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Use of diamines containing the α-phenylethyl group as chiral ligands in the asymmetric hydrosilylation of prochiral ketones

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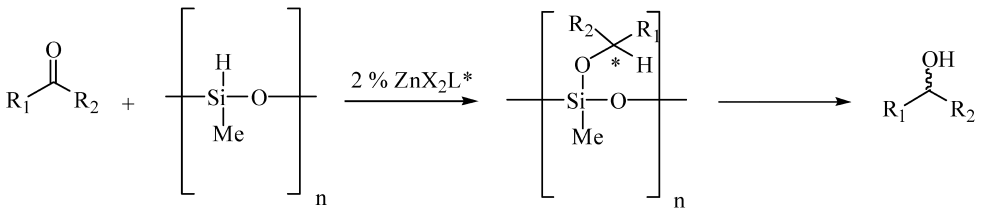
Abstract—Chiral diamines **1**–**7** were used in the enantioselective hydrosilylation of prochiral aromatic and aliphatic ketones. Some of these ligands combine chiral backbones and chiral *N*,*N*′-α-phenylethyl substituents that give rise to synergistic effects between these two groups and lead to catalysts that exhibit high enantioselectivity.

1. Introduction

The catalytic reduction of prochiral ketones to secondary alcohols with high enantioselectivity is an important goal in synthetic organic chemistry. Among the most efficient catalysts for this transformation are the ruthenium-BINAP hydrogenation catalysts developed by Noyori[1] and the chiral oxazaborolidine complexes of Itsuno,[2a] Corey,[2b] and others.[2c] A practical alternative to these methodologies is the asymmetric hydrosilylation of ketones, which affords secondary alcohols upon work-up. Several catalysts promote this reaction in an enantioselective fashion.[3] In some cases, polymethylhydrosiloxane (PMHS) has been used as the hydrosilylating reagent.[4] PMHS is a coproduct of the silicone industry that is inexpensive and can be easily handled in air. PMHS has been used with chiral *ansa*-titanocene catalysts in the reduction of ketones with high enantioselectivity by the Buchwald group.[5a] Additionally, the use of copper hydride in the hydrosilylation of aryl ketones has been reported by Lipschutz with excellent results.[5b,c]

Recent work in the enantioselective hydrosilylation of ketones by Mimoun and co-workers[6] has demonstrated that an efficient and enantioselective catalyst can be prepared from zinc precursors such as diethylzinc and zinc carboxylates in combination with homochiral diamine ligands and PMHS Eq. (1). The active species in the reduction is proposed to be L*ZnH_2, where L* is the chiral bidentate ligand. From a structure-enantioselectivity study, it was found that the ligands with the stilbene diamine backbone afforded better enantioselectivity than ligands derived from *trans*-1,2-diaminocyclohexane. They also observed that the catalyst generated from *N*,*N*′-ethylene bis(1-phenylethylamine) **1** (Chart 1), gave high enantioselectivities. Their results demonstrated that ligands with chiral backbones and achiral *N*,*N*′-dialkyl groups gave similar results to ligands with achiral backbones and chiral *N*,*N*′-dialkyl groups.[6]



PMHS (1)

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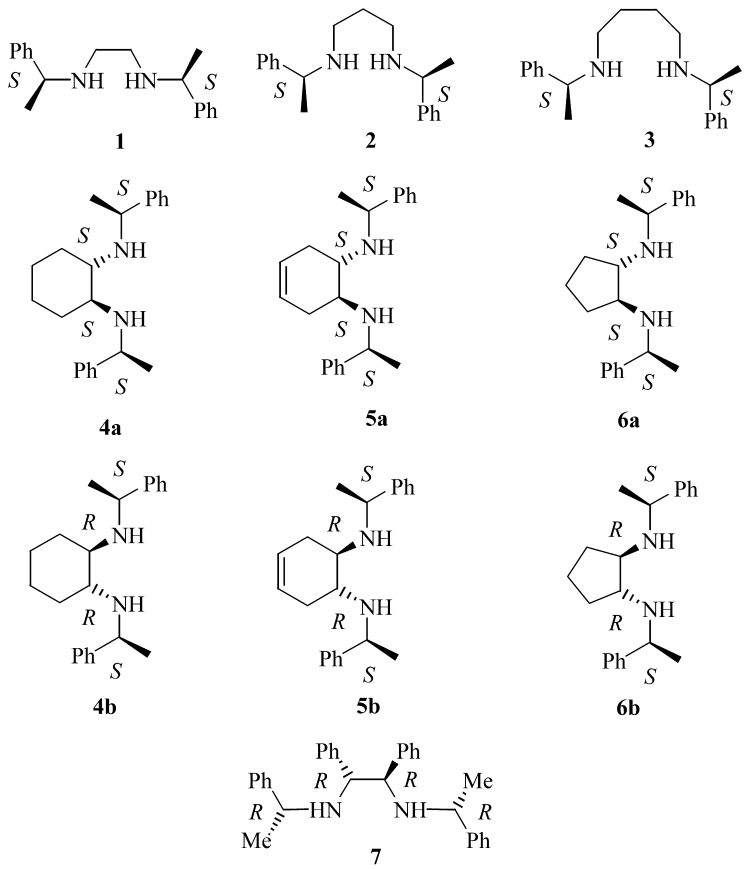


Chart 1.

Inspired by these results, we thought it would be informative to explore the structure-enantioselectivity relationship of ligands bearing both chiral backbones and chiral *N*,*N*′-dialkyl groups in the asymmetric hydrosilylation of ketones. We have, therefore, synthesized a series of such diamines and found that there is indeed a strong synergistic effect between these moieties in the catalytic asymmetric reduction of ketones.

