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Asymmetric addition of diethylzinc to aldehydes catalyzed by β-amino alcohols derived from limonene oxide†

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Abstract—A series of β-amino alcohols, conveniently prepared from limonene oxide, were evaluated as catalysts for the enantioselective addition of dialkylzinc to benzaldehyde. These limonene-based amino alcohols are of particular interest because they are easily synthesized in both enantiomeric forms. Ethylation of benzaldehyde using diethylzinc and catalyzed by limonene derived amino alcohols proceeded with enantioselection of up to 87% ee. This is an unusually high level of induction for amino alcohols possessing a *trans* relationship between the amino and alcohol functionalities. Both enantiomers of 1-phenyl-1-propanol can be synthesized with equal control since both enantiomers of the chiral catalyst are readily available. When (1*S*,2*S*,4*R*)-limonene amino alcohols are used as chiral catalysts, (*R*)-1-phenyl-1-propanol is obtained as the major product. A plausible mechanism is proposed to explain the facial selectivity determining the asymmetric induction observed in these reactions.

1. Introduction

The enantioselective additions of organometallic reagents to aldehydes is recognized as one of the most effective methods for generating optically active secondary alcohols.[1–4] Oguni and Omi first reported the ability of amino acid-derived β-amino alcohols to catalyze the enantioselective addition of diethylzinc to benzaldehyde, yielding up to 48.8% ee of (*R*)-1-phenyl-1-propanol.[5] In 1986, Noyori and co-workers used (−)-3-*exo*-(dimethylamino)isoborneol (DIAB) as the first highly enantioselective catalyst for diethylzinc addition to aldehydes, producing (*S*)-1-phenyl-1-propanol in 98% ee.[6] In 1987, Soai introduced a series of pyrrolidinylmethanols derived from (*S*)-proline that could produce both (*R*)- and (*S*)-enantiomers of 1-phenyl-1-propanol in high enantiomeric excess.[7] Since these initial efforts, an expansive body of work attaining high levels of enantioselectivity has been described in the literature.[4] In addition, mechanisms have been proposed to explain the facial selectivity observed in the catalytic asymmetric addition of diethylzinc to carbonyl compounds using enantiomerically pure β-amino alcohols.[8–12]

Recently, we reported the use of catalytic nopinone-derived amino alcohols in additions of diethylzinc to aromatic aldehydes, producing (*R*)-1-aryl-1-propanols in 52–80% ee.[13] In continuation of our work in this area, a new class of β-amino alcohols derived from limonene have been synthesized.[14] Herein we report the results of our study on the effectiveness of limonene-derived amino alcohols as chiral auxiliaries in diethylzinc additions. We also report the diastereoselective synthesis of structurally interesting, novel β-amino alcohols.

2. Results and discussion

2.1. Synthesis of limonene oxide-derived amino alcohols

Chiral, non-racemic β-amino alcohols derived from limonene oxide are easily synthesized and can be isolated with high diastereomeric purity in excellent yields. The limonene-derived β-amino alcohols used in our study are synthesized through epoxide ring opening of commercially available (*R*)-(+)- or (*S*)-(−)-limonene oxide with readily available amines.[14]

Usually, epoxidation of enantiomerically pure limonene results in a 1:1 mixture of *cis*- and *trans*-limonene oxides (**1**,**2** or **3**,**4**). The *cis* and *trans* mixture of limonene oxide diastereomers is not easily separable[15]

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† This paper is cordially dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

