Allylic Alcohols via Catalytic Asymmetric Epoxide Rearrangement

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Abstract: Optically active allylic alcohols can be prepared via rearrangement of epoxides using chiral lithium amides, but other than for a small subset of *meso*-epoxides, insufficient reactivity and enantioselectivity hamper the existing methods. Furthermore, the chiral reagents are often required in large excess. This study presents a general and highly enantioselective process that, in addition, is based on catalytic amounts (5 mol %) of enantiopure (1*S*,3*R*,4*R*)-3-(1-pyrrolidinyl)methyl-2-azabicyclo[2.2.1]heptane and lithium diisopropylamide as the stoichiometric base. The influence of structural modification of the catalyst is studied in terms of activity, enantioselectivity, and aggregation behavior. The utility of the process is demonstrated by its application to a variety of epoxide derivatives (≥94% ee for 11 out of 14 examples), including the formal syntheses of, e.g., a prostaglandin core unit, epibatidine, carbovir, faranal, and lasiol. The system is readily extended to the resolution of racemic epoxides, which allows access to highly enantioenriched epoxides or allylic alcohols, even at conversions near 50%.

Introduction

Allylic alcohols are versatile intermediates for organic synthesis, but multistep sequences are often required for their preparation. The lithium amide-mediated rearrangement of epoxides into allylic alcohols is an attractive approach, which has been thoroughly investigated due to its synthetic potential and its interesting mechanistic features.[1] The isomerization is known to occur via α- or *syn*-*β*-lithiation pathways,[2] of which the latter is more desirable because it leads exclusively to allylic alkoxides. In contrast, α-metalation may produce saturated alkoxides, enolates, or allylic alkoxides (Figure 1). Many synthetically useful systems have been developed, although the regioselectivity of the lithiation depends on the choice of base, solvent, and substrate.

Asymmetric versions of the epoxide rearrangement have been known for many years,[3] and this topic has been separately reviewed.[4] The best results have been obtained using bases derived from optically active diamines containing one secondary and one tertiary amine, and particularly lithium 2-(1-pyrrolidinyl)ethyl(alkyl)amides.[5] Enantioselective epoxide isomerization has been successfully applied to the synthesis of a number of natural products,[4a] and recent findings in the area include, for example, development of catalytic systems,[5a,b] and improved diamine syntheses.[5g,h] However, the process needs to be improved in terms of enantioselectivity, generality, and economy, before it can be considered as a useful synthetic tool (vide infra):

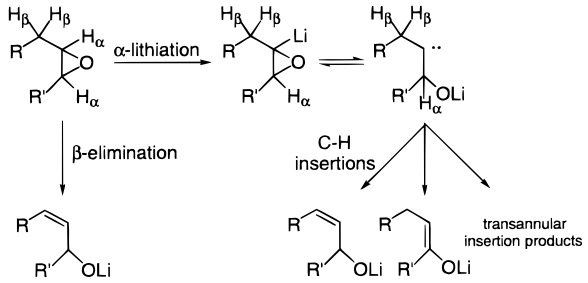

Figure 1. Mechanistic pathways for the isomerization of epoxides.

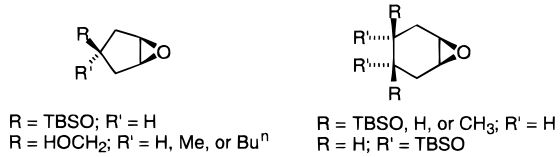

Figure 2. Epoxides suitable for asymmetric epoxide rearrangement.

(i) Only two types of *meso*-epoxide have been rearranged into allylic alcohols of enantiopurity exceeding 90% ee (Figure 2).[4−6]

(ii) None of the most frequently used lithium amides have reached >90% ee for more than one substrate.[4,5]

(1) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345−443.

(2) (a) Morgan, K. M.; Gronert, S. *J. Org. Chem.* **2000**, *65*, 1461−1466. (b) Ramírez, A.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 11114−11121. (c) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064−2067. (d) Hodgson, D. M.; Gibbs, A. R. *Tetrahedron Lett.* **1997**, *38*, 8907−8910.

(3) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755−756.

(4) For reviews, see: (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439−1457. (b) Asami, M. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 188−199. (c) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361−14384. (d) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1−26.

(5) (a) Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **1997**, *38*, 6425−6428. (b) Asami, M. Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793−796. (c) Tierney, J. P.; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1019−1222. (d) Asami, M.; Ogawa, M.; Inoue, S. *Tetrahedron Lett.* **1999**, *40*, 1563−1564. (e) de Sousa, S. E.; O'Brien, P.; Steffens, H. C. *Tetrahedron Lett.* **1999**, *40*, 8423−8425. (f) O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2435−2441. (g) de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483−1492. (h) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 167−170. (i) Khan, A. Z.-Q.; de Groot, R. W.; Arvidsson, P. I.; Davidsson, Ö. *Tetrahedron: Asymmetry* **1998**, *9*, 1223−1229. (j) Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1996**, *61*, 6108−6113.

(6) Dilithiated norephedrine has been successfully applied in the isomerization of *syn*-4-(hydroxymethyl)cyclopentene oxides; see, e.g.: Hodgson, D. M.; Gibbs, A. R. *Tetrahedron: Asymmetry* **1996**, *7*, 407−408.

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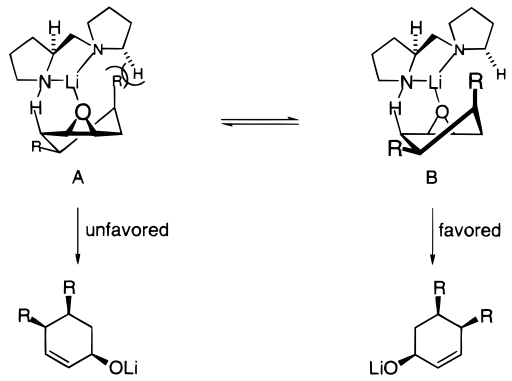
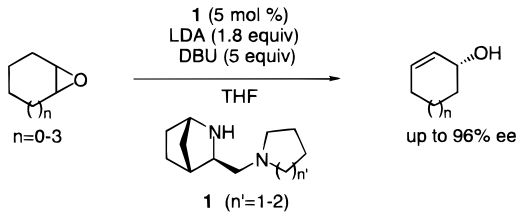


Figure 3. Proposed model for transition states A and B.

Scheme 1. Catalytic Asymmetric Isomerization of *meso*-Epoxides



(iii) Only one example of >90% ee has been achieved for catalytic isomerization (20 mol % chiral amine).[5a] The stoichiometric methods require up to 3 equiv of the chiral base.[5d,e,6]

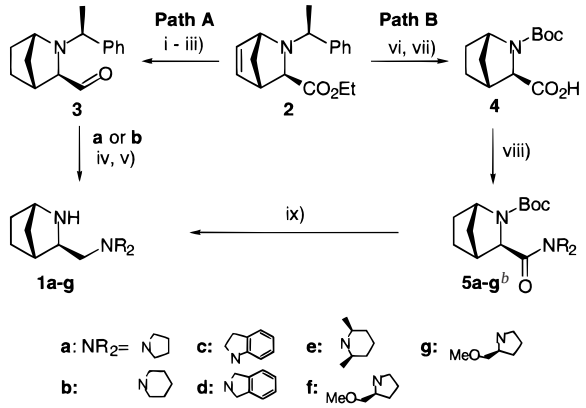
Recently, we reported that cyclic *meso*-epoxides can be rearranged with high levels of asymmetric induction by lithium diisopropylamide (LDA) in the presence of catalytic amounts (5 mol %) of homochiral 3-aminomethyl-2-azabicyclo[2.2.1]-heptanes **1** (Scheme 1).[7] The present paper describes studies of relationships between catalyst structure and activity, substrate generality, and kinetic resolution of racemic epoxides.

Results and Discussion

Because of the relatively limited knowledge about the design of efficient catalysts for the title reaction, we wanted to use an empirical approach to investigating the relationships between reactivity, enantioselectivity, and catalyst structure. The proposed model for asymmetric rearrangement of cyclohexene oxide suggests that enantiodifferentiation is controlled by steric repulsion between the substrate and the tertiary pyrrolidine unit in the lithium amide (Figure 3).[4b] Accordingly, our aim was to identify the influence of changes near the tertiary amine moiety. A set of diamines was chosen (**1a**−**g**, Scheme 2) to represent variations of electronic character (aliphatic **1a,b** vs anilinic **1c** and benzylic **1d**), steric hindrance (**1e**), and remote coordination sites and stereocentrers (**1f,g**).

Our route to diamines **1** (path A, Scheme 2)[7] was found to be less general than anticipated, as the reductive amination of aldehyde **3** gave low yields with most amines other than pyrrolidine and piperidine. Furthermore, hydrogenolytic debenzylation (step v, Scheme 2) turned out to be sensitive to catalyst poisoning, resulting in incomplete reactions. The desired diamines were instead prepared by means of a slightly modified version of the protocol reported by Asami (path B, Scheme 2).[8] The *aza*-Diels−Alder adduct **2**, readily accessible in both enantiomeric forms,[9] was converted into *N*-Boc amino acid **4**, and subsequent amide coupling, deprotection, and reduction gave diamines **1** in satisfactory overall yields.