Chiral diamines **1**–**7** (Chart 1) were selected with two considerations in mind: (1) The presence of C_2-symmetry was expected to confer a high degree of enantiotopic differentiation.[7] (2) Incorporation of the α-phenylethylamino group was deemed attractive as chiral moieties, because they have proven quite effective in asymmetric synthesis.[8]

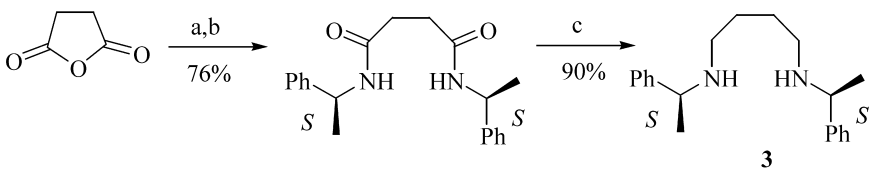
2. Results and discussion

2.1. Synthesis of chiral diamines 1–7

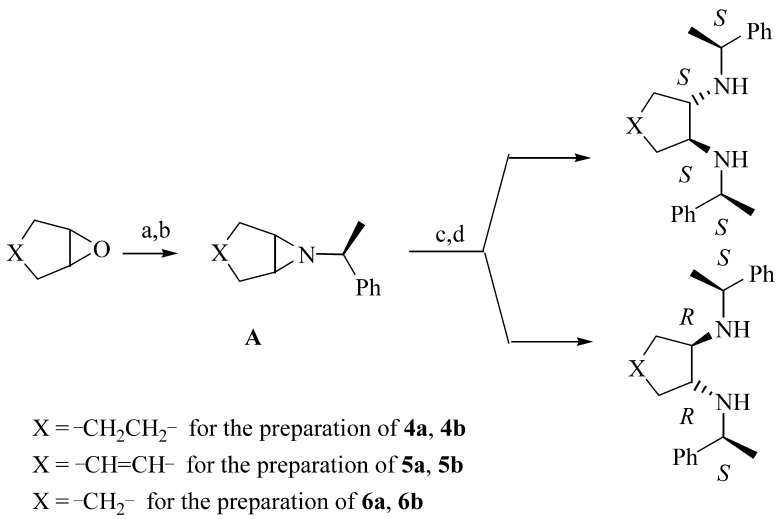
Convenient procedures for the preparation of *N*,*N*′-ethylene bis(1-phenylethylamine) **1** are available in the literature.[9] Higher homolog **2**[9b] was prepared according to our procedure.[10] The synthesis of diamine **3** was prepared from succinic acid as shown in Scheme 1.[11]

trans-Cyclohexane-1,2-diamines **4a** and **4b**, as well as unsaturated analogs **5a** and **5b** and *trans*-cyclopentane 1,2-diamines **6a** and **6b** were prepared from the appropriate epoxide precursors, via chiral aziridine intermediates **A**, as outlined in Scheme 2.[12b] The major products were **4a**, **5a** and **6a**, and the diastereomeric ratios were 2:1 in all cases.

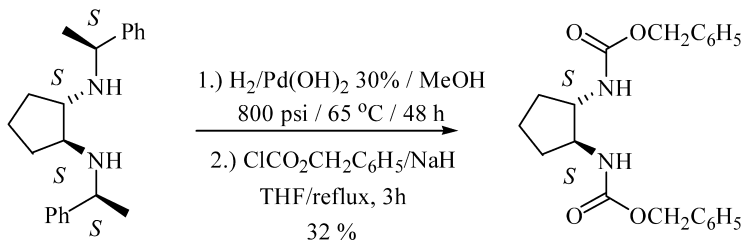
The separation of the diastereomeric pairs **4a/4b**, **5a/5b**, and **6a/6b** was accomplished by flash chromatography [hexane–EtOAc (12:1)]. The assignment of configuration of cyclopentane diamines **6a** (all *S* configurations) and **6b** [(*S*,*R*,*R*,*S*) isomer] was achieved by chemical correlation of **6a** with the known[10] *trans*-diamide (*S*,*S*)-**8** (Scheme 3). Likewise, the configuration of cyclohexene diamines **5a** and **5b** was possible via chemical correlation with **4a** and **4b**, respectively, by simple hydrogenation of the double bond (Scheme 4).



Scheme 1. Reagents and conditions: (a) (*S*)-$CH_3CH(Ph)NH_2$/Et_2O/rt/12 h. (b) (*S*)-$CH_3CH(Ph)NH_2$DCC/DMAP/CH_2Cl_2/rt/16 h. (c) $LiAlH_4$/THF/reflux/48 h.

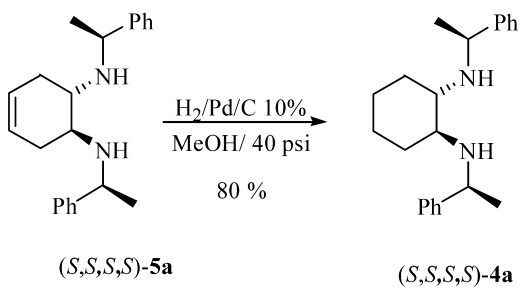


Scheme 2. Reagents and conditions: (a) (*S*)-α-Phenylethylamine/$LiClO_4$/CH_3CN/reflux/18 h. (b) $CH_3SO_2Cl/Et_3N/CH_2Cl_2$/rt/24 h. (c) (*S*)-α-Phenylethylamine/$LiClO_4$/CH_3CN/reflux/50 h. (d) Flash chromatography [hexane–EtOAc (12:1)].



Scheme 3.