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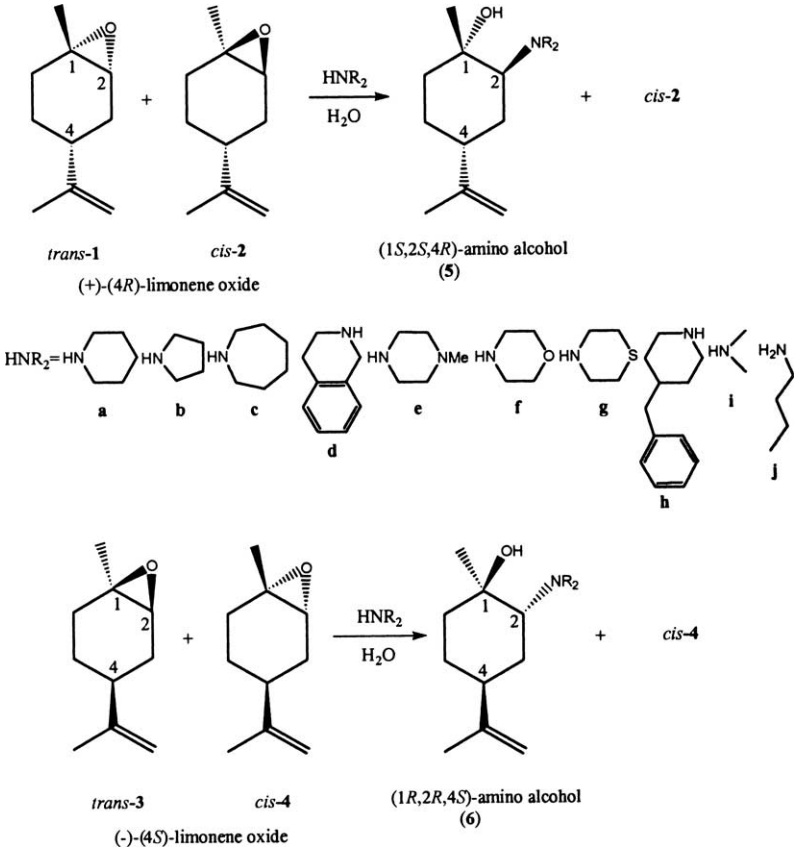
and consequently, the commercially available 1:1 mixture of limonene oxide has not previously been used in the synthesis of chiral auxiliaries.[16]

We recently reported a convenient method for resolution of limonene oxide diastereomers that involves selective epoxide ring opening by amines.[14] The difference in reactivity of *cis*- and *trans*-limonene oxides towards amines can be attributed to the unique conformation of limonene oxide. Conformational differences in the *cis*- and *trans*-limonene oxide result in kinetic resolution of the isomers, and allow a simple method by which to generate β-amino alcohols with high diastereoselectivity. There are two possible modes for nucleophilic attack of an amine on the epoxide ring of *cis*- and *trans*-limonene oxide. However, as shown in Scheme 1, only one of the possible diastereomers of limonene amino alcohol is obtained by nucleophilic attack of an amine on *trans*-limonene oxide. The S_N2 attack of a nucleophile on a cyclohexene oxide takes place by axial approach of the nucleophile on the epoxide moiety. The nucleophile is thus limited to attack on the *trans*-limonene oxide from the axial direction retaining the chair conformation in the transition state, leading to a regio- and stereospecific ring opening. In contrast, the *cis*-isomer must undergo ring flip to the unfavored boat transition state to allow for a traditional S_N2 backside attack to occur. The bicyclic nature of the epoxide ring in limonene oxide and the equatorial propenyl group at the C(4)-position provide a sizable energy barrier and prevent the conformational flip from occurring. Consequently, kinetic resolution of limonene oxide occurs by the *trans*-limonene oxide reacting with the amine, whereas the unreacted *cis*-limonene oxide is recovered by simple distillative workup.

It should be pointed out that these ring-opening reactions do not occur under normal uncatalyzed reaction conditions. Heating neat mixtures of limonene oxide and amines typically results in only 11% conversion after 7 days at 110°C. Water was subsequently found to be an excellent catalyst for this reaction. The addition of water facilitates the conversion of *trans*-limonene oxide to limonene amino alcohol, such that the reactions occur in essentially quantitative yield. All reactions are easily followed using gas chromatography by monitoring the consumption of *trans*-limonene oxide. Typical reaction times are 24 h. The amino alcohol products are easily separated from the unreacted *cis*-limonene oxide by simple distillation. The crude limonene amino alcohols thus obtained were purified further by formation and crystallization of the corresponding oxalate salts in methanol. The oxalate salts were converted back to the amine with potassium hydroxide and purified further by distillation or recrystallization.



Scheme 1. Synthesis of limonene β-amino alcohols **5a–j** and **6a–j**.

This reaction sequence provides limonene-based β-amino alcohols with high diastereomeric purity and also opens up an opportunity to use a wide range of amines resulting in a diverse library of useful β-amino alcohols. Using this reaction we have synthesized a collection of both enantiomers of β-amino alcohols derived from (+)- and (−)-limonene oxide. From (+)-limonene oxide, the (1*S*,2*S*,4*R*) stereoisomers **5a**–**j** are synthesized and (−) limonene oxide provided the (1*R*,2*R*,4*S*) stereoisomers **6a**–**j** (Scheme 1).

