = 1 dm), using Na and Hg lights, with the solvent and concentration indicated.

Compounds **2** and **3** have already been described: (*R*)-3-hydroxypyrrolidinium hydrogen maleate (**2**), see ref 6; (*R*)-3-hydroxypyrrolidine **3**, [2799-21-5].

Synthesis of Diamines 9 and 10. General Procedure for the Preparation of (*R*)-1-Alkyl-3-hydroxypyrrolidines 4. To a suspension of (*R*)-3-hydroxypyrrolidinium hydrogen maleate (**2**) (10.0 g, 49.3 mmol) in CH_2Cl_2 (250 mL) was added, at room temperature, 35% NaOH (16 mL, 197 mmol, 4.0 equiv). The mixture was stirred 1 h with K_2CO_3 (∼50 g) and charcoal and then filtered on Celite. The solid phase was extracted with CH_2Cl_2 (2 × 100 mL). Evaporation gave a yellow oil (4.11 g, 96%) which was utilized without further purification.

To a solution of the above crude pyrrolidinol (4.11 g, 47.2 mmol) and pyridine (18 mL, 222 mmol, 4.7 equiv) in CH_2Cl_2 (250 mL) was added, at 0 °C and under an argon atmosphere, the acid chloride (98 mmol, 2.1 equiv) dissolved in 15 mL of CH_2Cl_2. After 4 h of stirring at room temperature, the mixture was washed with water (50 mL) and then saturated $NaHCO_3$ (2 × 50 mL). The aqueous extracts were saturated by NaCl and extracted with CH_2Cl_2 (3 × 100 mL). After drying (Na_2SO_4), filtering, and evaporating, a very colored oil was obtained. This mixture of amido alcohol and amido ester was reduced without purification.

A THF (100 mL) solution of the crude amide was added to a stirred suspension of $LiAlH_4$ (6.27 g, 165.3 mmol, 3.5 equiv) in THF (120 mL) at 0 °C. After being stirred for 5 h at room temperature, the reaction mixture was cooled to 0 °C and quenched by the successive addition of 5.5 mL of H_2O, 5.5 mL of 4 M aqueous NaOH, and 16.5 mL of H_2O. The resulting white precipitate was removed by filtration and then extracted with CH_2Cl_2 (2 × 100 mL). Evaporation gave an oil, purified by an acid extraction followed by basic treatment (except for (*R*)-1-ethyl-3-hydroxypyrrolidine (**4a**), sufficiently clean to be used as such): A solution of the crude oil in Et_2O (150 mL) was vigorously stirred with 1 M HCl (100 mL) for 10 min. The ethereal phase was extracted with H_2O (100 mL). The aqueous acidic layer was extracted with AcOEt (3 × 100 mL) and triturated with solid $NaHCO_3$ and then with 4 M NaOH. Amino alcohol was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated.

***(R)*-1-Ethyl-3-hydroxypyrrolidine (4a):** yield (crude) 83% (yellow oil); ^{1}H NMR *δ* 4.33−4.24 (m, 1H), 3.57 (br s, OH), 2.87−2.74 (m, 1H), 2.55 (AB, 2H, J = 10.2, 5.2, 2.4), 2.44 (q, 2H, J = 7.2), 2.29−2.06 (m, 2H), 1.72−1.60 (m, 1H), 1.06 (t, 3H, J = 7.2); ^{13}C NMR *δ* 70.5, 62.6, 52.2, 49.9, 34.7, 13.4; IR (neat) 3354, 2988, 2806 cm^{-1}; CIMS (*t*-BuH) *m*/*z* (relative intensity) 116 (M + H$^+$, 100).

***(R)*-1-(2-Methoxyethyl)-3-hydroxypyrrolidine (4b):** yield (crude) 88% (GC purity ∼96%; colorless oil after Kugelrohr distillation (P ∼ 0.1 mmHg, T ∼ 85 °C) of a sample for spectral characterization); $[\alpha]_D^{25}$ −4.8 (*c* 4.85, CH_2Cl_2); ^{1}H NMR (C_6D_6) *δ* 4.24−4.15 (m, 1H), 3.67 (br s, OH), 3.31 (t, 2H, J = 5.8), 3.10 (s, 3H), 2.77 (td, 1H, J = 8.8, 5.0), 2.72 (dd, 1H, J = 9.9, 2.7), 2.51 (t, 2H, J = 5.8), 2.37 (dd, 1H, J = 9.9, 5.5), 2.08 (td, 1H, J = 8.5, 6.7), 2.01−1.84 (m, 1H), 1.77−1.57 (m, 1H); ^{13}C NMR (C_6D_6) *δ* 71.8, 71.0, 63.9, 58.4, 55.5, 53.3, 35.4; IR (neat) 3384, 2947, 2816, 1114 cm^{-1}; EIMS *m*/*z* (relative intensity) 145 (M$^{+\bullet}$, 8), 100 ([M − $MeOCH_2$]$^+$, 100).

***(R)*-1-(1-Naphthylmethyl)-3-hydroxypyrrolidine (4c):** yield 80% (viscous yellow oil); $[\alpha]_D^{25}$ −0.11 (*c* 4.50, toluene); ^{1}H NMR *δ* 8.26−8.21 (dd, 1H), 7.88−7.33 (m, 2H), 7.57−7.36 (m, 4H), 4.22−4.13 (m, 1H), 4.00 (s, 2H), 3.24 (s, OH), 2.84 (td, 1H, J = 8.6, 5.2), 2.56 (AB, 2H, J = 10.1, 5.2, 2.4), 2.36 (td, 1H, J = 8.7, 6.5), 2.18−2.00 (m, 1H), 1.72−1.56 (m, 1H); ^{13}C NMR *δ* 134.3, 133.5, 131.9, 128.2, 127.6, 126.5, 125.6, 125.3, 124.9, 124.0, 70.7, 62.8, 57.7, 52.4, 34.5; IR (neat) 3382, 3044, 2944, 2796, 1937, 1827, 1596, 1510 cm^{-1}; CIMS (*t*-BuH) *m*/*z* (relative intensity) 228 (M + H$^+$, 100).

***(R)*-1-(2-Naphthylmethyl)-3-hydroxypyrrolidine (4d):** yield 82% (white solid); mp 87−88 °C; $[\alpha]_D^{25}$ −0.47 (*c* 4.27,

(20) We have checked that the 1:1 stoichiometry of the complex was not altered by an excess of BuLi (up to 6 eq.)[4a] and that a 1:1 ratio provides 1-o-tolylpentanol with the same enantiomeric excess in the cases of amides **1c** and **9c**.[3b] Therefore, we believe the key species in this reaction to be the 1: 1 lithium amide/alkyllithium complex, which reacts faster toward the aldehyde than the regular butyllithium aggregates (tetramer/dimer) present in the solution.

toluene); ^{1}H NMR δ 7.81−7.71 (m, 4H), 7.48−7.39 (m, 3H), 4.35−4.26 (m, 1H), 2.92−2.81 (m, 1H), 2.62 (AB, 2H, J = 10.1, 5.3, 1.9), 2.66 (s, OH), 2.38−2.26 (m, 1H), 2.26−2.09 (m, 1H), 1.78−1.64 (m, 1H); ^{13}C NMR δ 135.9, 133.1, 132.4, 127.6, 127.5, 127.4, 127.1, 127.0, 125.7, 125.4, 70.7, 62.7, 60.2, 52.3, 34.6; IR (KBr) 3144, 2844, 1947, 1598, 1504, 1346 cm^{-1}; EIMS m/z (relative intensity) 227 ($M^{+\bullet}$, 38), 141 (100). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.29; H, 7.49; N, 6.17. Found: C, 78.92; H, 7.60; N, 6.10.

(*R*)-1-(*o*-Methoxyphenylmethyl)-3-hydroxypyrrolidine (4e): yield 80% (yellow oil); $[\alpha]_D^{25}$ −3.5 (*c* 4.39, toluene); ^{1}H NMR δ 7.30−7.16 (m, 2H), 6.93−6.81 (m, 2H), 4.30−4.21 (m, 1H), 3.78 (s, 3H), 3.70 (s, OH), 3.64 (s, 2H), 2.83 (td, 1H, J = 8.6, 5.2), 2.60 (AB, 2H, J = 10.3, 5.0, 3.1), 2.36 (td, 1H, J = 8.7, 6.5), 2.22−2.05 (m, 1H), 1.74−1.59 (m, 1H); ^{13}C NMR δ 157.4, 130.4, 128.0, 120.1, 110.1, 126.2, 70.8, 62.7, 55.1, 53.2, 52.3, 34.7; IR (neat) 3380, 2942, 2834, 1600 cm^{-1}; EIMS m/z (relative intensity) 207 ($M^{+\bullet}$, 42), 121 (100), 91 (71).

