New Catalysts for the Base-Promoted Isomerization of Epoxides to Allylic Alcohols. Broadened Scope and Near-Perfect Asymmetric Induction

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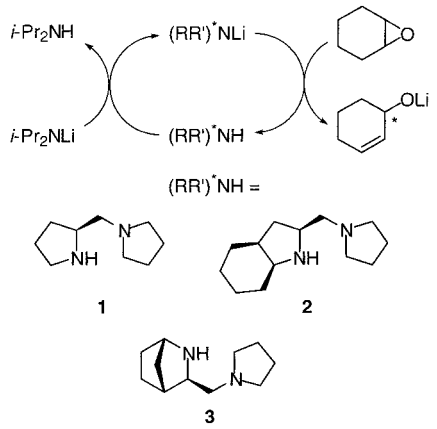
Optically active (1*S*,3*R*,4*R*)-3-[*N*-(*trans*-2,5-dialkyl)pyrrolidinyl]methyl-2-azabicyclo-[2.2.1]heptanes were evaluated as catalysts for the enantioselective *β*-elimination of *meso*-epoxides. The (2*R*,5*R*)-dimethylpyrrolidinyl-substituted catalyst **4** exhibited exceptionally high enantioselectivity and reactivity, and several substrates were rearranged with enantioselectivities of 98−99% ee. In addition, the use of **4** allowed the first successful, true catalytic rearrangement of the difficult substrates cyclopentene oxide (81%, 96% ee) and (*Z*)-4-octene oxide (80%, 91% ee).

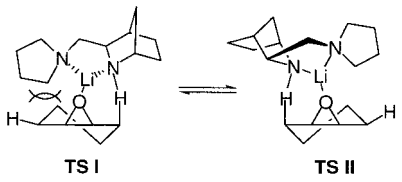
Introduction

Chiral allylic alcohols are valuable building blocks in organic synthesis.[1] They can be prepared in two steps from the corresponding alkene via epoxidation followed by asymmetric isomerization mediated by a chiral lithium amide. The isomerization reaction has been studied extensively during the last two decades,[2,3] and it has been applied to the synthesis of numerous drugs and natural products such as carbovir, lasiol, faranal, and prostaglandin precursors.[4] There are, however, some disadvantages with the methodology. Although the lithium amide of 2-(*N*-pyrrolidinyl)methylpyrrolidine **1** (Scheme 1) may be employed in substoichiometric amounts in the reaction using LDA as the stoichiometric base, the development of an efficient catalyst has proven to be difficult.[5] Most systems remain stoichiometric or substoichiometric in chiral base, and so far, only two diamines can be successfully used in catalytic amounts (**2** and **3**, Scheme 1).[6,7] The synthetic utility is further limited by the poor substrate generality exhibited by the majority of lithium amides studied to date.

Scheme 1



Scheme 2



Our contributions to the field include the development of Li-**3** (Scheme 1), which at present is the most potent and general catalyst for the rearrangement reaction. The use of a stoichiometric amount of LDA in the presence of 5 mol % of **3** allowed the isomerization of several epoxides with enantioselectivities up to 97% enantiomeric excess (ee).[6] However, despite the generality and efficiency of **3**, acyclic epoxides and some cyclopentene oxides could not be satisfactorily rearranged under catalytic conditions.[6]

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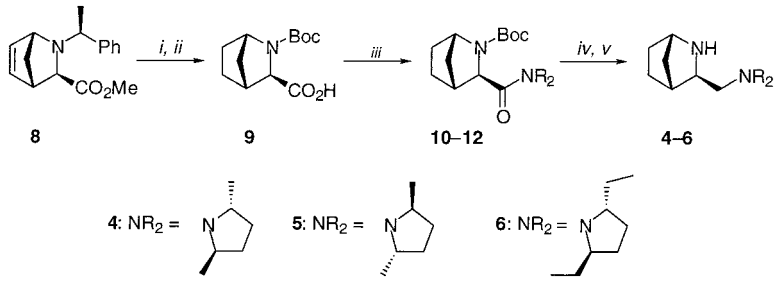
Scheme 3[a]



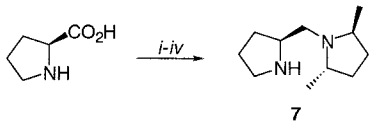
[a] Key: (*i*) H_2 (5 atm), Pd/C; (*ii*) LiOH, then Boc_2O (90% for *i*−*ii*); (*iii*) EDC, HOBt, Et_3N, R_2NH, CH_2Cl_2 (76−95%); (*iv*) HCl in dioxane; (*v*) LAH, THF (85−95% for *iv*−*v*).

The most well established selectivity model for the rearrangement of cyclohexene oxide, originally proposed by Asami, involves a syn-β-elimination pathway (Scheme 2).[3b] It suggests that the enantiodifferentiation is caused by a steric repulsion between the epoxide syn-γ-substituent and the tertiary pyrrolidine in transition state (TS) **I** (Scheme 2), thus favoring a reaction path via the diastereomeric TS **II**. Alternative models have been suggested on the basis of a variety of studies,[8] yet few observations contradict the original empirical model. In any event, it has been rigorously verified that modifications of the tertiary amine moiety significantly influence catalyst performance.[9] In a previous study by the authors, a systematic variation of the tertiary amine moiety in the chiral base was performed in order to collect information about design criteria for improved selectivity.[6b] However, all of the studied variations led to a loss of enantioselectivity and reactivity and no trends in the influence of steric or electronic properties on catalyst performance could be identified.