2.2. Evaluation of limonene-based amino alcohols in diethylzinc addition to benzaldehyde

With the β-amino alcohols **5a**–**j** and **6a**–**j** in hand, their efficiency in the addition of diethylzinc to benzaldehyde was evaluated. Four amino alcohols were originally examined: 2-(4-morpholinyl)-, 2-(1-pyrrolidinyl)-, 2-(1-piperidinyl), and 2-(benzylmethylamino)-(1*S*,2*S*,4*R*)-limonene amino alcohols. The initial work was done with 10 mol% of amino alcohol as a catalyst, and the enantiomeric excess observed was promising (in the range 78–85%).[14] We then wanted to investigate whether increasing the loading of the catalyst would influence the magnitude of the asymmetric induction in this reaction. The catalytic effectiveness of (1*R*,2*R*,4*S*)-(1-pyrrolidinyl)- and (1*S*,2*S*,4*R*)-dimethylamino limonene amino alcohols (**6b** and **5i**, respectively) were tested at 10–20 mol% catalyst loadings. The results, summarized in Table 1, show no dramatic effect on changing the amount of catalyst. Consequently, for the rest of our study, we employed 10 mol% of amino alcohol catalyst.

Following our initial study, all of the available limonene amino alcohols were screened to evaluate their ability to catalyze the asymmetric addition of diethylzinc to benzaldehyde. We also evaluated the limonene amino alcohols (**5a**–**j** and **6a**–**j**) derived from (+)- and (−)-limonene oxide respectively, to determine their facial selectivity in the asymmetric synthesis of 1-phenyl-1-propanol.

The highest enantioselectivity was obtained from the piperidine derived amino alcohols **5a** and **6a** with an induction of 87% ee (entry 1, Tables 2 and 3). The (1*S*,2*S*,4*R*)-limonene amino alcohols always delivered the ethyl group in such a way to form the (*R*)-1-phenyl-1-propanol as the major enantiomer. As expected, the (1*R*,2*R*,4*S*)-limonene amino alcohol-catalyzed reactions produced the (*S*)-1-phenyl-1-propanol, thus making it possible to synthesize both enantiomers of 1-phenyl-1-propanol.

Table 1. Effects of change in the percentage of catalyst used

	Catalyst	Amine	Mol%	Yield (%)[a]	Ee (%)[b]
1	**6b**	Pyrrolidine	10	90	70(*S*)
2	**6b**	Pyrrolidine	20	88	62(*S*)
3	**5i**	Dimethylamine	10	94	67(*R*)
4	**5i**	Dimethylamine	20	76	64(*R*)

[a] Isolated yield after distillation.
[b] Determined by chiral GC (Supelco β-Dex 120 30m) 125°C isothermal, 1-phenyl-1-propanol: $t_R(R)=18.41$ min, $t_R(S)=19.00$ min.

Table 2. Results for reactions catalyzed with (1*R*,2*R*,4*S*)-limonene amino alcohols **6**

	Catalyst	Amine	Mol%	Yield (%)[a]	Ee (%)[b]
1	**6a**	Piperidine	10	88	87(*S*)
2	**6b**	Pyrrolidine	10	90	70(*S*)
3	**6c**	Homopiperidine	10	84	80(*S*)
4	**6d**	Tetrahydroisoquinoline	10	70	77(*S*)
5	**6f**	Morpholine	10	98	80(*S*)
6	**6g**	4-Benzylpiperidine	10	94	83(*S*)

[a] Isolated yield after distillation.
[b] Determined by chiral GC (Supelco β-Dex 120 30m) 125°C isothermal, 1-phenyl-1-propanol: $t_R(R)=18.41$ min, $t_R(S)=19.00$ min.

Table 3. Results for reactions catalyzed with (1*S*,2*S*,4*R*)-limonene amino alcohols **5**

	Catalyst	Amine	Mol%	Yield (%)[a]	Ee (%)[b]
1	**5a**	Piperidine	10	89	87(*R*)
2	**5d**	Tetrahydroisoquinoline	10	80	78(*R*)
3	**5e**	4-Methylpiperizine	10	83	79(*R*)
4	**5i**	Dimethylamine	10	85	67(*R*)
5	**5j**	*n*-Butylamine	10	79	48(*R*)

[a] Isolated yield after distillation.
[b] Determined by chiral GC (Supelco β-Dex 120 30m) 125°C isothermal, 1-phenyl-1-propanol: $t_R(R)=18.41$ min, $t_R(S)=19.00$ min.