Scheme 2. Alternative Routes to Diamines **1**[a]



[a] Path A: (i) H_2 (1 atm), Pd/C; (ii) LAH (see ref 24 for i−ii); (iii) Swern oxidation (85% for i−iii); (iv) pyrrolidine or piperidine, $NaBH_3CN$; (v) H_2 (1 atm), $Pd(OH)_2/C$ (77−81% for iv−v). Path B: (vi) H_2 (5 atm), Pd/C (see ref 9); (vii) LiOH, then Boc_2O (90% for vi−vii); (viii) EDC, HOBt, Et_3N, amine (79−94%; 57% for **2e**); (ix) HCl, then LAH (83−96%). [b] **5g** was prepared from *ent*-**4**.

Diamine Evaluation. To evaluate the diamines in terms of both enantioselectivity and catalytic activity, reactions of cyclohexene and cyclooctene oxides were monitored at a point well before completion, as outlined in Table 1. As points of reference, **6**[5j] and **7**,[5e,10] which have previously been used in stoichiometric reactions, were included in the study. The results in Table 1 show that **1a** remains the most powerful catalyst (entry 1, Table 1), and that LDA alone reacts sluggishly under these conditions (cf. entries 1 and 12, Table 1). Nevertheless, Li-**6** and Li-**7** are outcompeted by LDA (entries 8 and 10, Table 1), and even when used in stoichiometric amounts, they react very slowly compared to the catalytic system based on **1a** (cf. entries 1 with 9 and 11, respectively, Table 1).

The similar performances exhibited by **1c** and **1d** (entries 3 and 4, Table 1) suggest that their inferiority compared to **1a** is attributable to conformational or steric differences and that the electronic properties of the pyrrolidine moiety are of minor importance (cf. entries 1 with 3 and 4, respectively, Table 1). Catalysts, which contain two independent units of chirality, are normally expected to show one matching and one mismatching combination with respect to effectiveness in a given application. However, the L-prolinol derivatives **1f,g** display a quasi-enantiomeric behavior (cf. entries 6 and 7, Table 1), which makes mechanistic interpretation difficult.

Solvent Studies. Epoxide metalation is usually very sensitive to the choice of substrate, base, and solvent, and these parameters are known to influence reactivity as well as chemo- and enantioselectivity.[2,5b,11] To optimize our system, cyclohexene oxide was isomerized using LDA (2 equiv) and **1a** (1 mol %) at 0 °C, in the presence of different solvents and a variety of Lewis basic additives (Table 2).

Relatively good results were obtained using THF in combination with (DBU), DBN, or HMPA (cf. entries 1, 2, and 7, Table

(7) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760−10761.

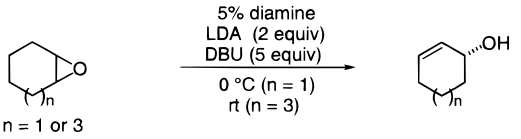
(8) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721−727.

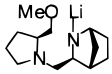
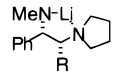
(9) See: Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530−2535 and references therein. Enantiomerically pure **3** is routinely prepared in our laboratories, on scales up to 1 mol.

(10) (a) Colman, B.; de Sousa, S. E.; O'Brien, P.; Towers, T. D.; Watson, W. *Tetrahedron: Asymmetry* **1999**, *10*, 4175−4182. (b) Amedjkouh, M.; Ahlberg, P. *11th Eur. Symp. Org. Chem.* July, **1999**.

(11) See, e.g.: Nilsson Lill, S. O.; Arvidsson, P. I.; Ahlberg, P. *Acta Chem. Scand.* **1998**, *52*, 280−284.

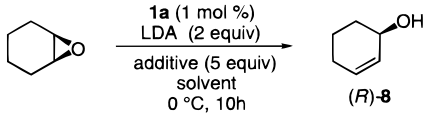
Table 1. Evaluation of Diamines **1**, **6**, and **7**



entry	R=	diamine	n = 1 % ee(%conv.)[a]	n = 3 % ee(%conv.)[a]
1		**1a**	96 (51)	63 (70)
2		**1b**	95 (50)	59 (65)
3		**1c**	73 (38)	54 (43)
4	 	**1d**	75 (46)	37 (40)
5		**1e**	46 (22)	35 (25)
6		**1f**	84 (24)	43 (22)
7[b]		**1g**[b]	-79 (32)	-40 (24)
8	Me	**6**	*rac.*[c] (3)	14 (16)
9[d]		**6**	90 (4)	61 (41)
10	H	**7**	*rac.*[c] (3)	9 (18)
11[d]	H	**7**	64 (5)	57 (41)
12		none	*rac.*[c] (5)	*rac.*[c] (13)

[a] Determined by GC (Chrompack Chirasil Dex-CB). Conversions based on epoxide consumption relative to an internal standard. Conversion is given after 2 h for $n = 1$ and after 18 h for $n = 3$. For $n = 1$, full conversion was reached within 5−24 h for entries 1−7. For entries 8−12 and $n = 1$, 50−70% conversion was observed after 24 h. [b] Prepared from *ent*-**4**. Negative ee values correspond to excess of (*S*)-isomers. [c] Nearly racemic (<5% ee). [d] Reaction run in the absence of LDA, using Li−**6** or Li−**7** (2.0 equiv.).

Table 2. Solvent and Additive Studies



entry	additive	solvent	ee[a] (%)	conv[a] (%)
1	none	THF	44	40
2	DBU[b]	THF	78	92
3	DBN[c]	THF	67	81
4	DABCO	THF	41	36
5	DMPU	THF	44	49
6	TMEDA	THF	40	67
7	HMPA	THF	69	80
8	Pyridine	THF	22	30
9	DMAP	THF	18	33
10	1-MeIm[d]	THF	rac.[e]	<5
11	1,3-dioxane	THF	41	72
12	DBU	PhH	35	58
13	DBU	Et_2O	38	63
14[f]	DBU	1,4-dioxane	65	70
15	DBU	THF	81	85

[a] See Table 1. [b] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [c] 1,5-Diazabicyclo[4.3.0]non-5-ene. [d] 1-Methylimidazole. [e] Nearly racemic (<5% ee). [f] 10 equiv of DBU was used.

2). The subsequent experiments were carried out in the presence of 5 equiv of DBU (ca. 0.6 M) in THF, although better enantioselectivity was observed at even higher DBU concentrations (cf. entries 2 and 15, Table 2).

Aggregates and Nonlinear Effects. It has been demonstrated that enantioselectivity in base-mediated reactions is often influenced by the aggregation state of the lithium amides.[5,12] Lewis basic additives, such as DBU, are believed to act in favor of a highly enantioselective, monomeric catalyst species, by inhibiting the formation of unselective aggregates $(Li^+\mathbf{1a}^-)_n$. The influence of aggregates was studied by monitoring the reaction of cyclohexene oxide (1 equiv) mediated by LDA (2 equiv) and **1a** (20 mol %) of enantiomeric purity ranging from 25 to 100% ee, in THF containing DBU in various concentrations. The results are shown in Figure 4, where the ee of (*R*)-cyclohex-2-en-1-ol (**8**) is plotted versus catalyst ee. At high DBU concentrations, the relationship between the ee's of **1a** and **8** was strictly linear, whereas a pronounced negative nonlinear correlation was observed at lower DBU loading.[13] Addition of DBU also improves enantioselectivity with an enantiopure catalyst, which indicates that the cosolvent does, indeed, prevent the formation of kinetically competent but less enantioselective aggregates $(Li^+\mathbf{1a}^-)_n$. The linear relationship between catalyst and product ee's at a sufficient DBU concentration suggests that the active catalyst is mainly monomeric (or, more likely, a $(Li^+\mathbf{1a}^-)$·DBU heterodimer). The nonlinear effects observed at low DBU concentrations and intermediate enantiopurity of **1a** could be due to DBU-induced dissociation occurring more readily for the heterochiral *meso*-aggregates $(Li^+\mathbf{1a}^-)_n$·$(Li^+$-*ent*-$\mathbf{1a}^-)_n$ than for the homochiral dimers. As a result, the ee of the monomeric catalyst would become lower than that of the total **1a** (i.e., ee $[Li^+\mathbf{1a}^-]$ < ee $[\mathbf{1a}]_{tot}$). Alternatively, these nonlinear effects could be attributable to the action of one (or several) *meso*-type species with superior catalytic activity for the production of racemic **8**. For the future development of this catalytic process, we believe that nonlinear effect studies should serve as a useful complement to other tools for mechanistic studies.[14]

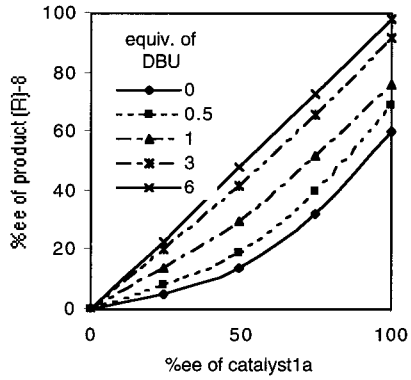
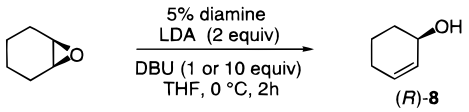


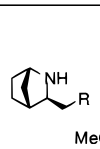
Figure 4. Nonlinear effects and influence of DBU.

The development of catalysts that are effective in the absence of cosolvents is clearly important, and **1e**−**g** were therefore compared with **1a** at lower loadings of DBU, as outlined in Table 3. It is again evident that an increased DBU concentration leads to improved enantioselectivity. Interestingly, a decrease in the DBU loading is less detrimental for the performance of **1g** than for the other catalysts (entry 4, Table 3). Obviously, $Li^+\mathbf{1g}^-$ exhibits different aggregation properties than the lithium amides of **1a**, **1e**, and **1f**.[15] This demonstrates that subtle differences can largely influence the aggregation properties of these catalysts and could certainly justify further elaboration of the diamine structures.