Finally, the preparation of (*R*,*R*,*R*,*R*)-*N*,*N*′-di(α-phenylethyl)-1,2-diphenyl-1,2-ethylenediamine **7**[14a] was accomplished following the procedure described in the literature, which involves the stereoselective addition of phenylmagnesium bromide to the chiral bis-imine,[14b,c] derived from glyoxal and 2 equiv. of (*R*)-α-phenylethylamine.



Scheme 4.

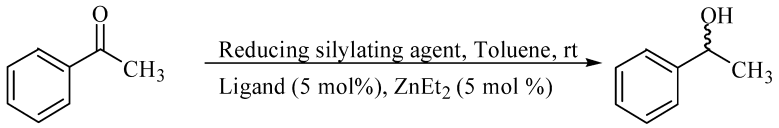
3. Enantioselective reduction of aromatic and aliphatic prochiral ketones

According to the general procedures described for the enantioselective reduction of prochiral ketones,[6] acetophenone was treated with 5 mol% of diethylzinc (1.0 M in hexanes), and 5 mol% of the chiral ligand in toluene solvent at ambient temperature in the presence of 2 equiv. of PMHS for 24 h (method A) or 1.5 equiv. of $(EtO)_3SiH$ for 18 h (method B). The results are collected in Table 1.

Examination of Table 1 indicates that highest enantioselection is achieved with chiral ligands **4a**, **5a** and **6a** where the α-phenylethylamino chiral groups are bonded to a fairly rigid cycloalkane (or cycloalkene in the case of **5a**) framework. As can be appreciated in entries 4, 5, 7, 8, and 11 in Table 1, the use of ligands **4a**, **5a** and **6a** (all *S*-configuration) afforded consistently high enantioselectivities (80–84%). In contrast, ligands **4b**, **5b** and **6b** [(*S*,*R*,*R*,*S*) configuration] led to reduced carbinol products of low enantiopurity (10–29%). These results demonstrate that the stereogenic centers of phenylethyl groups are important in the enantioselectivity determining step.[15]

Whereas ethylene diamine derivative **1** induces high enantioselectivity in the reduction process (79% ee, entry 1 in Table 1), higher homologs **2** and **3** proved to be inefficient ligands (5% ee and 17% ee, respectively). It has been known since early studies by Knowles and coworkers[16] that chiral ligands with stereogenic centers directly attached to the metal center can exhibit excellent enantioselectivities. We believe that a key factor in the control of enantioselectivity in the asymmetric hydrosilylation of ketones is the stereochemistry of coordination of the amino groups to the zinc center. Upon coordination nitrogen inversion ceases and the bound nitrogens become stereogenic centers. It is possible that the ligand **1** binds to the metal with high diastereoselectivity and that the chiral phenylethyl groups and stereogenic nitrogens contribute constructively to the enantioselectivity of the catalyst. In contrast, ligands **2** and **3**, with longer, more flexible

Table 1. Enantioselective reduction of acetophenone in the presence of diethylzinc and a chiral ligand



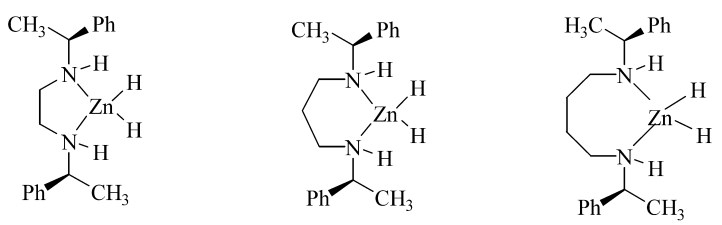
Entry	Chiral ligand	Reducing silylating agent[a]	Reaction time (h)	Yield (%)	ee (%)[b]
1	**1**	PMHS	24	100	79 (*R*)[c]
2	**2**	PMHS	24	85	5 (*R*)
3	**3**	PMHS	24	20	17 (*R*)
4	**4a**	$(EtO)_3SiH$	18	100	80 (*R*)
5	**4a**	PMHS	24	90	83 (*R*)
6	**4b**	PMHS	24	40	18 (*S*)
7	**5a**	$(EtO)_3SiH$	18	99	84 (*R*)
8	**5a**	PMHS	24	90	82 (*R*)
9	**5b**	$(EtO)_3SiH$	18	100	29 (*R*)
10	**5b**	PMHS	24	40	10 (*R*)
11	**6a**	PMHS	24	95	83 (*R*)
12	**6b**	PMHS	24	50	21 (*S*)
13	**7**	PMHS	24	18	2 (*R*)

[a] Experiments were carried out using 1.0 equiv. of acetophenone and 2.0 equiv. of PMHS or 1.5 equiv. of $(EtO)_3SiH$.
[b] The enantiomeric excess was determined by HPLC with a Chiralcel OD column.
[c] Mimoun et al.[6] reported 75% ee in this reaction using 2 mol% zinc-ligand catalyst, in the presence of 1.1 equiv. of PMHS.

backbones, may permit formation of diastereomeric catalysts (Chart 2) that are less enantioselective. The magnitude of the difference in enantioselectivity between the match and mismatched diastereoisomers is surprisingly large, being 101% (**4a/4b**), 92% (**5a/5b**), and 104% (**6a/6b**). We believe these results indicate that the enantioselectivities of the catalysts are highly sensitive to their chiral environments. It is also noteworthy that the mismatched ligands resulted in much slower catalysts. Although catalysts derived from **4a**, **5a** and **6a** proceeds to at least 90% yield in 24 h, those using catalysts prepared from **4b**, **5b** and **6b** did not exceed 50% in this time. It is also clear that the difference in enantioselectivities between the catalysts derived from (*S*,*S*,*S*,*S*)- and (*R*,*S*,*S*,*R*)-configured ligands arises from a mismatched combination between the stereogenic nitrogens and the phenylethyl groups. Amino groups that become stereochemically fixed on coordination have been shown to have a powerful impact on enantioselectivity in zinc(diamine)-based catalysts.[17]