The results summarized in Table 3 suggest that the steric requirement of the amine moiety plays an important role in the asymmetric induction observed. Whereas, the *n*-butylamine-derived amino alcohol **5j** showed poor asymmetric induction (entry 5, Table 3), increasing the steric requirements by use of a tertiary amine group, such as the dimethylamine-derived amino alcohol **5i**, increases the asymmetric induction significantly. Similarly, the sterically more demanding tetrahydoisoquinoline-derived amino alcohol **5d**, afforded the product with 78% ee (entry 2, Table 3). The highest asymmetric induction was obtained using the piperidine-derived amino alcohol **5a**, which suggests that the piperidine moiety is more sterically demanding than the other amino groups. Similar trends are observed in the results summarized in Table 2.

2.3. Effect of conformation on facial selectivity

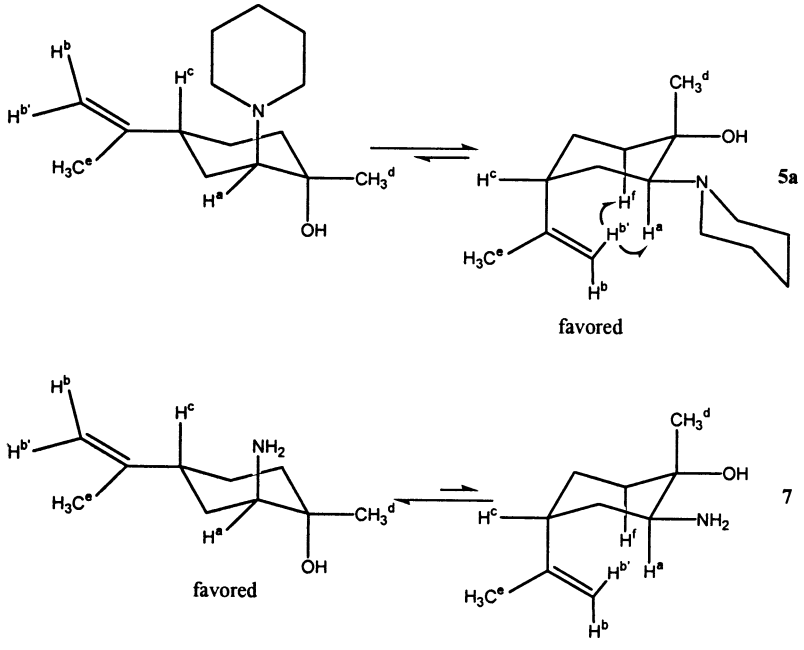
Comparison of the ^{1}H NMR spectra of the limonene amino alcohols derived from ammonia and piperidine clearly indicated the differences in the steric requirements of the two amino groups and the conformational preferences of these amino alcohols. The limonene oxide-derived amino alcohol chiral auxiliaries are unique because of the *trans* geometry of the amine and hydroxyl moieties. Most of the amino alcohols used as catalytic ligands in asymmetric diethylzinc addition reactions have the amine and hydroxyl groups in a *cis* relationship to each other. In spite of the *trans*-diaxial orientation of the amine and hydroxy groups, the limonene-derived amino alcohols are efficient chiral sources for these addition reactions of diethylzinc. This intriguing result can be explained using conformational analysis: with amino alcohols containing sterically demanding amino groups, such as piperidine, a conformational change occurs due to the large A-value of the bulky amino group with respect to the isopropenyl group (Scheme 2).[17] Consequently, limonene amino alcohols containing large amino groups are expected to be in a conformation where the amine and hydroxy groups are in a *trans*-diequatorial orientation (Scheme 2).

The ^{1}H NMR data of limonene amino alcohols derived from piperidine (**5a**) and ammonia (**7**) are compared in Table 4 to show the spectral differences between *trans* diaxial and *trans* diequatorial amino alcohol conformations. Amino alcohol **7** was chosen because the amine group by itself does not have an A-value high enough to induce ring flip. The ^{1}H NMR spectrum of **5a** clearly displays two different signals for protons **b** and **b′** (Scheme 2) which is characteristic of the axially oriented isopropenyl group.[18] In compound **7**, the hydrogens **b** and **b′** of the isopropenyl group are identical, indicative of equatorial orientation. ^{1}H NOESY analysis of the piperidinyl limonene amino alcohol **5a** shows vinylic proton $H^{b'}$ with a NOE crosspeak between axial protons H^a and H^f which is consistent with the isopro-

