Synthesis of Optically Active *β*-Aryloxy Alcohols and *β*-Arylthiol Alcohols *via* Asymmetric Transfer Hydrogenation Reaction

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Abstract: A series of optically active *β*-aryloxy alcohols and *β*-arylthiol alcohols were synthesized directly by asymmetric transfer hydrogenation of the corresponding *β*-carbonyl ethers or *β*-carbonyl sulfides in excellent yields (up to 99%) and excellent enantioselectivity (up to 100% *ee*) under mild reaction conditions.

Keywords: Asymmetric transfer hydrogenation, *β*-aryloxy alcohols, *β*-arylthiol alcohols, *β*-ketosulfide, *β*-ketoether.

INTRODUCTION

The asymmetric transfer hydrogenation (ATH) reaction of prochiral ketones and imines is a pivotal reaction for the synthesis of chiral secondary alcohols or amines which has attracted much attention in recent years [1]. The easily available hydrogen sources, mild reaction conditions and simple experimental setup have made it an area of interest for both industrial and academic researchers [2, 3]. Many catalysts have been developed for the hydrogenation process of various ketones, providing the corresponding products with high *ee* values, such as the reduction of acetophenones bearing CN, N_3, Cl, RNH, SO_2NH and NO_2 at the *α*-position [4–10]. Chiral *β*-aryloxy alcohols and *β*-arylthiol alcohols are important building blocks for many chiral compounds, such as chiral oxiranes, aziridines, thiiranes, tetrahydrofurans and *β*-hydroxy esters [11–17]. Few papers reported the synthesis of these compounds by biological method and the scope was limited [18, 19]. Herein, we report a highly efficient synthesis of optical acitive *β*-aryloxy alcohols and *β*-arylthiol alcohols with high enantiomeric purity *via* ATH reaction. Most of the products are new compounds.

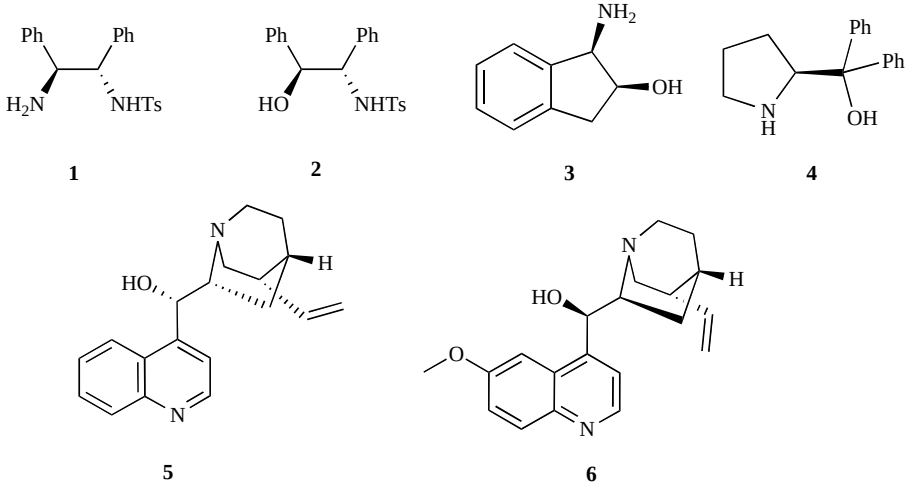

Fig. (1). Ligands chosen for the ATH reactions.

RESULTS AND DISCUSSION

Initially, 2-pehnoxy-1-phenylethanone was used as the model substrate and the asymmetric catalytic activities of six chiral amino alcohols (Fig. **1**) were examined for the ATH reaction. The results are summumrized in Table **1**.