It is also informative to compare the enantioselectivities of our matched and mismatched ligands with a ligand that has chirality in the diamine backbone and achiral *N*,*N*′-dialkyl groups. In the reduction of acetophenone with matched catalyst derived from **4a** and mismatched catalyst derived from **4b** the enantioselectivities and configurations were 83% (*R*) and 18% (*S*), respectively. The previously reported ligand (*R*,*R*)-*N*,*N*′-bis(1-naphthylenemethyl)-*trans*-1,2-cyclohexanediamine gave 70% enantioselectivity with acetophenone under the same conditions. These results suggest that the synergistic effects of the chiral *N*,*N*′-α-phenylethyl groups with the diamine backbone in **4a** can raise the level of enantioselectivity of the catalyst over that of a similar catalysts bearing only achiral *N*,*N*′-dialkyl groups. The poor stereoinduction achieved with ligand **7** (all *R*-configured) show again that a proper combination of stereogenic center on the α-phenylethylamino groups and the ligand's backbone is essential for good enantiofacial differentiation in this system.

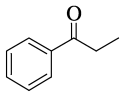
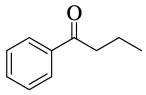
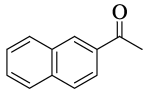
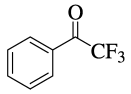
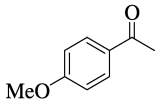
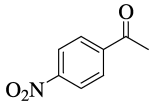
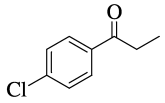
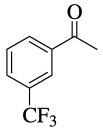
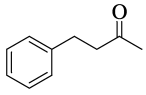
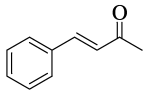
Since there is not a significant difference in the enantioselectivity of acetophenone reduction with diamines **4a**, **5a** and **6a** (Table 1), and **4a** can be prepared more economically, the use of diamine **4a** in the enantioselective reduction of other prochiral ketones with PMHS in the presence of $ZnEt_2$ has been explored (Table 2). Prochiral ketones were treated with 2 mol% diethylzinc (1.0 M in toluene), and 2 mol% of the chiral ligand in toluene solvent at ambient temperature and in the presence of 2 equiv. of PMHS for 24 h (method C). From Table 2, it can be seen that with aryl alkyl ketones better enantioselectivities were obtained with longer alkyl groups, that is, *n*-Pr>Et>Me (Table 2 entries 1 and 2, Table 1 entry 5). The enantioselectivity with β-acetonaphthone gave similar results to



1·ZnH$_2$ **2·ZnH$_2$** **3·ZnH$_2$**

Chart 2.

Table 2. Enantioselective reduction of prochiral ketones by PMHS in the presence of $ZnEt_2$ (2 mmol%) and diamine **4a** (2 mmol%)[a]

Entry	Ketones	Yield (%)	ee (%)
1		75	84 (*R*)[b]
2		80	89 (*R*)[b]
3		72	84 (*R*)[b]
4		95	19 (*S*)[c]
5		87	11 (*R*)[c]
6		80	68 (*R*)[b]
7		81	84 (*R*)[c]
8		95	82 (*R*)[c]
9		67	15 (*R*)[b]
10		70	84 (*R*)[b]

[a] Experiments were carried out using 1.0 equiv. of prochiral ketone and 2.0 equiv. of PMHS.
[b] The enantiomeric excess were determined by HPLC after purification on silica gel (hexane–ethyl acetate, 10:1).
[c] The enantiomeric excess were determined by GC on a β-Dex column.

acetophenone (entry 3). However, the enantioselective reduction of trifluoroacetophenone proceeded with low selectivity due to the electronic effect of the trifluoromethyl group (entry 4). Additionally, the reduction of prochiral ketones with substituents on the aromatic ring was performed. Enantioselectivity was significantly diminished when *p*-MeO and *p*-NO_2 group were present (entries 5 and 6). Nevertheless, *p*-Cl or *m*-CF_3-acetophenones were very good substrates, exhibiting (82–84% ee, entries 7 and 8). To examine the effect of substrate unsaturation on the catalyst enantioselectivity, we examined the use of 4-phenyl-2-butanone and *trans*-4-phenyl-3-buten-2-one (entries 9 and 10). The saturated derivative gave low enantioselectivity (15%). This is not surprising, given that the lone pair environments of the substrate are so similar and the catalyst cannot readily differentiate between them. On the other hand, the unsaturated substrate give very good enantioselectivity (84%) indicating the importance of the double bond in this asymmetric reduction.

In conclusion, chiral diamines **1**–**7** were used in the enantioselective hydrosilylation of prochiral acetophenone. Diamines **4a**, **5a**, and **6a** combine chiral backbones and chiral *N*,*N*′-α-phenylethyl substituents that give rise to synergistic effect between these two groups and lead to catalysts that exhibit high enantioselectivities. The enantioselectivities of prochiral aromatic ketones in the presence of **4a** were found to range from poor with dialkyl ketones to very good with acetophenone derivatives and α,β-unsaturated ketones.

4. Experimental

4.1. General

Melting points were determined on a Fischer Jones apparatus and are uncorrected. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were measured on a Varian Mercury spectrometer, with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm) and coupling constants *J* are given in Hz. Optical rotations $[\alpha]_D$ were measured at ambient temperature in 0.1 dm cells, using a Perkin–Elmer 241 spectrophotometer. IR-FT spectra were recorded on a BioRad instrument. Mass spectra were recorded on a Saturn Varian GC-mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. All reagents were purchased from Aldrich Chemical Co.