Another drawback, common for most systems related to **3**, was that optimum enantioselectivity was only accomplished in the presence of high concentrations of a cosolvent, typically DBU.[10] The role of this additive is not fully understood, although it is assumed to affect the aggregation properties of the catalyst. Spectroscopic studies have demonstrated that Li-**1** (Scheme 1) resides as a dimer in ethereal solution,[11] but it is plausible that the active species is monomeric under the conditions employed for catalysis, i.e., in the presence of epoxide, LDA, and DBU. Consistent with the idea of a monomeric catalyst is the fact that the only lithium amide reaching full efficiency without DBU is Li-**2** (Scheme 1), of which the bulky and rigid structure should lead to a less pronounced dimerization compared to Li-**1**.

In an earlier investigation, we demonstrated that the level of asymmetric induction in the rearrangement reaction is not linearly correlated to the optical purity of the catalyst unless the reactions are run under the influence of high concentrations of DBU. This negative nonlinear effect is most likely associated with the formation of homo- and heterochiral (*meso*-) catalyst dimers or aggregates, which have different stabilities relative to each other. However, from the study it was not possible to conclude whether the dimers are catalytically active because similar nonlinear effects would arise from either reactive and stable heterodimers or stable and inactive homodimers (i.e., a so-called reservoir effect).[12,13]

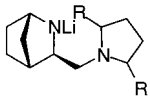
Scheme 4[a]



[a] Key: (*i*) Boc_2O (>95%); (*ii*) EDC, HOBt, Et_3N, R_2NH, CH_2Cl_2 (77%); (*iii*) HCl in dioxane; (*iv*) LAH, THF (>95% for *iii*−*iv*).

Results and Discussion

Strategy. As a continuation of our attempts toward a systematic variation of the tertiary amine moiety, the *trans*-2,5-dialkylpyrrolidines **4**−**6** were judged to be suitable catalyst candidates. The limited flexibility of the pyrrolidine ring was an attractive feature, as well as the C_2-symmetry, which does not allow the formation of diastereomerically heterogeneous catalysts. Furthermore, the access to both enantiomers of the dimethylpyrrolidine would not only provide information about the influence of steric hindrance but also reveal the preferred stereochemistry of the substituents at the tertiary amine.



Li-**4**: R = (*R*)-Me
Li-**5**: R = (*S*)-Me
Li-**6**: R = (*R*)-Et

Synthesis. The diamines **4**−**6** were prepared by the previously described method, in which aminoester **8** was converted into the common intermediate *N*-Boc-amino acid **9** via hydrogenation, hydrolysis, and subsequent N-protection (Scheme 3).[6b] Enantiopure *trans*-2,5-dialkylpyrrolidines, synthesized from commercially available diols,[14] were then attached via standard amide coupling to give **10**−**12**. Deprotection and reduction then afforded **4**−**6** in good overall yields.

The proline derivative **7** was also prepared and included in the study (Scheme 4).

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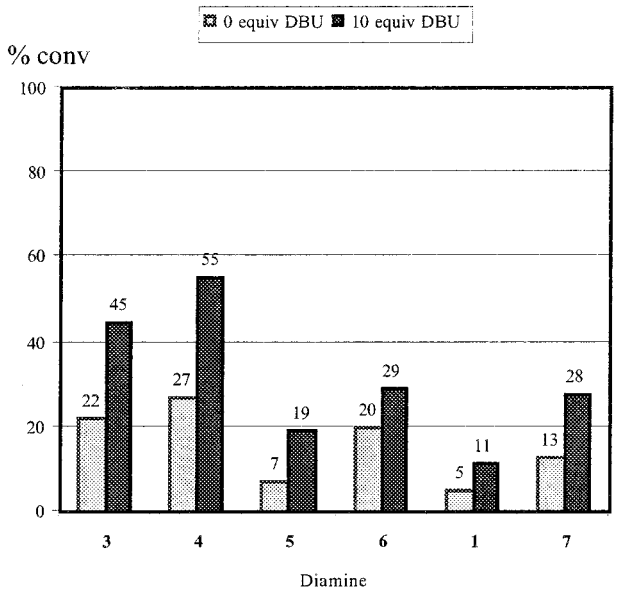


Figure 1. Reaction conditions **A**: 5 mol% of diamines **1** and **3**−**7**.

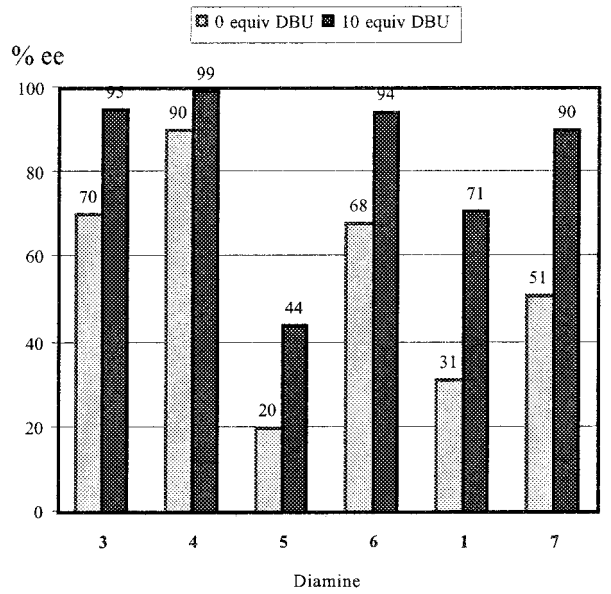


Figure 2. Reaction conditions **A**: 5 mol% of diamines **1** and **3**−**7**.