As expected, (1*R*, 2*R*)-Ts-DPEN, the well known ligand, gave the best result (Table **1**, entries **1-6**). The product was

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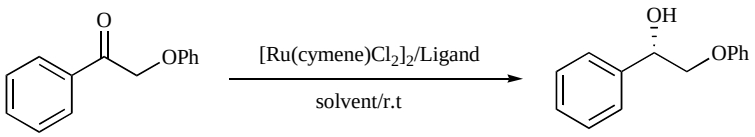
Table 1. Screening of Optimum Conditions for ATH Reaction[a]



Entry[a]	Ligand	Solvent	Yield (%)	*ee* (%)[e]
1	1	CH_3CN	96	93
2	2	CH_3CN	No reduction	-
3[b]	3	CH_3CN	76	86
4[b]	4	CH_3CN	trace	-
5[b]	5	CH_3CN	trace	-
6[b]	6	CH_3CN	trace	-
7	1	DMF	92	89
8	1	CH_3OH	95	91
9	1	THF	97	96
10	1	DCM	99	88
11	1	Et_2O	99	85
12	1	Toluene	95	89
13[c]	1	THF	96	88
14[d]	1	THF	94	91

[a]Reactions were performed at room temperature for 24 h, using 0.5 mmol substrate, 1.0 ml solvent, 0.25 mol% ligand, 3.8 mg $[Ru(cymene)Cl_2]_2$ and 0.2 ml $HCOOH/Et_3N$ (5 : 2).
[b]The reaction was carried out in ^{i}PrOH/KOH system.
[c]The amount of the ligand is 0.50 mol%.
[d]The amount of the ligand is 0.125 mol%.
[e]The enantiomeric excess was determined by chiral HPLC analysis of the corresponding products on a Chiralpak AD-H column. The absolute configuration is *S* according to the literature (see ref. [17]).

obtained with 96% yield and 93% *ee* in acetonitrile. Encouraged by the excellent result, we attempted to identify the optimal conditions for the ATH reaction using (1*R*, 2*R*)-Ts-DPEN as the chiral ligand. Solvent effect was firstly examined. Among the solvents explored, the best result was obtained when THF was used as the solvent (Table **1**, entry **9**). Then, the influence of the substrate/catalyst ratio on the ATH was investigated. Decreasing or increasing the amount of the ligand had no benefit on the reaction. Thus, the optimal conditions for the ATH reaction of 2-pehnoxy-1-phenylethanone required 0.25 mol% ligand and formic acid as the hydrogen donor in THF at room temperature.

With the optimized reaction conditions in hand, the scope of the reaction was investigated and the results are summarized in Table **2**. Various substrates (**1a-1j**) were reacted in the presence of chiral catalyst Ru(*p*-cymene)TsDPEN using the $HCOOH/Et_3N$ = 5 : 2 as hydrogen source in THF at ambient temperature. Regardless of the types of substituents on the R_1 ring or R_2 ring, be it electron-withdrawing or electron-donating, the reactions proceeded well to afford highly enantioselective adducts (up to 99%). When R_1 is heteroatomic ring, the product can aslo obtained with high *ee* (up to 98%, Table **2**, entry **10**).

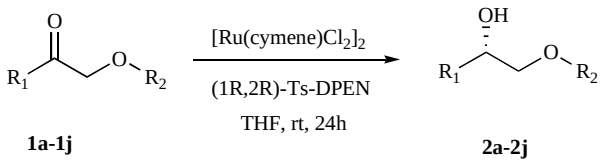
When the substrates were broaden to *β*-ketosulfides, the reaction can hardly react at the same conditions. However, the reaction can proceed smoothly with the reaction temperature enhancing to 40 ^{o}C. The results are summarized in Table **3**. As can be seen from the table, most of the reactions were completed within 24 h with excellent yields (88%–99%) and excellent enantioselectivities (79% to 100% *ee*).

In summary, we have presented the first asymmetric reduction of *β*-carbonyl ethers or *β*-carbonyl sulfides using chiral $[RuCl_2(p\text{-cymene})]$-TsDPEN as the catalyst, and $HCOOH/Et_3N$ as the hydrogen source. A series of optically active *β*-aryloxy alcohols and *β*-arylthiol alcohols were synthesized with good to excellent yields (up to 99% yield) and excellent enantioselectivity (up to 100% *ee*).