(12) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227−234.
(13) For a recent review on nonlinear effects in asymmetric synthesis, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2922−2959.
(14) See, e.g.: (a) Arvidsson, P. I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* **1999**, *121*, 1883−1887. (b) Olsson, R. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3991−3998. (c) Nilsson Lill, S. O.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1999**, *10*, 265−279.

Table 3. Effect of DBU Concentration



entry	diamine	R=	diamine	10 equiv. DBU %ee (%conv.)[a]	1 equiv. DBU %ee (%conv.)[a]
1			**1a**	97 (46)	70 (65)
2			**1e**	49 (20)	26 (22)
3			**1f**	85 (20)	24 (26)
4			**1g**[b]	-79 (31)	-64 (38)

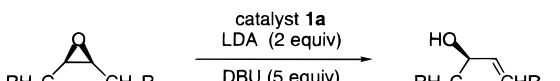
[a] Determined as indicated in Table 1. [b] Prepared from *ent*-**4**.

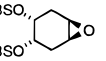
Substrate Screening. To test the scope and limitations of our system, a series of representative *meso*-epoxides[16] were subjected to LDA (2 equiv), **1a** (5−20 mol %), and DBU (5 equiv) in THF, as outlined in Table 4. Considering that no other lithium amide has achieved >90% ee for more than one substrate, the general efficiency of **1a** is remarkable (cf. entries 1−10, Table 4). Moreover, apart from our preliminary report, catalytic rearrangement has previously only been reported for the epoxides of cyclohexene, cyclooctene, and (*Z*)-octene.[5a−c]

Given the value of cyclopentene oxides as natural product precursors, it is somewhat unfortunate that their reactivity differs significantly from that of cyclohexene oxides. For example, nonsubstituted and *anti*-substituted derivatives react sluggishly (entries 1, 2, and 5, Table 4), whereas *syn*-4-substituted cyclopentene oxides tend to be very reactive (entries 3 and 4, Table 4). Moreover, both categories require larger or even stoichiometric amounts of **1a** in order to yield the corresponding alcohols with satisfactory ee (entries 1−5, Table 4). The differences in reactivity probably derive from conformational and chelation phenomena.[2c] A preference for conformations from which the desired syn-β-elimination is unfavorable may explain the low reactivity exhibited by nonsubstituted and *anti*-substituted substrates (cf. entries 1, 2, and 5, respectively, Table 4). It has also been demonstrated that rearrangement of similar epoxides may proceed partly via α-lithiation pathways, in which enantiodifferentiation is likely to be poor or reversed. In contrast, it has been suggested that cyclopentene oxides bearing *syn*-4-substituents prefer conformations in favor of vicinal elimination, particularly if the *syn*-substituent can assist in the coordination of Li^+. Accordingly, the modest ee obtained in the catalytic production of (*R*)-**10** (entry 3, Table 4) may be attributed to a silyloxy-induced activation, which enables the LDA-mediated rearrangement to compete with the enantioselective reaction.

Cyclohexene oxides normally undergo clean vicinal elimination, and the influence of substituents is less pronounced than that observed for epoxycyclopentanes.[2b] We find that the reactivity of *anti*-substituted derivatives resembles that of cyclohexene oxide itself, in terms both of asymmetric induction and reaction rates (cf. entries 6 with 7 and 9, respectively, Table 4). The single *syn*-substituted cyclohexene oxide included in the present study (entry 8, Table 4) requires a slightly prolonged reaction time. These observations are simply in line with what one would expect for a more hindered substrate. The lower ee's obtained for cyclooctene and (*Z*)-octene oxides (entries 11 and 12, Table 4) probably reflect the conformational flexibility of these substrates.[17]

Table 4. Catalytic Asymmetric Rearrangement of Epoxides



entry	epoxide	**1a** (mol%)	t (°C)/ time (h)	% yield[a]	%ee[b]	product[c]
1		20	rt/ 24	67[d]	49	(*R*)-**9**
2		120	rt/ 24	78[d]	95	(*R*)-**9**
3		5	0/ 4	60	67	(*R*)-**10**
4		120	0/ 4	85	95	(*R*)-**10**
5		20	rt/48	42	95	(*R*)-**11**
6		5	0/ 6	91	96	(*R*)-**8**
7[e]		5	0/ 6	95	94	(*R*)-**12**
8[e]		5	0/ 16	95	97	(*R*)-**13**
9		5	0/ 6	60	97	(*R*)-**14**
10		5	0/ 6	89	96	(*R*)-**15**
11		5	0/ 36	81	78	(*R*)-**16**
12		5	0/36	82	66	(*R*)-**17**

[a] Isolated. [b] Determined by GC (Chirasil Dex-CB). Entries 9 and 12 determined for (*R*)-Mosher esters (^{1}H and ^{19}F NMR). [c] Assignment by sign of optical rotation. [d] After benzoylation. [e] Reaction carried out with a 9:1 *trans*/*cis* mixture of epoxides. Reaction times refer to the times required for full conversion of each isomer, respectively. Enantiomeric determination carried out on isomeric mixture. Yield refers to an inseparable 9:1 mixture of **12** and **13**.

Application to Racemic Epoxides: Kinetic Resolution. The base-mediated isomerization applied to kinetic resolution of racemic epoxides is a potentially very useful process. Some stoichiometric reactions have been reported,[4b,18] but high levels of enantioselectivity are rare and typically accompanied with low isolated yields (<30%). As part of the present study, two racemic epoxides were investigated with very promising results, as outlined in Table 5. The allylic alcohols as well as the recovered epoxides were isolated in good yields and with high ee's, even at conversions near 50%.[19] It is noteworthy that efficient resolution can be realized for acyclic epoxides (entries

(15) It should be noticed that the species in solution have not been identified for Li^+**1e**$^-$ (entry 2, Table 3). Deprotonation of **1e** may lead to the formation of a mixture of diastereomeric lithium amides (i.e., having the methyl groups oriented either *syn* or *anti* relative to Li) which could, in principle, exhibit the opposite sense of enantioselectivity.

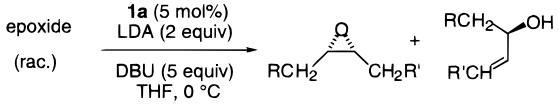
(16) Some of the allylic alcohols in Table 4 are precursors to natural products and drugs. (a) Prostaglandin core unit (entries 2 and 3): see ref 5j. (b) Carbovir (entry 5), cf.: Asami, M.; Inoue, S. *Tetrahedron* **1995**, *51*, 11725−11730. (c) Lasiol, cf. Kasai, T.; Watanabe, H,; Mori, K. *Bioorg. Med. Chem.* **1993**, *1*, 67−70. Faranal (entry 7), cf.: Mori, K.; Murata, N. *Liebigs Ann.* **1995**, 2089−2092. (d) Epibatidine (entry 10), cf.: Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1997**, *38*, 681−684. A subunit of manzamine A (entry 10), cf.: Kamenecka, T. M.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 4279−4282.

(17) The isomerization of cyclooctene oxide is known to produce bicyclo-[3.3.0]octan-2-ol under certain conditions (see, e.g., refs 2a and 11, respectively). This pathway appears to be unfavorable with Li−**1a**. Treatment of cyclooctene oxide with LDA/**1a** in Et_2O in the absence of DBU gave an approximately 8/1 mixture of the allylic/bicyclic alcohols. The bicyclo[3.3.0]octan-2-ol thus obtained held 23% ee.

(18) Mori, K.; Hazra, B. G.; Pfeiffer, R. J.; Gupta, A. K.; Lindgren, B. S. *Tetrahedron* **1987**, *43*, 2249−2254.

(19) For entry 4, a minor product, tentatively assigned as (1*S*)-2-methylene-1-cyclohexanol, was isolated in 11% yield (96% ee).

Table 5. Kinetic Resolution of Racemic Epoxides



entry	epoxide	% conv.[a]	epoxide[b] (% yield)	% ee[a] (epoxide)	alcohol[b] (% yield)	% ee[a] (alcohol)
1		48	(*S*)-**18** (87)	77	(*R*)-**19** (73)	88
2		55	(*S*)-**18** (89)	94	(*R*)-**19** (85)	84
3		43	(*S*)-**20** (81)	78	(*R*)-**21** (88)	96
4		52	(*S*)-**20** (63)	87	(*R*)-**21** (79)	94

[a] See Table 1. [b] Isolated yields, based on maximum recovery of each product at the given conversion. Reactions were quenched at the indicated conversion. Configurations based on optical rotation.

1 and 2, Table 5), and that the methodology can also be applied to the production of tertiary alcohols (entries 3 and 4, Table 5).

Conclusion

A set of easily accessible homochiral diamines **1** has been evaluated in the catalytic asymmetric LDA-mediated isomerization of epoxides to allylic alcohols. A catalytic system based on **1a** (typically 5 mol %) is superior to known stoichiometric reagents in terms of asymmetric induction and generality (≥94% ee for 11 out of 14 examples). The system works well for desymmetrization of *meso*-epoxides as well as for the kinetic resolution of racemic epoxides.

