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Synthesis of γ-amino alcohols from aldehydes, enamines, and trichlorosilane using Lewis base catalysts

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ABSTRACT

The reaction of aldehydes, enamines, and trichlorosilane in the presence of a Lewis base catalyst, particularly *N*-methylpyrrolidinone and DMF, affords γ-amino alcohols with a high diastereoselectivity. The method consists of C–C bond formation between an aldehyde and an enamine, and a subsequent intramolecular reduction of the resulting iminium ion intermediate. In most cases, one diastereomer is exclusively generated, and we propose a transition state model for the intramolecular reduction of the iminium ion intermediate. Enamines, prepared beforehand from the corresponding ketone and amine, can be used in the reaction without purification. Furthermore, enantioselective catalysis using a chiral Lewis base catalyst is possible, although the enantioselectivity is modest. The current tandem method offers the first, concise synthetic method of γ-amino alcohols from aldehydes and enamines.

1. Introduction

Tandem reactions enhance the efficiency of synthetic processes because reactive and unstable synthetic intermediates can be used without isolation and purification.[1] We have recently reported that P=O compounds as Lewis base catalysts promote the tandem conjugate reduction/aldol reaction (the reductive aldol reaction) of enones and aldehydes with trichlorosilane to provide β-hydroxy ketones in good yield with high stereoselectivity.[2] Herein, we disclose a novel synthetic method of γ-amino alcohols **3** from aldehydes **1**, enamines **2**, and trichlorosilane in the presence of a Lewis base catalyst (Fig. 1).

This method consists of a tandem C–C bond formation/reduction. The first C–C bond formation between aldehyde **1** and enamine **2** affords iminium ion intermediate **4**. Subsequently intermediate **4** is intramolecularly reduced by the hydrosilyl group to give γ-amino alcohol **3**.[3–8] Similar to the reductive aldol reaction,[2] we hypothesized that a Lewis base catalyst (LB)[9] promotes this reaction via activation of trichlorosilane.

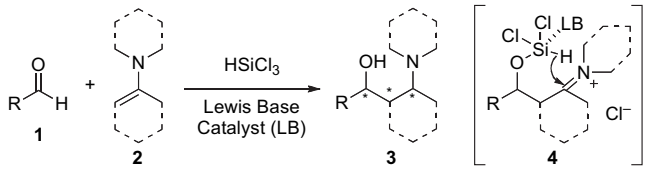

Fig. 1. Synthesis of γ-amino alcohols **3** from aldehydes **1** and enamines **2**.

Hosomi et al. have demonstrated that a tandem aldol/reduction of dimethylsilyl enol ethers with aldehydes in the presence of a catalytic amount of TBAF affords 1,3-diols.[10] Additionally, related reactions of *enol ethers*, electrophiles (acetals, aldehydes, or imines), and nucleophiles (methanol, triethylsilane, allyltrimethylsilane, etc.) in the presence of Lewis acids have also been reported.[11] However, the corresponding reaction of *enamines* has yet to be revealed.[12,13]

Enamines are valuable as enolate equivalents in organic synthesis.[14] Various transformations, including alkylation, acylation, and Michael addition, have been developed. In these processes, the amine moiety is hydrolytically removed during the workup to afford the corresponding carbonyl compounds. In contrast, the current method retains the amine moiety in the molecule as one of the useful functional groups. Thus, this work demonstrates a new aspect of enamine chemistry.

2. Optimization of reaction conditions

Initially, we investigated the reaction between benzaldehyde (**1a**) and *N*-1-cyclohexenylpiperidine (**2a**) (Eq. 1). Aldehyde **1a** (1.0 equiv) was added to a solution of **2a** (1.2 equiv) and

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trichlorosilane (1.5 equiv) in dichloromethane in the absence or presence of a Lewis base (20 mol %) (Table 1). The reaction proceeded without a Lewis base at −40 °C to give expected γ-amino alcohol **3a** in moderate yield with high diastereoselectivity (entry 1). As mentioned later, the major stereoisomer was 1,2-*anti*-2,3-*anti*. Either decreasing or increasing the reaction temperature lowered the chemical yield and/or diastereoselectivity (entries 2–4). The reaction at rt was accompanied by the reduction of **2a** to *N*-cyclohexylpiperidine, which decreased the yield of **3a** (entry 4). Hence, the effect of Lewis base catalysts was investigated at −40 °C (entries 5–9). Although all the Lewis bases examined improved the chemical yield, only DMF and *N*-methyl-2-pyrrolidone (NMP) retained a high diastereoselectivity (entries 6 and 8).

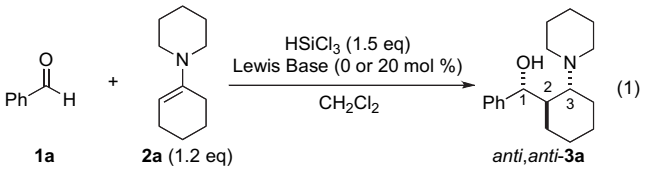


Table 1
Optimization of the reaction conditions

Entry	Lewis Base[a]	Conditions	Yield (%)	dr[b]
1	—	−40 °C, 1 h	35	96:1:1:2
2	—	−78 °C, 3 h	3	95:0:1:4
3	—	0 °C, 1 h	58	96:4:0:0
4	—	rt, 1 h	36	97:3:0:0
5	Ph_3PO	−40 °C, 1 h	67	89:10:1:0
6	DMF	−40 °C, 1 h	56	98:1:trace:1
7	DMPU	−40 °C, 1 h	68	94:5:1:0
8	NMP	−40 °C, 1 h	64	96:1:2:1
9	HMPA	−40 °C, 1 h	80	82:17:1:trace

[a] DMPU: *N*,*N*′-dimethylpropyreneurea, NMP: *N*-methyl-2-pyrrolidone.
[b] Diastereomeric ratio of **3a** (1,2-*anti*-2,3-*anti*:1,2-*syn*-2,3-*anti*:1,2-*syn*-2,3-*syn*:1,2-*anti*-2,3-*syn*). Determined by ^{1}H NMR analysis of the crude products.

3. Assignment of the relative configuration

The major isomer of product **3a** was isolated by column chromatography on silica gel as a crystalline compound. ^{1}H NMR analysis in $CDCl_3$ suggested the presence of intramolecular hydrogen bonding between the hydroxy group and piperidino nitrogen as a broad signal appeared at 9.3 ppm. NOESY analysis showed NOE correlations between H1 and H3 and between $H7_{ax}$ and H1, supporting the 1,2-*anti*-2,3-*anti* configuration depicted in Fig. 2.[15] Moreover, the coupling constants were consistent with this assignment.

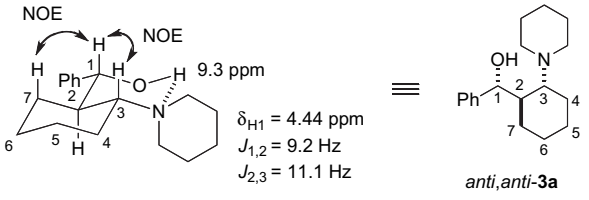
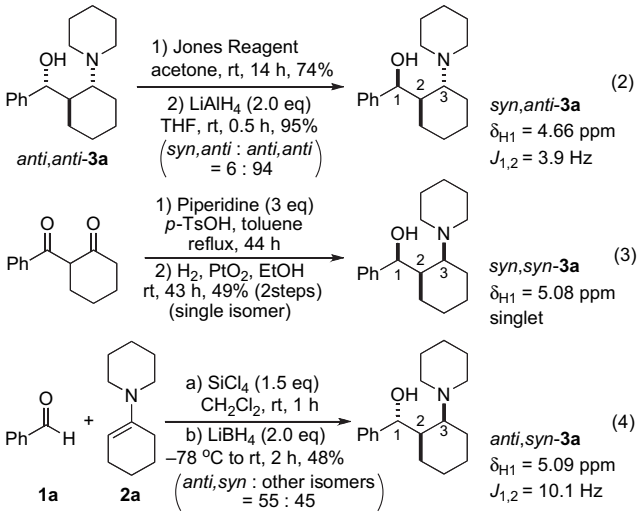


Fig. 2. Relative configuration of the major isomer of **3a**.