Table 4. ^{1}H NMR comparison of piperidinyl **5a** and primary amino **7**, limonene amino alcohols

H[1a]	Piperidinyl	Amino
a	3.68(t)	2.86(t)
b,b′	4.88(s),4.80(s)	4.74(s)
c	~2.63(m)	~2.25(m)
d	1.14(s)	1.21(s)
e	1.69(s)	1.72(s)

[a] Selected H^1 NMR shifts for (1*S*,2*S*,4*R*)-1-methyl-4-(1-methylethenyl)-2-(1-piperidinyl)cyclohexanol and (1*S*,2*S*,4*R*)-2-amino-1-methyl-4-(1-methylethenyl)cyclohexanol. All shifts determined in $CDCl_3$ at 25°C.



Scheme 2. Proposed conformations of (1*S*,2*S*,4*R*)-1-methyl-4-(1-methylethenyl)-2-(1-piperidinyl)cyclohexanol and (1*S*,2*S*,4*R*)-2-amino-1-methyl-4-(1-methylethenyl)cyclohexanol.

penyl group in the axial position. The single signals for protons **d** and **e** as well as ^{13}C NMR data (see Section 4) show that compounds **5a** and **7** are single diastereomers.

The conformation of limonene-based amino alcohols led us to propose a working transition state model for diethylzinc addition reactions catalyzed by these new chiral auxiliaries. Noyori has done extensive mechanistic work on the transition state model for the amino alcohol-catalyzed asymmetric diethylzinc addition reaction.[8–12] Based on the Noyori system of a six-membered cyclic transition state, we propose a transition state model for our limonene amino alcohol-catalyzed asymmetric diethylzinc ethylation reaction. This model reasonably predicts the facial selectivity observed in our system (Scheme 3).

As shown in Scheme 3, the facial selectivity observed in the present work is controlled by the amine moiety and the C(1)-methyl group. The β-hydroxyl group initially reacts with diethylzinc liberating ethane, the resulting zinc ion then coordinates with the amine lone pair to form a diequatorially oriented five-membered heterocyclic ring. Both the isopropenyl- and amino-groups hinder coordination of the aldehyde to the top face of the catalyst. The axial C(1)-methyl group of **5a** directs the *re*-face approach of benzaldehyde from below, while the oxygen of the aldehyde is coordinated to the zinc with the lone pairs *anti* to the phenyl group, to minimize the steric repulsion from the C(1)-methyl group. An ethyl group then adds to the activated aldehyde from the diethylzinc that is coordinated to a lone pair of the oxygen atom. The transition model proposed in Scheme 3 illustrates how (1*S*,2*S*,4*R*)-amino alcohols **5a**–**j** direct attack to the *re*-face leading to the (*R*)-1-phenyl-1-propanol and how (1*R*,2*R*,4*S*)-amino alcohols **6a**–**j** can direct attack to the *si*-face leading to the (*S*)-1-phenyl-1-propanol.

3. Conclusion

Several new β-amino alcohols derived from limonene oxide were screened as catalysts in the asymmetric synthesis of 1-phenyl-1-propanol using diethylzinc addition to benzaldehyde. The results presented in this paper demonstrate that (1*S*,2*S*,4*R*)-limonene amino alcohols **5** and (1*R*,2*R*,4*S*)-limonene amino alcohols **6** are efficient catalysts in the addition of diethylzinc to benzaldehyde. These ligands are easily prepared through simple kinetic resolution of the commercially available 1:1 diastereomeric mixture of limonene oxides. Both enantiomers of limonene amino alcohols are readily synthesized, providing an easy access to either (*R*)- or (*S*)-enantiomer of 1-phenyl-1-propanol. The limonene-derived amino alcohols reported herein are effective catalysts for the addition of diethylzinc to benzaldehyde. A plausible model has been proposed to explain the facial selectivity observed in this reaction. We are actively screening the utility of these limonene-derived amino alcohols in other types of asymmetric catalytic reactions.