Experimental Section

General. All reactions were run under argon or nitrogen using oven-dried glassware (140 °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. Methanol was heated at reflux over magnesium turnings for several hours and then distilled and stored over activated 3-Å molecular sieves under argon. 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 and DMSO were heated with powdered CaH_2, distilled at reduced pressure, and stored under argon over 3-Å molecular sieves. Epoxides and oxalyl chloride were freshly distilled. Flash chromatography was done using Matrex silica gel 60A (37−70 μm) or Merck Al_2O_3 90 (70−230 mesh) neutral, activity grade 1. Analytical TLC was carried out utilizing 0.25-mm precoated plates from Macherey-Nagel SIL G-60 UV_{254} 60-F or Merck Al_2O_3 60 F_{254} type E, 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 at ambient temperature for $CDCl_3$ solutions at 400 and 100.4 MHz, respectively (Varian Unity 400). Chemical shifts for protons are reported using the residual $CHCl_3$ as internal reference (δ 7.26). Carbon shifts are referred to the resonance of $CDCl_3$ (δ 77.0). Unless otherwise stated, enantiomeric determination was accomplished by analytical GC using a Chirasil Dex-CB column (25 m/0.25 mm i.d.) and N_2 (12 psi) as the carrier gas. Infrared spectra were recorded on a Perkin-Elmer 1600 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).

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-azabicyclo[2.2.1]heptane-3-carboxylic Acid (4). LiOH (0.33 g, 13.9 mmol) was added to a solution of (1*S*,3*R*,4*R*)-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid ethyl ester[9] (2.3 g, 12.6 mmol) in THF/H_2O (4:1, 25 mL), and the mixture was stirred vigorously at 40 °C until TLC indicated complete hydrolysis (ca. 5 min.). The solvent was evaporated in vacuo, and residual water was azeotropically removed with the aid of toluene and a Dean−Stark trap. The resulting lithium (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylate[20] was then protected with *N*-^{t}Boc as described for proline,[21] yielding **4** (2.9 g, 95%) as a white solid which was used without further purification.

4: mp 140−144 °C; $[\alpha]^{25}_D$ +175.5 (c = 1.0, CH_2Cl_2); IR (KBr) 3435, 2922, 1641, and 1460; ^{1}H NMR δ 4.15−4.12 (1H, m), 3.84−3.81 (1H, m), 2.95−2.90 (1H, m), 1.83−1.74 (2H, m), 1.68−1.62 (2H, m), 1.53−1.36 (2H, m), and 1.49 (9H, s); ^{13}C NMR δ 196.5, 135.7, 66.9, 57.1, 43.0, 40.2, 38.9, 36.9, 30.1, and 29.5; MS (EI) *m*/*z* (relative intensity) 242 (M^+ + 1, 6), 186 (16), 140 (100), and 112 (58); HRMS calcd for $C_{12}H_{19}NO_4$ 241.1314, found 241.1319.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-(*N*-pyrrolidinyl)carbonyl-2-azabicyclo[2.2.1]heptane (5a). 1-Ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (EDC) (3.90 g, 20.3 mmol), 1-hydroxybenzotriazole (HOBt) (2.55 g, 18.9 mmol), and **4** (3.50 g, 14.5 mmol) were dissolved in CH_2Cl_2 (20 mL) at 0 °C. Et_3N (2.81 mL, 20.3 mmol) was added dropwise via syringe, and the resulting mixture was stirred for 15 min. Pyrrolidine (2.50 mL, 29.0 mmol) was then added over a period of 2−3 min. The reaction mixture was warmed to room temperature and stirred overnight and then diluted with EtOAc (20 mL) and washed with 10% aqueous citric acid (2 × 10 mL). The aqueous phases were re-extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed sequentially with 10% citric acid (2 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). Then, drying with $MgSO_4$, evaporation, and purification by column chromatography (silica, pentane/EtOAc 3:1 to 1:3) gave **5a** (4.0 g, 94%) as a white solid.

5a: mp 108−110 °C; R_f 0.39 (silica, pentane/EtOAc 1:2); $[\alpha]^{24}_D$ +42.7 (c = 1.0, CH_2Cl_2); IR (KBr) 2971, 1679, and 1639 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 4.37 and 4.24 (1H, each s), 3.91 and 3.81 (1H, each s), 3.72−3.50 (2H, m), 3.47−3.35 (2H, m), 2.53−2.45 (1H, m), 2.33−2.19 (1H, m), 2.01−1.60 (7H, m), 1.50−1.39 (1H, m) 1.46 and 1.37 (9H, each s), and 1.24−1.18 (1H, m); ^{13}C NMR (mixture of rotamers) δ 168.8, 168.5, 154.2, 152.8, 79.2, 78.9, 63.4, 63.0, 57.0, 55.6, 45.82, 45.80, 41.9, 41.3, 34.7, 34.1, 30.5, 30.3, 28.3, 28.1, 26.16, 26.08, 23.9, and 23.7; GC−MS (EI) *m*/*z* (relative intensity) 293 (M^+ − 1, 3), 237 (14), 221 (10), 193 (8), 181 (10), 140 (100), 112 (32), and 98 (11). Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.56; H, 9.09; N, 9.70.

(1*S*,3*R*,4*R*)-3-(*N*-Pyrrolidinyl)methyl-2-azabicyclo[2.2.1]-heptane (1a). The Boc-protected amide **5a** (3.84 g, 13.0 mmol) was dissolved in anhydrous HCl (4 M in 1,4-dioxane, 65 mmol, 16.3 mL) and heated at reflux until TLC indicated complete consumption of **5a** (ca. 2 h). Volatile material was then removed by evaporation, and the residue was transferred to a suspension of LAH (1.48 g, 39.0 mmol) in THF (50 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 portionwise addition of a mixture of freshly ground Na_2SO_4·10 H_2O (12.6 g, 39.0 mmol) and Celite 545 (3.2 g). The resulting thick suspension was further stirred for 30 min and then filtered. The filter cake was washed with hot THF (100 mL), and the combined filtrates were concentrated and distilled to give **1a** as a colorless oil (2.3 g, 91%).

1a: bp (2.5 Torr) 94−96 °C; R_f 0.18 (Al_2O_3, CH_2Cl_2/MeOH 9:1); $[\alpha]^{25}_D$ −33.8 (c = 4.8, CH_2Cl_2); IR (neat) 3400 cm^{-1}; ^{1}H NMR δ 3.42 (1H, s), 2.80 (1H, dd, J = 7.5, 6.8 Hz), 2.53−2.41 (4H, m), 2.31 (1H, ddd, J = 11.7, 6.8, 3.9 Hz), 2.22 (1H, ddd, J = 11.7, 6.8, 3.9 Hz), 2.22−2.20 (1H, m), 1.75−1.69 (4H, m), 1.62−1.54 (3H, m), 1.49−1.43 (1H, m), 1.38−1.26 (2H, m), and 1.15 (1H, dt, J = 9.8, 1.4 Hz); ^{13}C NMR δ 62.8, 60.7, 55.8, 54.5, 40.0, 34.9, 32.4, 28.9, and 23.4; GC−MS (EI) *m*/*z* (relative intensity) 180 (M^+, <1), 111 (17), 109 (100), 95 (23), and 70 (17). Anal. Calcd for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.32; H, 11.17; N, 15.51.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-(*N*-indolinyl)carbonyl-2-azabicyclo[2.2.1]heptane (5c). The procedure described for **5a** was followed using indoline (0.36 g, 2.94 mmol) and **4** (0.70 g, 2.90 mmol) to give **5c** (0.43 g, 86%) as a white solid.

5c: mp 200−205 °C; R_f 0.55 (silica, pentane/EtOAc 1:2); $[\alpha]^{20}_D$ + 71.9 (c = 1.1, CH_2Cl_2); IR (KBr) 3151, 2921, 1694, and 1662 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 8.19 (1H, dd, J = 7.9, 5.9 Hz), 7.22−7.13 (2H, m), 7.05−6.96 (1H, m), 4.45 and 4.30 (1H, each s), 4.04 and 3.91 (1H, each s), 4.40−4.00 (2H, m), 3.30−3.15 (2H, m), 2.65−

(20) Södergren, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577−7580.

(21) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synlett* **1991**, 37−38.

2.60 (1H, m), 2.29−2−21 (1H, m), 1.86−1.62 (3H, m), 1.52−1.40 (1H, m) 1.46 and 1.33 (9H, each s), and 1.24−1.18 (1H, m); ^{13}C NMR (mixture of rotamers) δ 168.3, 168.1, 154.2, 152.6, 143.3, 142.9, 130.6, 130.5, 127.3, 127.1, 124.3, 124.1, 123.5, 123.4, 117.2, 116.8, 79.4, 79.3, 63.9, 63.8, 57.0, 55.6, 47.4, 47.3, 42.0, 41.4, 36.6, 34.0, 30.6, 30.4, 28.4, 28.2, 28.1, 28.0, 25.5, and 24.8; MS (EI) *m*/*z* (relative intensity) 342 (M^+, 12), 196 (16), 140 (100), 119 (42), 112 (17), and 96 (14). Anal. Calcd for $C_{20}H_{26}N_2O_3 \cdot 0.7H_2O$: C, 67.66; H, 7.78; N, 7.89. Found: C, 67.74; H, 7.45; N, 7.13.

(1*S*,3*R*,4*R*)-3-(*N*-Indolinyl)methyl-2-azabicyclo[2.2.1]heptane (1c). The procedure described for **1a** was followed using **5c** (0.31 g, 0.91 mmol), which gave **1c** (0.19 g, 96%) as a colorless oil.

