Design, Synthesis, and Application of a C_2 Symmetric Chiral Ligand for Enantioselective Conjugate Addition of Organolithium to α,β-Unsaturated Aldimine

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A C_2 symmetric chiral diether ligand, (1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane, was designed and synthesized on the basis of the concept of an asymmetric oxygen atom. Mediated by the chiral diether, high enantioselectivities were achieved in conjugate addition of organolithiums to naphthaldehyde imine and cyclic and acyclic α,β-unsaturated aldimines. The absolute configuration of the product is predictable by the model.

Introduction

Rational design of a chiral external ligand is a key for the success of an enantioselective reaction of organometallics.[1] The requirements of the ligand are (1) an activation of the reactivity of organometallics and subsequently (2) enhancement of the absolute stereochemistry control.[2] These demands may be satisfied by the formation of a rigid chelation structure between a chiral ligand and organometallics.[3] Although organometallics are aggregates in nonpolar solvents, chelation with a ligand is expected to give rise to a lower aggregate of higher reactivity.[4] Control of the absolute stereochemistry is simultaneously enhanced by the formation of the rigid chelate with a chiral ligand.

On the basis of the scenario described above, we designed a model (**1**) for the chiral chelate of organolithium, a powerful reagent[5] for a carbon−carbon bond-forming reaction (Figure 1). The steric control units, two balloons on heteroatoms X in **1**, are placed on the up and down faces of the chelation plane. Having this concept in hand,[6] we have reported a ligand-controlled enantioselective conjugate addition of organolithium.[7,8] We describe herein our design, synthesis, and application of the ligand to the reaction with α,β-unsaturated imine.[9]

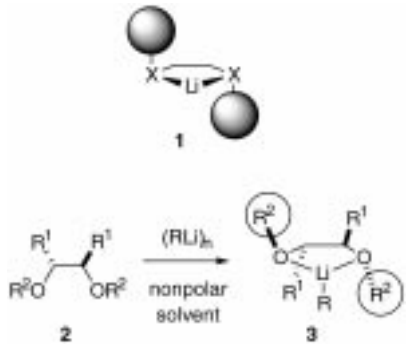

Figure 1.

Design of a Chiral Ligand. It is reasonable to assume that the chiral chelation structure **1**, where Li is the central lithium of the organometallic reagent and X is the coordinating atom to the lithium, provides a chiral environment around the central lithium due to the configurationally fixed bulk on X. The model has the advantage that a direct steric effect is operative by the coordinating chiral atom X just adjacent to the central lithium, because coordination to lithium by a substrate is the first step of the reaction.[10]

The chemical design of model **1** is of primary importance in our chemistry. It is reasonable to assume that

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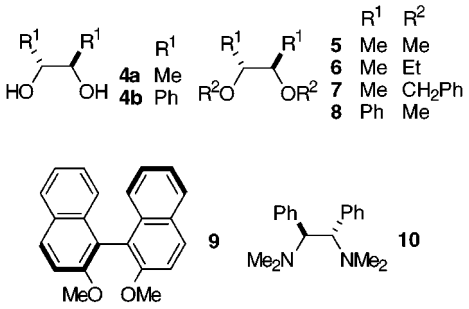

Figure 2.

a C_2 symmetric chiral diether **2** forms a five-membered chelation, **3**, with organolithium. The four substituents, two R^1 on the ethylene bridge and two R^2 on the ether oxygen atoms, take an all-trans arrangement due to steric factors. The arrangement of the two R^2 groups on the oxygen atoms, which represent the steric bulk shown in **1**, is important.

Generally, an oxygen atom is not an asymmetric center in itself. However, due to the steric effect of a neighboring asymmetric carbon of the ethylene bridge, the ether oxygen becomes an asymmetric center. Herein, we propose the concept of stereocontrol by formation of *an asymmetric oxygen atom*. Our proposal of chiral ether oxygen is supported by X-ray diffraction of the complex of dimethoxyethane and lithium enolate,[11] in which oxygen atoms of dimethoxyethane chelating to lithium appear to be tetrahedral. Formation of the chelate **3** enhances the reactivity of organometallics due to a lower aggregation.

Synthesis of Chiral Diethers. The C_2 symmetric chiral diethers in both enantiomeric forms are easily synthesized via dialkylation of the corresponding commercially or synthetically available chiral diols **4** (Figure 2). Chiral diethers **5**,[12] **6**,[13] and **7** were synthesized by dialkylation of sodium alkoxides of commercial chiral 2,3-butanediol **4a** in THF. A variety of C_2 symmetric chiral diols are also available in the necessary quantity and in high optical purity by the asymmetric dihydroxylation of olefins.[14] The chiral diether **8** was synthesized by dimethylation of optically pure hydrobenzoin **4b** and is a stable, nonhygroscopic, colorless, crystalline solid. The dimethyl ether **9** and bisdimethylamine **10** were prepared as reference ligands.