EXPERIMENTAL

All manipulations were carried out under an argon in degassed solvents. The reactions were monitored by TLC. NMR spectra were measured in $CDCl_3$ on a Varian-Inova-400 NMR spectrometer with TMS as an internal reference. Optical rotations were measured with a HORIBA SEPA-200 high-sensitivity polarimeter. The enantiomeric excess (*ee*) was determined by using a Chiralpak AD-H column or a Chiralpak IA column with hexane–^{i}PrOH as the solvent at a flow rate of 1 mL/min (unless otherwise stated), and UV detection at 254 nm (unless otherwise stated). MS spectra were recorded under EI conditions. IR spectra were recorded on a Varian FT-1000 IR spectrophotometer using KBr disks in the 4000–400 cm^{-1} region.

Table 2. Scopes of Reaction[a]

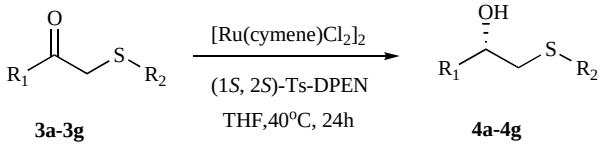


1a-1j **2a-2j**

Entry	R_1	R_2	Product	Yield (%)[b]	*Ee* (%)[c]
1	C_6H_5	C_6H_5	**2a**	97	96
2	*p*-MeC_6H_4	C_6H_5	**2b**	86	98
3	*p*-MeOC_6H_4	C_6H_5	**2c**	89	97
4	*p*-MeC_6H_4	2-Naphthyl	**2d**	89	99
5	C_6H_5	*p*-C_6H_4CHO	**2e**	92	99
6	*p*-ClC_6H_4	2-Naphthyl	**2f**	94	93
7	*p*-ClC_6H_4	C_6H_5	**2g**	90	93
8	*p*-MeOC_6H_4	2-Naphthyl	**2h**	87	98
9	C_6H_5	2-Naphthyl	**2i**	90	92
10	thiophene	C_6H_5	**2k**	86	98

[a]Reactions were performed at room temperature for 24 h, using 0.5 mmol substrate, 1.0 ml THF, 0.25 mol% (1*R*, 2*R*)-Ts-DPEN , 3.8 mg [Ru(cymene)Cl_2]$_2$ and 0.2 ml HCOOH/Et_3N (5 : 2).
[b]Isolated yield.
[c]Determined by chiral HPLC analysis using a Chiralpak AD–H or IA column. Absolute configuration probably *S* based on comparison of the elution order of HPLC analysis and/or the sign of the specific rotation value with those of the analogues reported. see ref. [17, 20-22].

Table 3. Scopes of the ATH Reaction for Ketosulfides[a]



3a-3g **4a-4g**

Entry	R_1	R_2	Product	Yield (%)[b]	*Ee* (%)[c]
1	C_6H_5	C_6H_5	4a	90	100
2	*p*-MeOC_6H_4	C_6H_5	4b	91	79
3	*p*-MeC_6H_4	*p*-MeC_6H_4	4c	91	95
4	*p*-MeC_6H_4	C_6H_5	4d	99	95
5	*p*-ClC_6H_4	C_6H_5	4e	92	91
6	*p*-ClC_6H_4	*p*-MeC_6H_4	4f	90	98
7	*p*-MeOC_6H_4	*p*-MeC_6H_4	4g	88	95

[a]Reactions were performed at 40 °C for 24 h, using 0.5 mmol substrate, 1.0 ml THF, 0.25 mol% (1*S*, 2*S*)-Ts-DPEN , 3.8 mg [Ru(cymene)Cl_2]$_2$ and 0.2 ml HCOOH/Et_3N (5 : 2).
[b]Isolated yield.
[c]Determined by chiral HPLC analysis using a Chiralpak AD–H or IA column. Absolute configuration except for **4a** is unknown, but probably *S* based on comparison of the elution order of HPLC analysis and/or the sign of the specific rotation value with those of the p-tolyl- analogues reported . See ref. [11, 12 and 22].