General Procedure for the Preparation of (*S*)-1-Alkyl-3-azidopyrrolidines 5. Preparation of Hydrazoic Acid Solutions. WARNING! *Hydrazoic acid is a highly toxic and volatile compound.*[7c] *These operations must be carried out under a well-ventilated hood.*

In a 250 mL three-necked-flask equipped with a dropping funnel, a thermometer, and a gas outlet tube, a paste was prepared from NaN_3 (13 g, 200 mmol) and 13 mL of hot water. To this paste, benzene (80 mL) was added, and the mixture was cooled to 0 °C. While it was vigorously stirred, concentrated sulfuric acid (5.4 mL, 100 mmol, 0.5 equiv) was added dropwise, maintaining temperature below 10 °C. The reaction mixture was stirred for 15 min, and the organic layer was decanted and then stored at 4 °C, on sodium sulfate and under an argon atmosphere. Its concentration, generally between 1.2 and 1.9 M, was determined with 1 M NaOH solution in the presence of phenolphthaleine and distilled water (20 mL for 2 mL of hydrazoic acid solution).

To a solution of (*R*)-1-alkyl-3-hydroxypyrrolidine (**4**) (10 mmol) and triphenylphosphine (3.41 g, 13 mmol, 1.3 equiv) in anhydrous benzene or toluene (60 mL) was added, at room temperature, hydrazoic acid solution (10 mL of 1.88 M solution, 18.8 mmol, 1.9 equiv) and then diethyl azodicarboxylate (2.26 g, 13 mmol, 1.3 equiv) dissolved in 24 mL of solvent. After 5 h at room temperature, the precipitate of diethyl hydrazodicarboxylate was filtered and the resulting filtrate was extracted with 1 M HCl (3 × 25 mL). The combined extracts were washed with a mixture Et_2O/AcOEt (∼70/30) and triturated with solid $NaHCO_3$ and then with 4 M NaOH before extraction by Et_2O or CH_2Cl_2 (3 × 100 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated to afford an oil, purified by flash chromatogaphy on silica gel, except for (*S*)-1-ethyl-3-azidopyrrolidine (**5a**).

(*S*)-1-Ethyl-3-azidopyrrolidine (5a): yield 74% (oil); ^{1}H NMR δ 3.99−3.88 (m, 1H), 2.72−2.60 (m, 1H), 2.57 (AB, 2H, J = 10.3, 6.2, 3.8), 2.50−2.31 (m, 1H), 2.41 (q, 2H, J = 7.2), 2.20−2.02 (m, 1H), 1.85−1.70 (m, 1H), 1.02 (t, 3H, J = 7.2); ^{13}C NMR δ 59.7, 59.2, 52.3, 49.6, 30.8, 13.6; IR (neat) 2968, 2098 cm^{-1}; CIMS (NH_3) m/z (relative intensity) 141 ($M + H^+$, 100).

(*S*)-1-(2-Methoxyethyl)-3-azidopyrrolidine (5b): yield 75% (green oil; flash 99/1 CH_2Cl_2/MeOH); $[\alpha]_D$ +18.0, $[\alpha]_{578}$ +18.7, $[\alpha]_{546}$ +21.0, $[\alpha]_{436}$ +32.4 (*c* 2.13, CH_2Cl_2, T = 26 °C); ^{1}H NMR δ 4.03−3.92 (m, 1H), 3.44 (t, 2H, J = 5.6), 3.30 (s, 3H), 2.82 (dd, 1H, J = 10.1, 6.5), 2.72−2.49 (m, 5H), 2.24−2.06 (m, 1H), 1.87−1.71 (m, 1H); ^{13}C NMR δ 71.1, 59.7, 59.6, 58.7, 54.9, 53.0, 30.7; IR (film) 2926, 2812, 2100 cm^{-1}; EIMS m/z (relative intensity) 170 ($M^{+\bullet}$, 7), 125 (100), 97 (27), 42 (66).

(*S*)-1-(1-Naphthylmethyl)-3-azidopyrrolidine (5c): yield 87% (green oil; flash 99.5/0.5 CH_2Cl_2/MeOH); ^{1}H NMR δ 8.32−8.27 (m, 1H), 7.89−7.75 (m, 2H), 7.58−7.38 (m, 4H), 4.06 (AB, 2H, J = 13.0), 3.95−3.84 (m, 1H), 2.87−2.69 (m, 3H), 2.52 (td, 1H, J = 8.6, 6.0), 2.30−2.12 (m, 1H), 1.97−1.81 (m, 1H); ^{13}C NMR δ 134.4, 133.6, 132.0, 126.2, 127.8, 126.4, 125.7, 125.5, 125.0, 124.4, 59.7, 59.6, 57.8, 52.6, 31.0; IR (neat) 2798, 2094, 1596, 1508 cm^{-1}; CIMS (*t*-BuH) m/z (relative intensity) 253 ($M + H^+$, 100).

(*S*)-1-(2-Naphthylmethyl)-3-azidopyrrolidine (5d): with (*R*)-1-(2-naphthylmethyl)-3-hydroxypyrrolidine (**4d**) being weakly soluble in toluene, it was necessary to add THF (15−20 mL) before PPh_3: yield 86% (green oil; flash 99.5−99.0/0.5−1.0 CH_2Cl_2/MeOH); $[\alpha]_D$ +8.6, $[\alpha]_{578}$ +8.9, $[\alpha]_{546}$ +9.8, $[\alpha]_{436}$ +13.7 (*c* 4.31, CH_2Cl_2, T = 25 °C); ^{1}H NMR δ 7.82−7.73 (m, 4H), 7.50−7.40 (m, 3H), 3.99−3.89 (m, 1H), 3.78 (AB, 2H, J = 12.6), 2.86−2.75 (m, 1H), 2.71 (AB, 2H, J = 10.3, 6.0, 4.1), 2.50 (td, 1H, J = 8.5, 6.0), 2.31−2.13 (m, 1H, J = 8.2), 1.97−1.82 (m, 1H); ^{13}C NMR δ 136.1, 133.2, 132.6, 127.8, 127.5, 126.8, 125.8, 125.4, 59.8, 59.7, 59.4, 52.5, 31.0; IR (film) 2960, 2796, 2100 cm^{-1}; EIMS m/z (relative intensity) 252 ($M^{+\bullet}$, 12), 196 (16), 141 (100), 115 (17), 83 (11).

(*S*)-1-((*o*-Methoxyphenyl)methyl)-3-azidopyrrolidine (5e): yield 81% (yellow oil; flash 99/1 CH_2Cl_2/MeOH); ^{1}H NMR δ 7.36−7.18 (m, 2H), 6.97−6.83 (m, 2H), 4.02−3.88 (m, 1H), 3.80 (s, 3H), 3.69 ("AB", 2H, J = 14.1), 2.85−2.73 (m, 1H), 2.79 (1/2AB, 1H, J = 10.3, 6.1), 2.66 (1/2AB, 1H, J = 10.1, 4.0), 2.54 (td, 1H, J = 8.6, 5.9), 2.28−2.10 (m, 1H), 1.94−1.78 (m, 1H); ^{13}C NMR δ 157.2, 130.0, 127.8, 120.1, 110.1, 126.2, 59.7, 59.2, 52.7, 52.3, 55.1, 30.8; IR (film) 2954, 2796, 2100 cm^{-1}; EIMS m/z (relative intensity) 232 ($M^{+\bullet}$, 10), 146 (61), 121 (100), 91 (69).

General Procedure for the Preparation of (*S*)-1-Alkyl-3-aminopyrrolidines 6. An ethereal solution (50 mL) of (*S*)-1-alkyl-3-azidopyrrolidine **5** (10 mmol) was added dropwise to a suspension of $LiAlH_4$ (1.33 g, 35 mmol, 3.5 equiv) in 30 mL of Et_2O. The mixture was stirred at room temperature for 3 h, cooled to 0 °C, and then quenched by 1.2 mL of water, 1.2 mL of 4 M NaOH, and 3.5 mL of water. The white precipitate was removed by filtration and extracted by AcOEt or CH_2Cl_2 (3 × 50 mL). The crude amine was utilized without purification.

(*S*)-1-Ethyl-3-aminopyrrolidine (6a): yield 93% (oil); ^{1}H NMR δ 3.43−3.31 (m, 1H), 2.59 (dd, 1H, J = 9.5, 6.6), 2.61−2.49 (m, 1H), 2.41−2.24 (m, 1H), 2.33 (q, 1H, J = 7.3), 2.32 (q, 1H, J = 7.1), 2.15 (dd, J = 9.6, 4.4), 2.14−1.97 (m, 1H), 1.82 (broad s, NH_2), 1.42−1.26 (m, 1H), 0.96 (t, 3H, J = 7.2); ^{13}C NMR δ 63.4, 52.8, 50.5, 49.9, 34.8, 13.5; IR (film) 3350, 3280, 2968, 2796 cm^{-1}; EIMS m/z (relative intensity) 114 ($M^{+\bullet}$, 34), 99 (12), 71(100), 56 (21).