1c: R_f 0.40 (Al_2O_3, CH_2Cl_2/MeOH 9:1); $[\alpha]^{24}_D$ − 23.3 (*c* = 0.9, CH_2Cl_2); IR (neat) 3318, 3047, and 2953 cm^{-1}; ^{1}H NMR δ 7.10−6.98 (2H, m), 6.63 (1H, dt, *J* = 7.5, 1.1 Hz), 6.45 (1H, td, *J* = 7.5, 0.6 Hz), 3.62−3.48 (1H, m), 3.47−3.45 (1H, m), 3.39 (2H, t, *J* = 8.4 Hz), 3.03−2.88 (3H, m), 2.80 (1H, dd, *J* = 12.8, 5.9 Hz), 2.35−2.32 (1H, m), 1.70−1.58 (4H, m), and 1.40−1.36 (2H, m); ^{13}C NMR δ 152.5, 129.3, 127.0, 124.1, 117.0, 106.1, 59.8, 55.7, 55.3, 53.8, 39.3, 34.2, 32.2, 28.6, and 28.4; MS (EI) *m*/*z* (relative intensity) 228 (M^+, 3), 132 (82), 118 (8), 96 (6), and 68 (16). Anal. Calcd for $C_{15}H_{20}N_2 \cdot CSA \cdot H_2O$: C, 63.00; H, 7.61; N, 5.88. Found: C, 62.91; H, 7.32; N, 5.53.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-(*N*-isoindolinyl)carbonyl-2-azabicyclo[2.2.1]heptane (5d). The procedure described for **5a** was followed using amino acid **4** (0.60 g, 2.48 mmol) and isoindoline[22] (0.33 g, 2.73 mmol), which gave **5d** (0.79 g, 93%) as an off-white solid.

5d: mp 185−190 °C; R_f 0.31 (silica, pentane/EtOAc 1:2); $[\alpha]^{25}_D$ +25.3 (*c* = 1.1, $CDCl_3$); IR (KBr) 3155, 2981, 1679, and 1657 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 7.12 and 7.06 (4H, each s), 4.94 and 4.83 (1H, each d, *J* = 13.3 Hz), 4.70−4.59 (2H, m), 4.66 and 4.52 (1H, each d, *J* = 16.0 Hz), 4.22 and 4.09 (1H, each s), 3.86 and 3.78 (1H, each s), 2.43−2.40 (1H, m), 2.19 and 2.13 (1H, each d, *J* = 9.8 Hz), 1.65−1.20 (4H, m), 1.28 and 1.17 (9H, each s), and 1.08 and 1.05 (1H, each d, *J* = 9.8 Hz); ^{13}C NMR (mixture of rotamers) δ 168.6, 168.4, 153.7, 152.2, 135.7, 135.6, 135.5, 135.4, 127.3, 127.04, 126.98, 126.8, 122.3, 122.2, 122.1, 122.0, 78.8, 78.6, 62.5, 62.4, 56.6, 55.2, 51.9, 51.8, 51.6, 51.5, 41.5, 41.0, 34.5, 33.7, 30.2, 30.0, 28.0, 27.9, 27.8, and 27.7; MS (EI) *m*/*z* (relative intensity) 342 (M^+, <1), 242 (54), 140 (100), 118 (79), and 96 (46). Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 69.97; H, 7.76; N, 8.17.

(1*S*,3*R*,4*R*)-3-(*N*-Isoindolinyl)methyl-2-azabicyclo[2.2.1]heptane (1d). The procedure described for **1a** was followed, using **5d** (2.53 g, 7.40 mmol), which gave **1d** (1.4 g, 83%) as a white solid.

1d: R_f 0.39 (Al_2O_3, CH_2Cl_2/MeOH 9:1); $[\alpha]^{24}_D$ −34.0 (*c* = 1.1, CH_2Cl_2); IR (KBr) 3413, 3047, and 2958 cm^{-1}; ^{1}H NMR δ 7.15 (4H, s), 3.92 (4H, s), 3.41 (1H, s), 2.88 (1H, t, *J* = 7.2 Hz), 2.62 (1H, dd, *J* = 11.8, 7.2 Hz), 2.48 (1H, dd, *J* = 11.8, 7.2 Hz), 2.32−2.29 (1H, m), 1.98 (1H, br s), 1.67−1.55 (2H, m), 1.54−1.48 (1H, m), 1.42−1.32 (2H, m), and 1.21−1.17 (1H, m); ^{13}C NMR δ 140.0, 126.4, 122.0, 62.0, 60.5, 59.3, 55.7, 39.6, 34.8, 32.3, and 28.8; MS (EI) *m*/*z* (relative intensity) 228 (M^+, 2), 132 (100), 118 (13), 96 (16), and 68 (34). Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 79.21; H, 8.52; N, 12.31.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-[*N*-(*cis*-2,6-dimethylpiperidinyl)]carbonyl-2-azabicyclo[2.2.1]heptane (5e). The procedure described for **5a** was followed, using **4** (0.50 g, 2.07 mmol) and *cis*-2,6-dimethylpiperidine (0.33 mL, 2.48 mmol), which gave **5e** as a gummy solid (0.4 g, 57%).

5e: R_f 0.44 (silica, pentane/EtOAc 1:2); $[\alpha]^{25}_D$ + 15.0 (*c* = 2.7, $CDCl_3$); IR (KBr) 2970, 1685, and 1625 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 4.83−4.76 and 4.70−4.63 (1H, each m), 4.38−4.35 and 4.23−4.20 (1H, each m), 4.04−3.92 (1H, m), 3.95 and 3.82 (1H, each s), 2.46−2.35 (1H, m), 2.11 and 1.99 (1H, each dt, *J* = 9.5, 2.0 Hz), 1.86−1.27 (11 H, m), 1.42 and 1.37 (9H, each s), and 1.33 and 1.17 (6H, each d, *J* = 7.1 Hz); ^{13}C NMR (mixture of rotamers) δ 166.9, 166.6, 153.9, 152.6, 79.3, 78.9, 63.0, 62.8, 57.3, 56.2, 47.2, 46.9, 44.0, 43.8, 43.2, 42.5, 34.8, 34.1, 30.5, 30.5, 29.9, 29.8, 28.5, 28.5, 21.7, 21.6, 20.5, and 20.5; GC−MS (EI) *m*/*z* (relative intensity) 236 (M^+, 2), 219 (2), 140 (2), 112 (21), 96 (98), and 68 (100). Anal. Calcd for $C_{19}H_{32}N_2O_3$: C, 67.82; H, 9.59; N, 8.33. Found: C, 67.69; H, 9.69; N, 8.18.

(1*S*,3*R*,4*R*)-3-[*N*-(*cis*-2,6-Dimethylpiperidinyl)]methyl-2-azabicyclo-[2.2.1]heptane (1e). The procedure described for **1a** was followed using **5e** (0.23 g, 0.67 mmol), which gave **1e** (0.14 g, 94%).

1e: R_f 0.48 (Al_2O_3, CH_2Cl_2/MeOH 9:1); $[\alpha]^{25}_D$ −8.8 (*c* = 2.2, $CDCl_3$); IR (neat) 3185 and 2926 cm^{-1}; ^{1}H NMR δ 3.39−3.37 (1H, m), 2.78 (1H, dd, *J* = 8.9, 4.5 Hz), 2.54−2.44 (2H, m), 2.47 (1H, dd, *J* = 14.9, 8.9 Hz), 2.36−2.34 (1H, m), 2.23 (1H, dd, *J* = 14.9, 4.5 Hz), 1.86 (1H, br s), 1.70−1.56 (3H, m), 1.50−1.42 (3H, m), 1.36−1.20 (5H, m), 1.16 (1H, dt, *J* = 10.2, 1.4 Hz), 1.12 (3H, d, *J* = 2.2 Hz), and 1.10 (3H, d, *J* = 2.2 Hz); ^{13}C NMR δ 61.0, 58.3, 57.3, 55.4, 54.9, 39.7, 34.3, 33.3, 33.0, 32.6, 29.0, 24.5, 22.1, and 22.0; GC−MS (EI) *m*/*z* (relative intensity) 220 (M^+ − 2, 2), 205 (11), 126 (100), 112 (54), and 96 (16); HRMS calcd for $C_{14}H_{26}N_2$ 222.2096, found 222.2098.

(1*S*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3-[*N*-((2*S*)-2-methoxymethyl)-pyrrolidinyl]carbonyl-2-azabicyclo[2.2.1]heptane (5f). The procedure described for **5a** was followed, using amino acid **4** (1.05 g, 4.35 mmol) and (*S*)-*O*-methylprolinol[23] (0.58 g, 5.72 mmol), which gave **5f** (1.5 g, 79%).

5f: R_f 0.25 (silica, pentane/EtOAc 1:2); $[\alpha]^{25}_D$ −10.8 (*c* = 1.0, $CDCl_3$); IR (neat) 3566, 2971, 2361, 1697, and 1654 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 4.24−4.22 and 4.11−4.09 (1H, each m), 4.16−4.05 (1H, m), 3.91, 3.80, 3.76 and 3.69 (1H, each s), 3.65−3.40 (2H, m), 3.35−3.14 (2H, m), 3.24 (1H, s), 3.22 and 3.20 (3H, each s), 2.42−2.35 (1H, m), 2.53−2.41 and 2.22−2.10 (1H, each m), 2.02−1.69 (4H, m), 1.67−1.46 (3H, m), 1.38−1.13 (1H, m), 1.33 (3H, s), and 1.28 (6H, t, *J* = 11.6 Hz); ^{13}C NMR (mixture of rotamers) δ 170.5, 168.8, 154.0, 152.9, 79.0, 75.2, 72.4, 71.8, 63.6, 62.0, 58.7, 58.6, 57.0, 56.8, 55.8, 55.7, 46.5, 46.4, 41.9, 41.3, 34.8, 34.7, 34.04, 33.98, 30.6, 30.3, 28.4, 28.2, 27.9, 27.1, 24.1, and 24.0; GC−MS (EI) *m*/*z* (relative intensity) 338 (M^+, 3), 196 (11), 140 (100), and 96 (29). Anal. Calcd for $C_{18}H_{30}N_2O_4 \cdot H_2O$: C, 60.65; H, 9.05; N, 7.86. Found: C, 60.40; H, 8.85; N, 7.72.

