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Asymmetric hydrogenation of β-amino ketones with the bimetallic complex RuPHOX-Ru as the chiral catalyst†

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Asymmetric hydrogenations of a series of β-amino ketones were carried out with a bimetallic complex (RuPHOX-Ru) as the chiral catalyst. Almost all the reactions (performed in a mixed solvent system of toluene and H_2O in the presence of KOH) gave quantitative conversions into their respective products with up to 99.9% ee. The RuPHOX-Ru catalyst is stable to both moisture and air. The procedure has the benefits of being inexpensive, environmentally friendly and highly efficient. Under a relatively low catalyst loading (TON = 2000), key intermediates of fluoxetine, tomoxetine and nisoxetine could be obtained in quantitative yield and in up to 99.9% ee. This methodology represents a promising alternative to the synthesis of the aforementioned drugs and their analogues.

1. Introduction

Fluoxetine, tomoxetine and nisoxetine are amongst the most important norepinephrine reuptake inhibiting antidepressants for the treatment of psychiatric disorders (Fig. 1).[1] Their asymmetric synthesis has received significant interest in recent years because both enantiomers of the aforementioned drugs show different curative effects.[2] Chiral γ-amino alcohol, (*R*)-3-methylamino-1-phenylpropan-1-ol, is the key building block for the synthesis of these molecules.

There are three common different pathways which can be used to prepare γ-amino alcohols: (1) utilising a chiral alcohol containing a facile leaving group (OMs, OTs, Cl, Br, *etc*.) at the γ-position, which can be replaced by an amine substituent (Scheme 1, Pathway 1);[3] (2) using a chiral ethylene oxide in place of a chiral alcohol (Scheme 1, Pathway 2);[4] and (3) the asymmetric hydrogenation of the corresponding β-amino ketones using a chiral metal-based catalyst (Scheme 1, Pathway 3).

The initial study on the asymmetric hydrogenation of β-amino ketones was performed by Achiwa. Up to 90.8% ee was obtained by using a (2*S*,4*S*)-MCPPM-Rh complex for the synthesis of 3-(*N*-benzyl-*N*-methylamino)propiophenone hydrochloride.[5] Noyori subsequently applied a chiral $RuCl_2$-(diphosphine)(1,2-diamine) complex to the reaction and obtained 97.5% ee and 96% yield for *N*,*N*-dimethyl-3-phenylpropanone[6] and 92.0% ee and 100% yield for 3-dimethylamino-1-(2-thienyl)-1-propanone.[7] Ding[8] and Huang[9] achieved the above utilizing ruthenium catalysts containing chiral diamines and achiral diphosphanes, with products being obtained in up to 99% yield and not more than 98% ee. Zhang prepared (*S*)-2-methyl-α-[2-(methylamino)ethyl]benzenemethanol in 92% yield and 99% ee utilizing a Rh-duanphos-catalyzed hydrogenation reaction of functionalized C=O.[10] Recently, Zhang developed a Ru-catalyzed asymmetric

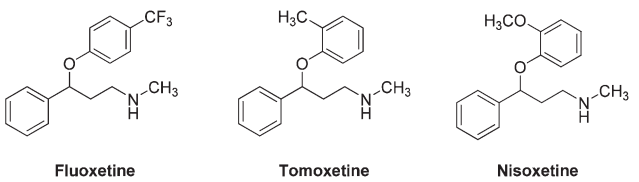
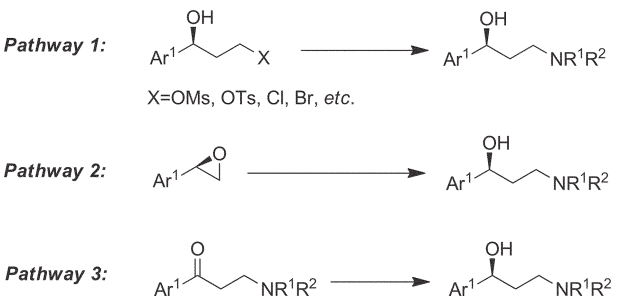


Fig. 1 The structure of fluoxetine, tomoxetine and nisoxetine.