4.1.1. *N*,*N*′-Bis[(*S*)-α-phenylethyl]propane-1,3-diamine, 2. In a dry two-necked flask fitted with an addition funnel, condenser, and magnetic stirrer was placed (*S*)-α-phenylethylamine (3.3 mL, 26 mmol) under a nitrogen atmosphere. The reaction flask was heated to 100 °C with stirring followed by slow addition of 2.0 g (13.0 mmol) of freshly prepared 1-mesylate-3-chloro-propane (prepared from 3-chloro-propanol) over 2 h. Stirring of the mixture was continued for 16 h at 100 °C, followed by cooling to 60 °C, and addition of 2 mL of saturated aqueous KOH. The resulting mixture was allowed to cool to ambient temperature and extracted with three 20 mL portions of CH_2Cl_2. The combined organic layers were washed with brine and dried over anh. Na_2SO_4, and concentrated in a rotary evaporator. The excess (*S*)-α-phenylethylamine was removed by vacuum distillation (40 °C/5 mm Hg) affording the desired product as a colorless liquid 1.3 g (50% yield). $[\alpha]_D=-64.6$ (c=1.1, $CHCl_3$); $[\alpha]_D=-66.3$ (c=0.55, $CHCl_3$).[9b] ^{1}H NMR ($CDCl_3$) δ: 1.3 (m, 2H), 1.4 (d, 6H, J=7 Hz), 2.1 (m, 2H), 3.7 (q, 1H, J=7 Hz), 7.2–7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 30.3, 46.4, 58.4, 126.5, 126.7, 128.3, 145.7.

4.1.2. *N*,*N*′-Bis[(*S*)-α-phenylethyl]butane-1,4-diamine, 3.[11] Succinic anhydride 0.7 g (7.0 mmol) was dissolved in 10 mL of diethyl ether at rt and a solution of (*S*)-α-phenylethylamine (0.90 mL, 7.0 mmol) in 2 mL of diethyl ether was added dropwise over 10 min with stirring. The mixture was stirred overnight at rt. The product was purified

by column chromatography [hexane–EtOAc (1:1)] and isolated as a white solid (1.4 g, 95% yield), mp=102–103 °C, $[\alpha]_D=-86.6$ (c=1.0, CH_3OH). ^1H NMR (CD_3OD) δ: 1.4 (d, 3H, J=6.6 Hz), 2.4 (m, 2H), 2.6 (m, 2H), 5.1 (q, 1H, J=6.6 Hz), 6.4 (m, 1H), 7.3 (m, 5H), 10.5 (b, 1H). ^{13}C NMR (CD_3OD) δ: 21.8, 29.7, 30.7, 49.2, 126.1, 127.4, 126.7, 142.8, 171.5, 176.6.[11a]

To a stirred solution of *N*-(*S*)-α-phenylethylsuccinamidic acid (0.44 mg, 2.1 mmol) in anhydrous CH_2Cl_2 (20 mL) under nitrogen at 0 °C was added 4-dimethylaminopyridine (10.3 g, 2.1 mmol), and 1,3-dicyclohexylcarbodiimide (10.4 g, 2.1 mmol). Then, (*S*)-α-phenylethylamine (0.27 mL, 2.1 mmol) was added. The reaction mixture was stirred at rt over 16 h, and filtered to remove the white precipitate. The filtrate was extracted with water and CH_2Cl_2 (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography [hexane–EtOAc (4:1)]. (1*S*,1′*S*)-*N*,*N*′-Bis-(α-phenylethyl)-1,4-succinil-diamide was obtained as a colorless solid (0.58 g, 80% yield), mp 206–207 °C, $[\alpha]_D=66.9$ (c=1.0, CH_3OH). ^1H NMR (CD_3OD) δ: 1.4 (d, 6H, J=7.0 Hz), 2.5 (m, 4H), 4.8 (q, 2H, J=7.0 Hz), 7.2–7.3 (m, 10H). ^{13}C NMR (CD_3OD) δ: 21.4, 31.0, 48.9, 125.9, 126.8, 128.3, 144.0, 172.4. MS (*m*/*z*): 42, 77, 195, 120 (base peak), 160, 188, 204, 221, 281, 303, 324.[11a]

A solution of (1*S*,1′*S*)-*N*,*N*′-bis-(α-phenylethyl)-1,4-succinildiamide (0.23 g, 0.70 mmol) in THF (2 mL) was added slowly to a vigorously stirred suspension of $LiAlH_4$ (0.13 g, 3.5 mmol) in THF (10 mL). The resulting mixture was refluxed over 48 h, and quenched by careful addition of an aqueous 10% NaOH solution (10 mL). The mixture was stirred vigorously for 30 min and filtered. The filtrate was concentrated, dissolved in CH_2Cl_2 (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography [hexanes–EtOAc (1:1)]. *N*,*N*′-Bis[(*S*)-α-phenylethyl]butane-1,4-diamine, **3**, was obtained as a colorless liquid (0.19 g, 90% yield), $[\alpha]_D=-67.5$ (c=1.0, $CHCl_3$), (*R*,*R*), $[\alpha]_D^{lit.}=+60$ (c=1.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.2 (s, 2H), 1.6 (d, 6H, J=6.6 Hz), 1.7 (m, 2H), 2.4 (m, 4H), 3.7 (q, 2H, J=6.6 Hz), 4.5 (b, 2H), 7.2–7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 23.2, 27.0, 46.9, 58.2, 126.7, 127.3, 128.6, 143.8.[11b]