(1*S*,3*R*,4*R*)-3-[*N*-((2*S*)-2-Methoxymethyl)pyrrolidinyl]methyl-2-azabicyclo[2.2.1]heptane (1f). The procedure described for **1a** was used to make **1f** (0.58 g, 85%) from **5f** (0.76 g, 2.26 mmol).

1f: R_f 0.39 (Al_2O_3, CH_2Cl_2/MeOH 9:1); $[\alpha]^{24}_D$ −28.4 (*c* = 2.6, CH_2Cl_2); IR (neat) 3360, 2922, and 2856 cm^{-1}; ^{1}H NMR δ 5.30 (1H, br s), 3.39−3.34 (1H, m), 3.30 (3H, s), 3.21 (1H, dt, *J* = 11.5, 3.9 Hz), 3.17−3.10 (1H, m), 2.81−2.73 (1H, m), 2.59−2.49 (2H, m), 2.27 (1H, dt, *J* = 11.5, 5.2), 2.20−2.12 (1H, m), 2.12−2.10 (1H, m), 1.87−1.77 (1H, m), 1.72−1.62 (3H, m), 1.58−1.46 (3H, m), 1.42−1.20 (3H, m), and 1.18−1.13 (1H, m); ^{13}C NMR δ 76.9, 63.4, 61.4, 60.9, 58.9, 55.7, 54.8, 40.0, 35.2, 31.7, 28.6, 28.3, and 23.2; GC−MS (EI) *m*/*z* (relative intensity) 225 (M^+ + 1, 5), 209 (3), 193 (3), 179 (9), 128 (75), 110 (21), 96 (22), and 84 (100); HRMS calcd for $C_{13}H_{24}N_2O$ 224.1889, found 224.1892.

(1*R*,3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-3-[*N*-((2*S*)-2-methoxymethyl)-pyrrolidinyl]carbonyl-2-azabicyclo[2.2.1]heptane (5g). The procedure described for **5a** was followed, using *ent*-**4** (0.50 g, 2.07 mmol) and (*S*)-*O*-methylprolinol[23] (0.28 g, 2.75 mmol), which gave amide **5g** (0.37 g, 75%).

5g: R_f 0.25 (silica, pentane/EtOAc 1:2); $[\alpha]^{25}_D$ −70.3 (*c* = 1.4, $CDCl_3$); IR (neat) 2975, 1738, and 1653 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 4.36−4.34 and 4.23−4.21 (1H, each m), 4.34−4.23 (1H, m), 3.92, 3.88, 3.84, and 3.79 (1H, each s), 3.54−3.32 (3H, m), 3.36 (1H, d, *J* = 2.2 Hz), 3.31 and 3.30 (3H, each s), 2.49−2.45 and 2.44−2.40 (1H, each m), 2.22−2.13 (1H, m), 2.10−1.77 (4H, m), 1.76−1.55 (3H, m), 1.50−1.30 (1H, m), 1.43 (6H, s), 1.38 and 1.35 (3H, each s), 1.34 (1H, s), and 1.18 (1H, dd, *J* = 10.5, 8.8 Hz); ^{13}C NMR (mixture of rotamers) δ 169.5, 168.7, 154.0, 153.6, 79.3, 79.2, 73.5, 72.2, 63.6, 63.2, 58.9, 57.2, 56.6, 56.5, 56.1, 55.8, 46.9, 46.8, 42.3, 41.7, 34.7, 34.1, 30.7, 30.5, 28.5, 28.33, 28.28, 28.0, 27.1, 26.9, 24.6,

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and 24.5; GC−MS (EI) *m*/*z* (relative intensity) 338 (M^+, 2), 196 (10), 140 (100), and 96 (30); HRMS calcd for $C_{18}H_{30}N_2O_4$ 338.2205, found 338.2210.

(1*R*,3*S*,4*S*)-3-[*N*-((2*S*)-2-Methoxymethyl)pyrrolidinyl]methyl-2-azabicyclo[2.2.1]heptane (1g). Deprotection and LAH reduction were carried out as described for **1a** using **5g** (0.3 g, 1.26 mmol) to give **1g** as a colorless oil (0.28 g, 100%).

1g: R_f 0.12 (Al_2O_3, CH_2Cl_2/MeOH 9:1); $[\alpha]^{24}_D$ −33.2 (c = 0.6, CH_2Cl_2); IR (neat) 3364, 2954, and 2872 cm^{-1}; ^1H NMR δ 6.27 (1H, br s), 4.06−4.03 (1H, m), 3.59 (1H, ddd, J = 11.0, 3.3, 1.1 Hz), 3.39−3.27 (3H, m), 3.17−3.10 (1H, m), 2.96 (1H, dd, J = 14.1, 5.3 Hz), 2.83−2.75 (1H, m), 2.72 (1H, dd, J = 14.1, 5.8 Hz), 2.46 (1H, dd, J = 16.2, 8.7 Hz), 2.12−2.00 (2H, m), 1.87−1.76 (2H, m), 1.74−1.35 (8H, m), and 1.22−1.14 (1H, m); ^{13}C NMR δ 76.1, 63.9, 61.8, 61.2, 58.9, 55.0, 54.8, 40.2, 35.4, 29.3, 27.9, 27.7, and 23.0; GC−MS (EI) *m*/*z* (relative intensity) 225 (M^+ + 1, 4), 193 (2), 179 (9), 128 (74), 110 (19), 96 (23), and 84 (100); HRMS calcd for $C_{13}H_{24}N_2O$ 224.1889, found 224.1892.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-2-azabicyclo[2.2.1]heptane-3-carbaldehyde (3). A solution of DMSO (6.39 g, 83 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 5 min to a solution of oxalyl chloride (4.82 g, 38 mmol) in CH_2Cl_2 (100 mL) at −78 °C. The resulting solution was stirred for 10 min at −78 °C. (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane-3-methanol[24] (8.0 g, 34 mmol) in CH_2Cl_2 (10 mL) was then slowly added, after which the reaction was stirred for 45 min. Triethylamine (17 g, 0.17 mol) was then added dropwise over a period of 5 min, and the resulting mixture was allowed to warm to room temperature over a period of 2 h before it was washed with water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were washed with brine (50 mL). Drying ($MgSO_4$), filtration, concentration, and purification by column chromatography gave **3** (7.5 g, 96%) as a white, low-melting solid.

3: R_f 0.62 (silica, pentane/EtOAc 4:1); $[\alpha]^{25}_D$ +78.6 (c = 2.0, $CHCl_3$); IR (KBr) 3062, 2970, and 1721 cm^{-1}; ^1H NMR δ 9.00 (1H, s), 7.33−7.17 (5H, m), 3.52 (1H, q, J = 6.4 Hz), 2.42 (1H, d, J = 3.2 Hz), 2.40 (1H, d, J = 3.2 Hz), 2.07−1.99 (1H, m), 1.73−1.63 (2H, m), 1.50−1.30 (4H, m), and 1.39 (3H, d, J = 6.4 Hz); ^{13}C NMR δ 205.0, 144.8, 128.4, 129.9, 127.6, 75.7, 60.8, 58.3, 42.3, 36.8, 29.2, 22.6, and 22.5; GC−MS (EI) *m*/*z* (relative intensity) 229 (M^+, <1), and 105 (100). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.64; H, 8.27; N, 6.23.

(1*S*,3*R*,4*R*)-3-(*N*-Pyrrolidinyl)methyl-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (22a). Powdered 3-Å molecular sieves (ca. 2 g) were added to a solution of aldehyde **3** (2.0 g, 7.7 mmol) in methanol (15 mL), and the resulting suspension was cooled in an ice/water bath. Pyrrolidine was added dropwise (0.65 g, 8.5 mmol), and the mixture was then stirred for 15 min. The cooling bath was removed, and a solution of sodium cyanoborohydride (0.32 g, 5.1 mmol) in methanol (10 mL) was added over a period of 4 h with the aid of a syringe pump. The reaction mixture was stirred for another 12 h at room temperature before it was filtered through a pad of Celite.[25] The filter cake was washed with methanol (50 mL), and the filtrate was concentrated at reduced pressure. Methanol (20 mL), KOH (12 g), and water (5 mL) were added to the residue, and the resulting mixture was agitated for 2 h and then concentrated again. The residue was partitioned between Et_2O (40 mL) and a mixture of saturated aqueous NaCl (15 mL) and water (15 mL). The aqueous phase was extracted with ether (3 × 10 mL). The combined ethereal phases were washed with brine (30 mL), dried (anhydrous K_2CO_3), concentrated, and purified by column chromatography, yielding **3** (2.0 g, 91%) as a white solid.