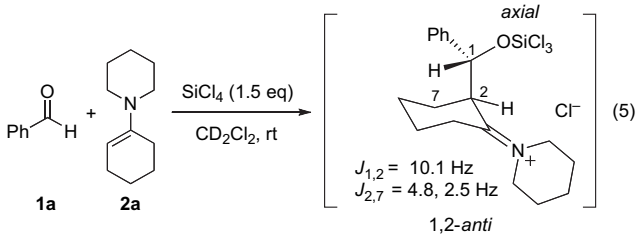
To further confirm the stereochemical outcome of the reaction, the other diastereomers of **3a** were prepared as follows. First *anti*,*anti*-**3a** was oxidized into the corresponding *trans*-ketone by Jones reagent, and was subsequently reduced by $LiAlH_4$ to give a mixture of *anti*,*anti*- and *syn*,*anti*-**3a** (94:6) (Eq. 2). Compound *syn*,*anti*-**3a** could be separated by column chromatography on silica gel. Second *syn*,*syn*-**3a** was prepared by Pt-catalyzed hydrogenation of the β-amino enone prepared from 2-benzoylcyclohexanone and piperidine (Eq. 3). Preparation of the corresponding *p*-methoxylphenyl



derivative using this procedure has been reported.[16] Third *anti*,*syn*-**3a** was prepared by treatment of **1a** and **2a** with $SiCl_4$ followed by $LiBH_4$ (Eq. 4). *anti*,*syn*-**3a**, which was the major product of this transformation, was isolated by column chromatography on silica gel (the stereochemistry of this reaction will be discussed in the next section). The ^{1}H NMR coupling constants between H1 and H2 were reasonable for the assignments. Thus, it was confirmed that the reaction of **1a** and **2a** with trichlorosilane afforded *anti*,*anti*-**3a** with a high diastereoselectivity.

4. Mechanistic insight into the stereochemistry

To provide insight into the formation of assumed iminium ion intermediate **4**, the reaction of benzaldehyde (**1a**) and enamine **2a** was performed using $SiCl_4$ instead of $HSiCl_3$ in CD_2Cl_2 at rt. The reaction was monitored by ^{1}H NMR spectroscopy. The spectra showed the consumption of **2a** and most of **1a** as well as the formation of several species whose ratios gradually changed. After 5 h, the spectrum remained constant, and the reaction mixture was analyzed by ^{1}H–^{1}H COSY analysis. The major component was assigned to the 1,2-*anti* iminium ion (Eq. 5).[17] A large $J_{1,2}$ coupling constant and small $J_{2,7}$ coupling constants suggested that the phenyl(silyloxy)methyl side chain was located in the pseudo *axial* position due to 1,3-allylic strain between the side chain and the methylene protons of the piperidine ring, which disfavors the pseudo *equatorial* orientation.[18]



As shown in Eq. 4, the reduction of this iminium ion with $LiBH_4$ afforded *anti*,*syn*-**3a** as the major isomer. The hydride of $LiBH_4$ likely attacked the iminium carbon from the bottom side (axial attack) to avoid the bulky phenyl(silyloxy)methyl group on the top side.

Based on this observation, it is speculated that the tandem reaction of **1a** and **2a** with $HSiCl_3$ generated a 1,2-*anti* iminium ion intermediate similar to that with $SiCl_4$. The formation of the 1,2-*anti* isomer would be kinetically favored over that of the 1,2-*syn* isomer

because the enamine can attack the $HSiCl_3$-activated aldehyde via the antiperiplanar acyclic transition state shown in Fig. 3. Sterically less congested transition state **A** would afford the 1,2-*anti* iminium ion, whereas transition state **B**, which would lead to the 1,2-*syn* isomer, has steric repulsion between the large trichlorosilyl group coordinated by the Lewis base and the cyclohexane ring of the enamine.[19]

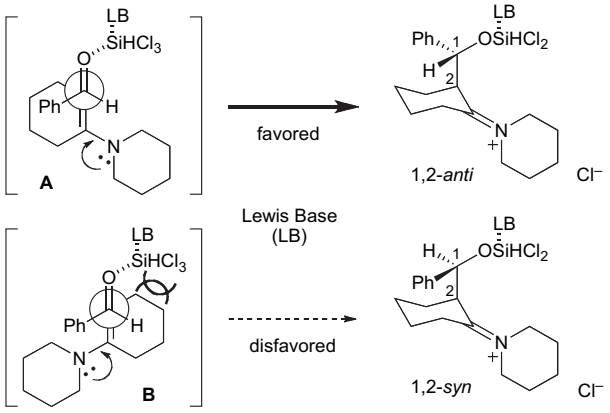


Fig. 3. Assumed transition states for C–C bond formation between **1a** and **2a**.

For the intramolecular reduction of the 1,2-*anti* iminium ion, the hydride could readily transfer from the axial silyloxy group to the iminium carbon to afford 1,2-*anti*-2,3-*anti*-**3a** (Fig. 4, first equation). On the other hand, hydride transfer in the 1,2-*syn* iminium ion would be disfavored due to steric repulsion between the phenyl group and cyclohexane ring (Fig. 4, second equation). Even this unfavorable hydride transfer might occur in the presence of a strong Lewis base. Indeed, employing HMPA gave 1,2-*syn*-2,3-*anti*-**3a** to a larger extent; thus, lowering the diastereoselectivity, but increasing the yield (see Table 1, entry 9). However, the minor 1,2-*syn* iminium ion barely reacted upon employing a weak Lewis base, such as DMF or NMP. This may explain the moderate yield, but high selectivity.

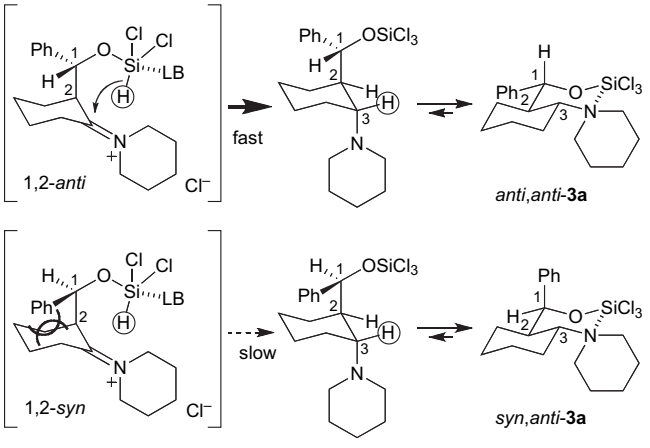
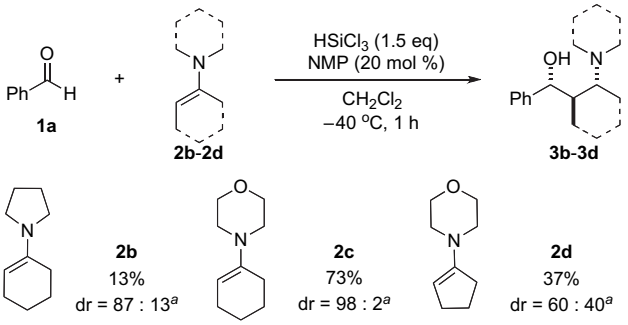


Fig. 4. Assumed transition states for intramolecular reduction of the iminium ions derived from **1a** with **2a**.