Scheme 1 The common different pathways to γ-amino alcohols.

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hydrogenation of β-ketoenamines to synthesize chiral γ-amino alcohols in up to 99% ee.[11] The above examples utilize high H_2 pressures, high temperatures and/or unstable catalyst systems, or provide somewhat low enantioselectivities, hampering their applicability to industrial processes. The efficient synthesis of β-amino ketones thus remains a challenge and is worthy of further investigation.

Recently, our group has focused on the development of novel planar chiral metallocenyl ligands and their applicability to different types of asymmetric syntheses.[12] Among them, C_2-symmetric metallocenyl planar P,N-ligands **1** (RuPHOX) have shown promising catalytic activity in many asymmetric reactions, most likely due to their dual reaction sites and large steric hindrance.[12e,f,h,n] Ligand **1b** especially has proven to be the most efficient ligand in the Ru-catalyzed asymmetric hydrogenation of simple ketones (Fig. 2).[12n] Herein we wish to disclose the asymmetric hydrogenation of β-amino ketones with a bimetallic RuPHOX-Ru complex **2** pre-prepared from **1b** and Ru(II)$(PPh_3)_3Cl_2$ as the chiral catalyst (Fig. 2).

2. Results and discussion

Initially, complex **2** was prepared *via* a simple procedure. As shown in Scheme 2, treatment of ligand **1b** and Ru(II)$(PPh_3)_3Cl_2$ in toluene at 90 °C provided complex **2** in 97% yield. This dark green solid is inert to both moisture and air, and could be preserved in air for more than one year without a decrease in catalytic activity. Asymmetric catalysis using readily prepared **2** or that prepared *in situ* from **lb** and Ru(II)-$(PPh_3)_3Cl_2$ performed similarly. Thus **2** could be used directly in subsequent reactions with the aim to facilitate the reaction procedure.

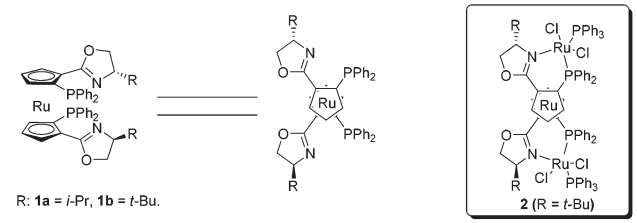
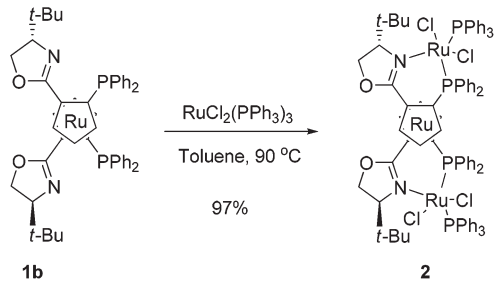
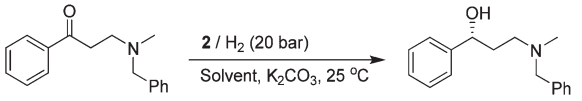


Fig. 2 RuPHOX **1** and its Ru-complex **2**.



Scheme 2 The synthesis of RuPHOX-Ru **2**.

Table 1 The effect of the solvent on the reaction[a]



Entry	Solvent	Conv.[b] (%)	ee[c] (%) (Config.[d])
1	MeOH	83.1	90.3 (*R*)
2	Toluene	25.3	69.4 (*R*)
3	Toluene + MeOH[e]	95.2	73.4 (*R*)
4	Toluene + H_2O[e]	96.0	90.7 (*R*)
5	MeOH + H_2O[e]	70.4	62.9 (*R*)

[a] Reactions were conducted with β-amino ketone (0.4 mmol) in a solvent (4 mL) using **2** (0.25 mol%) as a catalyst in the presence of K_2CO_3 (10 mol%) under an H_2 atmosphere (20 bar) at 25 °C for 12 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC using a Chiralcel OD-H column. [d] The absolute configuration of the product was assigned through the comparison of the sign of specific rotations with the literature data.[5f,e] The mixed solvent was composed of 3 mL MeOH (or toluene) and 1 mL H_2O (or MeOH).