(*S*)-1-(2-Methoxyethyl)-3-aminopyrrolidine (6b): yield 98% (green oil); $[\alpha]_D^{25}$ +3.6 (*c* 4.58, CH_2Cl_2); ^{1}H NMR δ 3.50−3.36 (m, 1H), 3.39 (t, 2H, J = 5.7), 3.26 (s, 3H), 2.72 (dd, 1H, J = 9.3, 6.7), 2.65−2.39 (m, 4H), 2.20 (dd, 1H, J = 9.4, 4.9), 2.14−2.01 (m, 1H), 1.45−1.29 (m, 1H + NH_2); ^{13}C NMR δ 71.0, 64.2, 58.6, 55.4, 53.5, 50.6, 34.8; IR (film) 3350, 2928, 2812 cm^{-1}; EIMS 145 ($M + H^+$, 1), 112 (20), 99 (100), 70 (16), 58 (19); CIMS (*t*-BuH) m/z (relative intensity) 145 ($M + H^+$, 100).

(*S*)-1-(1-Naphthylmethyl)-3-aminopyrrolidine (6c): yield 96% (oil); $[\alpha]_D^{25}$ −1.2 (*c* 5.06, CH_2Cl_2); ^{1}H NMR δ 8.30−8.25 (m, 1H), 7.86−7.73 (m, 2H), 7.55−7.35 (m, 4H), 4.00 (s, 2H), 3.50−3.39 (m, 1H), 2.82−2.66 (m, 2H), 2.47 (td, 1H, J = 8.7, 6.3), 2.36 (dd, 1H, J = 9.2, 4.0), 2.25−2.07 (m, 1H), 1.53−1.37 (m, 1H), 1.45 (broad s, NH_2); ^{13}C NMR δ 134.8, 133.4, 132.0, 128.1, 127.4, 126.2, 125.4, 125.2, 124.9, 124.2, 63.8, 58.0, 52.9, 50.7, 34.9; IR (film) 3328, 2960, 2788 cm^{-1}; EIMS m/z (relative intensity) 226 ($M^{+\bullet}$, 25), 209 (12), 141 (100), 182 (33).

(*S*)-1-(2-Naphthylmethyl)-3-aminopyrrolidine (6d): yield 98% (green oil); ^{1}H NMR δ 7.82−7.72 (m, 4H), 7.50−7.37 (m, 3H), 3.71 (AB, 2H, J = 13.1), 3.54−3.42 (m, 1H), 2.73 (dd, 1H, J = 9.2, 6.5), 2.77−2.65 (m, 1H), 2.48 (td, 1H, J = 8.5, 6.1), 2.30 (dd, 1H J = 9.5, 4.5), 2.26−2.08 (m, 1H), 1.54−1.39 (m, 1H + NH_2); ^{13}C NMR δ 136.6, 133.1, 132.5, 127.6, 127.5, 127.4, 127.0, 126.8, 125.7, 125.3, 63.8, 60.4, 53.0, 50.7, 34.9; IR (film) 3360, 3052, 2954, 2790 cm^{-1}; EIMS m/z (relative intensity) 226 ($M^{+\bullet}$, 21), 209 (21), 141 (100).

(*S*)-1-((*o*-Methoxyphenyl)methyl)-3-aminopyrrolidine (6e): yield 97% (yellow oil); $[\alpha]_D^{25}$ +0.35 (*c* 5.07, CH_2Cl_2); ^{1}H NMR δ 7.34−7.15 (m, 2H), 6.93−6.80 (m, 2H), 3.79 (s, 3H), 3.63 (s, 2H), 3.53−3.41 (m, 1H), 2.76 (dd, 1H, J = 9.4, 6.3), 2.71 (td, 1H, J = 8.6, 5.7), 2.51 (td, 1H, J = 8.5, 6.1), 2.31 (dd, 1H, J = 9.4, 4.5), 2.25−2.07 (m, 1H), 1.52−1.36 (m, 1H + NH_2); ^{13}C NMR δ 157.2, 130.0, 127.6, 120.0, 110.0, 126.8, 63.7,

55.1, 50.8, 53.2, 52.9, 35.0; IR (film) 3364, 3272, 2952, 2790 cm^{-1}; EIMS *m/z* (relative intensity) 206 ($M^{+\bullet}$, 5), 121 (100), 91 (37).

General Procedure for the Preparation of (*S*)-1-Alkyl-3-(alkylamino)pyrrolidines 1,[3] 9, and 10. Imines 7 and 8 were prepared according to one of the three methods described below:

Method A: A solution of (*S*)-1-alkyl-3-aminopyrrolidine **6** (10 mmol) and aldehyde or ketone (30 mmol, 3 equiv) in Et_2O or toluene (25 mL) was stirred overnight, at room temperature, with 4 Å molecular sieves and under an argon atmosphere.

Method B: In a system equipped with a Dean−Stark trap arranged for azeotropic removal of water, (*S*)-1-alkyl-3-aminopyrrolidine **6** (10 mmol) and cyclohexanone (2.94 g, 30 mmol, 3 equiv) were dissolved in toluene (20 mL) and heated to reflux overnight.

Method C: To an Et_2O solution (36 mL) of (*S*)-1-alkyl-3-aminopyrrolidine **6** (10 mmol) was added, at room temperature, ethereal 2.4 M HCl (4.2 mL, 10 mmol, 1 equiv). The mixture was stirred for 30 min and then concentrated. The chlorhydrate was taken up in 25 mL of CH_2Cl_2; to this suspension was added diphenylmethylenimine (1.99 g, 11 mmol, 1.1 equiv) dissolved in 18 mL of CH_2Cl_2. After 12 h at room temperature, the mixture was filtered on Celite and the filtrate was concentrated.

In all the cases, imines **7** or **8** were reduced without purification. For methods A and B, a 0.5 mL aliquot of the resulting solutions was concentrated for spectral characterization of crude imines.

The solution of imine **7** or **8** and excess of aldehyde or ketone in Et_2O or toluene was added, at 0 °C, to a stirred suspension of $LiAlH_4$ (1.71 g, 45 mmol, 4.5 equiv) in THF (59 mL). After 3 h at room temperature, the reaction was quenched at 0 °C with H_2O (1.5 mL), 4 M NaOH (1.5 mL), and H_2O (4.5 mL). The resulting white precipitate was removed by filtration, and the filtrate was concentrated. The residue was dissolved in Et_2O, and the diamine was extracted by 1 N hydrochloric acid. The acidic solution was washed with Et_2O or AcOEt and triturated with solid $NaHCO_3$ and then with 4 M NaOH. The diamine was then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and, after filtration, evaporated to give an oil chromatographed on silica gel (eluent: $MeOH/CH_2Cl_2$) or alumina (eluent: AcOEt/EP).

(*S*)-1-Benzyl-3-(benzylamino)pyrrolidine (1a):[3] yield 91% (orange oil, GC purity ∼98%); $[\alpha]_D$ +2.1, $[\alpha]_{578}$ +2.2 (*c* 2.14, $CHCl_3$, $T = 27$ °C); ^{1}H NMR (360 MHz): δ 7.25 (m, 10H), 3.71 (s, 2H), 3.60 (dd_{AB}, 2H), 3.35 (m, 1H), 2.75 (dd, 1H, J = 9.0, 6.5), 2.64 (m, 1H), 2.52 (m, 1H), 2.40 (dd, 1H, J = 9.0, 5.0), 2.13 (m, 1H), 1.75 (s, NH), 1.61 (m, 1H); ^{13}C NMR δ 139.9, 138.6, 128.5, 128.0, 127.9, 126.6, 60.3, 60.1, 56.4, 52.7, 52.0, 31.8; IR (film) 3304, 2914, 2788, 1950, 1872, 1810, 1674 cm^{-1}; EIMS *m/z* (relative intensity) 266 ($M^{+\bullet}$, 3), 91 (100); CIMS (CH_4) *m/z* (relative intensity) 267 ($M + H^+$, 100); HRMS calcd for $C_{18}H_{22}N_2$ 266.1783, found 266.1783.

(*S*)-1-Benzyl-3-((diphenylmethyl)amino)pyrrolidine (1b):[3] yield 69% (viscous green oil), after purification by acid extraction and then flash chromatography on silica gel (eluent: 87.0/12.5/0.5 EP/AcOEt/NEt_3); $[\alpha]_D^{21}$ −6.8 (*c* 4.34, CH_2Cl_2); ^{1}H NMR δ 7.41−7.15 (m, 15H), 4.83 (s, 1H), 3.57 (AB, 2H, J = 13.0), 3.30−3.17 (m, 1H), 2.70−2.59 (m, 2H, J = 9.2, 6.9), 2.51−2.38 (m, 2H, J = 4.6), 2.19−2.02 (m, 1H), 1.79 (broad s, NH), 1.73−1.57 (m, 1H); ^{13}C NMR δ 144.1, 139.1, 128.8, 128.4, 128.2, 127.4, 126.9, 65.4, 60.7, 60.5, 55.0, 53.0, 32.3; IR (film) 3300, 3024, 2952, 2784, 1949, 1890, 1827 cm^{-1}; EIMS *m/z* (relative intensity) 342 ($M^{+\bullet}$, 8), 182 (57), 175 (61), 167 (81), 161 (78), 133 (40), 120 (60), 91 (100); CIMS (*t*-BuH) *m/z* (relative intensity) 343 ($M + H^+$, 100); HRMS calcd for $C_{24}H_{26}N_2$ 342.2096, found 342.2097.