Conjugate Addition of Organolithium to 1-Naphthaldehyde Imine. The conjugate addition of an organolithium to an imine of 1-naphthaldehyde **11** has been developed by Meyers and is an established method for regioselective introduction of a carbonucleophile to naphthalene nucleus.[15] Extension to the diastereoselective asymmetric reaction and application to natural product synthesis[16] have been also developed using chiral oxazoline derivatives[17] or chiral imines.[18] Computational rationale for regioselective addition to unsaturated aldimines has been proposed by us.[19] Application of our chiral diether ligand was examined in the enantioselective addition reaction of organolithium to achiral imine **11**.[20]

With a stoichiometric amount of the simplest chiral diether ligand **5**, the enantioselective conjugate addition reaction of phenyllithium to the cyclohexyl aldimine **11a**[21] was examined. Toluene was used as a solvent because organolithiums are supposed to be much less reactive due to their high aggregation in less polar solvents.[22] In the presence of 1.1 equiv (to phenyllithium) of **5**, the reaction proceeded at −45 °C, and the reaction mixture showed a deep-red color that would indicate the formation of lithium azaenolate.[15] The reaction was quenched and hydrolyzed with acetate buffer (pH 4.5). The usual workup afforded 2-phenyl-1,2-dihydronaphthalene-1-carbaldehyde **12a**, which was immediately reduced with $NaBH_4$ in methanol to the corresponding trans alcohol **13a** in 68% overall yield after column chromatography. The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column to be as high as 90%. The absolute configuration was determined to be 1*S*,2*R* by optical rotation of **13a**[17] (Table 1, entry 1).

The reaction of butyllithium with the ligand **5** at −78 °C for 2 h gave (1*R*,2*S*)-**13b** in 92% yield and 53% ee (entry 2). In the absence of the ligand, the conjugate addition of butyllithium was sluggish in toluene to afford racemic **13b** in only 22% yield after 3 h (entry 15). Thus, the chiral diether **5** not only controls the absolute stereochemistry but also promotes the conjugate addition. Encouraged by these results, tuning of the chiral diethers was examined to improve the enantioselectivity.

Steric Requirements of the Ligand. Higher enantioselectivity would be achieved when the all-trans arrangement of the substituents on the five-membered chelate of **3** is more efficiently fixed. Therefore, bulkier substituents on the oxygen atoms of diether **3** were introduced at first. Contrary to our expectation, chiral diether **6** having an ethyl group on the oxygen atom

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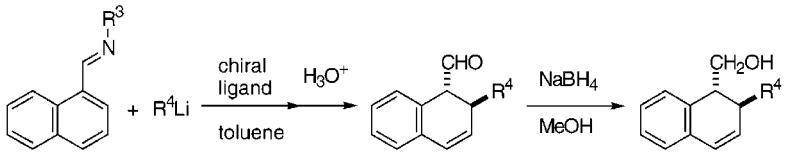
Table 1. Enantioselective Conjugate Addition of Organolithium to 1-Naphthaldehyde Imine 11 Controlled by Chiral Ligands 5−10



11a: R^3 = c-C_6H_{11} **11b**: R^3 = 1-adamantyl

12a: R^4 = Ph **12b**: R^4 = Bu

13a: R^4 = Ph **13c**: R^4 = Me **13b**: R^4 = Bu **13d**: R^4 = *t*-Bu

entry	aldimine	R^4	chiral ligand	temp/°C	time/h	product **13**[a]	ee/%[b]	yield/%[c]
1	**11a**	Ph	(*S*,*S*)-**5**	−45	13	(1*S*,2*R*)-**13a**	90	68
2	**11a**	Bu	(*R*,*R*)-**5**	−78	2	(1*R*,2*S*)-**13b**	53	92
3	**11a**	Ph	(*S*,*S*)-**6**	−45	15	(1*S*,2*R*)-**13a**	33	64
4	**11a**	Bu	(*S*,*S*)-**6**	−78	5	(1*S*,2*R*)-**13b**	28	83
5	**11a**	Ph	(*S*,*S*)-**7**	−45	12	(1*S*,2*R*)-**13a**	20	26
6	**11a**	Bu	(*S*,*S*)-**7**	−78	2	(1*R*,2*S*)-**13b**	15	89
7	**11a**	Ph	(*R*,*R*)-**8**	−45	13	(1*R*,2*S*)-**13a**	94	82
8	**11a**	Bu	(*R*,*R*)-**8**	−78	6	(1*R*,2*S*)-**13b**	91	80
9	**11a**	Bu	(*S*)-**9**	−78	7	(1*R*,2*S*)-**13b**	6	46
10	**11a**	Bu	(*S*,*S*)-**10**[d]	−78	4	(1*S*,2*R*)-**13b**	11	26
11	**11b**	Ph	(*S*,*S*)-**5**	−45	16	(1*S*,2*R*)-**13a**	92	80
12	**11b**	Ph	(*R*,*R*)-**8**	−45	22	(1*R*,2*S*)-**13a**	95	76
13	**11a**	Me	(*R*,*R*)-**8**	−23	20	(1*R*,2*R*)-**13c**	64	19[e]
14	**11a**	*t*-Bu	(*R*,*R*)-**8**	−78	1	(1*R*,2*S*)-**13d**	59	79
15	**11a**	Bu	none	−78	3	racemic-**13b**		22

[a] Determined by optical rotation.[17] [b] Determined by HPLC analysis using a chiral column. [c] Overall yield purified by silica gel column chromatography. [d] In ether. [e] The 1,2-adduct was obtained in 49% yield.

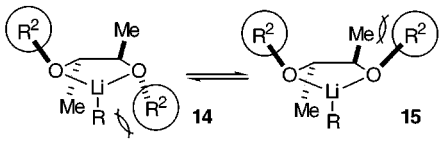


Figure 3.

afforded only 33% ee for **13a** and 28% ee for **13b** (entry 3, 4). The chiral diether **7** bearing a benzyl group on the oxygen gave **13a** and **13b** in poorer ee's of 20% and 15% (entries 5 and 6).