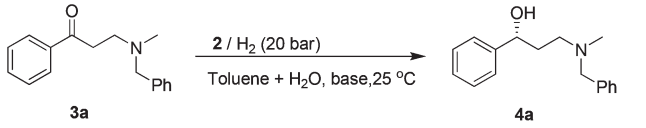
MeOH and toluene were used as solvents because they are very cheap and are frequently used in industry. Thus, asymmetric hydrogenation of 3-(benzyl(methyl)amino)-1-phenylpropanone (**3a**) was performed under 20 bar H_2 pressure at 25 °C with K_2CO_3 as a base.

However, as shown in Table 1, poor conversions to products and only moderate to good enantioselectivities were obtained when using only MeOH or toluene as the solvent (entries 1 and 2). When a mixed solvent system of toluene (3 mL) and MeOH (1 mL) were used, the reaction yield increased but with low enantioselectivity (entry 3). We believed that increasing the solubility of the K_2CO_3 could promote the reaction. H_2O was added to both MeOH and toluene. To our delight, the product was obtained in 96.0% yield and 90.7% ee in a system of toluene and H_2O (entry 4). However, a system of methanol and H_2O afforded low reaction activity and enantioselectivity (entry 5). According to the catalytic behavior described above, a solvent system of toluene and water was used for the hydrogenation reactions.

The effect of base on the reaction was then examined (Table 2). Inorganic bases were used because of their inexpensiveness and availability. Weak inorganic bases such as Na_2CO_3 and K_2CO_3 gave only middling results (entries 1 and 2). LiOH provided excellent enantioselectivity but low conversions (entry 3). Strong bases such as NaOH and KOH were used and found to greatly benefit the hydrogenation process. Reactions proceeded in quantitative yields and excellent enantioselectivities (99.9% ee, entries 4 and 5). Further reactions were thus performed with KOH as a base in the presence of **2**, using a mixed solvent system of toluene and H_2O at 25 °C.

With the optimal reaction conditions in hand, the applicability of our catalytic system to a number of substrates was explored. Hydrogenation of a series of β-amino ketones proceeded with excellent yields and enantioselectivities (Table 3).

Table 2 The effect of the base on the reaction[a]



3a 4a

Entry	Base	Conv.[b] (%)	ee[c] (%) (Config.[d])
1	K_2CO_3	96.0	90.7 (*R*)
2	Na_2CO_3	87.2	83.8 (*R*)
3	LiOH	22.4	99.9 (*R*)
4	NaOH	100	99.9 (*R*)
5	KOH	100	99.9 (*R*)

[a] Reactions were conducted with β-amino ketone (0.4 mmol) in toluene (3 mL)/H_2O (1 mL) using **2** (0.25 mol%) as a catalyst in the presence of a base (10 mol%) under an H_2 atmosphere (20 bar) at 25 °C for 12 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC using a Chiralcel OD-H column. [d] The absolute configuration of the product was assigned through the comparison of the sign of specific rotations with the literature data.[5f]

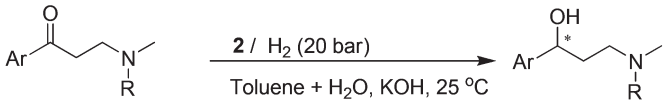
At first, β-amino ketones containing an electron-donating group (such as methyl and methoxyl substituents) at the *meta* and *para* positions were examined, and excellent catalytic results were obtained (entries 2–5). Substrates with electron-withdrawing groups such as F, Cl, Br, *etc.* were also amenable to the catalytic system (entries 6–10). Strong electron-withdrawing groups resulted in low reaction activity in addition to requiring lengthy reaction times. However, excellent enantioselectivities were obtained with these substrates (entries 8 and 9). Unfortunately, *ortho* substituted groups (such as Me and Cl) on the aromatic ring resulted in low reaction activity (less than 50% conversion). A substrate with a phenyl group at the *para* position also occurred with quantitative conversions to the product with 99.2% ee (entry 11).