5. Substrate scope

Using NMP (20 mol %) as a Lewis base catalyst, benzaldehyde (**1a**) was reacted with other cyclic enamines **2b**–**d** at −40 °C for 1 h for comparison (Scheme 1). *N*-1-Cyclohexenylmorpholine (**2c**) gave a slightly higher yield and diastereoselectivity than **2a**, whereas enamines **2b** and **2d** provided inferior results.[20]

Next, the reaction of enamine **2c** with various aldehydes was investigated under the same conditions (Table 2).[21] Aldehydes

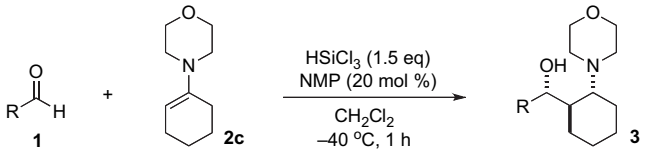


[a] Diastereomeric ratio of **3** (1,2-*anti*-2,3-*anti* : Σ other isomers). Estimated by ^{1}H-NMR analysis of the crude products.

Scheme 1. Reaction of **1a** and cyclic enamines **2b**–**d**.

1b–**e**, which possessed a variety of aromatic rings, respectively, afforded expected products **3e**–**h** in good yields with high selectivities (entries 2–5). However, hydrocinnamaldehyde (**1f**), a non-conjugated aldehyde did not produce the desired product (entry 6). Heteroaromatic aldehydes, 2-furfural (**1g**), and 2-pyridinecarboxaldehyde (**1h**) provided good yields albeit with inferior selectivities (entries 7 and 8). Hence, the stereochemical course may be influenced by coordination of the heteroatom to the silicon atom of reaction intermediates.

Table 2
Reaction of **2c** with various aldehydes



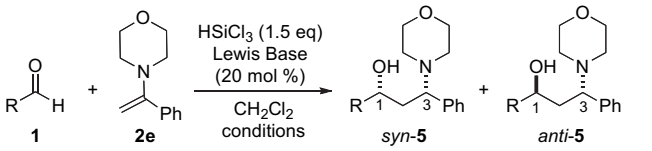
Entry	R in aldehyde (**1**)	**3**	Yield (%)	dr[a]
1	Ph (**1a**)	**3c**	73	98:2
2	*p*-$MeOC_6H_4$ (**1b**)	**3e**	72	99:1
3	*p*-$NO_2C_6H_4$ (**1c**)	**3f**	55	99:1
4	1-Naphthyl (**1d**)	**3g**	61	97:3
5	2-Naphthyl (**1e**)	**3h**	52	98:2
6	$PhCH_2CH_2$ (**1f**)	**3i**	0	—
7	2-Furyl (**1g**)	**3j**	69	90:10
8	2-Pyridyl (**1h**)	**3k**	70	15:85

[a] Diastereomeric ratio of **3** (1,2-*anti*-2,3-*anti*:Σ other isomers). Estimated by ^{1}H NMR analysis of the crude products.

The reaction of acetophenone-derived enamine **2e** with benzaldehyde (**1a**) showed a different tendency from that of cyclic enamine **2a** or **2c**. The use of NMP at −40 °C produced not desired product **5a**, but a complicated mixture, including chalcone and the dehydration product of **5a** (allylic amine) (Table 3, entry 1). On the other hand, employing Ph_3PO instead of NMP gave **5a** in moderate yield with good 1,3-*syn* selectivity (entry 2). In this case, bulkiness of the Lewis base might effectively suppress the side reactions. Lowering the reaction temperature to −78 °C improved the chemical yield (entry 3). Notably, when the aldehyde component was changed from benzaldehyde to 2-pyridinecarboxaldehyde (**1h**), 1,3-*anti* diastereoselectivity was observed. In this case, using Ph_3PO at −40 °C (entry 5) provided a better result than that of NMP at −40 °C or Ph_3PO at −78 °C (entries 4 and 6).

As depicted in Fig. 5, the coordination of the pyridine nitrogen of aldehyde **1h** to the silicon atom explains the reversal in the diastereoselectivity. In both $TS_{\mathbf{1a}-\mathbf{2e}}$ and $TS_{\mathbf{1h}-\mathbf{2e}}$, the morpholine moiety was located in the pseudo *equatorial* position to minimize the allylic strains. However, in $TS_{\mathbf{1a}-\mathbf{2e}}$ the phenyl group of the

Table 3
Reaction of **2e** with **1a** or **1h**



Entry	1	Lewis base	Conditions	5	Yield (%)	*syn*/*anti*[a]
1	**1a**	NMP	−40 °C, 1 h	**5a**	0	—
2	**1a**	Ph_3PO	−40 °C, 1 h	**5a**	37	90:10
3	**1a**	Ph_3PO	−78 °C, 5 h	**5a**	61	91:9
4	**1h**	NMP	−40 °C, 1 h	**5b**	33	10:90
5	**1h**	Ph_3PO	−40 °C, 1 h	**5b**	52	3:97
6	**1h**	Ph_3PO	−78 °C, 5 h	**5b**	18	5:95

[a] Diastereomeric ratio of **5**.

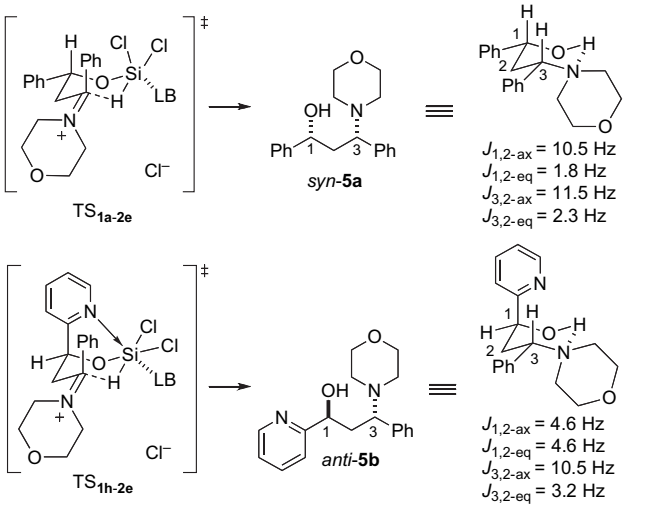
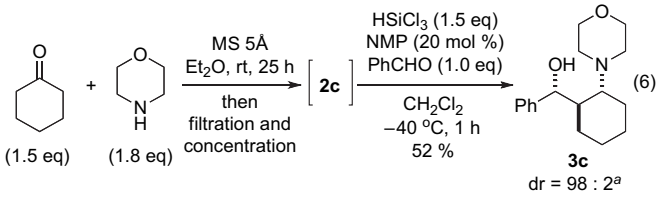


Fig. 5. Assumed transitions states for the reaction of enamine **2e** with **1a** or **1h**.

benzaldehyde was preferably oriented in the pseudo *equatorial* position to afford 1,3-*syn* product **5a**. On the other hand, in $TS_{\mathbf{1h}-\mathbf{2e}}$ coordination to the silicon atom forced the pyridine ring to be located in the pseudo *axial* position, leading to 1,3-*anti* product **5b**.

6. Use of enamine 2c without isolation

To extend the synthetic efficiency, we investigated the use of enamine **2c** without purification. Cyclohexanone and morpholine were mixed in diethyl ether in the presence of molecular sieves 5 Å[22] (Eq. 6). After 25 h, the mixture was filtered through Celite and concentrated under vacuum. The residue was diluted with dry dichloromethane, and the solution was cooled to −40 °C. NMP, trichlorosilane, and benzaldehyde were successively added to the solution, and the mixture was stirred for 1 h. After the usual workup, product **3c** was obtained in reasonable yield with high diastereoselectivity. We expect that this procedure will be applicable for enamines that are difficult to isolate.



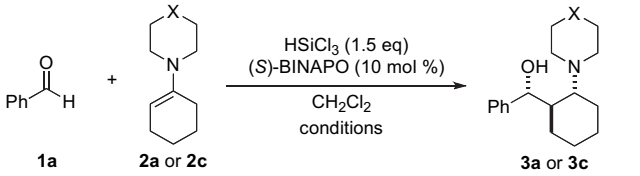
[a] Diastereomeric ratio (1,2-*anti*-2,3-*anti* : Σ other isomers). Estimated by ^{1}H-NMR analysis of the crude products.