22a: mp 43−46 °C; R_f 0.36 (Al_2O_3, CH_2Cl_2/MeOH 98:2); $[\alpha]^{25}_D$ +5.5 (c = 1.0, $CHCl_3$); IR (KBr) 3061, 2966, and 1561 cm^{-1}; ^1H NMR δ 7.33−7.16 (5H, m), 3.56−3.54 (1H, m), 3.41 (1H, q, J = 6.4 Hz), 2.29−2.25 (1H, m), 2.11−2.03 (4H, m), 2.01−1.94 (1H, m), 1.81−1.74 (2H, m), 1.72−1.66 (1H, m), 1.65−1.56 (1H, m), 1.55−1.45 (4H, m), 1.32−1.22 (3H, m), 1.29 (3H, d, J = 6.4 Hz), and 1.08 (1H, d, J = 9.4 Hz); ^{13}C NMR δ 146.0, 128.6, 127.9, 127.1, 67.7, 61.7, 61.2, 58.7, 54.2, 40.5, 35.2, 28.9, 23.1, 22.5, and 22.4; GC−MS (EI), *m*/*z* (relative intensity) 284 (M^+, 1), 200 (8), 172 (5), 105 (80), and 96 (100). Anal. Calcd for $C_{19}H_{28}N_2$: C, 80.23; H, 9.92; N, 9.84. Found: C, 79.98; H, 10.05; N, 9.97.

(1*S*,3*R*,4*R*)-3-(*N*-Pyrrolidinyl)methyl-2-azabicyclo[2.2.1]-heptane (1a). To a solution of diamine **22a** (1.8 g, 6.3 mmol) in acetic acid (4 mL) and MeOH (15 mL) was added $Pd(OH)_2$ (20% on carbon, 0.36 g). The resulting suspension was vigorously stirred under H_2 (1 atm) for 24 h at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. Toluene (3 × 10 mL) was evaporated from the residue to assist removal of acetic acid. The residue was partitioned between 6 M aqueous KOH (10 mL) and ether (20 mL). The phases were separated, and the aqueous phase was extracted with ether (3 × 10 mL). The organic fractions were combined, washed with brine (2 × 10 mL), dried over K_2CO_3, and concentrated. The resulting, yellowish oil was purified by column chromatography to give **1a** (1.1 g, 89%) as a colorless oil.

(1*S*,3*R*,4*R*)-3-(*N*-Piperidinyl)methyl-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (22b). The procedure described for **22a** was followed, using piperidine (0.53 g, 6.2 mmol) and **3** (1.3 g, 5.7 mmol), which gave **22b** (1.4 g, 83%) as a thick, colorless oil after flash chromatography.

22b: R_f 0.41 (Al_2O_3, CH_2Cl_2/MeOH 98:2); $[\alpha]^{25}_D$ +10.0 (c = 1.3, $CHCl_3$); IR (neat) 3059, 2966, and 1567 cm^{-1}; ^1H NMR δ 7.35−7.20 (5H, m), 3.59−3.56 (1H, m), 3.44 (1H, q, J = 6.6 Hz), 2.27−2.24 (1H, m), 2.07 (1H, dd, J = 12.1, 2.6 Hz), 2.05−1.91 (3H, m), 1.79 (1H, dd, J = 10.5, 2.1 Hz), 1.72−1.59 (4H, m), 1.36−1.20 (9H, m), 1.30 (3H, t, J = 6,6 Hz), and 1.16 (1H, dd, J = 12.1, 2.6 Hz); ^{13}C NMR δ 145.9, 128.6, 127.9, 127.0, 66.6, 64.3, 61.2, 58.7, 54.8, 40.8, 35.1, 28.9, 25.7, 24.2, 22.6, and 22.4; GC−MS (EI), *m*/*z* (relative intensity) 298 (M^+, 3), 214 (5), 221 (10), and 105 (100). Anal. Calcd for $C_{20}H_{30}N_2$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.58; H, 9.96; N, 9.46.

(1*S*,3*R*,4*R*)-3-(*N*-Piperidinyl)methyl-2-azabicyclo[2.2.1]heptane (1b). The reductive amination procedure given for **1a** was followed, using **22b** (1.3 g, 4.4 mmol) and $Pd(OH)_2$/C (0.26 g), to give **1b** (0.80 g, 93%) as a colorless oil after flash chromatography.

1b: bp (2.5 Torr) 105−115 °C; R_f 0.22 (Al_2O_3, CH_2Cl_2/MeOH 9:1); $[\alpha]^{25}_D$ −39.0 (c = 1.3, CH_2Cl_2); IR (neat) 3430 cm^{-1}; ^1H NMR δ 3.38 (1H, br s), 2.84, (1H, dd, J = 8.1, 6.1 Hz), 2.44−2.24 (4H, m), 2.21 (1H, dd, J = 12.2, 6.1 Hz), 2.15−2.13 (1H, m), 2.06 (1H, dd, J = 12.1, 8.1 Hz), 1.60−1.45 (6H, m), 1.45−1.28 (6H, m), and 1.15−1.11 (1H, m); ^{13}C NMR δ 64.9, 59.1, 54.8, 40.1, 35.1, 34.4, 31.4, 28.6, 25.8, and 24.3; GC−MS (EI) *m*/*z* (relative intensity) 194 (M^+, 2), 109 (100), and 96 (8). Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.17; H, 11.33; N, 14.36.

Catalytic Asymmetric Rearrangement of Epoxides into Allylic Alcohols: Procedure A. *n*-BuLi (0.63 mL 1.0 mmol, 1.6 M in hexane) was added dropwise over 5 min to a solution of diamine **1a** (2.0 mg, 25 μmol) and DIPA (0.14 mL, 1.0 mmol) in THF/DBU (4.0 mL/0.45 mL) at 0 °C. The resulting yellowish solution was stirred at 0 °C for 30 min, and the epoxide (0.5 mmol) in THF (4.0 mL) containing *n*-dodecane (ca. 20 mg, as 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 partitioned between saturated aqueous NH_4Cl (5 mL) and Et_2O (15 mL). The phases were separated, and the ether layer was washed with 10% aqueous citric acid (2 × 5 mL), water (5 mL), and brine (5 mL) and dried ($MgSO_4$). The crude alcohol was coated on Celite by evaporating the solvent and directly purified by column chromatography.

Catalytic Asymmetric Rearrangement of Epoxides into Allylic Alcohols: Procedure B. As procedure A but with the following modifications: after addition of the epoxide, the reaction mixture was stirred at the indicated temperature until the epoxide was consumed (according to TLC analysis). After workup and purification as in procedure A, the product was converted to the corresponding (*R*)-Mosher ester,[26] and its diastereomeric excess was determined by integration of the ^1H signals (^1H NMR spectroscopy).

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Catalytic Asymmetric Rearrangement of Epoxides into Allylic Alcohols: Procedure C. As procedure A but with the following modifications in amounts of reagents: diamine **1a**, 18 mg, 0.1 mmol; DIPA, 0.13 mL, 0.9 mmol; *n*-BuLi, 0.63 mL,1.0 mmol, 1.6 M in hexane; and epoxide, 0.5 mmol.

Asymmetric Rearrangement of Epoxides into Allylic Alcohols: Procedure D (Stoichiometric). As procedure A but with the following modifications in amounts of reagents: diamine **1a**, 108 mg, 0.60 mmol; DIPA, 35.0 μL, 0.25 mmol; *n*-BuLi, 0.53 mL, 0.85 mmol, 1.6 M in hexane; and epoxide, 0.5 mmol.

(1*R*)-Cyclopent-2-en-1-ol (9). Following procedure C, cyclopentene oxide (84 mg, 1.0 mmol) was transformed at room temperature to the corresponding allylic alcohol **9**. The reaction was judged to have ceased after 24 h (90% conversion, 49% ee). After workup, the crude allylic alcohol was benzoylated[8] and purified by column chromatography (silica, pentane/EtOAc 90:10) to give the benzoate of **9** (126 mg, 67%).

Similarly, procedure D gave **9** (24 h at room temperature, 95% conversion, 95% ee) from cyclopentene oxide (84 mg, 1.0 mmol). After workup, the crude allylic alcohol was benzoylated[8] and purified by column chromatography to give the benzoate of **9** (147 mg, 78%).

(*R*)-**9**: colorless oil; GC (68 °C isotherm) $t_R(S) = 18.17$ min, $t_R(R) = 18.64$ min.

***cis*-(1*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)cyclopent-2-en-1-ol (10).** Following procedure A, *syn*-4-(*tert*-butyldimethylsilyloxy)cyclopentene oxide (23 mg, 0.1 mmol) was rearranged to the allylic alcohol **10.** The reaction was judged to have ceased after 4 h at 0 °C (at 80% conversion). Workup and column chromatography (silica, pentane/EtOAc 90:10 to 80:20) gave pure **10** (14 mg, 60%, 67% ee) with spectroscopic properties identical to those reported.[27]

Similarly, procedure D gave **10** (9 mg, 85%, 95% ee) after 4 h at 0 °C (>90% conversion) from *syn*-4-(*tert*-butyldimethylsilyloxy)cyclopentene oxide (10 mg, 43 μmol).

(*R*)-**10**: GC (110 °C for 15 min, then 1 °C/min to 130 °C); $t_R(S) = 26.67$ min, $t_R(R) = 27.15$ min.

(1*R*,4*R*)-*trans*-4-(*tert*-Butyldimethylsilyloxymethyl)cyclopent-2-en-1-ol (11). Following procedure C, *anti*-4-(*tert*-butyldimethylsilyloxymethyl)cyclopentene oxide[28] (40 mg, 0.18 mmol) was rearranged to the allylic alcohol **11**. The reaction was judged to have ceased after 48 h at room temperature (at 50% conversion). Workup and column chromatography (silica, pentane/EtOAc 4:1) then gave **11** (17 mg, 42%, 95% ee) with spectroscopic properties identical to those reported.[28] To further verify the ee of the allylic alcohol, the (*R*)-Mosher ester was prepared, and its diastereomeric excess was determined by integration of the ^{1}H signals (^{1}H NMR spectroscopy) in the olefinic region (95% ee).