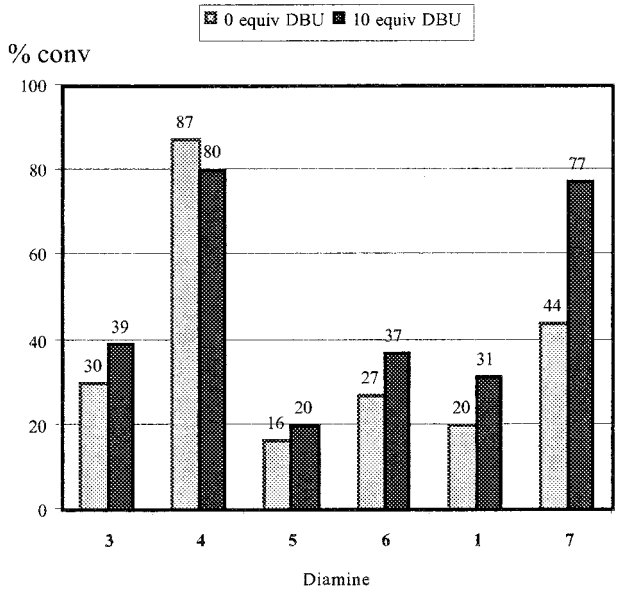


Figure 3. Reaction conditions **B**: 1.5 equiv of diamines **1** and **3**−**7**.

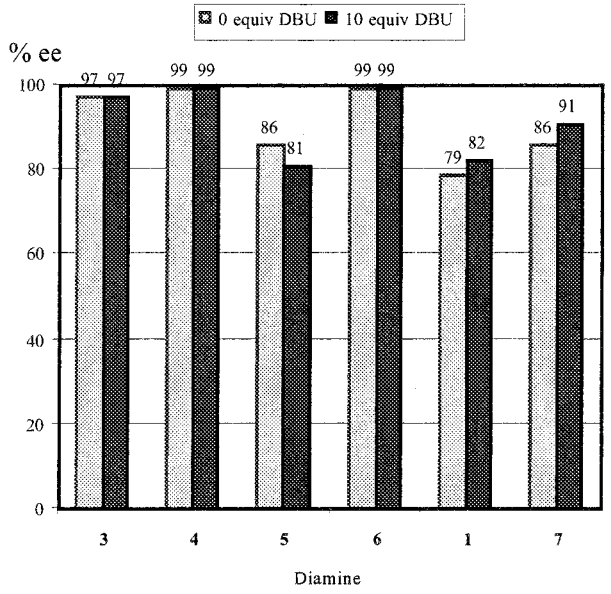
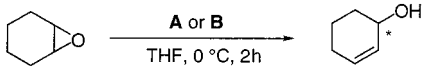


Figure 4. Reaction conditions **B**: 1.5 equiv of diamines **1** and **3**−**7**.

Evaluation. The diamines were evaluated both as catalysts (Scheme 5, **A**; and Figures 1−2) and as stoichiometric bases (Scheme 5, **B**; and Figures 3−4). To reveal differences in aggregation properties, each diamine was studied both in the absence and in the presence of DBU. As an approximate measure of the initial rates, conversions were measured after 2 h (Figures 1 and 3), whereas ees (Figures 2 and 4) were determined after full conversion.[15]

From the exceptional efficiency of **4**, it is clear that the introduction of appropriate steric hindrance on the pyrrolidine moiety can significantly improve both the level of asymmetric induction and the reaction rate (cf. **3** and **4**, Figures 1−4). It is important to bear in mind

Scheme 5

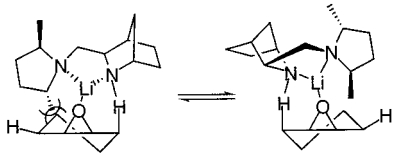


A: diamine (5 mol%), LDA (1.5 equiv), DBU (0 and 10 equiv).
B: diamine (1.5 equiv), *n*-BuLi (1.5 equiv), DBU (0 or 10 equiv).

that until now, the performance of Li-**3** has been outstanding in terms of both enantioselectivity and rate of conversion. The selectivity improvement achieved by **4** is best illustrated by the fact that the enantioselectivity observed in the stoichiometric reaction is *maintained* at 99% ee in the catalytic process, whereas that of Li-**3** drops from 97 to 95% ee (cf. Figures 2 and 4). Although the 95% ee achieved by **3** in the catalytic reaction may be sufficient for many practical applications, the improvement from 95 to 99% ee represents a signifi-

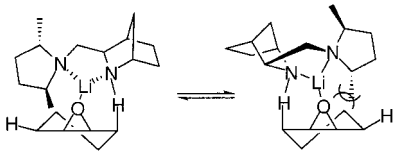
(15) Our attempts toward more detailed kinetic studies have failed to give consistent results so far mainly because our experimental setup does not readily allow multiple sampling without partial quenching of the reactions.

Scheme 6



TS I TS II

Scheme 7



TS I TS II

cant increase in $\Delta\Delta G^{\ddagger}$ between the two competing reaction paths. This may certainly prove to be valuable for the reaction of other, more challenging substrates. The enhanced reactivity exhibited by Li-**4** is more clearly demonstrated in the stoichiometric reaction, where after 2 h the conversion is nearly complete, i.e., 80−87%, whereas only 30−39% conversion is reached for **3** (cf. **3** and **4** in Figure 3).

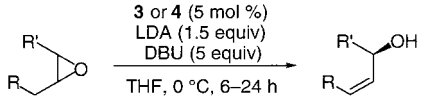
The poor performance of **5**, the diastereomer of **4**, illustrates that it is crucial to properly match the absolute stereochemistry of the pyrrolidine with that of the 2-azabicycloheptane (cf. **4** and **5**, Figures 1−4). The dramatic match/mismatch effects observed for **4** and **5** are consistent with the selectivity model proposed by Asami. For Li-**4**, the (2*R*,5*R*)-dimethyl groups do not interfere with the favored transition state **II**, whereas the unfavored pathway **I** is effectively blocked by the steric repulsion between the (2*R*)-methyl group and the cis-γ-proton of the epoxide (Scheme 6).

The slow reactions and much lower enantioselectivities observed by the mismatched Li-**5** can be related to the orientation of the (5*S*)-methyl substituent. In the favored TS **II**, the methyl group pointing toward the epoxide could cause a steric hindrance and interfere with the O−Li coordination (Scheme 7), hence raising the energy barrier for the process with a consequent loss of enantioselectivity and overall rate.