Replacement of the phenyl backbone by a naphthalene ring or a furan ring had little effect on the catalytic behavior (entries 12 and 13). Additionally, the frequently used *N*,*N*-dimethyl β-amino ketone was also subjected to the catalytic system (entry 14).

According to Wilkinson's catalytic cycle[13] and the reaction results above, the mechanism of our reaction can be proposed (Fig. 3). Initially, **2** reacts with a H_2 molecule in the presence of KOH to give Ru species. The carbonyl group of the β-amino ketone coordinates to the Ru, resulting in the release of PPh_3. The hydride is then transferred to the carbon atom of the carbonyl group. Another H_2 molecule is subsequently activated in the manner mentioned above *via* an alkoxyl anion instead of the KOH base. The hydrogenated product is then released and the catalyst is regenerated.

To examine the applicability of the catalyst system to an industrial process, the hydrogenation of **3a** was tested with a relatively low catalyst loading (TON = 2000). To our delight, the reaction proceeded smoothly with quantitative conversion of the substrate and 99.9% ee. The corresponding alcohol **4a** can be further extrapolated to several antidepressants, fluoxetine, tomoxetine and nisoxetine, according to the reported method (Scheme 3).[2] The present catalytic system shows potential for synthesis of several norepinephrine reuptake inhibiting antidepressants.

Table 3 The exploration of a series of β-amino ketones[a]



3a-n 4a-n

Entry	Sub.	Ar	R	TON	T (h)	Pro.	Conv.[b] (%)	ee[c] (%) (Config.[d])
1	**3a**	C_6H_5	Bn	400	12	**4a**	100	99.9 (*R*)
2	**3b**	3-$MeOC_6H_4$	Bn	400	12	**4b**	100	99.9 (*R*)
3	**3c**	4-$MeOC_6H_4$	Bn	400	12	**4c**	100	99.6 (*R*)
4	**3d**	3-MeC_6H_4	Bn	200	12	**4d**	100	99.9 (*R*)
5	**3e**	4-MeC_6H_4	Bn	200	12	**4e**	100	99.9 (*R*)
6	**3f**	3-ClC_6H_4	Bn	200	12	**4f**	100	99.3 (*R*)
7	**3g**	4-ClC_6H_4	Bn	200	12	**4g**	100	99.9 (*R*)
8	**3h**	3,4-diClC_6H_3	Bn	100	36	**4h**	100	99.9 (*R*)
9	**3i**	4-FC_6H_4	Bn	200	24	**4i**	100	99.3 (*R*)
10	**3j**	4-BrC_6H_4	Bn	200	12	**4j**	100	97.3 (*R*)
11	**3k**	4-PhC_6H_4	Bn	200	12	**4k**	100	99.2 (*R*)
12	**3l**	2-Naphthyl	Bn	200	12	**4l**	100	99.9 (*R*)
13	**3m**	2-Furan	Bn	200	12	**4m**	100	98.7 (*R*)
14	**3n**	Ph	Me	200	12	**4n**	100	99.6 (*S*)

[a] Reactions were conducted with β-amino ketone (0.4 mmol) in toluene (3 mL)/H_2O (1 mL) using **2** (0.25 mol%) as a catalyst in the presence of KOH (10 mol%) under an H_2 atmosphere (20 bar) at 25 °C for a certain time. [b] Determined by ^{1}H NMR. [c] Determined by HPLC using a Chiralcel OD-H or IC-3 column. [d] The absolute configuration of the product was assigned through the comparison of the sign of specific rotations with the literature data.[5f]