7. Enantioselective catalysis

Finally, we investigated enantioselective catalysis of the reaction using chiral Lewis base catalysts (Table 4). The reaction of benzaldehyde (**1a**) and enamine **2a** at −40 °C in the presence of BINAPO[23] (Fig. 6) gave desired product **3a** in good yield (76%) (entry 1). Although the diastereoselectivity was high, the enantioselectivity was very low. Meanwhile, when the same reaction was carried out at −78 °C, a moderate enantioselectivity (40% ee) was observed, but the yield decreased to 43% (entry 2). When the reaction was conducted at −78 °C for 1 h then at −40 °C for 1 h, the yield was largely improved, but the enantiomeric excess decreased to 9% (entry 3). Chiral Lewis bases other than BINAPO (Fig. 6) were also tested at −78 °C, but they provided inferior results (entries 4–7). The reaction of morpholine-derived enamine **2c** with (*S*)-BINAPO resulted in a low enantioselectivity even at −78 °C (entry 7).

These results can be rationalized by assuming that the enantioselectivity of the first C–C bond formation was very low, and that kinetic resolution of the iminium ion intermediate occurred in the subsequent intramolecular reduction process at low temperature (Fig. 7).[24] For the reaction of enamine **2a**, intramolecular reduction was relatively slow and hence, effectively catalyzed by BINAPO to show a moderate enantioselectivity at −78 °C (Table 4, entry 2). The yield was low because most of the other enantiomer of the *anti*

Table 4
Investigation of enantioselective catalysis



Entry	X in **2**	Conditions	**3**	Yield (%)	dr[a]	%ee[b]
1	CH_2 (**2a**)	−40 °C, 1 h	**3a**	76	94:6	8
2	CH_2 (**2a**)	−78 °C, 1 h	**3a**	43	97:3	40
3	CH_2 (**2a**)	−78 °C, 1h; −40 °C, 1 h	**3a**	88	94:6	9
4[c]	CH_2 (**2a**)	−78 °C, 1 h	**3a**	44	98:2	33
5[d]	CH_2 (**2a**)	−78 °C, 1 h	**3a**	44	97:3	8
6[e]	CH_2 (**2a**)	−78 °C, 1 h	**3a**	25	93:7	15[g]
7[f]	CH_2 (**2a**)	−78 °C, 1 h	**3a**	18	86:14	12
8	O (**2c**)	−78 °C, 1 h	**3c**	61	96:4	5

[a] Diastereomeric ratio of **3** (1,2-*anti*-2,3-*anti*:Σ other isomers). Estimated by ^{1}H NMR analysis of the crude products.
[b] The enantiomeric excess of the major 1,2-*anti*-2,3-*anti* diastereomer.
[c] (*S*)-SEGPHOSO (Fig. 6) was used instead of (*S*)-BINAPO.
[d] (*R*,*R*)-DIOPO (Fig. 6) was used instead of (*S*)-BINAPO.
[e] (*R*)-BIQNO (Fig. 6) was used instead of (*S*)-BINAPO.
[f] (*S*)-BQNO (Fig. 6) was used instead of (*S*)-BINAPO.
[g] The major enantiomer was opposite to that obtained with (*S*)-BINAPO.

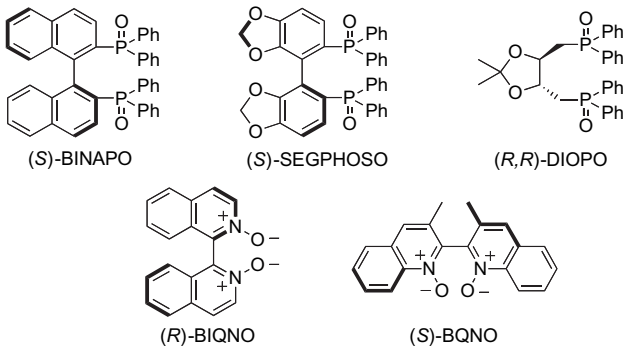


Fig. 6. Chiral Lewis base catalysts used in this study.

iminium intermediate remained intact. On the other hand, the *anti* iminium ion intermediate derived from enamine **2c** was sufficiently reactive even at −78 °C (Table 4, entry 8), presumably due to the inductive effect of the oxygen atom in the morpholine ring, and both enantiomers of the *anti* iminium ion reacted to give an almost racemic product. Thus, further investigations are necessary to improve the enantioselectivity.

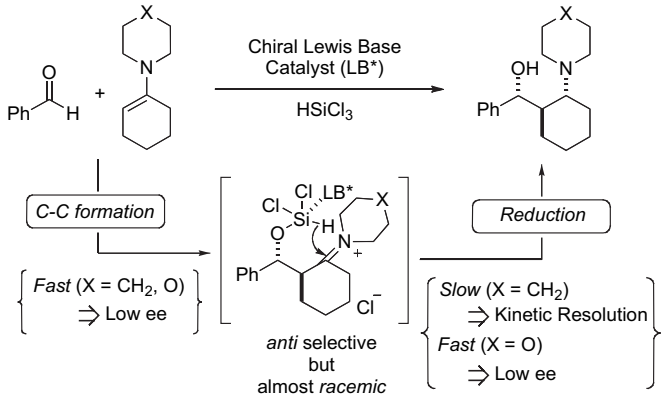


Fig. 7. Mechanistic insight into the enantioselective catalysis.

8. Conclusion

We have demonstrated that tandem C–C bond formation/reduction of aldehydes, enamines, and trichlorosilane in the presence of Lewis base catalysts affords γ-amino alcohols with a high diastereoselectivity. This method offers the first, concise synthetic method of γ-amino alcohols from aldehydes and enamines. Further investigations to improve the yield and enantioselectivity as well as to apply this method in the synthesis of useful molecules[6–8] are currently underway.

9. Experimental section

9.1. General

Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with JEOL JNM-ECX400 spectrometer otherwise noted. Tetramethylsilane (TMS) (δ=0 ppm) and $CDCl_3$ (δ=77.0 ppm) were used for internal standards for ^{1}H and ^{13}C NMR analyses, respectively. Infrared spectra were recorded on JEOL JIR-6500W. Mass spectra were measured with JEOL JMS-DX303HF mass spectrometer. Optical rotations were recorded on JASCO P-1010 polarimeter. High pressure liquid chromatography (HPLC) was performed with JASCO P-980 and UV-1575. Thin-layer chromatography (TLC) analysis was carried out using Merck silica gel plates. Visualization was accomplished with UV light, phosphomolybdic acid, and/or anisaldehyde. Column chromatography was performed using Kanto Chemical Silica Gel 60N (spherical, neutral. 63–210 μm). All reactions were performed under argon atmosphere using oven- and heat gun-dried glassware equipped with a rubber septum and a magnetic stirring bar.

Dichloromethane (dehydrated) was purchased from Kanto Chemical and stored over 4 Å MS prior to use. All other solvents were purified based on standard procedures. Trichlorosilane (>98%) and tetrachlorosilane were purchased from Tokyo Kasei Kogyo (TCI) and used without further purification. A dichloromethane solution of trichlorosilane (ca. 3 M) was prepared and stocked in a screw-top test tube with a Teflon packing. (*S*)-BINAPO was prepared by oxidation of (*S*)-BINAP with hydrogen peroxide in acetone.[23c] Enamines were prepared according to the literatures.[14c,25] All other chemicals were purified based on standard procedures.

9.2. General procedure for the synthesis of γ-amino alcohols from aldehydes, enamines, and trichlorosilane using NMP

Trichlorosilane (0.75 mmol, ca. 3 M CH_2Cl_2 solution, 1.5 equiv) was added to a solution of enamine **2** (0.6 mmol, 1.2 equiv) and NMP (20 mol %) in dichloromethane (2 mL) at −40 °C. Then aldehyde **1** (0.5 mmol, 1.0 equiv) was introduced to the mixture. After stirring for 1 h, the reaction was quenched with satd aqueous $NaHCO_3$ (5 mL). The mixture was diluted with AcOEt (5 mL) and stirred at rt for 1 h to precipitate the silicon byproducts. After filtration through a Celite pad with AcOEt, the filtrate was extracted with AcOEt (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (silica gel 15 g, hexane/AcOEt=2/1–AcOEt/EtOH=5/1) to give corresponding γ-amino alcohol **3** or **5**. The diastereomeric ratio of **3a** was determined by ^{1}H NMR analysis of the crude product and compared to the spectral data of the diastereomers (see Section 9.3–9.5). The diastereomeric ratios of **3b**–**k** were tentatively estimated by analogy.

