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Ruthenium-Catalyzed Enantioselective Synthesis of β-Amino Alcohols from 1,2-Diols by "Borrowing Hydrogen"

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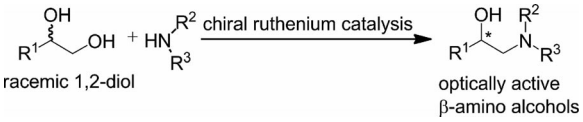
Enantioselective synthesis of β-amino alcohols from 1,2-diols by the use of $[RuCl_2(p\text{-cymene})]_2$/(*S*,*R*)-JOSIPHOS catalysis was developed. Several 1,2-diols were treated with secondary amines to afford the corresponding optically active β-amino alcohols in up to 99 % yield with 77 % *ee*.

Introduction

Since the last century, when asymmetric synthetic chemistry began being used, optically active β-amino alcohols have played important roles in organic chemistry and related research fields.[1] This class of organic compounds has been widely used as chiral ligands or chiral auxiliaries,[2] organocatalysts,[3] and versatile intermediates in the synthesis of various medicines[4] and unnatural amino acids.[5] In addition, various biologically active natural compounds contain β-amino alcohols.[6] Consequently, numerous methods for the preparation of optically active β-amino alcohols have been reported,[7] such as asymmetric reduction of amino ketones,[8] ring-opening of enantioenriched epoxides,[9] and Sharpless asymmetric aminohydroxylation of alkenes.[10]

An environmentally friendly method, the so-called "borrowing hydrogen" methodology, has recently received much attention as a highly atom-efficient synthetic strategy in organic synthesis.[11] Alcohols are usually converted into reactive haloalkanes and related compounds by treatment with halogenated reagents before the reaction with nucleophiles.[12] Under "borrowing hydrogen" methodology conditions, on the other hand, alcohols are transformed in situ into aldehydes or ketones, which are more reactive in nucleophilic addition reactions than alcohols. This in situ transformation provides a wide range of ways to deal with alcohols as alkylation reagents. The only byproduct expected is water, so the reaction proceeds with high atom efficiency. Although there are many reports on the use of ruthenium, iridium, and palladium catalysts in the alkylation of amines[13] and oxo nitriles,[14] examples in which 1,2-diols are used as substrates are limited.[15] One successful application of the "borrowing hydrogen" methodology for β-amino alcohol preparation from 1,2-diols was reported by Beller and co-workers, who used an $[Ru_3(CO)_{12}]$ catalyst.[15a] To the best of our knowledge, however, no application of this methodology for the preparation of optically active amino alcohols has been reported in spite of the importance of asymmetric synthesis of β-amino alcohols. Here we report the first enantioselective reaction of 1,2-diols with amines that provides an optically active β-amino alcohol (Scheme 1).



Scheme 1. Synthesis of optically active β-amino alcohols described in this work.

Results and Discussion

The reaction of 2 mol-equiv. of 1-phenyl-1,2-ethanediol (**1a**) and morpholine (**2a**) was initially carried out in the presence of $[RuCl_2(p\text{-cymene})]_2$ and chiral ligand (*S*)-BINAP at 120 °C for 24 h. The reaction proceeded successfully to give the desired β-amino alcohol **3a** in 88 % yield and 12 %*ee* (Table 1, Entry 1). Although the enantioselectivity was low, this result encouraged us to investigate the novel asymmetric reaction further. To enhance the enantioselectivity, we investigated such reaction conditions as the catalyst, the balance of starting materials, and the temperature (Table 1). Increasing the amount of (*S*)-BINAP to 1.2 equiv. of ruthenium increased the yield to 95 % with 17 %*ee*; further increasing the amount to 1.5 equiv. Ru, however, resulted in the formation of an almost racemic product. Addition of an excess amount of **1a** slightly increased the *ee* (Entries 4 and 5). Reducing of temperature

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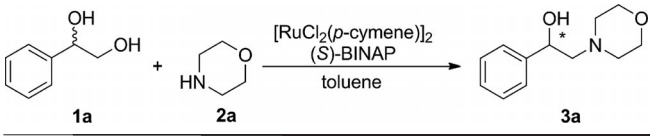
from 120 to 110 °C doubled the *ee* (32%), but decreased the yield by a factor of four, from 92 to only 23% yield of **3a** (Entry 6).