(*S*)-1-Benzyl-3-(cyclohexylamino)pyrrolidine (1c):[3] yield 75% (yellow oil), after flash chromatography on silica gel (eluent: ∼96.5/2.5/1.0 CH_2Cl_2/MeOH/NEt_3); $[\alpha]_D^{22}$ −0.76 (*c* 3.03, CH_2Cl_2); ^{1}H NMR δ 7.28−7.14 (m, 5H), 3.55 (s, 2H), 3.48−3.36 (m, 1H), 2.72 (dd, 1H, J = 9.2, 6.7), 2.62−2.42 (m, 2H), 2.42−2.31 (m, 1H), 2.25 (dd, 1H, J = 9.3, 5.4), 2.18−2.00 (m, 1H), 1.83−1.39 (m, 6H + NH), 1.28−0.91 (m, 5H); ^{13}C NMR δ 138.9, 128.7, 128.1, 126.8, 61.2, 60.5, 54.9, 53.8, 52.9, 33.8, 33.6, 32.6, 26.0, 25.0; IR (film) 3337, 2922, 2852, 2786 cm^{-1}; EIMS *m/z* (relative intensity) 258 ($M^{+\bullet}$, 27), 133 (100), 91 (64), 42 (62); CIMS (*t*-BuH) *m/z* (relative intensity) 259 ($M + H^+$, 100); HRMS calcd for $C_{17}H_{26}N_2$ 258.2096, found 258.2102.

(*S*)-1-Ethyl-3-(*N*-cyclohexylideneamino)pyrrolidine (7a). Method A was used ((*S*)-1-ethyl-3-aminopyrrolidine (**6a**), 1.14 g; cyclohexanone, 2.94 g): ^{1}H NMR (C_6D_6): δ 4.15−4.00 (m, 1H), 2.95 (dd, 1H), 2.75−2.50 (m, 3H), 2.45 (q, 2H), 2.25 (pseudo-t, 2H), 2.20−1.80 (m, 4H), 1.50, 1.40−1.25 (2m, 6H), 1.10 (t, 3H, J = 7.1); ^{13}C NMR (C_6D_6): δ 170.0, 62.0, 57.9, 53.6, 50.4, 41.8 or 40.0, 33.9, 29.5, 28.0, 27.3, 26.9 or 26.3, 14.3; IR (film) 1656 cm^{-1}.

(*S*)-1-Ethyl-3-(cyclohexylamino)pyrrolidine (9a): yield 56% (green oil; GC purity ∼98%); $[\alpha]_D^{25}$ +0.87 (*c* 1.60, CH_2Cl_2); ^{1}H NMR δ 3.46−3.33 (m, 1H), 2.69 (dd, 1H, J = 9.3, 6.8), 2.57−2.30 (m, 5H), 2.21 (dd, 1H, J = 9.4, 5.4), 2.16−1.98 (m, 1H), 1.81−1.36 (m, NH + 6H), 1.29−0.88 (m, 5H), 1.03 (t, 3H, J = 7.2); ^{13}C NMR δ 61.0, 54.8, 53.6, 52.7, 50.1, 33.7, 33.6, 32.5, 25.9, 24.9, 13.6; IR (film) 3280, 3154, 2926, 2852, 2790, 1450 cm^{-1}; EIMS *m/z* (relative intensity) 196 ($M^{+\bullet}$, 18), 71 (100); HRMS calcd for $C_{12}H_{24}N_{27}$ 196.1940, found 196.1941.

(*S*)-1-Ethyl-3-((*N*-diphenylmethylidene)amino)pyrrolidine (8a). Method C was used ((*S*)-1-ethyl-3-aminopyrrolidine (**6a**), 1.14 g): yield 95% (crude); ^{1}H NMR (C_6D_6): δ 7.92−7.83 (m, 2H), 7.17−7.09 (m, 6H), 6.97−6.88 (m, 2H), 4.14−4.01 (m, 1H), 2.79 (AB, 2H, J = 8.9, 6.9, 5.6), 2.70−2.53 (m, 2H), 2.444 (q, 1H, J = 7.3), 2.438 (q, 1H, J = 7.1), 2.11−1.83 (m, 2H), 1.07 (t, 3H, J = 7.2); ^{13}C NMR (C_6D_6): δ 166.1, 140.3, 137.7, 130.0, 128.9, 128.6, 128.5, 128.2, 128.1, 61.9, 61.3, 53.7, 50.3, 34.2, 14.3; IR (film) 2968, 1958, 1903, 1815, 1658, 1600 cm^{-1}.

(*S*)-1-Ethyl-3-((diphenylmethyl)amino)pyrrolidine (10a): yield 52% (green oil; GC purity ∼90%), after flash chromatography on alumina of type III (eluent: 98.5/1.0/0.5 EP/AcOEt/NEt_3); $[\alpha]_D^{25}$ −1.8 (*c* 2.29, CH_2Cl_2); ^{1}H NMR δ 7.43−7.14 (m, 10H), 4.86 (s, 1H), 3.31−3.19 (m, 1H), 2.64 (dd, 1H, J = 9.2, 7.2), 2.68−2.53 (m, 1H), 2.50−2.36 (m, 4H), 2.19−2.02 (m, 1H), 1.72−1.56 (m, 1H + NH), 1.08 (t, 3H, J = 7.2); ^{13}C NMR δ 143.9, 128.2, 127.1, 126.7, 65.3, 60.4, 54.7, 52.6, 50.0, 32.0, 13.5; IR (film) 3330, 2966, 2788, 1954, 1899, 1832 cm^{-1}; EIMS *m/z* (relative intensity) 280 ($M^{+\bullet}$, 3), 182 (63), 167 (100), 165 (96), 113 (46), 71 (48), 58 (40); HRMS calcd for $C_{19}H_{24}N_2$ 280.1939, found 280.1938.

(*S*)-1-(2-Methoxyethyl)-3-(*N*-cyclhexylideneamino)pyrrolidine (7b). Method B was used ((*S*)-1-(2-methoxyethyl)-3-aminopyrrolidine (**6b**), 1.44 g; cyclohexanone, 2.94 g): ^{1}H NMR (C_6D_6): δ 4.10−3.97 (m, 1H), 3.43 (t, 2H, J = 6.1), 3.13 (s, 3H), 3.01 (dd, 1H, J = 8.7, 7.3), 2.83−2.52 (m, 5H), 2.24 (m, 2H), 2.13−1.75, 1.49, 1.34−1.26 (3m, 10H); ^{13}C NMR (C_6D_6): δ 169.9, 72.4, 62.7, 58.4, 58.0, 55.8, 54.5, 40.0, 34.0, 29.4, 28.0, 27.3, 26.3; IR (film) 1656 cm^{-1}.

(*S*)-1-(2-Methoxyethyl)-3-(cyclohexylamino)pyrrolidine (9b): yield 84% (brown oil; GC purity ∼97%); $[\alpha]_D^{25}$ +2.5 (*c* 4.26, CH_2Cl_2); ^{1}H NMR δ 3.50−3.37 (m, 1H), 3.44 (t, 2H, J = 5.7), 3.31 (s, 3H), 2.79 (dd, 1H, J = 9.2, 6.9), 2.69−2.48 (m, 4H), 2.45−2.31 (m, 1H), 2.25 (dd, 1H, J = 9.2, 5.6), 2.18−2.00 (m, 1H), 1.82−1.38 (m, 6H + NH), 1.29−0.89 (m, 5H); ^{13}C NMR δ 71.0, 61.4, 58.6, 55.5, 54.7, 53.4, 53.3, 33.4, 33.3, 32.1, 25.8, 24.8; IR (film) 3300, 2926, 2852, 2810 cm^{-1}; EIMS *m/z* (relative intensity) 226 ($M^{+\bullet}$, 0.3), 225 ($[M - H]^+$, 2), 181 (65), 138 (60), 82 (83), 71 (76), 68 (40), 56 (99); CIMS (*t*-BuH) *m/z* (relative intensity) 228 (13), 227 ($M + H^+$, 100), 75 (96).