Unfavorable interactions between the bulky substituent R^2 on oxygen and the alkyl group R of the organolithium (**14**) would be greater than that with the methyl group on the chiral carbon and R^2 and would force the all-trans conformation **14** to take the conformation **15**, which would give rise to lower selectivity (Figure 3). Therefore, the chiral diether **8** having phenyl groups on the asymmetric carbons was expected to be more efficient than **5**.

In fact, the chiral diether **8** exerted better enantioselectivity 94% ee in the reaction of phenyllithium (entry 7). Furthermore, the reaction with butyllithium gave **13b** in dramatically improved 91% ee (entry 8). The chiral diether **8** was recovered quantitatively for reuse without any loss of optical purity.

The solvent effect on the ee was marginal. The reaction of **11a** with butyllithium in the presence of **8** in ether for 9 h at −78 °C gave (1*R*,2*S*)-**13b** in 89% ee and 61% yield.

The reaction of the adamantylimine of 1-naphthaldehyde **11b** with phenyllithium in the presence of **5** and **8** also gave conjugate adduct **13a** in 92% and 95% ee, respectively (entries 11 and 12).

It was disappointing that **9**[23] with a binaphthyl unit only induced a miserable ee of 6%, probably due to the lower coordinating ability of the phenolic oxygen atoms (entry 9). It is also important to note that diamine **10**[24] induced only 11% ee in ether, although it has a diphenylethane unit as in **8** (entry 10). This suggests that the direct stereocontrol factor is not the bulky groups on the asymmetric carbons but the "asymmetric oxygen" coordinated to the central lithium.

Other organolithiums, methyl- and *tert*-butyllithiums, reacted with **11a** to afford **13c**,**d** in 64% and 59% ee's (entries 13 and 14). The reaction of methyllithium gave the 1,2-adduct as the major product in 49% yield.[25]

The reaction of vinyllithium, prepared in situ from tetravinyltin and methyllithium in toluene, gave, after methylation in situ, **16** in 83% ee. On the other hand, crystallized vinyllithium reacted with **11a** in the presence of **8** in toluene at −35 °C for 16 h to afford, after methylation, the N-methylated 1,2-adduct in 22% yield, without production of **16** (Figure 4).

Conjugate Addition to Cyclic α,β-Unsaturated Aldimine. The present asymmetric reaction of organolithiums is applicable to other unsaturated aldimines. The reaction of phenyllithium with cyclic α,β-unsaturated aldimines **17a**,**b** proceeded smoothly. The initially formed cis aldehyde **18** was isomerized to *trans*-**19** by treating **18** with concentrated hydrochloric acid in THF.[26] Then

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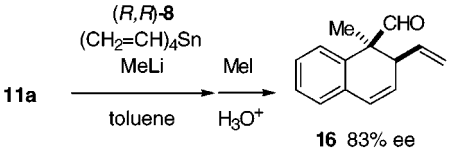
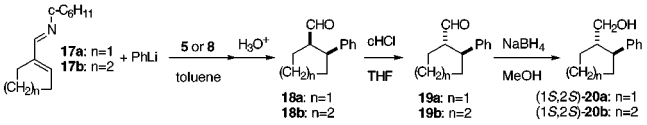


Figure 4.

Table 2. Enantioselective Conjugate Addition of Phenyllithium to Cyclic α,β-Unsaturated Aldimine 17 Mediated by Chiral Diethers 5 and 8



entry	aldimine	chiral ligand	temp/ °C	time/ h	product[a]	ee/ %[b]	yield/ %[c]
1	**17a**	(*R*,*R*)-**8**	−45	3	(1*S*,2*S*)-**20a**	91	59
2	**17a**	(*S*,*S*)-**5**	−45	4	(1*R*,2*R*)-**20a**	82	76
3	**17b**	(*R*,*R*)-**8**	−45	7	(1*S*,2*S*)-**20b**	96	61
4	**17b**	(*S*,*S*)-**5**	−45	1	(1*R*,2*R*)-**20b**	80	69

[a] Absolute configuration was determined by optical rotation.[27] [b] Determined by HPLC analysis using a chiral column. [c] Purified yield of **20**.

the *trans*-**19** was reduced with $NaBH_4$ to the corresponding alcohol **20**. As shown in Table 2, **20a**,**b** were obtained in over 90% ee with use of **8** from both of five- and six-membered imines **17a** and **17b**. The chiral diether **8** exhibited higher enantioselectivity than **5** (entry 1 vs entry 2 and entry 3 vs entry 4). The sense of asymmetric induction was the same as that of the naphthalene imines described above.[27]

Conjugate Addition to Acyclic α,β-Unsaturated Aldimine. Acyclic unsaturated imines were also good substrates for the asymmetric conjugate addition reaction. The reactivity was so high that the reaction proceeded at −78 °C even when phenyllithium was used. High enantioselectivity was achieved as shown in Table 3. Especially with phenyllithium as the nucleophile, nearly optically pure products **23** were obtained by the use of chiral diether ligand **8** (entries 1 and 3). Chemical yields were modest in some cases, since the 1,2-adducts were also obtained in 10−25% yield. The sense of asymmetric induction was the same as that of the naphthalene imines **11**.[28]

The reaction of phenylmagnesium bromide with **21a** in the presence of **8** in toluene at −23 °C for 3 h gave racemic **22** (R^5 = Me, R^4 = Ph). This result indicates that lithium is the essential metal in the reaction promoted by the diether ligand **8**.