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Ru/Ligand	**1a/2a**	Temp. [°C]	Yield [%][b]	*ee* [%][c]
1	1:1	2:1	120	88	12
2	1:1.2	2:1	120	95	17
3	1:1.5	2:1	120	95	4
4	1:1.2	3:1	120	92	21
5	1:1.2	5:1	120	92	16
6	1:1.2	3:1	110	23	32

[a] Reaction conditions: 1-phenyl-1,2-ethanediol, morpholine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol-%), (*S*)-BINAP, under Ar, toluene (1 mL), heated for 24 h. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Determined by HPLC analysis.

We next focused on the effect of the chiral ligand (Table 2, Figure 1). When (*S*)-Tol-BINAP was used, the racemic amino alcohol was obtained, although the reaction proceeded with up to 86% yield (Entry 1). Use of the SEGPHOS family of ligands in the reaction delivered high reactivity (up to 99% yield) but yielded almost racemic products (Entries 2–4). Employing chiral bis(oxazoline) ligand (*R*,*S*)-IndaBox(Me_2) afforded the desired amino alcohol in a yield of 45%, however, with little enantioselectivity (Entry 5). Both the catalytic activity and enantioselectivity were reduced when the phosphoramidite ligand (*S*)-MONOPHOS was used (Entry 6). We then tested other diphosphane ligands. (–)-DIOP provided 99% yield of the desired β-amino alcohol with 18%*ee* (Entry 8), and (*S*,*R*)-JOSIPHOS provided 99% yield of the desired amino alcohol with 25%*ee* (Entry 7). We investigated temperature effects on reactions with (*S*)-BINAP and (*S*,*R*)-JOSIPHOS. When (*S*,*R*)-JOSIPHOS was used, the highest *ee* value (48%) was obtained at 100 °C, and this was obtained without reduction in the chemical yield (Entry 11); no reaction took place when (*S*)-BINAP was used at 100 °C (Entry 10). The Ru/JOSIPHOS catalyst did not work well at 90 °C (Entry 12).

Table 2. Ligand and temperature effects.[a]

Entry	Ligand	Temp. [°C]	Yield [%][b]	*ee* [%][c]
1	(*S*)-Tol-BINAP	110	86	0
2	(*S*)-SEGPHOS	110	98	0
3	(*S*)-DM-SEGPHOS	110	99	4
4	(*S*)-DTBM-SEGPHOS	110	92	1
5	(*R*,*S*)-IndaBox(Me_2)	110	45	5
6	(*S*)-MONOPHOS	110	23	10
7	(*S*,*R*)-JOSIPHOS	110	99	25
8	(–)-DIOP	110	99	18
9	none	110	NR	–
10	(*S*)-BINAP	100	NR	–
11	(*S*,*R*)-JOSIPHOS	100	99	48
12	(*S*,*R*)-JOSIPHOS	90	50	29

[a] Reaction conditions: 1-Phenyl-1,2-ethanediol (3 mmol), morpholine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol-%), ligand (6 mol-%), under Ar, toluene (1 mL), heated for 24 h. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Determined by HPLC analysis.

With the conditions required to obtain good selectivity with Ru/JOSIPHOS catalysis established, we investigated the scope and limitations of the optimized enantioselective preparation of β-amino alcohols. We started by testing several secondary amines (Table 3). Five- and six-membered cyclic amines showed good reactivity under the optimized reaction conditions (Entries 1–4), and both piperidine (**2b**) and pyrrolidine (**2c**) reacted with 1-phenyl-1,2-ethandiol (**1a**) to afford the corresponding β-amino alcohols in almost quantitative yield with good enantioselectivity (62 and 55%*ee*, respectively). Tetrahydroisoquinoline (**2d**) afforded the desired product in 87% isolated yield with 64%*ee* (Entry 4). The present reaction was also used to prepare β-amino alcohol **3e** with an acetal protecting group with 48%*ee*, although the yield was only 62% (Entry 5). In contrast, acyclic amine, di-*n*-propylamine (**2f**), showed low reactivity and gave the product **3f** in only 25% yield as a racemic compound (Entry 6). Aromatic amine **2g** did not react under the optimized conditions (Entry 7).