The matched diethyl analogue **6** exhibits excellent enantioselectivity in the stoichiometric process despite its relatively poor kinetics (Figures 3 and 4). In analogy with Li-**4**, it is expected that transition state **I** will be highly disfavored for Li-**6** due to the steric repulsion between the (2*R*)-ethyl group and the pseudoaxial γ-epoxide proton (cf. Scheme 6). However, the low reactivity of **6** indicates that also the energy barrier for TS **II** is raised. One plausible explanation is that the (5*R*)-ethyl group may be capable of a steric interaction with the epoxide α-proton. The poor catalytic performance of Li-**6** is most likely related to its slow reaction rates, which allow competition from the LDA-mediated background reaction.

The positive influence of a matched 2,5-dimethylpyrrolidine applies also to Asami's proline-derived diamine **7**, for which the 90% ee obtained in the catalytic reaction could be compared with the maximum ee obtained using the parent unsubstituted analogue, i.e., 82% ee in the *stoichiometric* process (cf. Figures 2 and 4).[5]

Table 1. Screening of Substrates Using 3 and 4 as Catalytic Bases



			4		3	
entry	epoxide	allylic alcohol	yield[a] %	ee[b] %	yield[a] %	ee[b] %
1		(*R*)-**14**	81	96[c]	67	49[c, d]
2		(*R*)-**15**	95	99	91	96
3[e]		(*R*)-**16**	94	98	95	94
4[e]		(*R*)-**17**	85	99	95	97
5		(*R*)-**18**	93	>99	89	96
6		(*R*)-**19**	80	91	82	66

[a] Isolated. [b] By GC, entry 5 for (*R*)-Mosher ester (^{1}H and ^{19}F NMR). [c] Run at rt. [d] 15 mol% of catalyst. [e] 9:1 *trans*/*cis* mixture of epoxides. Ee determination carried out on isomeric mixture.

From the present study, it is evident that DBU gives rise to a more rapid conversion of the epoxide in the stoichiometric as well as the catalytic reactions (cf. Figures 1 and 3). However, whereas the presence of DBU leads to improved enantioselectivity in the catalytic reactions (Figure 2), little or no such effect is shown in the stoichiometric processes (Figure 4). With the presumption that DBU acts by dissociating catalyst aggregates, the lack of influence on enantioselectivity in the stoichiometric reactions indicates that the catalyst dimers are practically inactive compared to the monomers. Thus, the enhancement of enantioselectivity by DBU in the catalytic reactions could simply be the result of an increased concentration of active catalyst, which leads to a less pronounced LDA-mediated background reaction.[16] Alternatively, the role of DBU could be to intercept a species that is not present in the stoichiometric process, e.g. a catalyst/LDA heterocomplex. In light of the idea that the catalyst dimers are relatively inactive, the high reactivity exhibited by Li-**4** could to some extent be the result of a less pronounced dimerization compared to Li-**3**.

To test **4** for substrate generality, a series of representative *meso*-epoxides were subjected to the standard catalytic conditions, as outlined in Table 1. It was found that its efficiency applies to all substrates investigated, and the levels of enantioselectivities were improved. The result obtained with cyclopentene oxide (Table 1, entry 1) constitutes a new milestone in the field of asymmetric epoxide rearrangement and is worthy of further comment. Cyclopentene oxide is a notoriously difficult substrate for the title reaction, which tends to undergo unclean syn-β-elimination due to competing α-lithiation. Diagnostic of its challenging character is the fact that the asymmetric rearrangement of cyclopentene oxide has

(16) The LDA-mediated background reaction is not accelerated by the presence of DBU; see ref 6.

been reported only twice, namely, using stoichiometric Li-**1** (1.65 equiv), to give a 49% yield and 31% ee,[10a] and a high catalyst loading of Li-**3** (15 mol %), which afforded a 67% yield and 49% ee.[6] Likewise, the catalytic rearrangement of acyclic epoxides to give >90% ee is also purely novel.

Conclusions

It has been demonstrated that the catalyst performance in the base-mediated epoxide rearrangement can be significantly improved by the proper design of the tertiary amine moiety. The dramatically increased enantioselectivity, reactivity, and substrate versatility of catalyst **4** has allowed the transformation to produce several allylic alcohols of >98% ee. Furthermore, the new catalyst allows highly selective isomerization of particularly problematic substrates, including cyclopentene oxide and (*Z*)-4-octene oxide.

The set of *trans*-2,5-dialkylpyrrolidine-substituted diamines **4**−**7** uncovered marked substituent effects on reactivity and enantioselectivity. The observations were found to support the selectivity rationale proposed by Asami (Scheme 2) and allow for further refinements of the transition state model (Schemes 6−7). Moreover, results from combined stoichiometric and catalytic experiments indicate that the catalytically active species is monomeric, and that the catalyst dimers are relatively inactive.

Experimental Section

All reactions were conducted under argon or nitrogen using oven-dried glassware (130 °C for at least 6 h) and magnetic stirring. Molecular sieves were activated at 250 °C and 0.5 mTorr for 24 h and then stored in a drybox. THF was freshly distilled from a deep-blue solution of sodium-benzophenone ketyl under nitrogen. CH_2Cl_2 and amines were distilled from powdered CaH_2 under nitrogen just prior to use. DBU was heated with powdered CaH_2, distilled at reduced pressure, and stored under argon over 3 Å molecular sieves. Epoxides were freshly distilled. Flash chromatography was performed using Matrex silica gel 60A (37−70 μm). Analytical TLC was carried out utilizing 0.25 mm precoated plates from Macherey-Nagel SIL G-60 UV_{254} 60-F, and spots were visualized by the use of UV light and ethanolic phosphomolybdic acid followed by heating. ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 400 and 100.4 MHz, respectively. Chemical shifts for protons are reported using the residual $CHCl_3$ as the internal reference (δ 7.26). Carbon signals are referred to the shift from the ^{13}C signal of $CDCl_3$ (δ 77.0). Determination of enantiomeric purity was accomplished by analytical GC using a Chirasil Dex-CB column (25 m/0.25 mm i.d.) and N_2 (12 psi) as a carrier gas. Infrared spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Mass spectra were recorded using a Finnigan MAT GCQ PLUS system (EI; 70 eV).