4.1.3. (1*S*,2*S*,1′*S*,1″*S*)- and (1*R*,2*R*,1′*S*,1″*S*)-*N*,*N*′-Di(α-phenylethyl)-4-cyclohexene-1,2-diamines, 5a and 5b. Diamines **5a** and **5b** were prepared following the general procedure. The diastereomeric mixture of β-aminoalcohols were prepared from 1,4-cyclohexadiene monoxide (98% yield).[12a] The crude mixture was used immediately for the synthesis of 4-cyclohexen-1-aziridine following the literature procedure.[10] The product was obtained as a colorless liquid, 80% yield, after purification by flash chromatography [hexanes–ethyl acetate (30:1)], $[\alpha]_D=-90.0$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.4 (d, 3H, J=7 Hz), 1.6–1.8 (m, 2H), 2.2–2.4 (m, 4H), 2.6 (q, 1H, J=7 Hz), 5.5 (s, 2H), 7.2–7.5 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.2, 23.2, 23.6, 35.1, 36.4, 68.4, 121.3, 121.7, 125.1, 125.2, 126.6, 143.6. MS (*m*/*z*): 39, 41, 55, 67, 77, 79, 95, 96, 105, 120, 136, 154, 184, 198, 200 (M^++H). HRMS (FAB+) calcd for $C_{14}H_{17}N_1$ (M^++H) 200.1439 found 200.1446.

After purification, the aziridine was used to obtain the 1,2-diamines, which were separated by flash chromatography [hexanes–ethyl acetate (12:1)].

1,2-Diamine **5a** dihydrochloride. White crystals, mp 177–178 °C. Anal. calcd $C_{22}H_{28}N_2{\cdot}2HCl{\cdot}H_2O$: C 64.22%, H 7.84%; found C 64.55%, H 7.65%.

*Free 1,2-diamine (1S,2S,1′S,1″S)-**5a***. The main product is the *all-S* yielding 55%, $[\alpha]_D=+36.2$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.3 (d, 6H, J=6 Hz), 1.7–1.8 (m, 4H), 2.2 (d, 2H), 2.6 (t, 2H), 3.8 (q, 2H, J=6 Hz), 5.4 (s, 2H), 7.1–7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 32.5, 55.3, 56.5, 125.1, 126.7, 126.8, 128.4, 147.2.

1,2-Diamine **5b** dihydrochloride. White crystals, mp 240 °C. MS (*m*/*z*): 42, 79, 82, 105 (base peak), 120, 134, 161, 187, 201, 217, 266, 305, 321, 322 (M^+).

*Free 1,2-diamine (1R,2R,1′S,1″S)-**5b***. 18% yield, $[\alpha]_D=-75.0$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.3 (d, 6H, J=6 Hz), 1.6–1.8 (m 4H), 1.9 (s, 1H), 2.2–2.5 (m, 3H), 3.9 (q, 2H, J=6 Hz), 5.5 (s, 2H), 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 25.6, 31.7, 53.9, 54.6, 124.8, 126.5, 126.6, 128.3, 145.7. HRMS (FAB+) calcd for $C_{22}H_{28}N_2$ (M^++H) 321.2331; found 321.2332.

4.1.4. (1*S*,2*S*,1′*S*,1″*S*)- and (1*R*,2*R*,1′*S*,1″*S*)-*N*,*N*′-Di(α-phenylethyl)cyclopentane-1,2-diamines, 6a and 6b. Following the general procedure, the diastereomeric mixture of β-aminoalcohols was prepared from cyclopentene oxide, affording a yellow liquid (98% yield). Immediately, the mixture was used to prepare the *N*-[(*S*)-α-phenylethyl]-cyclopenteneaziridine. The crude product was purified by flash chromatography [hexanes–ethyl acetate (30:1)] to provide the aziridine (1.5 g, 80.0% yield) as a yellow liquid, $[\alpha]_D=-10.5$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.3 (d, 3H, J=7 Hz), 1.2–1.4 (m, 4H), 1.7–2.1 (m, 4H), 2.5 (q, 1H, J=7 Hz), 7.1–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 21.3, 23.5, 27.4, 27.8, 44.5, 45.2, 66.8, 126.4, 126.0, 128.0, 145.8. MS (*m*/*z*): 42, 53, 55, 68, 83, 91, 105 (base peak), 119, 130, 143, 144, 158, 172, 187 (M^+). HRMS (FAB+) calcd for $C_{13}H_{17}N_1$ (M^++H) 188.1439; found 188.1442.

The aziridine was then used to obtain the 1,2-diamines, which were separated by flash chromatography [hexanes–ethyl acetate (12:1)].

*Free 1,2-diamine (1S,2S,1′S,1″S)-**6a***. The main product is the *all-S* yielding 55%, $[\alpha]_D=+63.1$ (c=1.0, $CHCl_3$). ^1H NMR δ: 1.1 (m, 2H), 1.3 (d, 6H, J=6 Hz), 1.5 (m, 2H), 1.7 (m, 2H), 2.0 (broad, 2H), 2.7 (t, 2H), 3.8 (q, 2H, J=6 Hz), 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 21.1, 24.1, 31.5, 57.0, 63.6, 126.6, 126.7, 128.2, 146.4. IR (cm^{-1}) 3100, 2954–2862, 1450.

1,2-Diamine **6a** dihydrochloride. White crystals, mp 230–232 °C. MS (*m*/*z*): 308, 208, 189, 160, 120, 105 (base peak), 79, 56. Anal. calcd $C_{21}H_{28}N_2{\cdot}2HCl{\cdot}H_2O$: C 63.14%, H 8.07%; found C 62.92%, H 8.19%.