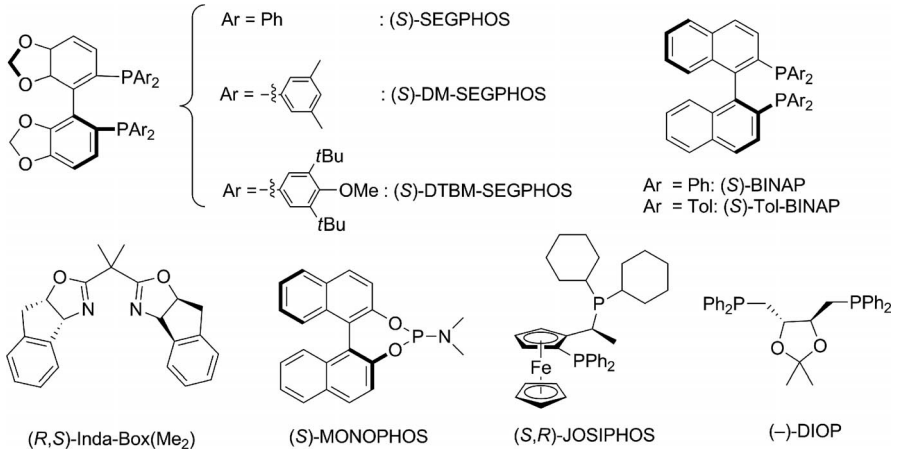
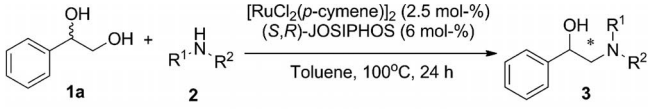
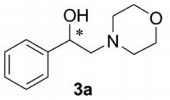
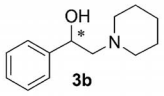
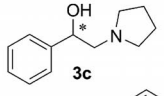
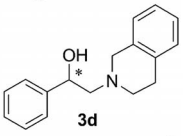
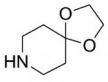
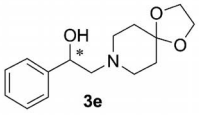
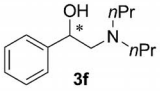
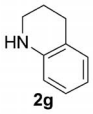
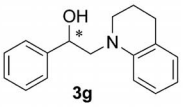


Figure 1. Chiral ligands screened for the asymmetric amination of 1,2-diol.

Table 3. Amination of 1-phenyl-1,2-ethanediol by secondary amines.[a]



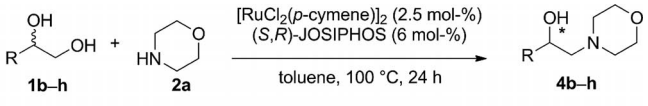
Entry	Amine	Product	Yield [%][b]	*ee* [%][c]
1	 **2a**	 **3a**	99	48
2	 **2b**	 **3b**	99	62
3	 **2c**	 **3c**	99	55
4	 **2d**	 **3d**	99 (87[d])	64
5	 **2e**	 **3e**	62	48
6	 **2f**	 **3f**	25	rac
7	 **2g**	 **3g**	n.d.	–

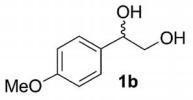
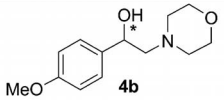
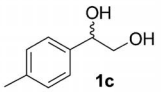
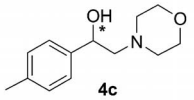
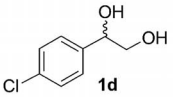
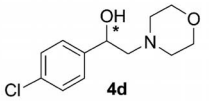
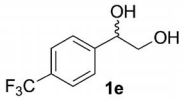
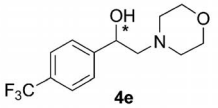
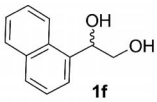
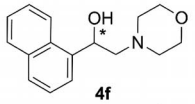
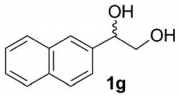
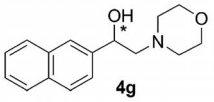
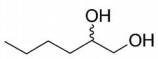
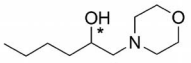
[a] Reaction conditions: 1-phenyl-1,2-diol (3 mmol), amine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol-%), (*S*,*R*)-JOSIPHOS (6 mol-%), toluene (1 mL), 100 °C, 24 h. [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by HPLC analsysis. [d] Isolated yield in parentheses.