*9.2.1. Phenyl[2-(piperidin-1-yl)cyclohexyl]methanol (**3a**). anti,anti-*Isomer: colorless solid; TLC: R_f 0.31 (AcOEt/EtOH=5/1, stained blue with phosphomolybdic acid/EtOH); mp 121–123 °C; IR (KBr, cm^{-1}) 2914, 1444, 1375, 1333, 1201, 1134, 1061, 1032, 766; ^{1}H NMR ($CDCl_3$): δ 0.79 (dddd, 1H, *J*=3.7, 11.9, 13.3, 13.3 Hz), 0.95 (ddddd, 1H, *J*=3.2, 3.2, 12.8, 12.8, 13.3 Hz), 1.07–1.33 (m, 4H), 1.47–1.83 (m, 8H), 1.86–1.95 (m, 1H), 2.21 (br t, 1H, *J*=10.4 Hz), 2.56 (ddd, 1H, *J*=3.6, 11.1, 11.1 Hz), 2.66 (br t, 1H, *J*=9.8 Hz), 2.82 (br d, 1H, *J*=9.8 Hz), 3.10 (br d, 1H, *J*=10.4 Hz), 4.44 (d, 1H, *J*=9.2 Hz), 7.21–7.26 (m, 1H), 7.28–7.37 (m, 4H), 9.27 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.1, 24.5, 25.4, 25.6, 25.8 (br), 26.8 (br), 29.3, 43.0, 46.4 (br), 53.3 (br), 70.7, 82.3, 127.1, 127.3, 128.0, 143.8; HRMS (FAB): calcd for $C_{18}H_{28}NO$ ($M+H^+$) 274.2171, found 274.2169.

*9.2.2. Phenyl[2-(pyrrolidin-1-yl)cyclohexyl]methanol (**3b**). anti,anti-*Isomer: colorless solid; TLC: R_f 0.26 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); mp 101–103 °C; IR (KBr, cm^{-1}) 2927, 2854, 1450, 1331, 1147, 1061, 1020, 758, 698; ^{1}H NMR ($CDCl_3$): δ 0.80 (dddd, 1H, *J*=3.7, 11.7, 12.4, 13.3 Hz), 0.98 (ddddd, 1H, *J*=3.7, 3.7, 12.8, 13.3, 13.3 Hz), 1.10–1.22 (m, 2H), 1.27 (dddd, 1H, *J*=3.2, 11.3, 12.1, 12.8 Hz), 1.53 (apparent d, 1H, *J*=13.3 Hz), 1.65 (dddd, 1H, *J*=3.7, 9.2, 11.0, 13.3 Hz), 1.71–1.82 (m, 5H), 1.86 (apparent d, 1H, *J*=12.4 Hz), 2.75 (br s, 2H), 2.87 (ddd, 1H, *J*=3.7, 11.0, 11.0 Hz), 2.87 (br s, 2H), 4.46 (d, 1H, *J*=9.2 Hz), 7.21–7.26 (m, 1H), 7.28–7.35 (m, 4H), 9.22 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.2, 23.5 (br), 25.5, 29.4, 44.9, 47.2 (br), 64.2, 82.6, 127.1, 127.3, 128.0, 143.9; HRMS (FAB): calcd for $C_{17}H_{26}NO$ ($M+Na^+$) 282.1834, found 282.1837. *Other isomers*: ^{1}H NMR ($CDCl_3$): δ 4.69 (d, *J*=4.1 Hz), 5.29 (s) (detectable carbinol protons).

*9.2.3. [2-(Morpholin-4-yl)cyclohexyl]phenylmethanol (**3c**). anti,anti-*Isomer: colorless solid; TLC: R_f 0.26 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); mp 124–126 °C; IR (KBr, cm^{-1}) 2954, 2854, 1452, 1446, 1117, 999, 760, 700; ^{1}H NMR ($CDCl_3$): δ 0.80 (dddd, 1H, *J*=3.2, 11.9, 13.2, 13.2 Hz), 0.97 (ddddd, 1H, *J*=3.2, 3.2, 12.8, 13.2, 13.2 Hz), 1.09–1.34 (m, 3H), 1.53 (apparent d, 1H, *J*=13.2 Hz), 1.68–1.84 (m, 2H), 1.90–1.98 (m, 1H), 2.51–2.68 (m, 3H), 2.96 (br s, 2H), 3.67 (br s, 2H), 3.89 (br s, 2H), 4.48 (d, 1H, *J*=9.2 Hz), 7.22–7.29 (m, 1H), 7.30–7.35 (m, 4H), 8.66 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.1, 25.2, 25.4, 29.2, 43.0, 45.7 (br), 51.7 (br), 66.9 (br), 67.3 (br), 70.3, 82.2, 127.19, 127.24, 128.0, 143.2; HRMS (FAB): calcd for $C_{17}H_{26}NO_2$ ($M+H^+$) 276.1964, found 276.1961. *Other isomers*: ^{1}H

NMR ($CDCl_3$): δ 4.71 (d, J=3.6 Hz), 5.09 (d, J=2.3 Hz) (detectable carbinol protons).

*9.2.4. [2-(Morpholin-4-yl)cyclopentyl]phenylmethanol (**3d**). anti,anti*-Isomer: colorless oil; TLC: R_f 0.14 (AcOEt/EtOH=5/1, stained blue with phosphomolybdic acid/EtOH); IR (NaCl, cm^{-1}) 2956, 2850, 1452, 1265, 1119, 1014, 874, 762, 702; ^1H NMR ($CDCl_3$): δ 1.10–1.33 (m, 2H), 1.48–1.74 (m, 4H), 2.07 (dddd, 1H, J=7.8, 9.6, 10.1, 11.0 Hz), 2.58–2.68 (m, 2H), 2.77–2.88 (m, 2H), 3.04 (ddd, 1H, J=7.8, 10.1, 10.1 Hz), 3.71–3.83 (m, 4H), 4.54 (d, 1H, J=9.6 Hz), 6.92 (br s, 1H), 7.22–7.26 (m, 1H), 7.29–7.38 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 21.0, 21.2, 26.0, 45.8, 49.4 (br), 67.3, 73.2, 81.4, 126.5, 127.4, 128.2, 144.0; HRMS (FAB): calcd for $C_{16}H_{24}NO_2$ ($M+Na^+$) 284.1626, found 284.1647. *Other isomers*: ^1H NMR ($CDCl_3$): δ 4.94 (d, J=5.0 Hz) (detectable carbinol proton).

*9.2.5. (4-Methoxyphenyl)[2-(morpholin-4-yl)cyclohexyl]methanol (**3e**). anti,anti*-Isomer: colorless oil; TLC: R_f 0.35 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); IR (film on NaCl, cm^{-1}) 2929, 2852, 1514, 1452, 1244, 1117, 1036, 1001, 860, 833; ^1H NMR ($CDCl_3$): δ 0.77 (dddd, 1H, J=3.7, 11.9, 13.3, 13.3 Hz), 0.97 (ddddd, 1H, J=3.2, 3.2, 12.8, 13.3, 13.3 Hz), 1.07–1.32 (m, 3H), 1.54 (apparent d, 1H, J=13.3 Hz), 1.70 (dddd, 1H, J=3.9, 9.2, 11.5, 13.3 Hz), 1.80 (apparent d, 1H, J=12.8 Hz), 1.93 (apparent d, 1H, J=12.4 Hz), 2.52–2.68 (m, 3H), 2.95 (br s, 2H), 3.67 (br s, 2H), 3.79 (s, 3H), 3.87 (br s, 2H), 4.44 (d, 1H, J=9.2 Hz), 6.86 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz) 8.58 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.1, 25.3, 25.5, 29.2, 43.1, 45.7 (br), 51.8 (br), 55.1, 66.9 (br), 67.4 (br), 70.3, 81.7, 113.3, 128.2, 135.6, 158.7; HRMS (FAB): calcd for $C_{18}H_{27}NO_3Na$ ($M+Na^+$) 328.1889, found 328.1883. *Other isomers*: ^1H NMR ($CDCl_3$): δ 4.66 (s) (detectable carbinol proton).