(*S*)-1-(1-Naphthylmethyl)-3-(*N*-cyclohexylideneamino)-pyrrolidine (7c). Method A was used ((*S*)-1-(1-naphthylmethyl)-3-aminopyrrolidine (**6c**), 2.26 g; cyclohexanone, 2.94 g): ^{1}H NMR (C_6D_6): δ 8.48 (d, 1H, J = 8.4), 7.70−7.60 (m, 2H), 7.44−7.21 (m, 4H), 3.96 (AB, 2H, J = 12.8), 4.02−3.93 (m, 1H), 2.99 (dd, 1H, J = 8.7, 7.3), 2.80−2.55 (m, 3H), 2.22 (pseudo-t, 2H), 2.14−1.74, 1.53−1.04 (2m, 10H); ^{13}C NMR (C_6D_6): δ 170.1, 136.1, 134.4, 133.0, 128.6, 128.1, 126.9, 125.9, 125.5, 125.4, 62.2, 59.3, 57.9, 54.1, 40.0, 34.0, 29.4, 28.0, 27.3, 26.3; IR (film) 1652 cm^{-1}; EIMS *m/z* (relative intensity) 306 ($M^{+\bullet}$, 14), 209 (50), 165 (59), 141 (100).

(*S*)-1-(1-Naphthylmethyl)-3-(cyclohexylamino)pyrrolidine (9c): yield 60% (yellow oil; GC purity ~97%), after flash chromatography on silica gel (eluent: 98.0/1.5/0.5 CH_2Cl_2/MeOH/NEt_3); $[\alpha]_D^{24}$ +2.8 (*c* 2.33, CH_2Cl_2); ^{1}H NMR δ 8.28−8.23 (m, 1H), 7.85−7.72 (m, 2H), 7.54−7.34 (m, 4H), 4.00 (AB, 2H, J = 13.3), 3.50−3.37 (m, 1H), 2.80 (dd, 1H, J = 9.1, 6.6), 2.71−2.51 (m, 2H), 2.45−2.31 (m, 1H), 2.37 (dd, 1H, J = 9.2, 5.4), 2.20−2.02 (m, 1H), 1.84−1.42 (m, 6H + NH), 1.30−0.93 (m, 5H); ^{13}C NMR δ 134.8, 133.5, 132.0, 128.1, 127.4, 126.3, 125.5, 125.3, 124.9, 124.2, 61.2, 58.2, 54.6, 53.7, 52.9, 33.6, 33.4, 32.3, 25.9, 24.9; IR (film) 3314, 2924, 2850, 2792, 1928, 1869, 1810 cm^{-1}; EIMS *m*/*z* (relative intensity) 308 ($M^{+\bullet}$, 18), 183 (63), 141 (100), 182 (65); HRMS calcd for $C_{21}H_{28}N_2$ 308.2253, found 308.2227.

(*S*)-1-(2-Naphthylmethyl)-3-(*N*-cyclohexylideneamino)-pyrrolidine (7d). Method A was used ((*S*)-1-(2-naphthylmethyl)-3-aminopyrrolidine (**6d**), 2.26 g; cyclohexanone, 2.94 g): ^{1}H NMR (C_6D_6): δ 7.78 (s, 1H), 7.71−7.63 (m, 4H), 7.32−7.21 (m, 2H), 4.18−4.02 (m, 1H), 3.72 (AB, 2H, J = 13.3), 3.02 (dd, 1H, J = 8.8, 7.3), 2.81−2.52 (m, 2H), 2.65 (dd, 1H, J = 8.8, 6.3), 2.25 (pseudo-t, 2H), 2.18−1.82 (m, 4H), 1.48, 1.39−1.23 (m, 6H); ^{13}C NMR (C_6D_6): δ 170.1, 138.1, 134.1, 133.4, 128.2, 128.1, 127.3, 126.1, 125.6, 62.2, 61.0, 58.0, 54.0, 40.0, 34.1, 29.4, 28.0, 27.3, 26.3; IR (film) 1652 cm^{-1}.

(*S*)-1-(2-Naphthylmethyl)-3-(cyclohexylamino)pyrrolidine (9d): yield 72% (green oil; GC purity ~98%), after flash chromatography on silica gel (eluent: 95.0/4.5/0.5 CH_2Cl_2/MeOH/NEt_3); $[\alpha]_D^{22}$ −3.8 (*c* 3.35, CH_2Cl_2); ^{1}H NMR δ 7.81−7.72 (m, 4H), 7.49−7.38 (m, 3H), 3.53−3.40 (m, 1H), 3.73 (AB, 2H, J = 13.4), 2.79 (dd, 1H, J = 9.2, 6.7), 2.69−2.51 (m, 2H), 2.38 (m, 1H), 2.31 (dd, 1H, J = 9.3, 5.5), 2.23−2.05 (m, 1H), 1.86−1.42 (m, 6H), 1.29−0.83 (m, NH + 5H); ^{13}C NMR δ 136.6, 133.2, 132.5, 127.6, 127.55, 127.46, 127.1, 127.0, 125.7, 125.3, 61.3, 60.6, 54.8, 53.8, 53.0, 33.8, 33.6, 32.6, 26.0, 25.0; IR (film) 3296, 2924, 2850, 2790 cm^{-1}; EIMS *m*/*z* (relative intensity) 308 ($M^{+\bullet}$, 19), 183 (100), 141 (96); HRMS calcd for $C_{21}H_{28}N_2$ 308.2253, found 308.2232.

(*S*)-1-(2-Naphthylmethyl)-3-((*N*-diphenylmethylidene)-amino)pyrrolidine (8d). Method C was used ((*S*)-1-(2-naphthylmethyl)-3-aminopyrrolidine (**6d**), 2.26 g): ^{1}H NMR (C_6D_6): δ 7.91−6.85 (m, 17H), 4.17−4.04 (m, 1H), 3.72 (s, 2H), 2.88 (d, 2H, J = 6.4), 2.84−2.58 (m, 2H), 2.14−1.84 (m, 2H); ^{13}C NMR (C_6D_6): δ 166.3, 140.3, 137.9, 137.7, 134.1, 133.4, 130.0−125.7, 62.2, 61.4, 60.9, 54.1, 34.3; IR (film) 3056, 2912, 2792, 1956, 1899, 1814, 1777, 1600, 1568 cm^{-1}.

(*S*)-1-(2-Naphthylmethyl)-3-((diphenylmethyl)amino)-pyrrolidine (10d): yield 35% (yellow viscous oil), after flash chromatography on silica gel (eluent: 80/19/1 EP/AcOEt/NEt_3). The workup was based on acidic hydrolysis (0.2 N HCl) of the remaining imine; the acidic aqueous layer was extracted by Et_2O (2 × 30 mL) and then basified before extracting again with AcOEt (3 × 40 mL): $[\alpha]_D^{25}$ −9.7 (*c* 4.37, CH_2Cl_2); ^{1}H NMR δ 7.89−7.78, 7.55−7.19 (2m, 17H), 4.88 (s, 1H), 3.78 (AB, 2H, J = 12.9), 3.38−3.25 (m, 1H), 2.80−2.68 (m, 2H), 2.61−2.47 (m, 2H), 2.27−2.09 (m, 1H), 1.84 (broad s, NH), 1.81−1.65 (m, 1H); ^{13}C NMR δ 144.0, 143.9, 136.6, 133.2, 132.5, 128.2, 127.6, 127.55, 127.46, 127.2, 127.1, 126.8, 125.7, 125.3, 65.3, 60.5, 54.9, 53.0, 32.2; IR (film) 3314, 3058, 2954, 2790, 1948, 1815, 1600 cm^{-1}; EIMS *m*/*z* (relative intensity) 392 ($M^{+\bullet}$, 1.4), 167 (60), 141 (100), 115 (64); HRMS calcd for $C_{24}H_{28}N_2$ 392.2253, found 392.2254.

(*S*)-1-((*o*-Methoxyphenyl)methyl)-3-(cyclohexylamino)-pyrrolidine (9e): yield 61% (dark orange oil), after flash chromatography on silica gel (eluent: 99.00/0.75/0.25 CH_2Cl_2/MeOH/NEt_3); $[\alpha]_D^{25}$ +0.68 (*c* 2.65, CH_2Cl_2); ^{1}H NMR δ 7.32−7.15 (m, 2H), 6.93−6.80 (m, 2H), 3.78 (s, 3H), 3.63 (s, 2H), 3.51−3.38 (m, 1H), 2.82 (dd, 1H, J = 9.4, 6.7), 2.69−2.52 (m, 2H), 2.40 (m, 1H), 2.32 (dd, 1H, J = 9.4, 5.6), 2.20−2.02 (m, 1H), 1.83−1.40 (m, 6H), 1.23−0.92 (m, 5H + NH); ^{13}C NMR δ 157.3, 130.2, 127.8, 120.1, 110.1, 126.7, 61.1, 55.2, 54.8, 53.8, 53.5, 52.9, 33.7, 33.6, 32.4, 26.0, 25.0; IR (film) 3322, 2926, 2790, 1600, 1588 cm^{-1}; EIMS *m*/*z* (relative intensity) 288 ($M^{+\bullet}$, 10), 163 (72), 121 (100); HRMS calcd for $C_{18}H_{28}N_2O$ 288.2202, found 288.2208.