*Free 1,2-diamine (1R,2R,1′S,1″S)-**6b***. 22% yield, $[\alpha]_D=-83.4$ (c=1.0, $CHCl_3$). ^1H NMR δ: 1.1 (m, 2H),

1.3 (d, 6H, J=6 Hz), 1.5 (m 2H), 1.9 (m, 4H), 2.4 (t, 2H), 3.7 (q, 2H, J=6 Hz), 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 21.0, 25.5, 30.3, 56.1, 62.2, 126.4, 126.5, 128.1, 146.1. MS (m/z): 27, 41, 43, 55, 77, 91, 105, 120, 136, 154, 160, 187, 188, 203, 224, 231, 252, 267, 289, 309 (M^++1). HRMS (FAB+) calcd for $C_{21}H_{28}N_2$ (M^++H) 309.2331; found 309.2332.

1,2-Diamine **6b** dihydrochloride. White crystals, mp 240–243 °C.

4.1.5. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di(α-phenylethyl)-1,2-diphenyl-1,2-ethylenediamine, 7. The *N*,*N*′-bis-[(*R*)-1-phenylethyl]-ethanediimine was prepared from 40% aqueous glyoxal and (*R*)-α-phenylethylamine (2 equiv.) following the reported procedure.[14b]

^{1}H NMR δ: 1.5 (d, 6H, J=6.5 Hz), 4.4 (q, 2H, J=6.5 Hz), 7.3 (m, 10H), 8.0 (s, 2H). ^{13}C NMR δ: 23.9, 69.6, 126.6, 127.2, 128.5, 160.6.[13c]

To a stirred solution of *N*,*N*′-bis-[(*R*)-1-phenylethyl]-ethanediimine (170 mg, 0.64 mmol) in Et_2O (3 mL) at −70 °C under a nitrogen atmosphere was added PhMgBr (2.57 mL of a 2 M solution in THF) over 10 min. A white precipitate formed immediately, and the mixture was then allowed to warm to rt over a period of 5 h. The mixture was then cooled to 0 °C, quenched by the addition of a saturated aqueous solution of NH_4Cl, and the organic product extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, the solvent removed under reduced pressure, and the residue was purified by column chromatography [hexanes–EtOAc (10:1)] to yield a yellowish oil 76 mg, 45% yield, $[\alpha]_D$=+190.0 (c=1.0, $CHCl_3$), 93% ee, $[\alpha]_D$=+205.0 (c=0.7, $CHCl_3$).[14a] ^{1}H NMR δ: 1.2 (d, 6H, J=6.6 Hz), 2.4 (broad, 2H), 3.4 (s, 2H), 3.5 (q, 2H, J=6.6 Hz), 6.9–7.4 (m, 20H). ^{13}C NMR δ: 25.2, 54.9, 65.7, 126.8, 127.7, 127.8, 128.20, 128.2, 141.5, 141.5.[14a]

4.1.6. (1*S*,2*S*)-*N*,*N*′-Cyclopentane-1,2-dibenzyldicarbamate, (*S*,*S*)-8. The hydrogenation flask was rinsed with methanol and 30 mol% palladium hydroxide was added followed by **5a** (100 mg, 0.3 mmol) in methanol (15 mL). The reaction vessel was purged three times with nitrogen, three times with hydrogen, pressurized with 800 psi of hydrogen, and heated with stirring to 60 °C for 48 h. After completion of the reduction the catalyst was filtered over celite and the solvent was removed in vacuo.

The reaction mixture was dissolved in THF (2 mL). NaH (14.4 mg, 0.6 mmol) and benzyl chloroformate (0.086 mL, 0.6 mmol) were added and the mixture was refluxed for 3 h. The resulting solution was extracted with CH_2Cl_2 (3×20 mL), dried, and evaporated under reduced pressure. The product was purified by flash chromatography [EtOAc–hexanes (1:10)] to afford an oil (35 mg, 32% yield), $[\alpha]_D$=+8.1 (c=1.75, $CHCl_3$), ee=69%. [mp=147–149 °C, $[\alpha]_D$=+10.2 (c=0.47, $CHCl_3$), ee=87%]. ^{1}H NMR ($CDCl_3$) δ: 1.4 (m, 2H), 1.7 (m, 2H), 2.2 (m, 2H), 3.7 (m, 2H), 4.9 (m, 2H, NH), 5.1 (m, 4H), 7.3 (s, 10H). ^{13}C NMR ($CDCl_3$) δ: 19.1, 28.6, 54.4, 66.3, 126.3, 127.7, 128.4, 136.1, 156.3.[13]

4.2. Enantioselective reduction of prochiral ketones. General procedure

Method A. In a Schlenk flask $ZnEt_2$ (0.08 mL, 1 M in hexanes, 0.082 mmol) and chiral ligand (0.082 mmol) were dissolved in 1 mL of toluene and stirred under nitrogen atmosphere for 10 min. Then 1.66 mmol of the corresponding ketone was added, and PMHS (0.13 g, 2 mmol) was added slowly to the mixture. The reaction was kept at rt for 24 h. The reaction mixture was poured on KOH 15% aqueous solution (5 mL) and extracted with CH_2Cl_2 (3 mL×3). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography on silica gel, with hexanes–EtOAc, 10:1, as eluent.

Method B. In a Schlenk flask $ZnEt_2$ (0.08 mL, 1 M in toluene, 0.082 mmol) and chiral ligand (0.082 mmol) were dissolved in 1 mL of toluene and stirred under nitrogen atmosphere for 10 min. Then 1.66 mmol of the corresponding ketone was added, and $(EtO)_3SiH$ (2 mmol) was added slowly to the mixture. The reaction was kept at rt for 18 h. The reaction mixture was poured on KOH 15% aqueous solution (5 mL) and extracted with CH_2Cl_2 (3 mL×3). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo.). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography on silica gel, with hexanes–EtOAc, 10:1, as eluent.