***trans*-(2*S*,5*S*)-2,5-Dimethylpyrrolidine·HCl and *trans*-(2*R*,5*R*)-2,5-Dimethyl-pyrrolidine·HCl.** The dimethylpyrrolidines were prepared according to a literature procedure, and physical and spectroscopic data were in complete agreement with the reported data.[14]

***trans*-(2*R*,5*R*)-2,5-Diethylpyrrolidine·HCl.** Diethylpyrrolidine was prepared according to a literature procedure[14] starting from (−)-(3*R*,6*R*)-3,6-octanediol (4.00 g, 27.4 mmol) to obtain the product in 81% yield over three steps (3.62 g): mp 173−174 °C; $[\alpha]^{25}_D$ +14.1 (*c* 1.02, 0.1 M HCl); IR (KBr) 2932, 2517, and 1604 cm^{-1}; ^{1}H NMR δ 9.50 (2H, br s), 3.68−3.43 (2H, m), 2.28−1.92 (4H, m), 1.86−1.54 (4H, m), and 1.03 (6H, t, J = 7.27 Hz); ^{13}C NMR δ 60.9, 29.8, 25.6, and 10.9; GC-MS (EI) *m*/*z* (relative intensity) 128 ($M^+ + 1$, 100), 98 (97), and 81 (54). Anal. Calcd for $C_8H_{17}N\cdot HCl\cdot 0.1H_2O$: C, 58.06; H, 11.09; N, 8.46. Found: C, 58.03; H, 11.22; N, 8.45.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-azabicyclo[2.2.1]-heptane-3-carboxylic Acid (9). Amino acid **9** was prepared from (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid methyl ester **8**[17] according to a published procedure.[6b]

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-[*N*-(*trans*-(2*R*,5*R*)-2,5-dimethyl)pyrrolidinyl]carbonyl-2-azabicyclo[2.2.1]-heptane (10). Et_3N (1.45 mL, 10.4 mmol) was added dropwise via syringe at 0 °C to a suspension of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) (1.11 g, 5.81 mmol), 1-hydroxybenzotriazole (HOBt) (0.76 g, 5.60 mmol), and **9** (1.02 g, 4.15 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred for 15 min before *trans*-(2*R*,5*R*)-dimethylpyrrolidine·HCl (0.85 g, 6.27 mmol) was added over a period of 2−3 min. The reaction mixture was warmed to room temperature, stirred overnight, and then diluted with EtOAc (30 mL) and washed with 10% aqueous citric acid (2 × 15 mL). The aqueous phases were extracted twice with EtOAc (20 mL), and the combined organic phases were washed sequentially with 10% citric acid (2 × 15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (15 mL). Drying with $MgSO_4$, evaporation, and purification by column chromatography (silica, pentane/EtOAc) gave **10** (1.27 g, 95%): mp 148−151 °C; R_f 0.27 (silica, pentane/EtOAc 1:2); $[\alpha]^{25}_D$ −2.7 (*c* 2.0, CH_2Cl_2); IR (neat) 2969, 1698, and 1646 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 4.36 and 4.16 (1H, each pent, J = 6.5 Hz), 4.28−4.26 and 4.16−4.14 (1H, each m), 4.21−4.11 (1H, m), 3.82 and 3.72 (1H, each s), 2.65 and 2.57 (1H, each dpent, J = 9.7, 2.0 Hz), 2.47−2.43 (1H, m), 2.35−1.93 (3H, m), 1.73−1.27 (6H, m), 1.38 and 1.36 (9H, each s), 1.23−1.13 (2H, m), 1.18 and 1.15 (3H, each d, J = 6.5 Hz), and 1.14−1.11 (1H, m); ^{13}C NMR (mixture of rotamers) δ 169.7, 169.6, 153.0, 153.9, 79.3, 79.1, 62.4, 62.3, 56.9, 55.8, 54.2, 54.0, 53.0, 52.7, 43.7, 42.9, 35.1, 34.3, 31.1, 31.0, 30.6, 30.3, 28.9, 28.8, 28.4, 28.3, 28.2, 28.0, 22.9, 22.7, 18.8, and 18.3; GC-MS (EI) *m*/*z* (relative intensity) 322 (M^+, <1), 196 (11), 140 (100), and 112 (15). Anal. Calcd for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69. Found: C, 66.93; H, 9.52; N, 8.70.