Synthesis of Diamines 13. (*R*)-1-(2-Naphthoyl)-3-(tosyloxy)pyrrolidine (11). To a solution of crude (*R*)-3-hydroxypyrrolidine (**3**) (obtained from 4.5 g (22.2 mmol) of (*R*)-3-hydroxypyrrolidinium hydrogen maleate (**2**)) and pyridine (14 mL, 173.1 mmol, 7.8 equiv) in CH_2Cl_2 was added, between 0 and 5 °C and under argon, 2-naphthoyl chloride (4.5 g, 23.5 mmol, 1.1 equiv) in CH_2Cl_2 (15 mL). The mixture was stirred between 5 and 10 °C for 2 h, before adding *p*-tosyl chloride (17.0 g, 89.3 mmol, 4.0 equiv) and a catalytic amount of DMAP. After 2 days at room temperature, the solvent and pyridine were evaporated; the residue was taken up with AcOEt (80 mL) and the precipitate of chlorhydrate filtered. The filtrate was concentrated and dissolved in Et_2O, and the addition to this solution of petroleum ether (30−40 mL) resulted in the precipitation of a brown oil. After separation from the supernatant, which contains principally the excess of *p*-tosyl chloride, this oil was washed once with 50/50 Et_2O/EP and then chromatographed on silica gel (eluent: ~50/50 AcOEt/EP) to afford 2.67 g of a translucent solid: yield 30%; $[\alpha]_D$ −7.4, $[\alpha]_{578}$ −9.0, $[\alpha]_{546}$ −14.1, $[\alpha]_{436}$ −49.0, $[\alpha]_{365}$ −111.9 (*c* 3.37, $CHCl_3$, T = 25 °C). The presence of 2 rotamers[20] a and b in a 58/42 ratio in $CDCl_3$ resulted in the splitting of several signals in ^{1}H and ^{13}C NMR ^{1}H NMR δ 7.99−7.15 (m, 11H), 5.15 (m, 0.58H^a), 5.03 (m, 0.42H^b), 3.87−3.50 (m, 4H), 2.44 (s, H^a), 2.27 (s, H^b), 2.27−1.90 (m, 2H); ^{13}C NMR δ 169.7, 145.2, 133.9, 133.4, 133.2, 132.4, 130.0, 128.5, 128.2, 127.7, 127.3, 126.7, 124.2, 80.1, 79.5, 54.6, 52.2, 47.0, 43.9, 33.1, 30.7, 21.6, 21.4; IR (film) 3058, 2954, 2892, 1622 cm^{-1}; CIMS (CH_4) *m*/*z* (relative intensity) 424 (M + $C_2H_5^+$, 6), 396 (M + H^+, 52), 242 (97), 240 (33), 224 (87), 173 (100), 155 (72), 93 (69), 65 (51).

(*S*)-1-(2-Naphthoyl)-3-[[1-(*S*)-phenylethyl]amino]pyrrolidine (12b). A mixture of (*R*)-1-(2-naphthoyl)-3-(tosyloxy)-pyrrolidine (**11**) (1.0 g, 2.6 mmol) and (*S*)-1-phenylethylamine (3.4 g, 28.1 mmol, 11.0 equiv) was heated for 20 h at 105 °C. After cooling, the reaction mixture, diluted by AcOEt (15 mL), was vigorously stirred with 4 M NaOH (10 mL). After decantation, the aqueous basic layer was extracted with AcOEt (2 × 10 mL); both organic layers were dried over $MgSO_4$, filtered, and then concentrated leading to a brown oil (3.21 g). After being washed with pentane to remove the excess of the primary amine, the residue was finally purified by flash chromatography on silica gel (eluent: ~98.5/1.5 CH_2Cl_2/MeOH) to afford 0.53 g of a yellow oil: yield 60%; $[\alpha]_D$ −102.8, $[\alpha]_{578}$ −107.6, $[\alpha]_{546}$ −123.4, $[\alpha]_{436}$ −224.0 (*c* 4.41, $CHCl_3$, T = 25 °C). This molecule has also 2 rotamers a and b in a quasi 50/50 ratio in $CDCl_3$, inducing a splitting of several signals in ^{1}H and ^{13}C NMR ^{1}H NMR δ 7.97, 7.84, 7.60−7.47, 7.34−7.17 (4m, 12H), 3.92−3.72, 3.64−3.11 (2m, 6H), 2.08−1.56 (m, 2H), 1.41 (broad s, NH), 1.37 (d, H^a, J = 6.6), 1.25 (d, H^b, J = 6.5); ^{13}C NMR δ 169.8, 145.1, 134.1, 133.9, 133.7, 132.5, 128.5, 128.0, 127.7, 127.0, 126.5, 126.3, 124.4, 56.7, 56.6, 55.6, 54.0, 55.2, 52.1, 47.9, 44.7, 33.2, 31.4, 24.8, 24.7; IR (film) 3304, 3058, 2968, 2876, 1614, 1470, 1418 cm^{-1}; EIMS *m*/*z* (relative intensity) 344 ($M^{+\bullet}$, 80), 329 (38), 239 (77), 225 (97), 197 (50), 184 (91), 156 (99).

(*S*)-1-(2-Naphthoyl)-3-[[1-(*R*)-phenylethyl]amino]pyrrolidine (12a). By the same procedure using 1.4 g of (*R*)-1-(2-naphthoyl)-3-(tosyloxy)pyrrolidine (**11**) (3.5 mmol) and 4.8 g of (*R*)-1-phenylethylamine (39.4 mmol, 11.2 equiv), a milky viscous oil (0.61 g) was obtained after flash chromatography on silica gel (eluent: 99/1 CH_2Cl_2/MeOH): yield 50%; ^{1}H NMR δ 7.96, 7.86−7.77, 7.59−7.45, 7.32−6.99 (4m; 12H), 3.91−3.04 (m, 6H), 2.25−1.62 (m, 2H), 1.52 (broad s, NH), 1.37 (d, H^a, J = 6.6), 1.29 (d, H^b, J = 6.6); ^{13}C NMR δ 169.6, 145.1, 133.9, 133.7, 132.4, 128.5, 127.9, 127.6, 127.0, 126.4, 124.4, 56.6, 56.0, 56.2, 53.9, 55.6, 52.6, 47.9, 44.6, 32.2, 30.7, 24.6.

For the reduction of amides **12** into amines **13**, the procedure was the same as that described for the preparation of amino alcohols **4**.

(*S*)-1-(2-Naphthylmethyl)-3-[[1-(*S*)-phenylethyl]amino]-pyrrolidine (13b). (*S*)-1-(2-Naphthoyl)-3-[[1-(*S*)-phenylethyl]-amino]pyrrolidine (**12b**), 0.5 g (1.5 mmol), in 20 mL of THF with $LiAlH_4$, 0.3 g (7.4 mmol, 4.8 equiv), in 10 mL of THF (flash chromatography on silica gel (eluent: ~97/3 CH_2Cl_2/MeOH))

afforded 0.38 g of a green oil: yield 75%; $[\alpha]_D$ −89.6, $[\alpha]_{578}$ −93.6, $[\alpha]_{546}$ −106.9 (*c* 2.74, $CHCl_3$, *T* = 22 °C); ^{1}H NMR (500 MHz): *δ* 7.84−7.75 (m, 4H), 7.51−7.41 (m, 3H), 7.36−7.18 (m, 5H), 3.80 (AB, 2H, *J* = 12.9), 3.77 (q, 1H), 3.23−3.18 (m, 1H), 2.75−2.70 (m, 1H), 2.72 (dd, 1H, *J* = 9.4, 6.5), 2.57 (dd, 1H, *J* = 9.4, 4.9), 2.51 (pseudo-q, 1H), 2.12−2.05 (m, 1H + NH), 1.60−1.53 (m, 1H), 1.37 (d, 3H, *J* = 6.6); ed ∼95% (determined by comparison of intensities of **13b**'s multiplet (1.60−1.53 ppm) and **13a**'s dd (2.32 ppm)); ^{13}C NMR *δ* 145.2, 136.4, 133.3, 132.6, 128.4, 127.8, 127.7, 127.6, 127.2, 126.9, 126.7, 125.9, 125.5, 60.6, 60.3, 56.5, 54.6, 53.0, 32.5, 24.5; IR (film) 3329, 3056, 2960, 2790 cm^{-1}; EIMS *m*/*z* (relative intensity) 330 ($M^{+\bullet}$, 5), 211 (82), 183 (93), 182 (78), 141 (92), 115 (74), 105 (100), 56 (69); HRMS calcd for $C_{23}H_{26}N_2$ 330.2096, found 330.2101.