*9.2.6. [2-(Morpholin-4-yl)cyclohexyl](4-nitrophenyl)methanol (**3f**). anti,anti*-Isomer: colorless solid; TLC: R_f 0.19 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); mp 116–118 °C; IR (KBr, cm^{-1}) 3078, 2931, 2850, 1605, 1514, 1454, 1350, 1130, 1113, 1005, 856; ^1H NMR ($CDCl_3$): δ 0.86 (dddd, 1H, J=3.7, 11.4, 12.8, 13.3 Hz), 0.97 (ddddd, 1H, J=3.2, 3.2, 12.8, 12.8, 13.3 Hz), 1.08–1.35 (m, 3H), 1.56 (apparent d, 1H, J=12.8 Hz), 1.68 (dddd, 1H, J=3.7, 9.2, 11.0, 12.8 Hz), 1.82 (apparent d, 1H, J=12.8 Hz), 1.96 (apparent d, 1H, J=12.8 Hz), 2.56–2.71 (m, 3H), 2.84–3.07 (m, 2H), 3.67 (br s, 2H), 3.93 (br s, 2H), 4.61 (d, 1H, J=9.2 Hz), 7.50 (d, 2H, J=8.7 Hz), 8.19 (d, 2H, J=8.7 Hz), 9.02 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.2, 25.1, 25.3, 29.0, 43.0, 45.8 (br), 51.8 (br), 66.8 (br), 67.5 (br), 70.4, 81.4, 123.4, 128.2, 147.3, 150.7; Anal. calcd for $C_{17}H_{24}N_2O_4\cdot 0.5H_2O$ C, 61.99; H, 7.65; N, 8.50; found C, 62.07; H, 7.79; N, 8.32. No other isomers could be detected.

*9.2.7. [2-(Morpholin-4-yl)cyclohexyl](naphthalene-1-yl)methanol (**3g**). anti,anti*-Isomer: colorless oil; TLC: R_f 0.30 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); IR (film on NaCl, cm^{-1}) 2927, 2852, 1452, 1119, 1061, 864, 798, 779, 735; ^1H NMR ($CDCl_3$): δ 0.78–1.04 (m, 3H), 1.16 (dddd, 1H, J=3.2, 3.2, 12.8, 12.8 Hz), 1.32 (dddd, 1H, J=3.7, 12.4, 12.8, 12.8 Hz) 1.44 (apparent d, 1H, J=12.4 Hz), 1.79 (apparent d, 1H, J=12.8 Hz), 1.98 (apparent d, 1H, J=12.4 Hz), 2.06–2.17 (m, 1H), 2.60–2.76 (m, 3H), 2.99–3.09 (m, 2H), 3.73 (br s, 2H), 3.95 (br s, 2H), 5.30 (d, 1H, J=9.2 Hz), 7.42–7.51 (m, 3H), 7.56 (d, 1H, J=6.8 Hz), 7.77 (d, 1H, J=7.8 Hz), 7.82–7.88 (m, 1H), 8.39 (d, 1H, J=7.8 Hz), 8.69 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.2, 25.3, 25.4, 29.4, 43.3, 45.9 (br), 51.9 (br), 66.9 (br), 67.5 (br), 70.8, 79.1, 124.2, 125.2, 125.4, 125.5, 127.7, 128.7, 131.6, 133.8, 139.0 (one aromatic carbon is overlapped); HRMS (FAB): calcd for $C_{21}H_{27}NO_2Na$ ($M+Na^+$) 348.1934, found 348.1924. *Other isomers*: ^1H NMR ($CDCl_3$): δ 4.66 (d, J=9.2 Hz) (detectable carbinol proton).

*9.2.8. [2-(Morpholin-4-yl)cyclohexyl](naphthalene-2-yl)methanol (**3h**). anti,anti*-Isomer: colorless oil; TLC: R_f 0.29 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); IR (film on NaCl, cm^{-1}) 3055, 2929, 2852, 1452, 1119, 1061, 1003, 860, 823, 746; ^1H NMR ($CDCl_3$): δ 0.79–1.01 (m, 2H), 1.09–1.22 (m, 2H), 1.28 (dddd, 1H, J=3.2, 12.4, 12.4, 12.4 Hz), 1.49 (apparent d, 1H, J=12.8 Hz), 1.74–1.88 (m, 2H), 1.94 (apparent d, 1H, J=12.4 Hz), 2.56–2.71 (m, 3H), 2.98 (dd, 2H, J=2.3, 11.4 Hz), 3.71 (br s, 2H), 3.91 (br s, 2H), 4.67 (d, 1H, J=9.2 Hz), 7.41–7.48 (m, 2H), 7.52 (dd, 1H, J=1.4, 8.2 Hz), 7.73 (s, 1H), 7.78–7.85 (m, 3H), 8.80 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.1, 25.2, 25.4, 29.2, 42.9, 45.7 (br), 51.8 (br), 66.9 (br), 67.4 (br), 70.4, 82.3, 125.1, 125.4, 125.7, 126.1, 127.5, 127.8, 132.9, 133.0, 140.6 (one aromatic carbon is overlapped); HRMS (FAB): calcd for $C_{21}H_{28}NO_2$ ($M+H^+$) 326.2120, found 326.2111. *Other isomers*: ^1H NMR ($CDCl_3$): δ 4.89 (d, J=3.7 Hz), 5.26 (s) (detectable carbinol protons).

*9.2.9. (Furan-1-yl)[2-(morpholin-4-yl)cyclohexyl]methanol (**3j**). anti,anti*-Isomer: colorless solid; TLC: R_f 0.44 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); mp 110–112 °C; IR (KBr, cm^{-1}) 2931, 2850, 1450, 1151, 1117, 1059, 1034, 1005, 858, 733; ^1H NMR ($CDCl_3$): δ 0.81 (dddd, 1H, J=3.7, 12.4, 12.4, 12.6 Hz), 1.02–1.35 (m, 4H), 1.59 (apparent d, 1H, J=11.5 Hz), 1.78–1.86 (m, 1H), 1.93 (apparent d, 1H, J=12.8 Hz), 2.01 (dddd, 1H, J=4.1, 9.6, 11.0, 11.0 Hz), 2.52 (ddd, 1H, J=3.2, 11.0, 11.4 Hz), 2.54–2.63 (m, 2H), 2.93 (apparent d, 2H, J=9.6 Hz), 3.66 (br s, 2H), 3.85 (br s, 2H), 4.56 (d, 1H, J=9.6 Hz), 6.22 (d, 1H, J=2.8 Hz), 6.28–6.32 (m, 1H), 7.38 (d, 1H, J=1.4 Hz), 8.62 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.1, 25.1, 25.4, 28.8, 40.7, 45.8 (br), 51.7 (br), 67.11 (br), 67.20 (br), 70.1, 75.0, 107.1, 109.6, 141.8, 155.2; Anal. calcd for $C_{15}H_{23}NO_3$ C, 67.90; H, 8.74; N, 5.28; found C, 67.70; H, 8.76; N, 5.16. *Other isomers*: ^1H NMR ($CDCl_3$): δ 4.63 (d, J=3.6 Hz), 5.10 (d, J=2.3 Hz) (detectable carbinol protons).