Several 1,2-diols were also tested under the optimized reaction conditions (Table 4). First, 1-aryl-1,2-ethanediols (**1b**–**g**) were examined. Use of diol **1c**, with a methyl group at the *para* position, gave 78% yield of the desired β-amino alcohol **4c** with 59%*ee* (Entry 2). Substrates with other substituents, such as a methoxy group, a chlorine atom, or a trifluoromethyl group, suppressed the reaction (Entries 1, 3, and 4). Use of 1-(1-naphthyl)-1,2-ethanediol (**1f**) gave only 55% isolated yield with 22%*ee* (Entry 5). On the other hand, we were pleased to find that 1-(2-naphthyl)-1,2-ethanediol (**1g**) afforded the highest *ee* (77%*ee*, 76% yield; Entry 6). We also examined aliphatic 1,2-diols and found that the reaction of acyclic aliphatic diol 1,2-hexanediol (**1h**) and morpholine (**2a**) gave β-amino alcohol **4h** in 80% yield with 38%*ee* (Entry 7).

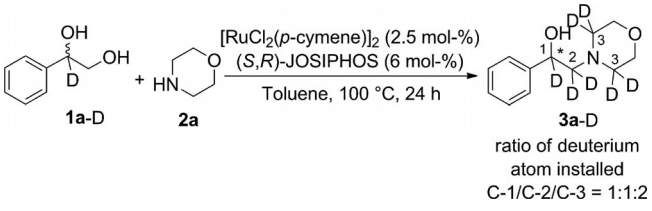
We examined several possible reaction mechanisms. Checking the enantiopurity of recovered diol **1a** by chiral HPLC revealed that **1a** was recovered as a racemic product.

Table 4. Amination of 1,2-diols with morpholine.[a]

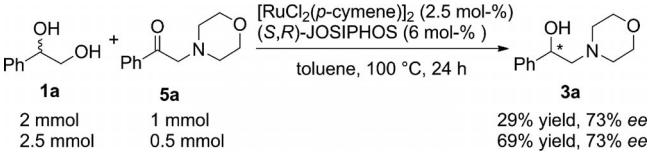


Entry	1,2-Diol	Product	Yield [%][b]	*ee* [%][c]
1	 **1b**	 **4b**	28	28
2	 **1c**	 **4c**	78	59
3	 **1d**	 **4d**	46	29
4	 **1e**	 **4e**	n.d.	–
5	 **1f**	 **4f**	55[d]	22
6	 **1g**	 **4g**	76	77
7	 **1h**	 **4h**	80[d]	38

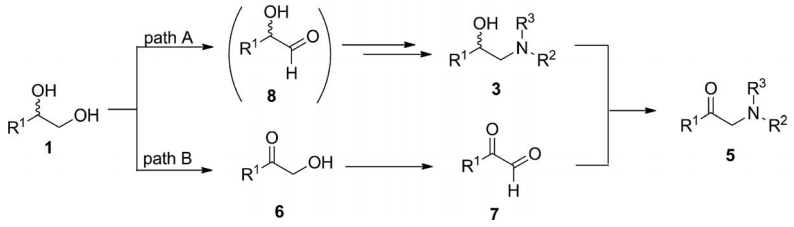
[a] Reaction conditions: 1,2-diol (3 mmol), morpholine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol-%), (*S*,*R*)-JOSIPHOS (6 mol-%), under Ar, toluene (1 mL), 100 °C, 24 h. [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by HPLC analysis. [d] Isolated yield.



Scheme 2. Reaction of deuterium-labeled 1-phenyl-1,2-ethanediol (**1a**-D) with morpholine (**2a**).



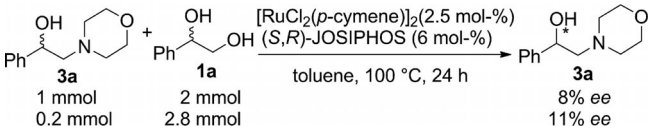
Scheme 3. Asymmetric reduction of amino ketone **5a** to β-amino alcohol **3a**.



Scheme 4. Possible pathways from diols **1** to amino ketones **5**.