(*S*)-1-(2-Naphthylmethyl)-3-[[1-(*R*)-phenylethyl]amino]-pyrrolidine (13a). (*S*)-1-(2-Naphthoyl)-3-[[1-(*R*)-phenylethyl]-amino]pyrrolidine (**12a**), 0.6 g (1.8 mmol), in 18 mL of THF with $LiAlH_4$, 0.3 g (8.4 mmol, 4.8 equiv), in 10 mL of THF afforded **13a**: yield 75% (green oil), after flash chromatography on silica gel (eluent: 97/3 CH_2Cl_2/MeOH); $[\alpha]_{578}$ +28.0, $[\alpha]_{546}$ +31.5 (*c* 2.46, $CHCl_3$, *T* = 22 °C); ^{1}H NMR (500 MHz) *δ* 7.82−7.74 (m, 3H), 7.68 (s, 1H), 7.49−7.39 (m, 3H), 7.32−7.14 (m, 5H), 3.81 (q, 1H, *J* = 6.6), 3.74 (AB, 2H, *J* = 12.8), 3.23−3.18 (m, 1H), 2.72−2.65 (m, 1H), 2.67 (dd, 1H, *J* = 9.4, 7.0), 2.58 (td, 1H, *J* = 8.5, 6.1), 2.32 (dd, 1H, *J* = 9.4, 5.4), 2.15−2.08 (m, 1H), 1.70−1.64 (m, 1H + NH), 1.37 (d, 3H, *J* = 6.6); ed ∼93% (determined comparing integrations of **13a**'s dd (2.32 ppm) and of the multiplet (3.23−3.18 ppm) corresponding to both diastereoisomers); ^{13}C NMR *δ* 145.3, 136.4, 133.2, 132.5, 128.2, 127.6, 127.5, 127.4, 127.1, 127.0, 126.8, 126.5, 125.7, 125.3, 60.9, 60.5, 56.0, 54.5, 53.0, 31.7, 24.1.

Synthesis of Diamines 16 and 18. (*R*)-1-Tosyl-3-(tosyloxy)pyrrolidine (14). To a mixture of the crude (*R*)-3-hydroxypyrrolidine (**3**) (obtained from 4.5 g (22.2 mmol) of (*R*)-3-hydroxypyrrolidinium maleate (**2**)), pyridine (8.6 mL, 106.0 mmol, 4.8 equiv), and a catalytic amount of DMAP in CH_2Cl_2 (50 mL) was added, at 0 °C, *p*-tosyl chloride (21.3 g, 112.0 mmol, 5.0 equiv). After being stirred for 48 h at room temperature and under an argon atmosphere, the solvent and pyridine were evaporated and the resulting solid was at first washed by 50/50 Et_2O/petroleum ether to remove the excess of *p*-tosyl chloride and then chromatographed on silica gel (eluent: 45/55 AcOEt/EP), leading to 4.86 g of a white solid: yield 55%; mp 110 °C; $[\alpha]_D$ +8.1, $[\alpha]_{578}$ +8.4, $[\alpha]_{546}$ +9.3, $[\alpha]_{436}$ +16.0, $[\alpha]_{365}$ +28.2 (*c* 3.26, CH_2Cl_2, *T* = 25 °C); ^{1}H NMR *δ* 7.62 (d, 2H, *J* = 8.3), 7.61 (d, 2H, *J* = 8.3), 7.28 (d, 2H, *J* = 8.1), 7.27 (d, 2H, *J* = 8.1), 4.92−4.86 (m, 1H), 3.46−3.29 (m, 3H), 3.18 (td, 1H, *J* = 9.5, 7.3), 2.40, 2.38 (2s, 6H), 2.08−1.80 (m, 2H); ^{13}C NMR *δ* 145.0, 143.7, 133.1, 133.0, 129.8, 129.6, 127.4, 127.3, 79.2, 53.3, 45.6, 31.9, 21.5, 21.3; IR (KBr): 2962, 1924, 1594 cm^{-1}; CIMS (CH_4) *m*/*z* (relative intensity) 424 (M + $C_2H_5^+$, 9), 396 (M + H^+, 100), 242 (94), 225 (85), 92 (69). Anal. Calcd for $C_{18}H_{21}NO_5S_2$: C, 54.68; H, 5.32; N, 3.54. Found: C, 54.57; H, 5.35; N, 3.48.

(*S*)-1-Tosyl-3-morpholinopyrrolidine (15). A solution of (*R*)-1-tosyl-3-(tosyloxy)pyrrolidine (**14**) (3.3 g, 8.4 mmol) and morpholine (15 mL, 172.0 mmol, 21.0 equiv) was heated for 6 h at 85 °C. After cooling, the reaction mixture, diluted with AcOEt (15 mL), was vigorously stirred with 4 M NaOH (10 mL). After decantation, the aqueous basic layer was extracted with AcOEt (2 × 10 mL); both organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by flash chromatography on silica gel (eluent: 45/55 AcOEt/CH_2Cl_2) to afford 2.3 g of a yellow oil: yield 90%; $[\alpha]_D$ −19.0, $[\alpha]_{578}$ −19.8, $[\alpha]_{546}$ −22.4, $[\alpha]_{436}$ −38.2, $[\alpha]_{365}$ −59.8 (*c* 3.57, $CHCl_3$, *T* = 25 °C); ^{1}H NMR *δ* 7.62 (d, 2H, *J* = 8.2), 7.25 (d, 2H, *J* = 8.1), 3.56 (pseudo-t, 4H, *J* ∼ 4.6), 3.44 (dd, 1H, *J* = 9.1, 7.0), 3.33−3.09 (m, 2H), 2.86 (pseudo-t, 1H), 2.63 (qt, 1H, *J* ∼ 7.7), 2.35 (s, 3H), 2.40−2.20 (m, 4H), 2.01−1.87 (m, 1H), 1.67−1.47 (m, 1H); ^{13}C NMR *δ* 143.3, 132.9, 129.4, 127.3, 66.3, 63.9, 51.7, 50.9, 46.3, 28.6, 21.2; IR (film) 2956, 2814, 1938, 1827, 1731, 1598 cm^{-1}; EIMS *m*/*z* (relative intensity) 310 ($M^{+\bullet}$, 2.5), 127 (68), 112 (69), 70 (85), 69 (76), 56 (100).

(*S*)-3-Morpholinopyrrolidine (16). To 100 mL of liquid ammonia in a three necked-flask equipped with a dry ice condenser and a mechanical stirrer was introduced carefully a solution of (*S*)-1-tosyl-3-morpholinopyrrolidine (**15**) (2.3 g, 7.4 mmol) and *tert*-butyl alcohol (2.6 g, 34.7 mmol, 4.7 equiv) in THF (25 mL). To this mixture was added, at −70 °C, sodium cut in small pieces until a blue persistent color was reached. The reaction mixture was then neutralized with solid NH_4Cl before evaporating ammonia. The residue was taken up with CH_2Cl_2, and the resulting suspension was filtered on Celite and the filtrate evaporated. A flash chromatography on silica gel (eluent: 90/9/1 CH_2Cl_2/MeOH/NEt_3) afforded 0.51 g of a yellow oil: yield 44%; $[\alpha]_D$ −14.6, $[\alpha]_{578}$ −15.2, $[\alpha]_{546}$ −17.6, $[\alpha]_{436}$ −32.5 (*c* 4.47, $CHCl_3$, *T* = 25 °C); ^{1}H NMR (C_6D_6): *δ* 3.57 (t, 4H, *J* = 4.7), 2.87−2.53 (m, 4H, *J* = 10.4, 7.2), 2.32 (qt, 1H, *J* = 7.3), 2.23−2.04 (m, 4H), 1.90 (bd s, NH), 1.60−1.28 (m, 2H); ^{13}C NMR (C_6D_6): *δ* 67.2, 67.1, 53.1, 51.3, 46.4, 30.5; IR (film) 3276, 2956, 2854, 2808 cm^{-1}; EIMS *m*/*z* (relative intensity) 156 ($M^{+\bullet}$, 15), 114 (55), 43 (100), 42 (55); HRMS calcd for $C_8H_{16}N_2O$: 156.1263; found: 156.1267.