Stereochemical Aspects of the Reaction. The sense of asymmetric induction exhibited by the chiral diether ligand **8** is the same regardless of whether 1-naphthyl-, cyclic, or acyclic imines are used as the substrates. Organolithium attacks from the top face of imines **11**, **17**, and **21**. The assumption that coordination of nitrogen of the imine to tetravalent lithium[10,29] is the initial event leads to two model structures, **24** and **25**, for the reactive complexes involving **8**, R−Li, and cyclohexylimine of crotonaldehyde (**21a**), where the migrating C−Li bond is almost parallel to the p orbital of the imine (Figure 5). Obviously, there are less unfavorable steric interactions in **24** than in **25**.[30] The absolute configuration predicted from **24** is identical with the experimental results.

Conclusion

The chiral C_2 symmetric ligands **5** and **8** show the powerful effect on the activation of the addition of organolithium to α,β-unsaturated imines as well as on the enantioselectivity of the reaction.[31] The methyl group on the ether oxygen seems to be critical to the enantioselectivity of the addition. This principle is very simple for designing chiral ligands and is applicable in a variety of asymmetric reactions.

Experimental Section

General. ^1H and ^{13}C NMR were recorded in $CDCl_3$, unless otherwise noted. Chemical shift values are presented in parts per million downfield from tetramethylsilane. Data are reported as follows: integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (hertz), and assignment where relevant. Mass spectra were recorded under electron impact (EI) conditions. Analytical HPLC was performed using Waters Optipak-TA, XC, PC, TC, Daicel Chiralcel AD. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254), with UV light, ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as the developing agent. Melting points are uncorrected. Boiling points are uncorrected. THF, Et_2O, DME, and toluene were distilled from sodium benzophenone ketyl.

(2*S*,3*S*)-2,3-Dimethoxybutane, 5.[12] **5** was prepared from (2*S*,3*S*)-2,3-butanediol. $[\alpha]^{20}_D$ −3.65 (neat). ^1H NMR: 1.10 (6H, d, *J* = 6 Hz), 3.10−3.70 (8 H, m). IR (neat): 3000, 2960, 2900, 2840 cm^{-1}.

(2*S*,3*S*)-2,3-Diethoxybutane, 6.[13] Prepared from (2*S*,3*S*)-2,3-butanediol. $[\alpha]^{25}_D$ +4.86 (neat), $[\alpha]^{25}_D$ +10.7 (*c* 5.45, CH_2Cl_2). ^1H NMR: 1.09 (6H, d, *J* = 6 Hz), 1.18 (6H, t, *J* = 7 Hz), 3.30−3.80 (6H, m). ^{13}C NMR: 15.0 (q), 15.6 (q). 64.7 (t), 77.3 (d). IR (neat): 2900, 1120 cm^{-1}.

(2*S*,3*S*)-2,3-Dibenzyloxybutane, 7. (2*S*,3*S*)-2,3-Butanediol (2.00 g, 22.2 mmol) in THF (10 mL) was added dropwise over 10 min to a suspension of 2.22 g (55.5 mmol) of sodium hydride (60% in mineral oil, washed 3 times with hexane (5 mL)) in THF (40 mL). After being stirred at room temperature for 30 min, the viscous mass was refluxed for 30 min until hydrogen evolution ceased. Then, 9.49 g (55.5 mmol) of benzyl bromide in THF (10 mL) was added dropwise during 10 min. After being stirred at room temperature for 13 h, the reaction mixture was refluxed for 1 h, poured into saturated NH_4Cl (50 mL), and extracted with Et_2O (50 mL). The extract was washed with brine and dried over $MgSO_4$. Concentration provided a yellow oil, which was chromatographed over silica gel (hexane/Et_2O = 10:7) to yield **7** (5.19 g, 86%) as a pale-yellow oil of bp 130−132 °C at 0.4 mmHg. $[\alpha]^{25}_D$ +20.3 (*c* 1.48, $CHCl_3$). ^1H NMR: 1.17 (6H, d, *J* = 6 Hz), 3.4 (2H, m), 4.57 (2H, d, *J* = 12 Hz), 4.59 (2H, d, *J* = 12 Hz), 7.1−7.4 (10H, m). ^{13}C NMR: 15.0 (q), 71.3 (t), 77.1 (d), 127.4 (d), 127.6 (d), 128.3 (d), 139.0 (s). IR (neat): 1615, 1590 cm^{-1}. MS *m*/*z*: 270 (M^+). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.68; H, 8.26.

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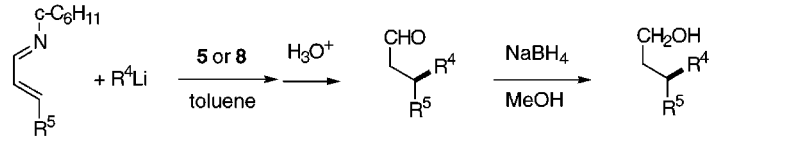
(30) Cache calculation indicates the stability of **24** is higher than that for **25** by a factor of around 2 kcal/mol.

(31) Unfortunately, the attempted catalytic reaction of phenyllithium with **11a** using 0.2 equiv of **5** or **8** gave **12a** in at most 10% yield.