Given this, we hypothesized that the reaction did not proceed through kinetic resolution of the racemic diol by the chiral ruthenium complex and that the secondary alcohols in diols participate in a "borrowing hydrogen" reaction. To test this hypothesis, we used deuterium-labeled diol **1a**-D (Scheme 2). Diol **1a**-D was treated with morpholine **2a** in the presence of Ru/(*S*,*R*)-JOSIPHOS catalyst at 100 °C to afford the desired amino alcohol **3a**-D in 99% yield. Deuterium atoms were found at the C-1 and C-2 positions and even at the α-position of the morpholine ring. This scrambling of deuterium atoms revealed that the hydrogen transfer reaction from **1a** to the ruthenium complex occurred to form hydroxy ketone **6a**, oxo aldehyde **7a**, and/or amino ketone **5a** (see Scheme 4 below). To determine which intermediates were mainly formed under the present reaction conditions, a GC–MS analysis of the crude reaction was performed at an early stage (5 h). Oxo aldehyde **7a** and hydroxy ketone **6a**, accompanied by amino ketone **5a** and amino alcohol **3a**, were detected, whereas hydroxy aldehyde **8a** (a possible oxidized product) was not observed. This result suggested that the double oxidation of diols to oxo aldehydes occurred under our catalytic conditions and that the amino ketone is an important intermediate in the process leading to enantioenriched amino alcohols. We therefore next examined the reaction of amino ketone **5a** by using starting diol **1a** and the present chiral ruthenium catalysis (Scheme 3). Thus, amino ketone **5a** was treated with 2 equiv. of 1-phenyl-1,2-ethanediol (**1a**) under the optimized reaction conditions to obtain the corresponding amino alcohol **3a** in 29% yield with 73%*ee*. The reaction using 5 equiv. **1a** also afforded **3a** in 69% yield with 73%*ee*. The formation of amino alcohol **3a** with reasonable optical purity from **1a** is consistent with amino ketone **5a** being a key intermediate in the enantiodetermining step. Two possible routes to form amino ketone intermediate **5a** are depicted in (Scheme 4): (1) oxidation of product amino alcohol **3a** (Path A); (2) reaction of morpholine after the double oxidation of the starting diol (Path B), which is supported by GC–MS analysis of the reaction mixture at an early stage of the reaction.

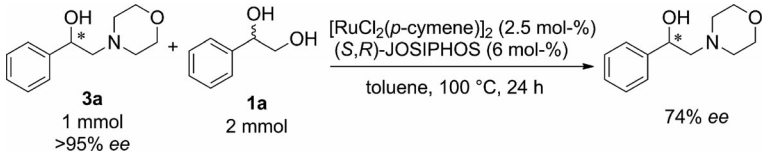
To verify the feasibility of Path A, we first investigated the change of the *ee* value for amino alcohol **3a** under the optimized reaction conditions. When racemic **3a**, prepared independently, was exposed to the reaction conditions, the *ee* value of recovered **3a** was less than 11% (Scheme 5).



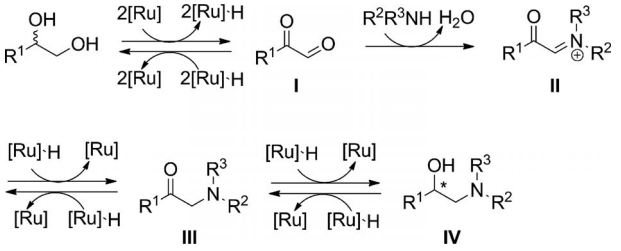
Scheme 5. Treatment of *rac*-**3a** with **1a** and chiral ruthenium catalysis.

In addition, almost optically pure amino alcohol **3a** (>95%*ee*), which was prepared by an authentic procedure,[8] was slightly racemized under the optimized reaction conditions to afford **3a** with an *ee* of 74% (Scheme 6). These results suggested that an enantioselective redox reaction took place at the benzylic position under the optimized reaction conditions, although the reaction rate is considered to be relatively slow. We therefore thought that the oxidation of amino alcohol **3** (Path A) is not the main route for the formation of amino ketone **5**. Although the secondary alcohol in aliphatic diols is expected to be oxidized slower than the primary alcohol, this trend is also inconsistent with the feasibility of Path A. In addition, several selective oxidations of secondary alcohols in 1,2-diol[16] and isomerization of hydroxy aldehyde to hydroxy ketone[17] have been reported, supporting the possibility that double oxidation could have taken place on the aliphatic diols under the present reaction conditions.

Given the results of these mechanistic studies, we propose the following main reaction pathway (Scheme 7). The starting diol is converted into oxo aldehyde **I** by ruthenium-catalyzed double dehydrogenation. Oxo aldehyde **I** reacts with the amine to afford iminium ion intermediate **II**, which is converted into amino ketone **III**. Amino ketone **III** is finally converted into the desired amino alcohol **IV** by a second transfer hydrogenation reaction. Enantioselection occurs in the final step.