(1*S*,3*R*,4*R*)-3-[*N*-(*trans*-(2*R*,5*R*)-2,5-Dimethyl)pyrrolidinyl]methyl-2-azabicyclo[2.2.1]heptane (4). The Boc-protected amide **10** (1.27 g, 3.94 mmol) was dissolved in anhydrous HCl (4 M in 1,4-dioxane, 39.4 mmol, 9.87 mL) and heated at reflux until TLC indicated complete consumption of the amide (ca. 2 h). Volatile material was then removed by evaporation, and the residue was transferred to a suspension of LAH (0.39 g, 11.8 mmol) in THF (60 mL) at 0 °C. The mixture was then heated at reflux overnight. The reaction mixture was cooled to 0 °C and vigorously stirred during the portion-wise addition of a mixture of freshly ground $Na_2SO_4\cdot 10H_2O$ (3.0 g, 9.3 mmol) and Celite 545 (0.9 g). The resulting, thick suspension was further stirred for 30 min and then filtered. The filter cake was washed with hot THF (40 mL), and the combined filtrates were concentrated to give **4** (0.70 g, 85%): $[\alpha]^{25}_D$ −94.0 (*c* 1.04, CH_2Cl_2); IR (neat) 3395, and 1636 cm^{-1}; ^{1}H NMR δ 3.35−3.33 (1H, m), 3.03−2.95 (2H, m), 2.75 (1H, dd, J = 9.5, 5.6 Hz), 2.42 (1H, dd, J = 12.5, 5.6 Hz), 2.14 (1H, dd, J = 12.5, 9.5 Hz), 2.09−2.06 (1H, m), 1.96−1.83 (2H, m), 1.60−1.45 (2H, m), 1.40−1.19 (5H, m), 1.15 (1H, ddd, J = 9.7, 1.4, 0.9 Hz), and 0.87 (6H, d, J = 6.3 Hz); ^{13}C NMR δ 60.2, 55.7, 54.9, 52.3, 40.2, 35.5, 31.4, 30.6, 28.6, and 16.9; GC-MS (EI) *m*/*z* (rel intensity) 208 (M^+, 9), 193 (14), 112 (100), 98 (69), and 96 (15). Anal. Calcd for $C_{13}H_{24}N_2\cdot 0.4H_2O$: C, 72.44; H, 11.60; N, 13.00. Found: C, 72.70; H, 11.29; N, 12.75.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-[*N*-(*trans*-(2*S*,5*S*)-2,5-dimethyl)pyrrolidinyl]carbonyl-2-azabicyclo[2.2.1]-heptane (11). The procedure for **10** was followed using amino acid **9** (0.30 g, 1.24 mmol) and *trans*-(2*S*,5*S*)-dimethylpyrrolidine·HCl (0.25 g, 1.87 mmol) to obtain **11** (0.37 g, 93%): mp 149−151 °C; R_f 0.27 (silica, pentane/EtOAc 1:2);

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$[\alpha]_D^{25}$ +55.4 (*c* 0.48, CH_2Cl_2); IR (neat) 2976, 1688, and 1649 cm^{-1}; ^1H NMR (mixture of rotamers) δ 4.41−4.38 and 4.26−4.22 (1H, each m), 4.22 (1H, sept, J = 6.3 Hz), 4.00 and 3.95 (1H each t, J = 6.5 Hz), 3.92 and 3.83 (1H, each s), 2.43−2.38 (1H, m), 2.21−2.02 (3H, m), 1.79−1.67 (2H, m), 1.66−1.54 (2H, m), 1.54−1.36 (2H, m), 1.44 and 1.37 (9H, each s), 1.34 and 1.24 (3H, each d, J = 6.5 Hz), 1.17−1.12 (1H, m), 1.11 and 1.09 (3H, each d, J = 6.3 Hz); ^{13}C NMR (mixture of rotamers) δ 168.2, 168.1, 154.1, 153.1, 79.3, 78.9, 63.65, 63.60, 57.2, 56.0, 52.8, 52.54, 52.47, 52.4, 42.9, 42.2, 34.3, 33.6, 30.8, 30.7, 30.6, 30.4, 28.43, 28.38, 28.3, 28.22, 28.20, 28.1, 21.84, 21.81 18.8, and 18.7; GC-MS (EI) *m*/*z* (rel intensity) 323 (M^+ + 1, 11), 249 (18), 196 (30), 140 (100), and 98 (30). Anal. Calcd for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69. Found: C, 66.87; H, 9.48; N, 8.59.

(1*S*,3*R*,4*R*)-3-[*N*-(*trans*-(2*S*,5*S*)-2,5-Dimethyl)pyrrolidinyl]methyl-2-azabicyclo[2.2.1]heptane (5). The procedure described for **4** was followed using **11** (0.37 g, 1.15 mmol), which gave **5** (0.22 g, 91%): $[\alpha]_D^{25}$ + 49.9 (*c* 3.30, $CHCl_3$); IR (neat) 3436, and 1639 cm^{-1}. ^1H NMR δ 3.36−3.38 (1H, m), 3.01−2.93 (2H, m), 2.75 (1H, dd, J = 9.5, 4.8 Hz), 2.33−2.37 (1H, m), 2.28 (1H, dd, J = 12.5, 9.5 Hz), 2.21 (1H, dd, J = 12.5, 4.8 Hz), 1.98−1.85 (2H, m), 1.70 (1H, br s), 1.64−1.51 (2H, m), 1.47 (1H, dpent, J = 9.8, 2.0 Hz), 1.36−1.23 (4H, m), 1.10 (1H, dt, J = 9.8, 1.3 Hz), and 0.90 (6H, d, J = 6.3 Hz); ^{13}C NMR δ 59.9, 55.7, 55.0, 53.4, 39.1, 34.2, 32.7, 30.7, 28.9, and 17.0; GC-MS (EI) *m*/*z* (rel intensity) 208 (M^+, <1), 112 (100), 98 (92), and 96 (12). Anal. Calcd for $C_{13}H_{24}N_2 \cdot 0.2H_2O$: C, 73.67; H, 11.60; N, 13.22. Found: C, 73.81; H, 11.65; N, 13.07.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-[*N*-(*trans*-(2*R*,5*R*)-2,5-diethyl)pyrrolidinyl]carbonyl-2-azabicyclo[2.2.1]heptane (12). The procedure for **10** was followed using **9** (1.00 g, 4.14 mmol) and *trans*-(2*R*,5*R*)-diethylpyrrolidine·HCl (1.02 g, 6.22 mmol) to obtain **12** (1.10 g, 76%): mp 134−135 °C; $[\alpha]_D^{25}$ −8.74 (*c* 1.0, CH_2Cl_2); IR (neat) 2969, 1695, and 1645 cm^{-1}; ^1H NMR (mixture of rotamers) δ 4.32−4.30 and 4.21−4.19 (1H, each m), 4.15−4.08 and 3.94−3.82 (2H, each m), 3.79 and 3.67 (1H, each s), 2.73 and 2.66 (1H, each dt, J = 9.5, 2.0 Hz), 2.52−2.47 (1H, m), 2.19−1.59 (8H, m), 1.53−1.23 (3H, m), 1.43 and 1.40 (9H, each s), 1.19−1.23 (1H, m), 1.13−1.01 (1H, m), 0.94 and 0.83 (6H, each t, J = 7.3 Hz); ^{13}C NMR (mixture of rotamers) δ 170.0, 169.9, 153.9, 153.1, 79.4, 79.1, 62.6, 60.5, 60.3, 59.3, 58.9, 56.9, 55.9, 43.9, 43.0, 35.2, 34.4, 30.8, 30.3, 29.3, 28.9, 28.51, 28.45, 28.40, 28.3, 27.6, 27.4, 25.9, 25.7, 25.0, 24.5, 11.5, 10.9, 10.8, and 10.7; GC-MS (EI) *m*/*z* (rel intensity) 351 (M^+ + 1, 10), 140 (100), and 126 (24). Anal. Calcd for $C_{20}H_{34}N_2O_3$: C, 68.54; H, 9.78; N, 7.99. Found: C, 68.28; H, 9.87; N, 8.00.