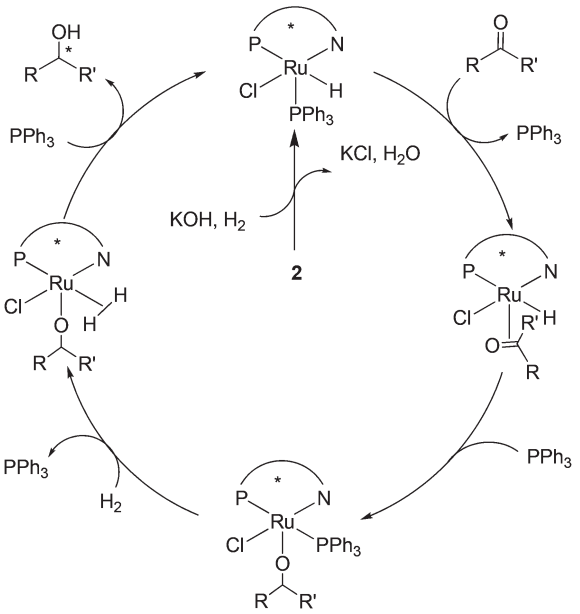
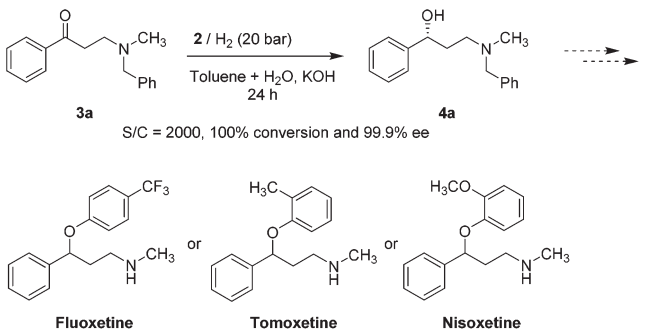


Fig. 3 The possible asymmetric hydrogenation mechanism.



Scheme 3 The asymmetric synthesis of tomoxetine.

3. Conclusions

In conclusion, asymmetric hydrogenations of a series of β-amino ketones were performed using a stable bimetallic chiral catalyst, RuPHOX-Ru complex **2**. Almost all the examples gave quantitative yields of products with up to 99.9% ee. The procedure has the advantages of being inexpensive, environmentally beneficial, and highly efficient (even under relatively low catalyst loadings (TON = 2000)).

4. Experimental section

General information

All reactions were performed under a nitrogen atmosphere, and workups were carried out in air. Toluene, MeOH, EtOH and *i*-PrOH were distilled over dehydrating reagents. Commercially available reagents were used without further purification. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{31}P NMR (162 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. The enantioselectivity was measured by high performance liquid chromatography (HPLC) using a Daicel Chiralcel OD-H or IC-3 column with hexane–2-propyl alcohol as the eluent and 0.1% Et_3N as the additive. Column chromatography was performed using 100–200 mesh silica gel. All commercially available substrates were used as received. β-Amino ketones were prepared through Mannich reaction according to literature procedures.[8]

General procedure for the synthesis of catalyst 2

A solution of ligand **1b** (69.5 mg) and Ru(II)$(PPh_3)_3Cl_2$ (156.8 mg) in toluene (20 mL) was heated to 90 °C for 5 h. The solvent was removed and the residue was purified by flash column silica-gel chromatography (PE–EA = 5/1) to give the catalyst **2** (96.8% yield) as a dark green solid. mp. 210–211 °C. $[\alpha]_D^{25}$ 18.5° (*c* = 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66–6.75 (m, 50H), 5.60–5.50 (m, 2H), 5.43 (s, 2H), 4.93 (t, *J* = 9.2 Hz, 2H), 4.66 (t, *J* = 8.4 Hz, 2H), 4.45 (s, 2H), 4.4 (t, *J* = 8.8 Hz, 2H), 0.8 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 138.1, 137.6, 135.5, 135.4, 135.3, 134.9, 134.6, 133.9, 133.8, 133.1, 133.0, 131.3, 130.7, 130.2, 129.5, 129.2, 128.7, 127.7, 127.6, 127.4, 127.3, 127.2, 127.1, 93.2, 86.9, 86.2, 85.8, 81.9, 77.8, 77.6, 77.3, 77.2, 76.9, 75.8, 75.7, 69.6, 39.8, 33.4, 32.1, 29.9, 27.6; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 68.76, 43.58.