Scheme 6. Racemization of enantioenriched β-amino alcohol **3a**.



Scheme 7. Proposed reaction mechanism of enantioselective amination of 1,2-diols.

Conclusions

We have achieved the first enantioselective preparation of β-amino alcohols from 1,2-diols by application of the ruthenium-catalyzed "borrowing hydrogen" methodology. Our mechanistic studies suggest that the reaction proceeds mainly through amino ketone intermediates that are converted into the corresponding optically active β-amino alcohols. Investigations aimed at improving the enantioselectivity and applying the present method for the synthesis of bioactive compounds are in progress in our laboratory.

Experimental Section

General Information: NMR spectra were recorded with Varian Mercury Plus 300-4N spectrometers by using TMS (δ = 0 ppm) as an internal standard for ^{1}H NMR and $CDCl_3$ (δ = 77 ppm) for ^{13}C NMR spectroscopy. Enantiomeric excess (*ee*) values were measured with a Hitachi L-7100 HPLC with a chiral column (Daicel Chiralcel OD-H or OJ-H) under the conditions described below. All reactions were carried out under argon in a sealed tube. Reagents obtained from commercial sources were used without further purification. Toluene was dried by a standard method and distilled under argon. Molecular sieves (4 Å) were activated by heating at 350 °C for 2 h before use.

General Procedure for the Synthesis of β-Amino Alcohols from 1,2-Diols: To an argon-purged reaction tube containing 4 Å molecular sieves (0.62 g) was added the respective 1,2-diol (3 mmol), amine (1 mmol), $[RuCl_2(p\text{-cymene})Cl_2]_2$ (0.0154 g, 0.025 mmol), (*S*,*R*)-JOSIPHOS (0.0356 g, 0.060 mmol), and anhydrous toluene (1 mL). The mixture was degassed by using three freeze-pump-thaw cycles and then purged with argon. The reaction mixture was stirred at 100 °C for 24 h, then filtered, and the filtrate was concentrated under reduced pressure. The inorganic wastes and excess amount of the starting diol were removed by Kugelrohr distillation. The crude product was purified by column chromatography or extracted by using an acidic aqueous solution to give the corresponding β-amino alcohol.

2-Morpholino-1-phenylethanol (3a): White solid; m.p. 78–79 °C; 48%*ee* by HPLC [Daicel Chiralcel OD-H; λ = 225 nm; *i*PrOH/hexane = 20:80; flow = 0.5 mL/min; t_R = 15.86 (minor), 17.22 (major) min]. ^{1}H NMR: δ = 2.42–2.57 (m, 4 H), 2.73–2.76 (m, 2 H), 3.73–3.81 (m, 4 H), 4.75 (dd, *J* = 10.2, 3.9 Hz, 1 H), 7.24–7.35 (m, 5 H) ppm. ^{13}C NMR: δ = 53.4, 66.6, 67.0, 68.5, 125.8, 127.5, 128.3, 141.8 ppm. GC-MS: *m*/*z* = 207. FAB-MS: *m*/*z* = 208 [M + H$^+$].

1-Phenyl-2-(piperidin-1-yl)ethanol (3b): White solid; m.p. 65–66 °C; 62%*ee* by HPLC [Daicel Chiralcel OJ-H; λ = 225 nm; EtOH/hexane = 3:97; flow = 0.15 mL/min; t_R = 43.20 (minor), 46.40 (major) min]. ^{1}H NMR: δ = 1.47–1.49 (m, 2 H), 1.61–1.64 (m, 4 H), 2.34–2.51 (m, 4 H), 2.69–2.71 (m, 2 H), 4.73 (dd, *J* = 10.5, 3.6 Hz, 1 H), 7.24–7.37 (m, 5 H) ppm. ^{13}C NMR: δ = 24.2, 26.1, 54.4, 66.9, 68.60, 125.8, 127.4, 128.2, 142.4 ppm. FAB-MS: *m*/*z* = 206 [M + H$^+$].