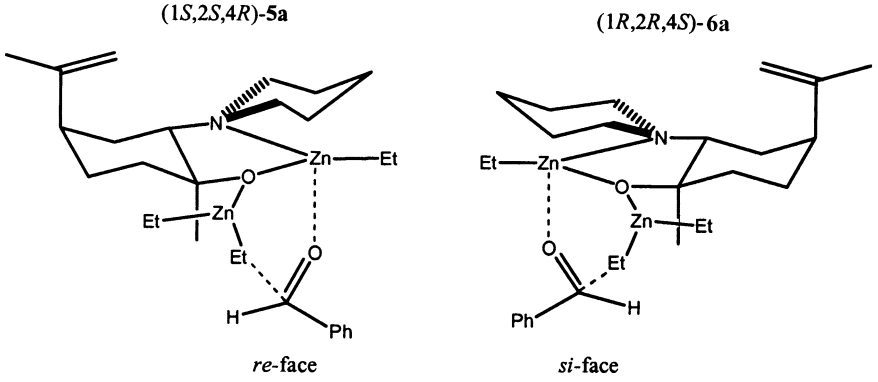
4. Experimental

4.1. General

Reactions were carried out in oven-dried glassware under an inert atmosphere. *cis*/*trans*-(+)-Limonene oxide, benzaldehyde and the diethylzinc reagents used were supplied by the Aldrich Chemical Company and used as received. ^1H NMR spectra were recorded on a Bruker at 250 MHz and ^{13}C at 62.9 MHz. Optical rotations were recorded on a Jasco DIP-371 polarimeter, with samples dissolved in either cyclohexane or methanol. Analysis of enantioselectivity was accomplished using an HP 5890 gas chromatograph with a flame-ionization detector equipped with a Supelco β-cyclodextrin 120 chiral GC column (30 m×0.25 mm). Samples of known stereochemistry were used to associate the major isomer formed by (+)-limonene β-amino alcohols with (*R*)-1-phenyl-1-propanol, thus permitting the monitoring of the aromatic alcohol products. GC conditions for 1-phenyl-1-propanol: 125°C isothermal; t_R, (*R*)-alcohol: 18.41 min, t_R, (*S*)-alcohol: 19.01 min.

4.2. Representative procedure for synthesis of β-amino alcohols from limonene oxide

4.2.1. (1*S*,2*S*,4*R*)-1-Methyl-4-(1-methylethenyl)-2-(1-piperidinyl)cyclohexanol. *cis*/*trans*-(+)-Limonene oxide mixture (60 mmol, 9.13 g, 4.9 mL) was combined with



Scheme 3. Facial selectivity of diethylzinc addition with 2-piperidine limonene amino alcohols.

deionized water (18 mL) and piperidine (300 mmol, 5.36 g, 6.23 mL.) The reaction flask was fitted with a reflux condenser and maintained at 100°C for 24 h. The majority of *trans*-(+)-limonene oxide had reacted according to GC analysis, so the reaction was cooled and fitted with a distillation head. The excess piperidine and *cis*-limonene oxide were distilled at reduced pressure (2.5 torr) resulting in 13.85g of oil. The oil was dissolved in methanol (15 mL). To this solution, a solution of oxalic acid (5.50 g, 61 mmol) in methanol (50 mL) was slowly added. A heavy slurry of white crystals quickly formed. The slurry was cooled to 0°C and stirred for 0.5 h. The solid was isolated by filtration, washed with cold methanol (15 mL), air dried, and vacuum dried at 40°C to give oxalate salt as a white, crystalline solid (7.48 g), mp 217–218°C. A sample of the oxalate salt (4.59 g) was converted to the free base with potassium hydroxide to give 5a (1*S*,2*S*,4*R*)-1-methyl-4-(1-methylethylenyl)-2-(1-piperidinyl)cyclohexanol as a colorless oil (3.32 g). A sample of this material (3.11 g) was distilled at reduced pressure to give pure piperidinyl amino alcohol (2.86 g); bp 133–135°C (3.5 torr) $[\alpha]_D^{23}=+13.5$ (*c*, 4.0, methanol). IR (neat): 3479.4, 2933 cm^{-1}; ^1H NMR (250 MHz, DMSO): $\delta=1.11$ (s, 3H), 1.35 (m, 2H), 1.45 (m, 5H), 1.52 (m, 2H), 1.61 (m, 1H), 1.69 (m, 4H), 1.72 (m, 1H), 2.30 (m, 2H), 2.38 (m, 2H), 2.65 (m, 2H), 3.80 (s, 1H), 4.74 (s, 1H), 4.80 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) $\delta=22.03$, 22.44, 24.39, 24.68, 25.01, 26.91, 35.84, 39.14, 53.07, 67.62, 72.40, 99.33, 110.89, 145.67.