General procedure for the asymmetric hydrogenation of β-amino ketones

2 (0.25 mol%) and β-amino ketone (0.4 mmol) were dissolved in a degassed solution of toluene (3 mL) under a nitrogen atmosphere. KOH (10 mol%) was added to degassed H_2O (1 mL) and both solutions were mixed in a glove box under a nitrogen atmosphere. The reaction began when the solution was transferred to an autoclave in the presence of H_2 (20 bar). After several hours, the reaction mixture was concentrated under reduced pressure. The percentage conversion of the product was determined by ^{1}H NMR of the crude residue. The mixture was purified by flash chromatography with ethyl acetate–petrol ether (1 : 1) to give pure product **4** for the determination of the ee using a Daicel Chiralcel OD-H or IC-3 column with hexane–2-propyl alcohol as the eluent and 0.1% Et_3N as the additive.

(*R*)-3-(Benzyl(methyl)amino)-1-phenylpropan-1-ol (4a).[14] As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.20 (m, 10H), 4.91 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.65 (d, *J* = 12.8 Hz, 1H), 3.48 (d, *J* = 12.8 Hz, 1H), 3.87–2.76 (m, 1H), 2.64–2.55 (m, 1H), 2.27 (s, 3H), 1.95–1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 138.0, 129.6, 128.8, 128.5, 127.7, 127.2, 125.8, 75.6, 62.9, 56.6, 41.9, 35.9; $[\alpha]_D^{22}$ 20.572° (*c* = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 0.8 mL min^{-1}, t_R = 14.52 min (major) and t_R = 13.17 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(3-methoxyphenyl)propan-1-ol (4b). As a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.20 (m, 6H), 7.01–6.88 (m, 2H), 6.84–6.72 (m, 1H), 4.89 (dd, *J* = 7.6, 3.6 Hz, 1H), 3.81 (s, 3H), 3.65 (d, *J* = 12.8 Hz, 1H), 3.48 (d, *J* = 12.4 Hz, 1H), 2.88–2.76 (m, 1H), 2.65–2.53 (m, 1H),