1-Phenyl-2-(pyrrolidin-1-yl)ethanol (3c): White solid; m.p. 44–48 °C; 53%*ee* by HPLC [Daicel Chiralcel OJ-H; λ = 225 nm; *i*PrOH/hexane = 10:90; flow = 0.5 mL/min; t_R = 15.82 (minor), 16.99 (major) min]. ^{1}H NMR: δ = 1.78–1.82 (m, 4 H), 2.45–2.57 (m, 3 H), 2.72–2.82 (m, 3 H), 3.81 (br., 1 H), 4.70 (dd, *J* = 10.6, 3.3 Hz, 1 H), 7.24–7.41 (m, 5 H) ppm. ^{13}C NMR: δ = 23.6, 53.8, 64.1, 70.7, 125.8, 127.3, 128.2, 142.5 ppm.

1-Phenyl-2-(tetrahydroisoquinolin-2-yl)ethanol (3d): Light-yellow oil; 28%*ee* by HPLC [Daicel Chiralcel OD-H; λ = 225 nm; *i*PrOH/hexane = 20:80; flow = 0.5 mL/min; t_R = 14.07 (minor), 15.19 (major) min]. ^{1}H NMR: δ = 2.65–2.78 (m, 3 H), 2.94–3.04 (m, 3 H), 3.68 (d, *J* = 15 Hz, 1 H), 3.94 (d, *J* = 14.7 Hz, 1 H), 4.86 (dd, *J* = 9.8, 4.2 Hz, 1 H), 7.04–7.43 (m, 9 H) ppm. ^{13}C NMR: δ = 29.2, 50.9, 55.8, 66.0, 69.0, 125.7, 125.8, 126.2, 126.4, 127.4, 128.3, 128.6 ppm. FAB-MS: *m*/*z* = 254 [M + H$^+$].

2-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-1-phenylethanol (3e): White solid; m.p. 104–107 °C; 48%*ee* by HPLC [Daicel Chiralcel OJ-H; λ = 225 nm; EtOH/hexane = 96:4; flow = 0.7 mL/min; t_R = 22.38 (minor), 23.43 (major) min]. ^{1}H NMR: δ = 1.75–1.80 (m, 4 H), 2.42–2.53 (m, 4 H), 2.82–2.84 (m, 2 H), 3.95 (s, 4 H), 4.70 (dd, *J* = 10.3, 3.9 Hz, 1 H), 7.24–7.37 (m, 5 H) ppm. ^{13}C NMR: δ = 34.9, 51.3, 64.3, 65.7, 68.9, 107.0, 125.8, 127.5, 128.3, 142.1 ppm. FAB-MS: *m*/*z* = 264 [M + H$^+$].

2-(Dipropylamino)-1-phenylethanol (3f): Yellow oil; racemic by HPLC (Daicell Chiralcell OJ-H; λ = 225 nm; EtOH/hexane = 2:98; flow = 0.4 mL/min; t_R = 12.26, 12.71 min). ^{1}H NMR: δ = 0.92 (t, *J* = 7.5 Hz, 6 H), 1.46–1.56 (m, 4 H), 2.40–2.53 (m, 4 H), 2.56–2.63 (m, 2 H), 4.64 (dd, *J* = 10.5, 3.6 Hz, 1 H), 7.26–7.39 (m, 4 H) ppm. ^{13}C NMR: δ = 11.9, 20.4, 56.0, 63.2, 69.3, 125.7, 127.2, 128.2, 142.4 ppm. FAB-MS: *m*/*z* = 222 [M + H$^+$].

1-(4-Methoxyphenyl)-2-(morpholin-4-yl)ethanol (4b): White solid; m.p. 76–77 °C; 28%*ee* by HPLC [Daicel Chiralcel OJ-H; λ = 225 nm; EtOH/hexane = 20:80; flow = 0.5 mL/min; t_R = 28.03 (minor), 31.74 (major) min]. ^{1}H NMR: δ = 2.41–2.51 (m, 4 H), 2.70–2.77 (m, 2 H), 3.69–3.77 (m, 4 H), 3.79 (s, 3 H), 4.70 (dd, *J* = 8.85, 4.8 Hz, 1 H), 6.85–6.90 (m, 2 H), 7.27–7.21 (m, 2 H) ppm. ^{13}C NMR: δ = 53.5, 55.3, 66.7, 67.0, 68.2, 113.8, 127.1, 133.8, 159.1 ppm. FAB-MS (*m*/*z*): 238 [M + H$^+$].