4.2.2. (1*R*,2*R*,4*S*)-1-Methyl-4-(1-methylethenyl)-2-(1-pyrrolidinyl)cyclohexanol, 6b. Bp 128–131°C (3.0 torr), $[\alpha]_D^{23}=-34.9$ (*c*, 4.0, methanol), IR (neat): 3460.5, 2873.4, 2795.2, 1640.9, 1455, 1368.8, 1123.8, 1089.5 cm^{-1}, ^1H NMR (250 MHz, DMSO): $\delta=1.25$ (s, 3H), 1.37–1.68 (m, 9H), 1.68 (s, 3H), 1.90 (m, 1H), 2.25 (m, 1H), 2.54 (m, 2H), 2.68 (m, 2H), 3.94 (m, 1H), 4.79 (s, 2H). ^{13}C NMR (62.5 MHz, DMSO) $\delta=21.59$, 23.50, 24.01, 25.73, 26.98, 29.29, 36.14, 52.80, 66.47, 71.88, 109.56, 148.86.

4.2.3. (1*R*,2*R*,4*S*)-1-Methyl-4-(1-methylethenyl)-2-(1-hexamethyleneiminyl)cyclohexanol, 6c. Mp 45–47°C, $[\alpha]_D^{23}=+2.4$ (*c*, 4.0, methanol IR (neat): 3481.4, 2982–2844, 1660.7, 1441.8, 1376.4, 1121.9, 885.3 cm^{-1}, ^1H NMR (300 MHz, DMSO): $\delta=1.11$ (s, 3H), 1.70 (s, 3H), 1.30–1.90 (mult, 14H), 2.25–2.40 (mult, 1H), 2.40–2.50 (mult, 1H), 2.50–2.65 (mult, 2H), 2.70–2.90 (mult, 2H), 3.83 (s, 1H, OH), 4.78 (s, 1H), 4.84 (s, 1H). ^{13}C NMR (75 MHz, DMSO): $\delta=21.70$, 23.58, 24.92, 26.05, 26.47, 29.56, 36.53, 39.10, 53.35, 67.91, 71.84, 109.91, 147.00.

4.2.4. (1*R*,2*R*,4*S*)-1-Methyl-4-(1-methylethenyl)-2-[2-(1,2,3,4-tetrahydroisoquinolinyl)]cyclohexanol, 6d. Mp 86–88°C, $[\alpha]_D^{23}=-5.2$ (*c*, 4.0, methanol), ^1H NMR (250 MHz, DMSO): $\delta=1.16$ (s, 3H), 1.52 (m, 3H)1.76–1.91 (m, 6H), 2.32b (s, 1H), 2.49–2.8 (m, 4H), 3.01 (m, 1H), 3.67–3.95 (q, 2H), 4.02 (s, 1H), 4.80 (s, 1H), 4.84 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) $\delta=21.95$, 24.82, 25.37, 25.60, 29.93, 36.83, 48.61, 55.15, 66.71, 72.16, 110.19, 125.54, 125.98, 126.64, 128.68, 135.00, 136.46.

4.2.5. (1*S*,2*S*,4*R*)-1-Methyl-4-(1-methylethenyl)-2-(4-methyl-1-piperazinyl)cyclohexanol, 5e. Bp 143–147°C (2.6 torr), $[\alpha]_D^{23}=+27.1$ (*c*, 4.0, methanol), IR 3480, 2964, 27.91, 1640, 1454, 1372, 1285, 1173, 1160, 1145, 1136, 1116, 1098, 1013, 948, 888, 794 cm^{-1}, ^1H NMR (300 MHz, DMSO): $\delta=1.11$ (s, 3H), 1.66 (s, 3H), 2.12 (s, 3H), 2.20–2.70 (mult, 10H), 3.87 (s, 1H, OH), 4.73 (s, 1H), 4.78 (s, 1H). ^{13}C NMR (75 MHz, DMSO) $\delta=21.29$, 24.90, 25.14, 25.25, 38.66, 45.72, 51.22, 55.54, 66.64, 71.43, 109.45, 147.80.

4.2.6. (1*S*,2*S*,4*R*)-1-Methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol, 5f. Mp 43–44°C, $[\alpha]_D^{23}=+37.5$ (*c*, 4.0, methanol), IR (neat): 3474.3, 2949.6–2851.4, 1639.4, 1449.7, 1118.2, 882.4 cm^{-1}, ^1H NMR (250 MHz, DMSO): δ 1.13 (s, 3H), 1.48–1.46 (m, 2H), 1.60 (m, 1H), 1.70 (s, 3H), 1.84 (m, 1H), 2.29 (m, 2H), 2.49 (m, 2H), 2.64 (m, 2H), 3.52 (m, 2H), 3.60 (m, 2H), 3.94 (s, 1H), 4.75 (s, 1H), 4.80 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) $\delta=21.41$, 24.86, 24.92, 25.33, 36.34, 39.45, 52.13, 66.89, 67.18, 71.62, 109.64, 147.72.