Gereral Experimental Procedure

A suspension of [$RuCl_2$(p-cymene)]$_2$ (3.8 mg) and (1*R*, 2*R*)-Ts-DPEN ligand (4.5 mg) in THF (1.0 mL) was stirred at r.t. for 2 h. HCOOH/Et_3N (5 : 2; 0.2 mL) and substrate (0.5 mmol) were added, and the mixture was stirred for 24 h. The product was then extracted with EtOAc (3 × 10 mL), and the combined extracts were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography [silica gel H, EtOAc–PE (1 : 6)] to give the pure product. For ketosulfieds **3a–3g**, the reaction conditions were identical, except that the ligand was (1*S*,2*S*)-Ts-DPEN and the reaction temperature was 40 °C.

Spectral Data

(S)-2-phenoxy-1-phenylethanol (2a)

$[\alpha]_D^{25}$ = + 35.4 ° (*c* 0.97, CH_2Cl_2); 97% yield. 96% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA

: hexane = 15 : 85). Retention time: t_{minor} = 8.65 min, t_{major} =11.25 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.36–7.28 (m, 3H), 6.98 (t, J = 7.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 5.14 (d, J = 8.8 Hz, 1H), 4.12 (dd, J_1 = 2.8 Hz, J_2 = 9.6 Hz, 1H), 4.01 (t, J = 9.2 Hz, 1H), 2.78 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 129.6, 128.6, 128.2, 126.3, 121.3, 114.7, 96.4, 73.32, 72.63; IR (cm^{-1}) : 3219, 1598, 1585, 1498, 1456, 1243; MS [ESI] m/z for $[C_{14}H_{14}O_2 + H]^+$ found (exceped): 215.0928 (215.1027).

(S)-2-phenoxy-1-p-tolylethanol (2b)

$[\alpha]_D^{25}$ = + 38.6 ^{o} (*c* 0.96, CH_2Cl_2); 86% yield. 98% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 9.5 min, t_{major} = 13.8 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 5.10 (d, J = 8.8 Hz, 1H), 4.10 (dd, J_1 = 3.0 Hz, J_2 = 9.4 Hz, 1H), 4.00 (t, J = 8.8 Hz, 1H), 2.73 (d, J = 2.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 138.0, 136.7, 129.6, 129.3, 126.2, 121.3, 114.7, 73.3, 72.5, 21.2; IR (cm^{-1}) : 3197, 2918, 1599, 1586, 1499, 1459, 1242; MS [ESI] m/z for $[C_{15}H_{16}O_2 + Na]^+$ found (exceped): 251.1038 (251.1048).

(S)-1-(4-methoxyphenyl)-2-phenoxyethanol (2c)

$[\alpha]_D^{25}$ = + 36.1 ^{o} (*c* 0.28, CH_2Cl_2); 89% yield. 97% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 13.8 min, t_{major} =19.3 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.8 Hz, 2H), 7.31–7.26 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 8.0 Hz, 4H), 5.08 (td, J_1 = 2.0 Hz, J_2 = 9.2 Hz, 1H), 4.07 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 4.00 (t, J = 9.2 Hz, 1H), 3.82 (s, 3H), 2.75 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.8, 126.7, 126.5, 125.8, 122.9, 117.7, 113.0, 112.2, 72.4, 71.2, 54.4; IR (cm^{-1}) : 3503, 2943, 2834, 1600, 1584, 1510, 1246, 1170; MS [ESI] m/z for $[C_{15}H_{16}O_3+Na]^+$ found (exceped): 267.0984 (267.0997).

(S)-2-(naphthalen-2-yloxy)-1-p-tolylethanol (2d)

$[\alpha]_D^{25}$ = + 31.9 ^{o} (*c* 0.48, CH_2Cl_2); 89% yield. 99% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 11.81 min, t_{major} = 21.10 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.75 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.45–7.33 (m, 4H), 7.24–7.19 (m, 3H), 7.12 (d, J = 2.0 Hz, 1H), 5.18 (d, J = 8.8 Hz, 1H), 4.21 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 2.76 (d, J = 2.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.1, 136.7, 134.5, 129.6, 129.3, 127.7, 126.8, 126.5, 126.3, 123.9, 118.7, 113.2, 107.1, 73.4, 72.5, 21.2; IR (cm^{-1}) : 3327, 2931, 1628, 1510, 1454, 1246, 1218, 1179; MS [ESI] m/z for $[C_{19}H_{18}O_2 + Na]^+$ found (exceped): 301.1193 (301.1204).