*9.2.10. [2-(Morpholin-4-yl)cyclohexyl](pyridin-2-yl)methanol (**3k**). anti,anti*-Isomer: colorless oil; TLC: R_f 0.30 (AcOEt/EtOH=5/1, stained blue with phosphomolybdic acid/EtOH); IR (NaCl, cm^{-1}) 2927, 2852, 1591, 1452, 1433, 1117, 1068, 1003, 860, 785; ^1H NMR ($CDCl_3$):δ 0.85–0.98 (m, 1H), 1.02 (ddddd, 1H, J=3.2, 3.2, 12.8, 12.8, 12.8 Hz), 1.10–1.22 (m, 2H), 1.29 (dddd, 1H, J=3.7, 12.4, 12.4, 12.4 Hz), 1.55 (apparent d, 1H, J=12.8 Hz), 1.80 (apparent dq, 1H, J=12.8, 2.8 Hz), 1.90–2.02 (m, 2H), 2.56–2.65 (m, 2H), 2.92–3.00 (m, 2H), 3.77 (br s, 4H), 4.66 (d, 1H, J=8.7 Hz), 7.17 (ddd, 1H, J=0.9, 4.8, 7.3 Hz), 7.37 (br d, 1H, J=7.8 Hz), 7.67 (ddd, 1H, J=1.8, 7.3, 7.8 Hz), 8.50 (br s, 1H), 8.58 (br d, 1H, J=4.8 Hz); ^{13}C NMR ($CDCl_3$): δ 24.2, 25.3, 25.5, 28.8, 42.4, 67.3 (br), 70.1, 82.4, 122.2, 122.4, 136.4, 148.9, 162.0; HRMS (FAB): calcd for $C_{16}H_{24}N_2O_2Na$ ($M+Na^+$) 299.1735, found 299.1726. *Other isomers*: ^1H NMR ($CDCl_3$): δ 4.76 (s), 4.97 (d, J=4.3 Hz), 5.12 (s) (detectable carbinol protons).

*9.2.11. 3-(Morpholin-4-yl)-1,3-diphenylpropan-1-ol (**5a**).* 1,3-*syn*-Isomer: colorless oil; TLC: R_f 0.16 (hexane/AcOEt=1/1, stained blue with phosphomolybdic acid/EtOH); IR (film on NaCl, cm^{-1}) 2920, 2850, 1452, 1265, 1117, 1063, 1024, 760, 702; ^1H NMR ($CDCl_3$): δ 1.82 (ddd, 1H, J=1.8, 2.3, 14.8 Hz), 2.37 (br s, 2H), 2.46 (ddd, 1H, J=10.5, 11.5, 14.8 Hz), 2.67–2.78 (m, 2H), 3.66–3.80 (m, 4H), 4.01 (dd, 1H, J=2.3, 11.5 Hz), 5.02 (dd, 1H, J=1.8, 10.5 Hz), 6.86 (br s, 1H), 7.13 (d, 2H, J=6.4 Hz), 7.22–7.28 (m, 1H), 7.29–7.37 (m, 5H), 7.38–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 38.6, 49.5 (br), 67.1, 70.1, 75.43, 75.46, 125.4, 127.1, 127.9, 128.1, 128.3, 128.8, 135.4, 144.8; HRMS (FAB): calcd for $C_{19}H_{24}NO_2$ ($M+H^+$) 298.1807, found 298.1833. 1,3-*anti*-Isomer: ^1H NMR ($CDCl_3$): δ 5.08 (dd, 1H, J=4.6, 4.6 Hz) (the carbinol proton).

*9.2.12. 3-(Morpholin-4-yl)-3-phenyl-1-(pyridin-2-yl)propan-1-ol (**5b**).* 1,3-*anti*-Isomer: colorless oil; TLC: R_f 0.43 (AcOEt/EtOH=5/1, stained blue with phosphomolybdic acid/EtOH); IR (film on NaCl, cm^{-1}) 2956, 2852, 1591, 1452, 1117, 1070, 768, 704; ^1H NMR ($CDCl_3$): δ 2.22 (ddd, 1H, J=3.2, 4.6, 14.4 Hz), 2.33 (br s, 2H), 2.57–2.69 (m,

2H), 2.74 (ddd, 1H, *J*=4.6, 10.5, 14.4 Hz), 3.59 (dd, 1H, *J*=3.2, 10.5 Hz), 3.68–3.80 (m, 4H), 5.11 (dd, 1H, *J*=4.6, 4.6 Hz), 6.67 (br s, 1H), 7.09–7.19 (m, 3H), 7.26–7.35 (m, 3H), 7.55–7.60 (m, 1H), 7.70 (ddd, 1H, *J*=1.8, 7.6, 7.6 Hz), 8.52 (dd, 1H, *J*=0.9, 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ 35.4, 49.8 (br), 66.33, 66.36, 67.2, 73.03, 73.12, 120.2, 121.8, 127.7, 128.1, 128.7, 136.2, 136.4, 148.9, 163.7; HRMS (FAB): calcd for $C_{18}H_{22}N_2O_2Na$ (M+Na$^+$) 321.1579, found 321.1584. 1,3-*syn*-Isomer: ^{1}H NMR ($CDCl_3$): δ 5.02 (dd, 1H, *J*=2.1, 10.3 Hz) (the carbinol proton).

9.3. Preparation of *syn*,*anti*-3a

Jones reagent (0.16 mL of 1.23 M solution, 0.19 mmol) [prepared from CrO_3 (1.41 g), water (10 mL), and concd H_2SO_4 (1.2 mL)] was added to a solution of *anti*,*anti*-**3a** (42.5 mg, 0.16 mmol, 1.0 equiv) in acetone (1.6 mL) at rt. After being stirred for 14 h, the solution was evaporated. The resulting residue was diluted with water (0.8 mL). After cooling at 0 °C, 15% aqueous NaOH (0.22 mL) was added to the solution, and extracted by dichloromethane (4×5 mL). The combined organic layers were washed by water (1×5 mL) and brine (1×5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (silica gel 15 g, hexane/AcOEt=3/1 to 1/1) to give the corresponding 1,2-*trans*-ketone (31.6 mg, 74%). Then, $LiAlH_4$ (3.1 mg, 0.093 mmol) was added to a solution of the 1,2-*trans*-ketone (12.6 mg, 0.046 mmol) in THF (0.38 mL) under an argon atmosphere at rt. After being stirred for 0.5 h, the reaction was quenched by adding water (3.4 μL), aqueous NaOH (6M, 3.4 μL), and water (10.2 μL). The mixture was stirred for 2 h and filtered through a Celite pad with dichloromethane. The filtrate was evaporated to give **3a** (12.1 mg, 95%, *anti*,*anti*/*syn*,*anti*=94/6).

*9.3.1. Phenyl[2-(piperidin-1-yl)cyclohexyl]methanol (**3a**). syn,anti*-Isomer: colorless solid; TLC: R_f 0.47 (AcOEt/EtOH=5/1, stained blue with phosphomolybdic acid/EtOH); mp 121–123 °C; IR (KBr, cm^{-1}) 2912, 1446, 1375, 1333, 1201, 1134, 1061, 1032, 787, 758; ^{1}H NMR ($CDCl_3$): δ 0.69 (dddd, 1H, *J*=3.7, 11.9, 12.8, 13.3 Hz), 0.83 (ddddd, 1H, *J*=3.2, 3.2, 13.0, 13.0, 13.3 Hz), 1.08–1.31 (m, 4H), 1.49–1.82 (m, 9H), 2.12–2.30 (m, 2H), 2.42–2.84 (m, 2H), 3.00–3.19 (m, 1H), 4.66 (d, 1H, *J*=3.9 Hz), 7.21–7.27 (m, 2H), 7.29–7.36 (m, 3H), 8.43 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.7, 24.7, 24.8 (br), 24.9, 26.4, 26.9 (br), 29.9, 42.5, 46.8 (br), 53.3 (br), 64.6, 79.7, 126.6, 127.4, 127.5, 142.9; HRMS (FAB): calcd for $C_{18}H_{28}NO$ (M+H$^+$) 274.2171, found 274.2188.