Table 3. Enantioselective Conjugate Addition of Organolithium to Acyclic α,β-Unsaturated Aldimine 21 Mediated by Chiral Diethers 5 and 8



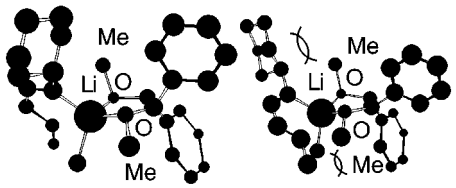
21a: R^5 = Me
21b: R^5 = Bu
21c: R^5 = Ph

22

23a: R^5 = Me, R^4 = Ph
23b: R^5 = Bu, R^4 = Ph
23c: R^5 = Ph, R^4 = Bu

entry	R^5	R^4	chiral ligand	temp/°C	time/h	product[a]	ee/%[b]	yield/%
1	Me	Ph	(*R*,*R*)-**8**	−78	3	(*S*)-**23a**	>99	48
2	Me	Ph	(*S*,*S*)-**5**	−78	1	(*R*)-**23a**	94	42
3	Bu	Ph	(*R*,*R*)-**8**	−78	4	(*S*)-**23b**	>99	58
4	Bu	Ph	(*S*,*S*)-**5**	−78	3	(*R*)-**23b**	93	45
5	Ph	Bu	(*R*,*R*)-**8**	−78	1	(*R*)-**23c**	82	40

[a] Absolute configuration was determined by optical rotation of **23**, which was obtained from the corresponding ester with the established absolute configuration.[28] [b] Determined by HPLC analysis using a chiral column.



24 **25**

The reactive complexes involving **8**, MeLi, and **21a**.

Figure 5.

(1*R*,2*R*)-1,2-Dimethoxy-1,2-diphenylethane, 8. (*R*,*R*)-(+)-Hydrobenzoin (10.0 g, 46.7 mmol) in THF (50 mL) was added dropwise during 10 min to a suspension of sodium hydride (4.67 g, 117 mmol, 60% in mineral oil, washed 3 times with hexane) in THF (100 mL). After the mixture was refluxed for 30 min, dimethyl sulfate (12.4 g, 98.1 mmol) was added dropwise under ice bath cooling. The hard viscous mass was stirred for 15 h at room temperature. The mixture was quenched with saturated NH_4Cl (10 mL) and extracted with Et_2O (200 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$. Concentration afforded a colorless solid (11.1 g), which was recrystallized from hexane to give **8** as colorless prisms (9.33 g, 82%) of mp 99−100 °C. $[\alpha]^{25}_D$ −15.2 (*c* 1.22, $CHCl_3$). ^{1}H NMR: 3.27 (6H, s), 4.31 (2H, s), 6.85−7.25 (10H, m). ^{13}C NMR: 57.1 (q), 87.7 (d), 127.6 (d), 127.8 (d), 138.2 (s). IR (KBr): 1490, 1450 cm^{-1}. MS *m*/*z*: 241 ($M^+ - 1$). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.41; H, 7.52.

(*S*,*S*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diphenylethylenediamine, 10. To a solution of (1*S*,2*S*)-1,2-diphenylethylenediamine (1.90 g, 8.9 mmol, 98.7% ee) in formic acid (90%, 4.1 mL, 214 mmol) and H_2O under reflux was added formalin (37%, 5.2 mL, 138 mmol) dropwise. After the mixture refluxed for 3 days, formic acid (4.1 mL) and formalin (5.2 mL) were added, and reflux was continued for 3 days. To the mixture, 10% HCl (150 mL) was added, and then the aqueous layer was washed with Et_2O (50 mL). After addition of 50% NaOH (pH 11), it was extracted with AcOEt (200 mL) and the organic layer was washed with brine and then dried over K_2CO_3. Concentration gave 2.86 g of a colorless solid, which was chromatographed over silica gel (AcOEt/hex = 1:4) to yield **10** (2.11 g, 88%) as colorless needles of mp 88.0−89.5 °C (hexane). $[\alpha]^{20}_D$ +57.2 (*c* 1.09, $CHCl_3$). ^{1}H NMR: 2.25 (12H, s), 4.25 (2H, s), 6.9−7.4 (10H, m). IR (KBr): 1450, 1035 cm^{-1}. MS *m*/*z*: 269 ($M^+ + 1$), 268 (M^+). Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.79; H, 9.11; N, 10.68.

***N*-(1-Naphthylmethylidene)-1-adamantanamine, 11b.** A solution of 1-naphthaldehyde (1.67 g, 10.7 mmol), 1-adamantanamine (2.00 g, 12.8 mmol), and BF_3OEt_2 (0.06 mL, 0.5 mmol) in benzene (100 mL) was refluxed for 3 h with a Dean−Stark trap. The mixture was washed with cold saturated $NaHCO_3$ and cold brine and dried over K_2CO_3. Concentration gave a yellow solid, which was recrystallized from EtOH (20 mL) to yield **11b** (2.43 g, 80%) as colorless needles of mp 119−120.5 °C. ^{1}H NMR: 1.7−2.1 (12H, m), 2.1−2.4 (3H, m), 7.4−7.7 (3H, m), 7.7−8.1 (3H, m), 8.7−8.9 (1H, m), 8.97 (1H, s). ^{13}C NMR: 29.6 (d), 36.6 (t), 43.3 (t), 58.3 (s), 124.1 (d), 125.3 (d), 125.8 (d), 126.7 (d), 127.5 (d), 128.6 (d), 130.3 (d), 131.4 (s), 132.8 (s), 133.8 (s), 154.3 (d). IR (KBr): 1630, 1615, 1510 cm^{-1}. MS *m*/*z*: 289 (M^+). Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.09; H, 8.11; N, 4.68.