2.26 (s, 3H), 1.98–1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 146.9, 137.9, 135.9, 129.4, 128.7, 127.7, 118.1, 112.7, 111.2, 75.9, 63.0, 56.8, 55.4, 41.9, 34.7; $[\alpha]_D^{22}$ 20.373° (c = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 1.0 mL min^{-1}, t_R = 19.25 min (major) and t_R = 15.44 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(4-methoxyphenyl)propan-1-ol (4c). As a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.20 (m, 7H), 6.93–6.84 (m, 2H), 4.86 (dd, J = 8.4, 2.8 Hz, 1H), 3.79 (s, 3H), 3.65 (d, J = 12.8 Hz, 1H), 3.47 (d, J = 12.8 Hz, 1H), 2.87–2.75 (m, 1H), 2.63–2.54 (m, 1H), 2.27 (s, 3H), 1.95–1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 138.0, 137.5, 129.5, 128.7, 127.6, 126.9, 113.8, 75.6, 63.0, 56.7, 55.5, 42.0, 34.9; $[\alpha]_D^{22}$ 46.538° (c = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 1.0 mL min^{-1}, t_R = 19.38 min (major) and t_R = 14.84 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(*m*-tolyl)propan-1-ol (4d). As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.00 (m, 9H), 4.88 (dd, J = 8.4, 2.8 Hz, 1H), 3.66 (d, J = 12.8 Hz, 1H), 3.49 (d, J = 12.8 Hz, 1H), 2.89–2.76 (m, 1H), 2.66–2.55 (m, 1H), 2.35 (s, 3H), 2.28 (s, 3H), 1.99–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 138.0, 137.9, 129.5, 128.8, 128.3, 127.9, 127.7, 126.5, 122.9, 76.0, 63.0, 56.9, 42.0, 34.7, 21.7; $[\alpha]_D^{22}$ 21.571° (c = 0.5, methanol). HRMS (ESI-TOF) Calcd for $C_{18}H_{24}NO$ $[M + H]^+$ 270.1858, Found: 270.1862. HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 0.8 mL min^{-1}, t_R = 13.51 min (major) and t_R = 12.05 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(*p*-tolyl)propan-1-ol (4e).[15] As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.26 (m, 7H), 7.20–7.14 (m, 2H), 4.90 (dd, J = 8.0, 3.6 Hz, 1H), 3.66 (d, J = 12.8 Hz, 1H), 3.49 (d, J = 12.8 Hz, 1H), 2.87–2.78 (m, 1H), 2.66–2.56 (m, 1H), 2.35 (s, 3H), 2.27 (s, 3H), 1.97–1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 137.2, 131.5, 130.1, 129.4, 129.2, 128.8, 125.8, 70.7, 53.4, 39.6, 33.5, 21.3; $[\alpha]_D^{22}$ 26.621° (c = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 0.8 mL min^{-1}, t_R = 14.19 min (major) and t_R = 11.07 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(3-chlorophenyl)propan-1-ol (4f). As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.15 (m, 9H), 4.87 (dd, J = 7.6, 4.8 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 3.48 (d, J = 12.4 Hz, 1H), 2.87–2.75 (m, 1H), 2.64–2.52 (m, 1H), 2.27 (s, 3H), 1.95–1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 137.8, 134.4, 129.7, 129.5, 128.8, 127.7, 127.2, 126.1, 123.9, 75.3, 62.9, 56.6, 42.0, 34.6; $[\alpha]_D^{22}$ 13.182° (c = 0.5, methanol). HRMS (ESI-TOF) Calcd for $C_{17}H_{21}ClNO$ $[M + H]^+$ 290.1312, Found: 290.1317; HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 1.0 mL min^{-1}, t_R = 12.08 min (major) and t_R = 9.18 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(4-chlorophenyl)propan-1-ol (4g).[16] As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.24 (m, 9H), 4.87 (t, J = 5.2 Hz, 1H), 3.64 (d, J = 12.8 Hz, 1H), 3.47 (d, J = 12.8 Hz, 1H), 2.85–2.76 (m, 1H), 2.62–2.54 (m, 1H), 2.27 (s, 3H), 1.87–1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 137.8, 132.6, 129.5, 128.8, 128.5, 127.7, 127.2, 75.4, 63.1, 56.5, 42.1, 34.6; $[\alpha]_D^{22}$ 19.374° (c = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 210 nm, 0.6 mL min^{-1}, t_R = 21.47 min (major) and t_R = 16.09 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(3,4-dichlorophenyl)propan-1-ol (4h). As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.45 (m, 1H), 7.42–7.24 (m, 6H), 7.18–7.10 (m, 1H), 4.84 (t, J = 6.0 Hz, 1H), 3.64 (d, J = 12.8 Hz, 1H), 3.47 (d, J = 12.4 Hz, 1H), 2.87–2.76 (m, 1H), 2.63–2.53 (m, 1H), 2.27 (s, 3H), 1.87–1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 137.7, 132.5, 130.7, 130.3, 129.5, 128.8, 127.9, 127.8, 125.2, 74.9, 63.0, 56.5, 42.0, 34.4; $[\alpha]_D^{22}$ 19.973° (c = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 1.0 mL min^{-1}, t_R = 13.56 min (major) and t_R = 10.39 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(4-fluorophenyl)propan-1-ol (4i).[15] As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.20 (m, 7H), 7.04–6.94 (m, 2H), 4.88 (dd, J = 8.0, 3.6 Hz, 1H), 3.65 (d, J = 12.8 Hz, 1H), 3.48 (d, J = 12.8 Hz, 1H), 2.87–2.76 (m, 1H), 2.66–2.54 (m, 1H), 2.28 (s, 3H), 1.94–1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.5, 128.8, 127.7, 127.4, 127.3, 115.3, 115.0, 75.5, 63.1, 56.6, 42.1, 34.8, 29.9; $[\alpha]_D^{22}$ 23.221° (c = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 0.8 mL min^{-1}, t_R = 14.26 min (major) and t_R = 11.12 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(4-bromophenyl)propan-1-ol (4j). As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.15 (m, 9H), 4.85 (t, J = 5.6 Hz, 1H), 3.63 (d, J = 12.8 Hz, 1H), 3.48 (d, J = 12.8 Hz, 1H), 2.86–2.75 (m, 1H), 2.64–2.53 (m, 1H), 2.27 (s, 3H), 1.92–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 137.8, 131.5, 129.5, 128.8, 127.7, 127.6, 120.8, 75.4, 63.0, 56.5, 42.1, 34.6; $[\alpha]_D^{22}$ 1.398° (c = 1.0, methanol); HRMS (ESI-TOF) Calcd for $C_{17}H_{21}BrNO$ $[M + H]^+$ 334.0807, Found: 334.0808; HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 90 : 10, UV 200 nm, 0.6 mL min^{-1}, t_R = 14.94 min (major) and t_R = 12.41 min (minor).