9.4. Preparation of *syn*,*syn*-3a

A solution of 2-benzoylcyclohexanone (202.1 mg, 1.0 mmol), piperidine (0.3 mL, 3.0 mmol), and *p*-toluenesulfonic acid monohydrate (4 mol %) was heated under reflux in toluene (10 mL) using a Dean–Stark apparatus. After being stirred for 44 h, the reaction mixture was cooled to rt and evaporated. To the residue was added dry EtOH (3 mL) and platinum oxide (10 mg) under an argon atmosphere at rt. Then, the argon was replaced by hydrogen, and the reaction mixture was stirred for 43 h at rt. The mixture was filtered through a Celite pad with EtOH, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (silica gel 15 g, hexane/AcOEt=2/1–AcOEt/EtOH=5/1) to give *syn*,*syn*-**3a** (133.7 mg, 49%).

*9.4.1. Phenyl[2-(piperidin-1-yl)cyclohexyl]methanol (**3a**). syn,syn*-Isomer: yellow oil; TLC: R_f 0.27 (AcOEt/EtOH=5/1, stained blue with phosphomolybdic acid/EtOH); IR (NaCl, cm^{-1}) 2931, 2852, 2808, 1450, 1448, 1126, 1101, 977, 701; ^{1}H NMR ($CDCl_3$): δ 1.02–1.18 (m, 2H), 1.36–1.78 (m, 12H), 2.14 (apparent d, 1H, *J*=12.8 Hz), 2.62 (br s, 2H), 2.88–3.41 (m, 3H), 5.08 (s, 1H), 7.18–7.23 (m, 1H), 7.25 (br s, 1H), 7.29–7.38 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 19.4, 22.8, 23.8, 24.2, 25.5, 26.8, 47.5, 54.2 (br), 65.0, 77.1, 125.6, 126.1, 127.6, 143.4; HRMS (FAB): calcd for $C_{18}H_{27}NONa$ (M+Na$^+$) 296.1990, found 296.1983.

9.5. Preparation of *anti*,*syn*-3a

Benzaldehyde (52.8 mg, 0.5 mmol, 1.0 equiv) and $SiCl_4$ (0.086 mL, 0.75 mmol, 1.5 equiv) was added to a solution of enamine **2a** (0.6 mmol, 1.2 equiv) in dichloromethane (2 mL) under an argon atmosphere at 0 °C. The reaction was immediately allowed to reach rt and stirred for 1 h. The mixture was added to $LiBH_4$ (1 mmol) in THF (2 mL) via a cannula under an argon atmosphere at −78 °C. The mixture was allowed to warm to rt over 2 h and quenched with satd aqueous $NaHCO_3$ (5 mL). The mixture was diluted with AcOEt (5 mL) and stirred for 1 h to precipitate silicon byproducts. After filtration through a Celite pad with AcOEt, the filtrate was extracted with AcOEt (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (silica gel 15 g, hexane/AcOEt=2/1–AcOEt/EtOH=5/1) to give *anti*,*syn*-**3a** (37.6 mg, 27%).

*9.5.1. Phenyl[2-(piperidin-1-yl)cyclohexyl]methanol (**3a**). anti,syn*-Isomer: colorless solid; TLC: R_f 0.36 (AcOEt/EtOH=5/1, stained blue with phosphomolybdic acid/EtOH); mp 129–131 °C; IR (KBr, cm^{-1}) 2943, 1446, 1362, 1342, 1275, 1103, 1041, 972, 870, 758; ^{1}H NMR ($CDCl_3$): δ 1.12 (dddd, 1H, *J*=4.1, 4.1, 13.7, 13.7 Hz), 1.22–1.37 (m, 4H), 1.45 (dddd, 1H, *J*=3.7, 3.7, 13.7, 13.7, 13.7 Hz), 1.62–1.82 (m, 6H), 1.86–2.06 (m, 4H), 2.25–2.34 (m, 1H), 2.49 (ddd, 1H, *J*=3.2, 3.4, 12.8 Hz), 3.18 (br s, 1H), 3.48 (br s, 1H), 5.09 (d, 1H, *J*=10.1 Hz), 7.20–7.29 (m, 1H), 7.31–7.48 (m, 4H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.5, 24.2, 24.4, 26.0 (br), 26.2, 26.6 (br), 27.4, 40.0, 49.5 (br), 53.5 (br), 67.6, 73.9, 127.0, 127.1, 128.1, 144.4; HRMS (FAB): calcd for $C_{18}H_{28}NO$ (M+H$^+$) 274.2171, found 274.2164.

9.6. Observation of iminium ion intermediate by NMR spectroscopy

Under an argon atmosphere, benzaldehyde (0.15 mmol, 1.0 equiv) was added to a solution of enamine **2a** (0.18 mmol, 1.2 equiv) in deuterated dichloromethane (0.6 mL) in an NMR tube at rt. After cooling at −78 °C, $SiCl_4$ (0.23 mmol, 1.5 equiv) was introduced to the mixture. The mixture was stood at rt for 5 h, before NMR measurements were conducted.[17]

9.7. Reaction of benzaldehyde with enamine 2c prepared beforehand

Cyclohexanone (0.16 mL, 1.5 mmol) and morpholine (0.16 mL, 1.8 mmol) was mixed in diethyl ether (1.5 mL) in the presence of molecular sieves 5 Å pellet (600 mg) at rt. After being stirred for 25 h at rt, the mixture was filtered through a Celite pad in a pipet and concentrated under vacuum. The residue was diluted with dichloromethane (4 mL) and cooled to −40 °C. NMP (20 mol %), trichlorosilane (ca. 3 M, 1.5 mmol), and benzaldehyde (112.5 mg, 1.06 mmol) were successively added to the solution, and the mixture was stirred at −40 °C for 1 h. The reaction was quenched by satd aqueous $NaHCO_3$. The mixture was stirred at rt for 1 h, filtered through a Celite pad, and extracted with AcOEt (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (silica gel 15 g, hexane/AcOEt=2/1–AcOEt/EtOH=5/1) to give *anti*,*anti*-**3c** (151.4 mg, 52%).

9.8. Enantioselective reaction of benzaldehyde with enamine 2a catalyzed by (*S*)-BINAPO

Trichlorosilane (0.75 mmol, ca. 3 M CH_2Cl_2 solution) was added to a solution of enamine **2a** (0.6 mmol), and (*S*)-BINAPO (32.9 mg, 10 mol %) in dichloromethane (2 mL) at −40 °C. Then benzaldehyde (**1a**) (55.4 mg, 0.52 mmol) was introduced to the mixture. After being stirred for 1 h, the reaction was quenched with satd aqueous $NaHCO_3$ (5 mL). The mixture was diluted with AcOEt (5 mL) and stirred at rt for 1 h to precipitate silicon byproducts. After filtration through a Celite pad with AcOEt, the filtrate was extracted with AcOEt (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (silica gel 15 g, hexane/AcOEt=2/1–AcOEt/EtOH=5/1) to give *anti*,*anti*-**3a** (62.0 mg, 43%, 40% ee).

*9.8.1. Phenyl[2-(piperidin-1-yl)cyclohexyl]methanol (**3a**). anti,anti*-Isomer: $[\alpha]_D^{32}$ −3.9 (*c* 1.02, $CHCl_3$) for 40% ee; HPLC (Chiralcel OD-H, hexane/2-Propanol=39/1, flow rate=1.0 mL/min, UV detection at 254 nm) t_R=9.0 min (minor), 11.1 min (major).

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Supplementary data

Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.10.075. These data include MOL files and InChIKeys of the most important compounds described in this article.

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24. The first C–C bond formation would be almost *anti* selective as depicted in Fig. 3 (see also Ref. 19) at low temperature. However, the enantioselectivity of this step would be low. If the enantio-determining step had been mainly this step, the enantiomeric excess of product **3a** obtained under the conditions of entry 3 (Table 4) would have been at least 24% according to the results shown in entries 1 and 2. This assumption is evidently inconsistent with the actual result (9% ee). Therefore, the kinetic resolution of the *anti* iminium ion via the second intramolecular reduction would be mainly enantio-determining.
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