1-(4-Methylphenyl)-2-(morpholin-4-yl)ethanol (4c): White solid; m.p. 75–76 °C; 59%*ee* by HPLC [Daicel Chiralcel OJ-H; λ = 225 nm; *i*PrOH/hexane = 10:90; flow = 0.5 mL/min; t_R = 45.68 (minor), 49.66 (major) min]. ^{1}H NMR: δ = 2.33 (s, 3 H), 2.41–2.50 (m, 4 H), 2.71–2.73 (m, 2 H), 3.72–3.76 (m, 4 H), 4.72 (dd, *J* = 9.45, 4.2 Hz, 1 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.26 (d, *J* = 5.1 Hz, 2 H) ppm. ^{13}C NMR: δ = 21.1, 53.4, 66.7, 67.0, 68.3, 125.8, 129.0, 137.2, 138.8 ppm. FAB-MS: *m*/*z* = 222 [M + H$^+$].

1-(4-Chlorophenyl)-2-(morpholin-4-yl)ethanol (4d): White solid; m.p. 69–70 °C; 29%*ee* by HPLC [Daicel Chiralcel OJ-H; λ = 225 nm; *i*PrOH/hexane = 20:80; flow = 0.5 mL/min; t_R = 22.82 (minor), 26.80 (major) min]. ^{1}H NMR: δ = 2.41–2.50 (m, 4 H), 2.70–2.77 (m, 2 H), 3.72–3.77 (m, 5 H), 4.70 (dd, *J* = 10.5, 3.6 Hz, 2 H), 7.31 (m, 4 H) ppm. ^{13}C NMR: δ = 53.4, 66.5, 67.0, 67.9, 127.2, 128.5, 133.2, 140.3 ppm. FAB-MS: *m*/*z* = 242 [M + H$^+$].

2-Morpholino-1-(1-naphthyl)ethanol (4f): White viscous oil; 22%*ee* by HPLC [Daicel Chiralcel OJ-H; λ: 225 nm; EtOH/hexane = 10:90; flow = 0.5 mL/min; t_R = 28.51 (minor), 30.22 (major) min]. ^{1}H NMR: δ = 2.50–2.63 (m, 3 H), 2.81–2.86 (m, 3 H), 3.75–3.83 (m, 4 H), 5.60 (dd, J = 10.5, 3.0 Hz, 1 H), 7.47–7.53 (m, 3 H), 7.78 (d, J = 7.8 Hz, 2 H), 7.87 (d, J = 18.3 Hz, 1 H), 8.0 (d, J = 10.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 53.6, 65.6, 65.7, 67.1, 122.5, 123.1, 123.4, 125.7, 126.0, 127.9, 129.0, 130.4, 133.7, 137.2 ppm. FAB-MS: *m*/*z* = 258 [M + H$^+$].

2-Morpholino-1-(2-naphthyl)ethanol (4g): White solid; m.p. 92–100 °C; 77%*ee* by HPLC [Daicel Chiralcel OJ-H; λ = 225 nm; *i*PrOH/hexane = 20:80; flow = 0.5 mL/min; t_R = 38.70 (minor), 44.63 (major) min]. ^{1}H NMR: δ = 2.47–2.65 (m, 4 H), 2.75–2.79 (m, 2 H), 3.09–3.82 (m, 5 H), 4.92 (dd, J = 10.05, 3.6 Hz, 1 H), 7.45 (dd, J = 9.3, 6.6 Hz, 3 H), 7.80–7.84 (m, 4 H) ppm. ^{13}C NMR: δ = 53.51, 66.56, 67.03, 68.65, 123.76, 124.52, 125.64, 125.97, 127.56, 127.76, 128.01, 132.88, 133.20, 139.16 ppm. FAB-MS: *m*/*z* = 258 [M + H$^+$].

1-Morpholino-2-hexanol (4h): Colorless oil; 38%*ee* by HPLC [Daicel Chiralcel OD-H; λ = 225 nm; *i*PrOH/hexane = 10:90; flow = 1 mL/min; t_R = 10.11 (minor), 10.63 (major) min]. ^{1}H NMR: δ = 0.84 (t, J = 6.6 Hz, 3 H), 1.22–1.40 (m, 6 H), 2.15–2.35 (m, 4 H), 2.55–2.57 (m, 2 H), 2.60 (br., 1 H), 3.62–3.69 (m, 5 H) ppm. ^{13}C NMR: δ = 14.0, 22.7, 27.7, 34.4, 53.5, 64.7, 65.8, 66.9 ppm. FAB-MS: *m*/*z* = 188 [M + H$^+$].

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of the amino alcohols.

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