(1*R*,2*S*)-(2-Phenyl-1,2-dihydronaphthyl)methan-1-ol, 13a[17] **(Table 1, entry 7).** To a suspension of the naphthylimine **11a** (237 mg, 1.00 mmol)[21] and (*R*,*R*)-**8** (582 mg, 2.40 mmol) in 10 mL of toluene at −78 °C was added dropwise a solution of phenyllithium (0.97 mL, 2.2 mmol). The solution was stirred for 13 h at −45 °C, and then 20 mL of 10% HCl was added to the red mixture. After being stirred for 4 h at room temperature, the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with 10% HCl (20 mL), saturated $NaHCO_3$, and brine and then dried over $MgSO_4$. Concentration gave an oily solid. The crude aldehyde was reduced with $NaBH_4$ (0.12 g) in MeOH (6 mL) at 0 °C for 10 min and quenched with 20% NH_4Cl (3 mL). After concentration, 20% NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (20 mL). The extract was washed with brine and dried over $MgSO_4$. Concentration and subsequent purification by column chromatography on silica gel (hexanes-Et_2O = 3:1) gave (1*R*,2*S*)-**13a** (193 mg, 82%) as a colorless oil of $[\alpha]^{26}_D$ +519.7 (*c* 1.09, $CHCl_3$). The spectral data were identical with those reported. The ee was determined to be 94% by HPLC analysis (Waters Optipak-TA; hexane/2-propanol = 9:1; 0.5 mL/min; major peak, 26 min; minor peak, 21 min). The ligand **8** (0.59 g) was recovered quantitatively.

(1*R*,2*S*)-(2-Butyl-1,2-dihydronaphthyl)methan-1-ol, 13b[17] **(Table 1, entry 8).** To a solution of the naphthylimine **11a** (237 mg, 1.00 mmol) and (*R*,*R*)-**8** (339 mg, 1.40 mmol) in 10 mL of toluene at −78 °C was added dropwise a solution of butyllithium (0.82 mL, 1.30 mmol). The mixture was stirred for 6 h at −78 °C, and then 20 mL of 10% HCl was added. After the mixture was stirred for 15 h at room temperature, workup as above gave an oil (0.67 g), which was reduced with $NaBH_4$ (0.12 g) in MeOH (5 mL) at 0 °C. After 10 min, workup as above and purification by chromatography on silica gel (hexane/AcOEt = 15/1) gave (1*R*,2*S*)-**13b** (172 mg, 80%) as a colorless oil of $[\alpha]^{20}_D$ +403.8 (*c* 2.43, $CHCl_3$). The spectral data were identical with those reported. The ee was determined to be 91% by HPLC analysis (Waters Optipak-TA; hexane/2-propanol = 9:1; 0.5 mL/min; major peak, 13.0 min; minor peak, 14.5 min).

(1*R*,2*R*)-(2-Methyl-1,2-dihydronaphthyl)methan-1-ol, 13c[17] **(Table 1, entry 13).** To a solution of **11a** (237 mg, 1.0 mmol) and (*R*,*R*)-**8** (800 mg, 3.3 mmol) in 20 mL of toluene at

−78 °C was added dropwise a solution of methyllithium (2.2 mL, 3.0 mmol, 1.36 M in Et_2O, low halide). After 20 h at −23 °C, acetate buffer (20 mL) was added. After the mixture was stirred for 3 h at room temperature, the usual workup gave an oil, which was reduced with $NaBH_4$ (0.12 g) in MeOH (3 mL) at 0 °C. After 10 min, the usual workup and purification by column chromatography over silica gel (hexane/Et_2O = 5:1) gave (1*R*,2*R*)-**13c** (36 mg, 19%) of $[\alpha]^{24}_D$ +274.3 (*c* 0.63, $CHCl_3$) in 64% ee. The spectral data were identical with those reported.

(1*R*,2*S*)-(2-*tert*-Butyl-1,2-dihydronaphthyl)methan-1-ol, 13d[17] **(Table 1, entry 14).** To a solution of **11a** (237 mg, 1.00 mmol) and (*R*,*R*)-**8** (339 mg, 1.40 mmol) in 20 mL of toluene at −78 °C was added dropwise a solution of *tert*-butyllithium (0.78 mL, 1.3 mmol, 1.67 M in pentane). After 1 h, acetate buffer (20 mL) was added to the deep-red reaction mixture. After the mixture was stirred for 3 h at room temperature, the usual workup gave an oil, which was reduced with $NaBH_4$ (0.12 g) in MeOH (3 mL) at 0 °C. After 10 min, the usual workup and purification by column chromatography over silica gel (hexane/Et_2O = 5:1) gave (1*R*,2*S*)-**13d** (171 mg, 79%) of $[\alpha]^{20}_D$ +253.8 (*c* 3.0, $CHCl_3$). The spectral data were identical with those reported. The ee was determined to be 59% by HPLC analysis (Waters Optipak-TA; hexane/2-propanol = 9:1; 0.5 mL/min; major peak, 20 min; minor peak, 11 min).