Method C. In a Schlenk flask $ZnEt_2$ (0.03 mL, 1 M in toluene, 0.033 mmol) and chiral diamine **4a** (0.033 mmol) were dissolved in 1 mL of toluene and stirred under nitrogen atmosphere for 10 min. Then 1.66 mmol of the corresponding ketone was added, and PMHS (0.13 g, 2 mmol) was added slowly to the mixture. The reaction was kept at rt for 24 h. The reaction mixture was poured on KOH 15% aqueous solution (5 mL). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography on silica gel, with hexanes–EtOAc, 10:1, as eluent.

4.3. Conditions for the analysis and assignment of configuration of the chiral secondary alcohol products from the enantioselective reductions

Chiral capillary GC: Supelco β-Dex 120 column 30 m×0.25 mm (i.d.), 0.25 μm film. Carrier gas He. Detector FID, 270 °C. Injector 250 °C.

Chiral HPLC: Chiralcel OB or Chiralcel OD column, 254 nm UV detector.

Specific optical rotations of the secondary alcohols were measured and compared with those reported on the literature to assign configuration.[18]

The racemic alcohol products were obtained by addition of $NaBH_4$ to the ketones in MeOH. The retention times of the racemic products under the given conditions are listed below.

4.3.1. 1-Phenyl-1-ethanol. t_R=19.90 min, t_S=24.80 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). (*R*)-1-Phenyl-1-ethanol: $[\alpha]_D^{lit.}$=+33.0 (*c*=1, $CHCH_3$).[18a]

4.3.2. 1-Phenyl-1-propanol. t_R=21.47 min, t_S=29.27 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D$=+34 (*c*=1, $CHCl_3$). (*R*)-1-Phenyl-1-propanol: $[\alpha]_D^{lit.}$=+48 (*c*=1, $CHCl_3$).[18a]

4.3.3. 1-Phenyl-1-butanol. t_R=18.01 min, t_S=20.72 min (HPLC OD column, hexanes–*i*-PrOH 97:3, 0.5 mL/min). $[\alpha]_D$=+34 (*c*=1, $CHCl_3$). (*S*)-1-Phenyl-1-butanol: $[\alpha]_D^{lit.}$=−48 (*c*=1, $CHCl_3$).[18b]

4.3.4. 1-(β-Naphtyl)-ethanol. t_R=36.84 min, t_S=40.10 min (HPLC OB column, hexanes–*i*-PrOH 98:2, 0.5 mL/min). $[\alpha]_D$=+29 (*c*=1, $CHCl_3$). (*S*)-1-(β-Naphtyl)-ethanol: $[\alpha]_D^{lit.}$=−31 (*c*=1, $CHCl_3$).[18c]

4.3.5. 2,2,2-Trifluoro-1-phenyl-ethanol. t_S=14.44 min, t_R=15.85 min (GC 115 °C, 2.8 mL/min). $[\alpha]_D$=+6 (*c*=0.5, $CHCl_3$). (*S*)-2,2,2-Trifluoro-1-phenyl-ethanol: $[\alpha]_D^{lit.}$=+30.4 (*c*=1.56, $CHCl_3$).[18d]

4.3.6. 1-(*p*-Methoxyphenyl)-ethanol. t_R=61.75 min, t_S=65.6 min (GC 120 °C, 1.0 mL/min). $[\alpha]_D$=+5 (*c*=0.7, $CHCl_3$). (*S*)-1-(*p*-Methoxyphenyl)-ethanol: $[\alpha]_D^{lit.}$=−40.6 (*c*=1.12, $CHCl_3$).[18c]

4.3.7. 1-(*p*-Nitrophenyl)-ethanol. t_R=32.21 min, t_S=34.11 min (HPLC OB column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D$=+18 (*c*=1, $CHCl_3$). (*S*)-1-(*p*-Nitrophenyl)-ethanol: $[\alpha]_D^{lit.}$=−30.5 (*c*=1, $CHCl_3$).[18e]

4.3.8. 1-(*p*-Chlorophenyl)-propanol. t_R=18.38 min, t_S=19.76 min (GC 136 °C, 2.6 mL/min). $[\alpha]_D$=+23 (*c*=1.6, C_6H_6). (*S*)-1-(*p*-Chlorophenyl)-propanol: $[\alpha]_D^{lit.}$=+28.59 (*c*=5.1, C_6H_6).[18f]

4.3.9. 1-(*m*-Trifluoromethylphenyl)-ethanol. t_R=13.56 min, t_S=14.64 min (GC 115 °C, 1.6 mL/min). $[\alpha]_D$=+14 (*c*=0.9, MeOH). (*S*)-1-(*m*-Trifluoromethylphenyl)-ethanol: $[\alpha]_D^{lit.}$=−17.1 (*c*=2.92, MeOH).[18g]

4.3.10. *trans*-4-Phenyl-3-buten-2-ol. t_R=27.66 min, t_S=46.17 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D$=+27 (*c*=0.5, $CHCl_3$). (*S*)-*trans*-4-Phenyl-3-buten-2-ol: $[\alpha]_D^{lit.}$=−32.16 (*c*=5, $CHCl_3$).[18h]

4.3.11. 4-Phenyl 2-butanol. t_R=19.17 min, t_S=28.07 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D^{lit.}$=−2.0 (*c*=0.5, $CHCl_3$). (*S*)-4-Phenyl-2-butanol: $[\alpha]_D^{lit.}$=+15.8 (*c*=1.00, $CHCl_3$).[18i]

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