(*R*)-1-([1,1′-Biphenyl]-4-yl)-3-(benzyl(methyl)amino)propan-1-ol (4k). As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.26 (m, 14H), 4.96 (dd, J = 4.0 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H), 3.50 (d, J = 13.2 Hz, 1H), 2.90–2.78 (m, 1H), 2.68–2.57 (m, 1H), 2.28 (s, 3H), 2.01–1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 141.3, 140.0, 137.9, 129.5, 128.9, 128.8, 75.8, 63.1, 56.7, 42.0, 34.6, 30.0; $[\alpha]_D^{22}$ 28.961° (c = 1.0, methanol); HRMS (ESI-TOF) Calcd for $C_{23}H_{26}NO$ $[M + H]^+$ 332.2014, Found: 332.2042; HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel IC-3), Hex–*i*-PrOH 90 : 10, UV 230 nm, 0.8 mL min^{-1}, t_R = 31.48 min (major) and t_R = 16.94 min (minor).

(*R*)-3-(Benzyl(methyl)amino)-1-(naphthalen-2-yl)propan-1-ol (4l).[17] As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.80–7.50 (m, 5H), 7.35–7.10 (m, 9H), 4.90 (dd, J = 8.0, 4.4 Hz, 1H), 3.45 (d, J = 12.8 Hz, 1H), 3.30 (d, J = 12.8 Hz, 1H), 2.90–2.78 (m, 1H), 2.66–2.57 (m, 1H), 2.10 (s, 3H), 2.07–1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 139.1, 138.1, 133.7, 133.1, 129.5, 128.9, 128.3, 128.2 127.9, 127.8, 126.2, 125.8, 124.5, 124.3, 75.9, 63.0, 56.7, 42.0, 34.8, 25.6; $[\alpha]_D^{22}$ 19.574° (c = 2.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 1.0 mL min^{-1}, t_R = 24.65 min (major) and t_R = 17.84 min (minor).

(*R*)-(Benzyl(methyl)amino)-1-(furan-2-yl)propan-1-ol (4m). As a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 6H), 6.30 (dd, J = 3.2, 2.0 Hz,1H), 6.20 (m, 1H), 4.91 (dd, J = 8.0, 3.2 Hz, 1H), 3.61 (d, J = 12.4 Hz, 1H), 3.48 (d, J = 11.2 Hz, 1H), 2.82–2.70 (m, 1H), 2.69–2.60 (m, 1H), 2.25 (s, 3H), 2.16–1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 141.7, 137.9, 129.4, 128.7, 127.6, 110.3, 105.5, 69.9, 62.9, 56.2, 41.9, 30.9; $[\alpha]_D^{22}$ 2.796° (c = 1.0, methanol); HRMS (ESI-TOF) Calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$ 246.1494, Found: 246.1480; HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 200 nm, 0.5 mL min^{-1}, t_R = 20.74 min (major) and t_R = 18.38 min (minor).

(*S*)-3-(Dimethylamino)-1-phenylpropan-1-ol (4n).[18] As a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.45–7.20 (m, 5H), 4.93 (dd, J = 8.0, 4.0 Hz, 1H), 2.70–2.60 (m, 1H), 2.52–2.43 (m, 1H), 2.30 (s, 6H), 1.89–1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 128.0, 126.7, 125.7, 73.2, 57.0, 53.7, 44.9, 35.9; $[\alpha]_D^{22}$ −33.641° (c = 1.0, methanol). HPLC conditions: the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex–*i*-PrOH 95 : 5, UV 254 nm, 1.0 mL min^{-1}, t_R = 8.61 min (major) and t_R = 12.49 min (minor).

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