(1*S*,3*R*,4*R*)-3-[*N*-(*trans*-(2*R*,5*R*)-2,5-Diethyl)pyrrolidinyl]methyl-2-azabicyclo[2.2.1]heptane (6). The procedure described for **4** was followed using **12** (0.82 g, 2.34 mmol), which gave **6** (0.52 g, 95%): $[\alpha]_D^{25}$ −63.9 (*c* 1.5, CH_2Cl_2); IR (neat) 3430, and 1637 cm^{-1}; ^1H NMR δ 3.39−3.37 (1H, m), 2.83−2.75 (2H, m), 2.76 (1H, dd, J = 9.6, 5.7 Hz), 2.57 (1H, dd, J = 12.4, 5.7 Hz), 2.17 (1H, dd, J = 12.4, 9.6 Hz), 2.12−2.09 (1H, m), 2.04 (1H, br s), 1.60−1.48 (4H, m), 1.46−1.29 (7H, m), 1.21−1.17 (1H, m), 1.12−0.98 (2H, m), and 0.81 (6H, t, J = 7.3 Hz); ^{13}C NMR δ 62.4, 61.9, 60.5, 55.7, 52.0, 40.2, 35.6, 34.9, 31.5, 28.7, 27.5, 23.1, 18.9, 13.9, and 10.6; GC-MS (EI) *m*/*z* (rel intensity) 236 (M^+, <1), 209 (11), 140 (91), and 112 (100). Anal. Calcd for $C_{15}H_{28}N_2 \cdot 0.1H_2O$: C, 75.64; H, 11.93; N, 11.76. Found: C, 75.73; H, 11.70; N, 11.59.

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-[*N*-(*trans*-(2*S*,5*S*)-2,5-dimethyl)pyrrolidinyl]-carbonylpyrrolidine (13). Boc-amide **13** (0.53 g, 1.78 mmol) was prepared in 77% yield from *N*-Boc-proline[18] (0.50 g, 2.32 mmol) following the procedure described for **10**. **13**: mp 128−130 °C; R_f 0.24 (silica, pentane/EtOAc 1:2); $[\alpha]_D^{22}$ + 25.6 (*c* 0.9, CH_2Cl_2); ^1H NMR (mixture of rotamers) δ 4.46 and 4.36 (1H, each m), 4.21 (2H, pent, J = 6.5 Hz), 3.67 and 3.60 (1H, each ddd, J = 9.5, 8.1, 4.3 Hz), 3.46 and 3.39 (1H, each dt, J = 10.1, 7.2 Hz), 2.44−1.95 (4H, m), 1.84 (1H, m), 1.66−1.40 (2H, m), 1.44 and 1.43 (9H, each s), 1.23 (3H, d, J = 6.5 Hz), 1.18 (3H, d, J = 6.5 Hz), and 1.16 (1H, t, J = 6.0 Hz); ^{13}C NMR (mixture of rotamers) δ 172.1, 172.0, 154.3, 153.4, 79.3, 79.1, 57.1, 57.0, 54.0, 53.8, 53.1, 52.7, 47.1, 47.0, 31.9, 30.9, 30.4, 28.9, 28.8, 28.3, 28.2, 24.5, 23.4, 23.0, 22.7, 18.9, and 18.2; MS (EI) *m*/*z* (rel intensity) 296 (M^+, 7), 223 (15), 114 (100), 98 (54), and 70 (87). Anal. Calcd for $C_{16}H_{28}N_2O_3$: C, 64.83; H, 9.52; N, 9.45. Found: C, 64.64; H, 9.50; N, 9.50.

(2*S*)-2-[*N*-(*trans*-(2*S*,5*S*)-2,5-Dimethyl)pyrrolidinyl]-methylpyrrolidine (7). The procedure described for **4** was followed using **13** (0.53 g, 1.78 mmol), which gave **7** (0.32 g, 1.76 mmol) in quantitative yield: $[\alpha]_D^{25}$ + 66.8 (*c* 1.25, CH_2Cl_2); IR (neat) 3406, and 1632 cm^{-1}; ^1H NMR δ 3.17−3.35 (1H, m), 3.10−3.00 (2H, m), 2.94 (1H, dt, J = 13.4, 9.9 Hz), 2.83 (1H, dt, J = 13.4, 9.4 Hz), 2.42 (1H, dd, J = 12.2, 4.0 Hz), 2.33 (1H, dd, J = 12.2, 10.3 Hz), 2.03−1.80 (3H, m), 1.73 (2H, pent, J = 7.2 Hz), 1.43−1.22 (3H, m), and 0.93 (6H, d, J = 6.3 Hz); ^{13}C NMR δ 55.8, 54.6, 51.8, 45.3, 30.8, 29.6, 24.7, and 17.0; GC-MS (EI) *m*/*z* (rel intensity) 183 (M^+ + 1, 1), 112 (100), 98 (90), and 70 (32). Anal. Calcd for $C_{11}H_{22}N_2 \cdot H_2O$: C, 65.95; H, 12.08; N, 13.98. Found: C, 65.76; H, 11.88; N, 13.34.