4.2.7. (1*R*,2*R*,4*S*)-2-(4-Benzyl-1-piperidinyl)-1-methyl-4-(1-methylethenyl)cyclohexanol, 6g. Mp 78–81°C, $[\alpha]_D^{23}=-14.45$ (*c*, 4.0, methanol), IR 3480.8, 3081.9–2721.5, 16.37.4, 1445.0, 1134.9, 1102.4, 890.6, 747.5, 702.2 cm^{-1}, ^1H NMR (250 MHz, DMSO): $\delta=1.09$ (s, 3H), 1.37–3.34 (m, 23H), 3.82 (s, 1H), 4.51 (s, 1H), 4.73 (s, 1H), 4.77 (s, 1H), 6.87–7.52 (m, 5H). ^{13}C NMR (62.5 MHz, DMSO) $\delta=21.79$, 25.17, 25.32, 25.35, 32.95, 33.30, 36.72, 37.98, 42.92, 49.36, 55.24, 67.49, 71.85, 109.94, 125.98, 128.39, 129.25, 140.79, 148.03.

4.2.8. (1*S*,2*S*,4*R*)-2-(Dimethylamino)-1-methyl-4-(1-methylethenyl)cyclohexanol, 5i. See citations in Ref. 15.

4.2.9. (1*S*,2*S*,4*R*)-2-(1-Butylamino)-1-methyl-4-(1-methylethenyl)cyclohexanol, 5j. This sample was a mixture of three diastereomers, with the illustrated diastereomer being the predominant one. The ratio of diastereomers was 77:3:19 by capillary GC, and 75:4:20 by integration of the singlet methyl signals of the methyl group on the cyclohexane ring in the 300 MHz ^1H NMR (DMSO): $\delta=1.09$, 1.00, 0.97.

4.3. Representative procedure for the enantioselective alkylation of benzaldehyde with diethylzinc

4.3.1. 1-Phenyl-1-propanol. To the catalyst (1 mmol) was slowly added diethylzinc (11 mL of 1 M solution in hexanes, 11 mmol). The resulting solution was stirred at room temperature for 20 min and cooled to 0°C. Benzaldehyde (10 mmol, 1.06 g, 1.1 mL) was added dropwise over 2 min causing the solution to acquire a pale yellow color. The reaction was maintained at 0°C for 24 h, during which time the yellow color faded. The metallic reagent was quenched by addition of 45 mL saturated NH_4Cl solution and then washed with water (1×25 mL) and brine (1×25 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL) and the combined organic fractions were dried over $MgSO_4$ and then concentrated under reduced pressure. GC conditions (Supelco β-cyclodextrin 120) for 1-phenyl-1-

propanol: 125°C isothermal; t_R, (*R*) alcohol: 18.41 min, t_R, (*S*) alcohol: 19.01 min. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 6.9$, 3H), 1.81 (m, 2H), 1.97 (bs, OH), 4.6 (t, $J = 6.9$, 3H), 7.3–7.5 (Ar, 5H).

4.3.2. Recovery of catalyst. In order to demonstrate the recovery of the catalyst in this procedure, ligand **5a** was extracted from the crude product. This residue was dissolved in 45 mL EtOAc, and combined with 9 mL of 1 M HCl at 0°C with stirring. 3 M HCl was added dropwise until the solution was slightly acidic to litmus. The organic phase was washed with 0.5 M HCL (2×25 mL) and the combined aqueous fractions were then washed with CH_2Cl_2 (2×25 mL). While stirring at 0°C with CH_2Cl_2 (45 mL) the catalyst hydrochloride salt was treated with 3 M aqueous NaOH until basic to litmus (approx. 3 mL). The aqueous layer was washed with CH_2Cl_2 (2×25 mL) and the solvent was evaporated from the combined organic fractions. The resulting crude oil was distilled at 200 millitorr and β-amino alcohol **5a** (FW = 223, 0.21 g, 0.94 mmol) was recovered in 91% of the 1 mmol theoretical yield.

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