(*R*)-**11**: colorless oil; R_f 0.41 (silica, pentane/EtOAc 2:1); GC (110 °C isotherm) $t_R(S) = 27.17$ min, $t_R(R) = 27.24$ min.

Mosher ester of (*R*)-**11**: ^{1}H NMR (diastereomers) δ 6.14 (0.02H, dd, $J = 13.6$, 5.4 Hz), and 6.10 (0.98H, dd, $J = 13.6$, 5.4 Hz).

(1*R*)-Cyclohex-2-en-1-ol (8). Following procedure A, cyclohexene oxide (49 mg, 0.5 mmol) was rearranged to allylic alcohol **8.** The reaction was judged to have ceased after 4 h at 0 °C (at >95% conversion). Workup and column chromatography (pentane/Et_2O 90:10 to 60:40) then gave **8** (45 mg, 91%, 96% ee) with spectroscopic properties identical to those reported.[29]

(*R*)-**8**: GC (100 °C isotherm) $t_R(S) = 11.50$ min, $t_R(R) = 11.98$ min.

(1*R*,4*S*,5*S*)-4,5-Dimethylcyclohex-2-en-1-ol (12) and (1*R*,4*S*,5*R*)-4,5-Dimethylcyclohex-2-en-1-ol (13). Following procedure A, 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 (140 mg, 1.11 mmol)[16c] was transformed to the allylic alcohols **12** and **13**. The reaction was judged to have ceased after 6 h at 0 °C (at >95% conversion). Workup and column chromatography (pentane/Et_2O 95:5 to 60:40) gave a 92:8 mixture of **12** and **13** (133 mg, 95%, **12**: 94% ee, **13**: 97% ee) with spectroscopic properties identical to those reported.[16c]

(*R*)-**12**: GC (105 °C isotherm) $t_R(S) = 27.8$ min, $t_R(R) = 28.4$ min.

(*R*)-**13**: GC (105 °C isotherm) $t_R(S) = 17.40$ min, $t_R(R) = 17.89$ min.

(1*R*,4*S*,5*R*)-4,5-Bis(*tert*-butyldimethylylsilyloxy)cyclohex-2-en-1-ol (14). Following procedure B, (1*S*,2*R*,4*R*,5*S*)-4,5-bis(*tert*-butyldimethylsilyloxy)cyclohexene oxide (25 mg, 0.07 mmol)[5g] was transformed to the corresponding allylic alcohol **14**. The reaction was quenched after 16 h at 0 °C. Workup and column chromatography (pentane/Et_2O 99:1 to 80:20) then gave **14** (15 mg, 60%, 97% ee) with spectroscopic properties identical to those reported.[5g]

(*R*)-**14**: R_f 0.11 (silica, pentane/EtOAc 9:1).

Mosher ester of (*R*)-**14**: ^{1}H NMR (diastereomers) δ 5.51 (0.99H, dd, $J = 10.4$, 3.6 Hz), and 5.46 (0.02H, dd, $J = 10.4$, 3.6 Hz); ^{19}F NMR (diastereomers, Mosher acid chloride as reference) δ −334 (2.95F, s), and −355 (0.05F, s).

(1*R*)-Cyclohept-2-en-1-ol (15). Following procedure A, cycloheptene oxide (56 mg, 0.5 mmol) was transformed to the corresponding allylic alcohol **15**. The reaction was judged to have ceased after 6 h at 0 °C (at >95% conversion). Workup and column chromatography (pentane/Et_2O 95:5 to 60:40) gave **15** (50 mg, 89%, 96% ee) with spectroscopic properties identical to those reported.[30]

(*R*)-**15**: colorless oil; GC (110 °C isotherm) $t_R(S) = 7.35$ min, $t_R(R) = 7.74$ min.

(1*R*)-Cyclooct-2-en-1-ol (16). Following procedure A, cyclooctene oxide (63 mg, 0.5 mmol) was transformed to the corresponding allylic alcohol **16**. The reaction was judged to have ceased after 36 h at 0 °C (at >95% conversion). Workup and column chromatography (pentane/Et_2O 95:5 to 60:40) then gave **16** (51 mg, 81%, 78% ee) with spectroscopic properties identical to those reported.[31]

(*R*)-**16**: GC (150 °C, isotherm) $t_R(R) = 7.35$ min, $t_R(S) = 7.74$ min.

(4*R*)-Oct-5-enol (17). Following procedure A, (*Z*)-4-octene oxide (64 mg, 0.5 mmol) was transformed to the corresponding allylic alcohol **17**. The reaction was quenched after 36 h at 0 °C. Workup and column chromatography (pentane/Et_2O 95:5 to 60:40) then gave **17** (52 mg, 82%) with spectroscopic properties identical to those reported.[8] Enantiomeric excess was determined by analysis of the (*R*)-MTPA derivative (^{1}H and ^{19}F NMR, 66% ee).

Kinetic Resolution of Racemic Epoxides by Rearrangement into Allylic Alcohols: Procedure A. *n*-BuLi (0.63 mL 1.0 mmol, 1.6 M in hexane) was added dropwise over 5 min to a solution of diamine **1a** (9.0 mg, 50 μmol) and DIPA (0.14 mL, 1.0 mmol) in THF/DBU (4.0 mL/0.45 mL) at 0 °C. The resulting yellowish solution was stirred at 0 °C for 30 min, and the racemic epoxide (0.5 mmol) in THF (4.0 mL) containing *n*-dodecane (ca. 20 mg, as internal standard for GC analysis) was then added dropwise over a period of 5 min. The reaction mixture was stirred at 0 °C until about 40% conversion of the epoxide (according to GC analysis, which was also used for determining the ee of the allylic alcohol and the epoxide). The reaction mixture was then partitioned between saturated aqueous NH_4Cl (5 mL) and Et_2O (15 mL). The phases were separated, and the ether layer was washed with 10% aqueous citric acid (2 × 5 mL), water (5 mL), and brine (5 mL) and dried ($MgSO_4$). The crude reaction mixture was coated on Celite by evaporation of the solvent and directly purified by column chromatography.

Kinetic Resolution: Procedure B. As procedure A but with the following modification: after addition of the epoxide, the reaction mixture was stirred at 0 °C until about 60% conversion of the epoxide.

***cis*-β-Methylstyrene Oxide (18) and 1-Phenyl-2-propen-1-ol (19).** Following procedure A, racemic *cis*-β-methylstyrene oxide[32] (20 mg, 0.15 mmol) was transformed to the optically enriched epoxide (*S*)-**18** and allylic alcohol (*R*)-**19**. After 4 h at 0 °C, a conversion of 48% was reached (according to GC) and the reaction quenched. Workup and column chromatography (silica, pentane/Et_2O 95:5 to 60:40) gave

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epoxide (*S*)-**18** (9 mg, 87%, 77% ee) and allylic alcohol (*R*)-**19** (7 mg, 73%, 88% ee) with spectroscopic properties identical to those reported.[32,33]

Similarly, following procedure B, (*S*)-**18** (12 mg, 89%, 94% ee) and (*R*)-**19** (14 mg, 85%, 84% ee) was isolated from racemic *cis*-*β*-methylstyrene oxide **18** (30 mg, 0.23 mmol) after 8 h at 0 °C (55% conversion according GC).

(*S*)-**18**: GC (120 °C) $t_R(S) = 9.35$ min, $t_R(R) = 9.67$ min.

(*R*)-**19**: GC (120 °C) $t_R(S) = 12.09$ min, $t_R(R) = 12.20$ min.

(1*S*)-1-Methylcyclohexene Oxide (20) and (1*R*)-1-Methylcyclohex-2-en-1-ol (21). Following procedure A, racemic 1-methylcyclohexene oxide (40 mg, 0.36 mmol)[34] was transformed to the (*S*)-**20** and (*R*)-**21**. After 4 h at 0 °C, a conversion of 43% was reached (GC) and the reaction quenched. Workup and column chromatography (pentane/Et_2O 99:1 to 95:5) gave epoxide (*S*)-**20** (18 mg, 81%, 78% ee) and allylic alcohol (*R*)-**21** (15 mg, 88%, 96% ee), with spectroscopic properties identical to those reported.[18,34] Similarly, following procedure B, (*S*)-**20** (12 mg, 63%, 87% ee) and (*R*)-**21** (16 mg, 79%, 94% ee) were isolated from racemic 1-methylcyclohexene oxide **20** (40 mg, 0.36 mmol) after 48 h at 0 °C (52% conversion according to GC).

(*S*)-**20**: R_f 0.63 (silica, pentane/EtOAc 4:1); GC (105 °C) $t_R(S) = 5.86$ min, $t_R(R) = 5.95$ min.

(*R*)-**21**: R_f 0.42 (silica, pentane/EtOAc 4:1); GC (105 °C) $t_R(S) = 10.6$ min, $t_R(R) = 10.9$ min.

Not fully characterized byproduct: (1*R*)-*2*-methylene-1-cyclohexanol; GC (105 °C isotherm) $t_R(S) = 13.0$ min, $t_R(R) = 13.23$ min (11% yield at 64% conversion, 96% ee).

Nonlinear Effect Studies. Experiments were run as described in the procedure, except that 20 mol % of the catalyst was used. Partly racemic **1a** was prepared by mixing appropriate amounts of **1a** and *ent*-**1a** to correspond to optical purity of 25, 50, 75, and 100% ee, respectively. Using this set of catalyst precursors, reactions were run at different concentrations of DBU (0, 0.5, 1, 3, and 6 equiv relative to the *meso*-epoxide) The reactions were run at 0 °C, and the ee of the formed product was determined after 12 h.

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