Catalytic Rearrangement of Epoxides: General Procedure. *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexane) was added dropwise over 5 min to a solution of diamine **1** or **3**−**7** (15 μmol), diisopropylamine (0.64 mL, 0.46 mmol), and DBU (5 equiv for the substrate screening, otherwise as indicated in the tables) in THF (1.5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, and the epoxide (0.3 mmol) in THF (1.0 mL) containing *n*-dodecane (ca. 10 mg, as the internal standard for GC analysis) was then added dropwise over a period of 5 min. The reaction mixture was stirred at the temperature indicated until the reaction ceased (according to GC analysis, which was also used for determining the ee of the formed allylic alcohol). The reaction mixture was then diluted with Et_2O (15 mL) and washed with 10% aqueous citric acid (2 × 5 mL), water (5 mL), and brine (5 mL) and dried ($MgSO_4$). The crude alcohol was purified by column chromatography.

Stoichiometric Rearrangement of Epoxides: General Procedure. This procedure was performed as described for the catalytic reaction but with the following modifications in amounts of reagents: diamine, 0.60 mmol; *n*-BuLi, 0.41 mL (0.65 mmol, 1.6 M in hexane); and epoxide, 0.5 mmol.

(1*R*)-Cyclopent-2-en-1-ol (14). Cyclopentene oxide (26 mg, 0.31 mmol) was transformed at room temperature to the corresponding allylic alcohol (*R*)-**14**. The reaction was judged to have ceased after 14 h (90% conversion, 96% ee). After workup, the crude allylic alcohol was benzoylated[9a] and purified by column chromatography (silica, pentane/EtOAc 90:10) to give the benzoate ester of **14** (47 mg, 81%). (*R*)-**14**: colorless oil; GC (68 °C isotherm): t_R (*S*) = 18.17 min, t_R (*R*) = 18.64 min.

(1*R*)-Cyclohex-2-en-1-ol (15). Cyclohexene oxide (30 mg, 0.31 mmol) was rearranged at 0 °C to the allylic alcohol (*R*)-**15**, using diamines **1** and **4**−**7**. The conversion was determined after 2 h (on the basis of epoxide consumption relative to the internal standard, *n*-dodecane). When the reactions were complete, workup and column chromatography (silica, pentane/Et_2O from 90:10 to 60:40) gave **15** in the yield and with the ee indicated in the Table 1. The spectroscopic properties of the isolated allylic alcohol were identical to those reported.[19] (*R*)-**15**: GC (100 °C isotherm): t_R (*S*) = 11.50 min, t_R (*R*) = 11.98 min.

(1*R*,4*S*,5*S*)-4,5-Dimethyl-cyclohex-2-en-1-ol (16) and (1*R*,4*S*,5*R*)-4,5-Dimethyl-cyclohex-2-en-1-ol (17). A 90:10 mixture of (1*R**,2*S**,4*R**,5*S**)-(1,4-*syn*,4,5-*syn*)-4,5-dimethyl-1-oxabicyclo[4.1.0]heptane and (1*R**,2*S**,4*S**,5*R**)-(1,4-*anti*,4,5-*syn*)-4,5-dimethyl-1-oxabicyclo[4.1.0]heptane (39 mg, 0.31 mmol) was transformed into the allylic alcohols **16** and **17**. The reaction was judged to have ceased after 6 h at 0 °C (at >95%

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conversion for *trans*-epoxide). Workup and column chromatography (silica, pentane/Et_2O from 95:5 to 60:40) gave a mixture of **16** and **17** (**16**: 33 mg, 94%, 98% ee; **17**: 3.5 mg, 85%, 99% ee) with spectroscopic properties identical to those reported.[4c,i] (*R*)-**16**: GC (105 °C isotherm): t_R (*S*) = 27.8 min, t_R (*R*) = 28.4 min. (*R*)-**17**: GC (105 °C isotherm): t_R (*S*) = 17.40 min, t_R (*R*) = 17.89 min.

(1*R*)-Cyclohept-2-en-1-ol (18). Cycloheptene oxide (34 mg, 0.31 mmol) was transformed into the corresponding allylic alcohol **18**. The reaction was judged to have ceased after 6 h at 0 °C (at >95% conversion). Workup and column chromatography (silica, pentane/Et_2O from 95:5 to 60:40) gave **18** (32 mg, 93%, >99% ee) with spectroscopic properties identical to those reported.[20] (*R*)-**18**: colorless oil; GC (100 °C isotherm): t_R (*S*) = 18.37 min, t_R (*R*) = 18.47 min.

(4*R*)-Oct-5-en-4-ol (19). (*Z*)-4-Octene oxide (39 mg, 0.31 mmol) was transformed into the corresponding allylic alcohol **19**. The reaction was quenched after 24 h at 0 °C. Workup and column chromatography (silica, pentane/Et_2O from 95:5 to 60:40) then gave **19** (31 mg, 80%) with spectroscopic properties identical to those reported.[9] The enantiomeric excess was determined by analysis of the (*R*)-MTPA derivative (^1H and ^{19}F NMR, 91% ee).[21]

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