(*S*)-1-Acetyl-3-morpholinopyrrolidine (17). This amide was also obtained by deprotection of (*S*)-1-tosyl-3-morpholinopyrrolidine (**15**) (2.3 g, 7.4 mmol) according to the procedure described above. After evaporation of ammonia, the residue was stirred with AcOEt (100 mL) for 1 h at room temperature. After filtration and concentration was obtained an oil (1.45 g), used in the following step without purification. Yield: ∼100% of a mixture of 2 rotamers[21] a and b in a 50/50 ratio in C_6D_6, responsible for the splitting of several signals in ^{1}H and ^{13}C NMR ^{1}H NMR (C_6D_6): *δ* 3.80−3.63 (m, $^1/_2H^a$, $^1/_2H^{a\ or\ b}$, *J* = 11.5, 7.0), 3.52 (t, $4H^{a\ or\ b}$, *J* = 4.7), 3.51 (t, $4H^{b\ or\ a}$, *J* = 4.7), 3.31−2.55 (m, $^1/_2H^a$, $1H^b$, $^1/_2H^{a\ or\ b}$, $1H^{b\ or\ a}$), 2.24−1.82 (m, 5H), 1.73, 1.69 (2s, 3H), 1.48−1.07 (m, 2H); ^{13}C NMR (C_6D_6): *δ* 167.9, 66.9, 64.8, 63.4, 52.5, 52.3, 50.8, 49.7, 45.6, 44.4, 29.9, 28.3, 22.1, 21.6; IR (film) 2954, 2856, 2812, 1650, 1454 cm^{-1}; EIMS *m*/*z* (relative intensity) 155 (14), 126 (100), 111 (30), 88 (38), 43 (94), 42 (83); CIMS (CH_4) *m*/*z* (relative intensity) 227 (M + $C_2H_5^+$, 19), 199 (M + H^+, 100), 112 (43).

(*S*)-1-Ethyl-3-morpholinopyrrolidine (18). The procedure of the reduction is similar to that for the preparation of amino alcohols **4**: (*S*)-1-acetyl-3-morpholinopyrrolidine (**17**), 1.3 g (6.6 mmol) in THF (25 mL); $LiAlH_4$, 0.8 g (21.1 mmol, 3.2 equiv) in THF (30 mL); yield 80% (colorless oil), after flash chromatography on silica gel (eluent: 94.0/5.5/0.5 CH_2Cl_2/MeOH/NEt_3); $[\alpha]_D$ −1.0, $[\alpha]_{578}$ −1.2, $[\alpha]_{546}$ −1.7, $[\alpha]_{436}$ -7.2, $[\alpha]_{365}$ −20.1 (*c* 4.84, $CHCl_3$, *T* = 25 °C); ^{1}H NMR *δ* 3.60 (t, 4H, *J* = 4.7), 2.82−2.61 (m, 3H), 2.50−2.12 (m, 8H), 1.97−1.79 (m, 1H), 1.69−1.52 (m, 1H), 0.98 (t, 3H, *J* = 7.2); ^{13}C NMR *δ* 66.6, 64.6, 57.5, 52.7, 52.1, 50.0, 28.0, 13.5; IR (film) 2964, 2804 cm^{-1}; EIMS *m*/*z* (relative intensity) 184 ($M^{+\bullet}$, 4), 71 (100), 43 (50); HRMS calcd for $C_{10}H_{20}N_2O$ 184.1576; found 184.1579.

Amines 19. (*S*)-*N*-Cyclopentyl-1-phenylethylamine (19a): oil; $[\alpha]_D$ −73.3, $[\alpha]_{578}$ −76.3, $[\alpha]_{546}$ −86.8 (*c* 4.10, toluene, *T* = 20 °C); ^{1}H NMR *δ* 7.36−7.17 (m, 5H), 3.80 (q, 1H, *J* = 6.6), 2.87 (qt, 1H, *J* = 6.9), 1.85−1.16 (m, 8H + NH), 1.33 (d, 3H *J* = 6.6); ^{13}C NMR *δ* 146.0, 128.3, 126.7, 126.5, 57.1, 56.5, 33.7, 32.8, 24.6, 23.9, 23.8; IR (film) 3306, 2956, 2866, 1944, 1878, 1810 cm^{-1}; EIMS *m*/*z* (relative intensity) 189 ($M^{+\bullet}$, 5), 174 (100), 106 (42), 105 (90); HRMS calcd for $C_{13}H_{19}N$ 189.1517, found 189.1524.

(*S*)-*N*-[(*N*-Benzyl)piperidin-4-yl]-1-phenylethylamine (19b): oil; $[\alpha]_D$ −57.0, $[\alpha]_{578}$ −59.3, $[\alpha]_{546}$ −67.2 (*c* 4.05, toluene, *T* = 20 °C); ^{1}H NMR *δ* 7.35−7.17 (m, 10H), 3.94 (q, 1H, *J* = 6.5), 3.44 (s, 2H), 2.84−2.70 (m, 2H), 2.30 (tt, 1H, *J* = 10.6, 4.1), 1.98−1.82 (m, 3H), 1.73−1.60 (m, 1H), 1.46−1.22 (m, 2H + NH), 1.31 (d, 3H, *J* = 6.6); ^{13}C NMR *δ* 146.2, 138.6, 129.0, 128.4, 128.1, 126.8, 126.7, 126.5, 63.0, 54.4, 52.5, 52.4, 51.9, 33.6, 32.5, 25.1; IR (film) 3324, 2994, 2800, 2758, 1948, 1874, 1808 cm^{-1}; EIMS *m*/*z* (relative intensity) 294 ($M^{+\bullet}$, 3), 189 (43), 91 (100); HRMS calcd for $C_{20}H_{26}N_2$ 294.2096, found 294.2091.

(21) (a) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219. (b) Bowers-Nemia, M. M.; Joullié, M. M. *Heterocycles* **1983**, *20*, 817. (c) Lambert J. B., Takeuchi Y. *Acyclic Organonitrogen Stereodynamics*; VCH: New York, 1992.

General Procedure for the Condensation of Alkyllithium Compounds onto Aldehydes in the Presence of (*S*)-3-Aminopyrrolidine Lithium Amides. To a solution of (*S*)-3-aminopyrrolidine (0.75 mmol, 1.5 equiv) in anhydrous THF (27 mL) was added, between −20 and −10 °C and under an argon atmosphere, alkyllithium (2.00 mmol, 2.5 equiv). The mixture was stirred at −10 °C for 30 min and cooled to −78 °C. The aldehyde (0.50 mmol) in THF (1 mL) was then added over 5 min. After 1 h at −78 °C, the reaction was quenched at this temperature with 3 N hydrochloric acid (3 mL). The organic layer, diluted with ether, was washed with H_2O. The aqueous medium was then extracted by 3 × 10 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica gel (eluent: Et_2O/EP).

All alcohols obtained here have been described previously in the literature (in the following, the CAS numbers are reported between parentheses). The ee were determined by chiral shift using $Eu(hfc)_3$ in $CDCl_3$ or by HPLC. The HPLC separations of enantiomers have been achieved on a CHIRALCEL-OD column, using hexane/2-propanol mixtures, the UV detector being set at 254 nm and the debit of eluent being 1 mL/min: *1-phenyl-ethan-1-ol* (*R*, 1517-69-7; *S*, 1445-91-6), 97.5/2.5 hexane/*i*-PrOH, $R_t(R)$ = 13.3 min, $R_t(S)$ = 15.7 min; *1-phenyl-butan-1-ol* (*R*, 22144-60-1; *S*, 22135-49-5), 97.5/2.5 hexane/*i*-PrOH, $R_t(R)$ = 19.2 min, $R_t(S)$ = 20.3 min; *1-phenyl-pentan-1-ol* (*R*, 19641-53-3; *S*, 33652-83-4), 99/1 hexane/*i*-PrOH, $R_t(R)$ = 20.9 min, $R_t(S)$ = 22.7 min; *1-(o-methoxyphenyl)-pentan-1-ol* (91671-39-5), *1-(o*-methylphenyl)-pentan-1-ol (73178-44-6), 99.5/0.5 hexane/*i*-PrOH, $R_t(R)$ = 33.9 min, $R_t(S)$ = 31.3 min, $[\alpha]_D^{23}$ = +44.2, *c* = 3.52 (C_6H_6), ee = 75% (*R*); *1-(1-naphthyl)-pentan-1-ol* (*R*, 172927-11-6; *S*, 172927-12-7), 96/4 hexane/*i*-PrOH, R_t(minor) = 19.0 min, R_t(major) = 38.3 min; *1-(2-naphthyl)-pentan-1-ol* (*R*, 91464-57-2; *S*, 172927-13-8), 96/4 hexane/*i*-PrOH, $R_t(R)$ = 29.5 min, $R_t(S)$ = 25.9 min; *2,2-dimethyl-heptan-3-ol* (*R*, 51716-29-1; *S*, 35147-17-2).

Recovery of Ligands. The acidic aqueous layer, obtained after the workup of the preceding series of condensations of alkyllithium compounds onto aldehydes, could be stored at −20 °C for few weeks. It was possible to recover the ligands from combined aqueous layers by stirring them with $NaHCO_3$ and then with 4 M NaOH. The diamine was then extracted with ether and/or ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The mass of the crude residue is the same as that used for the different reactions in the case of (*S*)-1-(benzyl and 2-naphthylmethyl)-3-(cyclohexylamino)pyrrolidines **1c** and **9d**, but it was necessary to purify them by flash chromatography before reusing. For **1a**, we have checked for the absence of racemization during the condensation of butyllithium onto benzaldehyde in the presence of its amide.

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Supporting Information Available: NMR spectra for most of the compounds described in this work (51 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.

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