(1*S*,2*S*)-(1-Methyl-2-vinyl-1,2-dihydronaphthyl)methan-1-ol 16.[17] To a solution of tetravinyltin (81.9 mg, 0.36 mmol) in 10 mL of toluene was added dropwise a solution of methyllithium (0.96 mL, 1.3 mmol, 1.36 M in Et_2O, low halide) at room temperature. The resulting slightly white suspension was stirred for 1 h at room temperature. The vinyllithium solution was added to a solution of naphthylimine **11a** (237 mg, 1.0 mmol) and (*R*,*R*)-**8** (339 mg, 1.4 mmol) via cannula at −78 °C. The mixture was stirred for 36 h at −78 °C, for 24 h at −40 °C, and finally for 5 h at −30 °C. Then, HMPA (0.87 mL, 5 mmol) and THF (15 mL) were added to the resulting deep-red mixture at −78 °C. After 10 min, methyl iodide (0.25 mL, 4 mmol) was added and the mixture was allowed to warm gradually to room temperature for 1.5 h. Acetate buffer (20 mL) was added to the pale-yellow solution. After being stirred for 3 h at room temperature, the mixture was extracted with Et_2O (20 mL), and the combined organic layer was washed with 10% HCl (20 mL), saturated $NaHCO_3$, and brine and then dried over $MgSO_4$. Concentration and subsequent purification by chromatography on silica gel (hexane/Et_2O = 50:1) gave (1*S*,2*S*)-**16** (27 mg, 14%) as an oil of $[\alpha]^{22}_D$ +71.3 (*c* 2.54, $CHCl_3$) in 83% ee and the starting aldehyde (64.8 mg, 65%). ^1H NMR: 1.40 (3H, s), 3.15 (1H, ddd, *J* = 2, 4, 9 Hz), 4.95−5.40 (2H, m), 5.6−6.1 (2H, m), 6.55 (1H, dd, *J* = 2, 9 Hz), 6.9−7.6 (4H, m), 9.75 (1H, s). IR (neat): 1730 cm^{-1}. MS *m*/*z*: 198 (M^+). HRMS: calcd for $C_{14}H_{14}O$, 198.1045; found, 198.1047.

***N*-(1-Cyclopentenylmethylidene)cyclohexylamine, 17a.** To 1-cyclopentenecarbaldehyde[32] (1.79 g) in hexane (20 mL) was added cyclohexylamine (2.03 g, 20.5 mmol) and molecular sieves (4 Å). After being stirred for 14 h, the reaction mixture was filtered and concentrated. Distillation (bp 115 °C/12 mmHg) gave **17a** (2.36 g, 72%) as a yellow oil. ^1H NMR: 0.8−1.7 (16H, m), 1.7−2.2 (1H, m), 6.00−6.20 (1H, m), 8.13 (1H, s). ^{13}C NMR: 23.0 (t), 24.9 (t), 25.5 (t), 30.6 (t), 33.0 (t), 34.2 (t), 70.1 (d), 139.6 (d), 144.7 (s), 156.4 (d). IR (neat): 1645, 1610, 1450 cm^{-1}. HRMS: calcd for $C_{12}H_{19}N$, 177.1517; found, 177.1512.

***N*-(1-Cyclohexenylmethylidene)cyclohexylamine, 17b.** To 1-cyclohexenecarbaldehyde[33] (1.95 g) in hexane (30 mL) was added cyclohexylamine (1.93 g, 19.5 mmol) and molecular sieves (4 Å). After being stirred for 2 days, the reaction mixture was filtered and concentrated. Distillation (bp 111 °C/6 mmHg) provided **17b** (2.09 g, 70%) as a pale-yellow oil. ^1H NMR: 0.8−2.2 (18H, m), 2.75−3.12 (1H, m), 6.12 (1H, m), 7.81 (1H, s). ^{13}C NMR: 22.0 (t), 22.4 (t), 23.9 (t), 24.9 (t), 25.6 (t), 26.0 (t), 34.4 (t), 69.8 (d), 137.8 (d), 138.1 (s), 161.9 (d). IR (neat): 1650, 1630, 1450 cm^{-1}. MS *m*/*z*: 191 (M^+). HRMS: calcd for $C_{13}H_{21}N$, 191.1674; found, 191.1663.

(1*S*,2*S*)-*trans*-2-Phenylcyclopentanemethanol, 20a[27] **(Table 2, entry 1).** To a solution of **17a** (177 mg, 1.0 mmol) and (*R*,*R*)-**8** (339 mg, 1.4 mmol) in toluene (10 mL) at −78 °C was added dropwise a solution of phenyllithium (0.57 mL, 1.3 mmol, 2.27 M). The yellow solution was stirred for 3 h at −45 °C, and then 20 mL of acetate buffer was added. After being stirred for 1.5 h at room temperature, the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$. Concentration gave a yellow oil (**18a** trans/cis = 4:3 by NMR; C*H*O trans 9.55 ppm, cis 9.20 ppm), which was dissolved in THF (4 mL) and concentrated HCl (2 drops) and stirred for 2 h at room temperature. The mixture was neutralized with saturated $NaHCO_3$ and extracted 3 times with Et_2O (15 mL). The extract was washed with brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel (hexane/AcOEt = 2:1) afforded *trans*-**19a** of $[\alpha]^{20}_D$ +87.2 (c 1.20, PhH), which was reduced with $NaBH_4$ (0.12 g) in MeOH (3 mL) at 0 °C. After 10 min, 20% NH_4Cl (3 mL) was added. The usual workup, concentration, and purification by column chromatography over silica gel (hexane/Et_2O = 2:1) gave **20a** (104 mg, 59% from **17a**) as a colorless oil. The spectral data were identical with those reported. The ee was determined to be 91% by HPLC analysis (Waters Optipak-XC; hexane/2-propanol = 9:1; 0.5 mL/min; major, 15 min; minor, 12 min).

(1*S*,2*S*)-*trans*-2-Phenylcyclohexanemethanol, 20b[27] **(Table 2, entry 3).** A solution of **17b** (191 mg, 1.0 mmol), (*R*,*R*)-**8** (339 mg, 1.4 mmol), and phenyllithium (0.57 mL, 1.3 mmol, 2.27 M) in 10 mL of toluene was stirred for 7.5 h at −45 °C. A workup as above and chromatography over silica gel (hexane/AcOEt = 20:1) gave a colorless oil (116 mg, 61%) of **19b**. The trans aldehyde (77.0 mg) was reduced with $NaBH_4$ (0.12 g) in MeOH (1 mL) at 0 °C. A workup as above and chromatography over silica gel (hexane/Et_2O = 5:1) afforded **20b** (66.5 mg) as colorless needles of mp 71.5−73.5 °C. $[\alpha]^{27}_D$ +34.8 (*c* 0.09, MeOH). $[\alpha]^{25}_D$ +33.3 (*c* 1.04, $CHCl_3$). The ee was determined to be 80% by HPLC analysis (Waters Optipak-XC; hexane/2-propanol = 9:1; 0.5 mL/min; UV, 254 nm; major, 11.7 min; minor, 10.7 min).

The alcohol **20b** was recrystallized twice from hexane to afford colorless needles of mp 76−77 °C. $[\alpha]^{25}_D$ +35.3 (*c* 0.93, $CHCl_3$). ^1H NMR: 1.00−2.50 (11H, m), 3.20 (1H, dd, *J* = 6, 11 Hz), 3.39 (1H, dd, *J* = 4, 11 Hz), 7.0−7.4 (5H, m). IR (KBr): 3260, 1600, 1490 cm^{-1}. MS *m*/*z*: 190 (M^+). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.08; H, 9.57.

(*S*)-3-Phenylbutanol, 23a[28] **(Table 3, entry 1).** A mixture of **21a**[34] (151 mg, 1.0 mmol), (*R*,*R*)-**8** (582 mg, 2.4 mmol), and phenyllithium (0.97 mL, 2.2 mmol) in toluene (20 mL) was stirred for 3 h at −78 °C. A workup as above and purification by column chromatography over silica gel (hexane/Et_2O = 5:1−1:1) gave, after distillation (100−150 °C, 5 mmHg), **23a** (71.9 mg, 48%) as a colorless oil of $[\alpha]^{25}_D$ +25.5 (*c* 1.52, $CHCl_3$). The spectral data were identical with those reported. The ee was determined to be >99% by HPLC analysis (Waters Optipak-PC; hexane/2-propanol = 9:1; 0.2 mL/min; major, 20 min; minor, 22 min).

***N*-(2-Heptenylidene)cyclohexylamine, 21b.** To 2-heptenal (8.48 g, 75.6 mmol) was added cyclohexylamine (8.25 g, 83.2 mmol) dropwise at 0 °C. After the mixture was stirred for 10 min, Na_2SO_4 (20 g) was added. The mixture was stirred for 1.5 h and then filtered. The residue was washed with Et_2O, and the combined organic layer was concentrated to afford 15.5 g of a pale-yellow oil, which was distilled (bp 125 °C/10 mmHg) to give labile **21b** as a yellow oil (8.23 g, 60%). ^1H NMR: 0.70−3.40 (20H, m), 6.08−6.32 (2H, m, CH=CH), 7.75−8.00 (1H, m, CH=N). ^{13}C NMR: 13.6 (q), 22.0 (t), 24.6 (t), 25.4 (t), 30.4 (t), 32.0 (t), 34.2 (t), 69.2 (d), 130.7 (d), 144.8 (d), 150.3 (d). IR (neat): 1660, 1650, 1625 cm^{-1}. HRMS: calcd for $C_{13}H_{23}N$, 193.1832; found, 193.1780.

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(*S*)-3-Phenylheptanol, 23b[35] **(Table 3, entry 3).** A solution of **21b** (193 mg, 1.0 mmol), (*R*,*R*)-**8** (582 mg, 2.4 mmol), and phenyllithium (0.97 mL, 2.2 mmol, 2.27 M) in toluene (10 mL) was stirred for 4 h at −78 °C. A workup as above and purification by column chromatography over silica gel (hexane/Et_2O = 5:1) gave **23b** (112 mg, 58%) as a colorless oil (200 °C, 3 mmHg) of $[\alpha]^{25}_{365}$ −12.1 (*c* 0.98, $CHCl_3$). ^{1}H NMR: 0.50−2.0 (12H, m), 2.55 (1H, m), 3.50 (2H, t, *J* = 6), 6.9−7.6 (5H, m). IR (neat): 3380, 1610 cm^{-1}. MS *m*/*z*: 193 (M^+). HRMS: calcd for $C_{13}H_{20}O$, 192.1515; found, 192.1518. The ee was determined to be 99% by HPLC analysis (Waters Optipak TA; hexane/2-propanol = 9:1; 0.20 mL/min; major, 21 min; minor, 23 min).

(*R*)-3-Phenylheptanol, 23c (Table 3, entry 4). To a solution of **21c** (213 mg, 1.0 mmol)[36] and (*R*,*R*)-**8** (582 mg, 2.4 mmol) in 15 mL of toluene at −78 °C was added dropwise a solution of butyllithium (1.38 mL, 2.2 mmol). The violet solution was stirred for 1 h at −78 °C, and then 20 mL of acetate buffer was added. After being stirred for 3 h at room temperature, the mixture was extracted with Et_2O. The combined organic layer was washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$. Concentration gave an oil (0.82 g), which was reduced with $NaBH_4$ (0.10 g) in MeOH (3 mL) at 0 °C. After 10 min, 20% NH_4Cl (3 mL) was added. The usual workup and purification through column chromatography over silica gel (hexane/Et_2O = 5:1) gave **23c** (77.7 mg, 40%) as a colorless oil (200 °C, 3 mmHg) of $[\alpha]^{25}_{365}$ +9.80 (c 1.22, $CHCl_3$). The ee was determined to be 82% by HPLC analysis.

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