(S)-2-(4-(hydroxymethyl)phenoxy)-1-phenylethanol (2e)

$[\alpha]_D^{25}$ = + 17.6 ^{o} (*c* 0.46, CH_2Cl_2);; 92% yield. 99% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 25.93 min, t_{major} =28.70 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 6.8 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.36–7.28 (m, 3H), 6.91 (d, J = 8.8 Hz, 2H), 5.15 (dd, J_1 = 3.2 Hz, J_2 = 8.8 Hz, 1H), 4.63 (s, 2H), 4.1 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 4.03 (t, J = 9.2 Hz, 1H), 2.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 139.7, 133.8, 128.7, 128.6, 128.2, 126.3 114.8, 73.5, 72.6, 65.0; IR (cm^{-1}) : 3254, 2923, 2865, 1610, 1512, 1454, 1249; MS [ESI] m/z for $[C_{15}H_{16}O_3+Na]^+$ found (exceped): 267.0999 (267.0997).

(S)-1-(4-chlorophenyl)-2-(naphthalen-2-ylox y)ethanol (2f)

$[\alpha]_D^{25}$ = + 21.9 ^{o} (*c* 0.46, CH_2Cl_2); 94% yield. 93% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 11.65 min, t_{major} =23.08 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79–7.76 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.46–7.34 (m, 6H), 7.20–7.17 (m, 1H), 7.12 (d, J = 2.0 Hz, 1H), 5.30 (td, J_1 = 2.8 Hz, J_2 = 9.2 Hz, 1H), 4.21 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 4.10 (t, J = 9.2 Hz, 1H), 2.83 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.2, 134.4, 134.0, 129.7, 129.3, 128.8, 127.7, 127.6, 126.8, 126.6, 124.0, 118.5, 107.2, 73.2, 72.0;

IR (cm^{-1}) : 3559, 1596, 1576, 1487, 1217; MS [ESI] m/z for $[C_{18}H_{15}ClO_2+Na]^+$ found (exceped): 321.0623 (321.0658).

(S)-1-(4-chlorophenyl)-2-phenoxyethanol (2g)

$[\alpha]_D^{25}$ = + 35.8 ^{o} (*c* 0.74, CH_2Cl_2); 90% yield. 93% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 9.07 min, t_{major} =13.86 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.36 (m, 4H), 7.30 (t, J = 7.8 Hz, 2H), 6.99 (t, J = 3.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 5.11 (d, J = 8.0 Hz, 1H), 4.09 (dd, J_1 = 3.4 Hz, J_2 = 9.4 Hz, 1H), 3.97 (t, J = 9.2 Hz, 1H), 2.80 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 138.2, 133.9, 129.6, 128.8, 127.9, 121.5, 114.6, 73.1, 72.0; IR (cm^{-1}) : 3244, 1601, 1588, 1499, 1243; MS [ESI] m/z for $[C_{14}H_{13}O_2Cl+Na]^+$ found (exceped): 271.0493 (271.0502).

(S)-1-(4-methoxyphenyl)-2-(naphthalen-2-yloxy)ethanol (2h)

$[\alpha]_D^{25}$ = + 31.8 ^{o} (*c* 0.50, CH_2Cl_2); 87% yield. 98% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 16.91 min, t_{major} =28.15 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78–7.75 (m, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 3H), 7.35 (t, J = 6.8 Hz, 1H), 7.20 (dd, J_1 = 3.2 Hz, J_2 = 8.8 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 5.16 (td, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 1H), 4.19 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 4.13 (t, J = 9.2 Hz, 1H), 3.84 (s, 3H), 2.76 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 156.4, 134.5, 131.8, 129.6, 129.2, 127.7, 127.6, 126.8, 126.4, 123.9, 118.7, 114.1, 107.1, 73.4, 72.2 55.4; IR (cm^{-1}) : 3327, 2931, 1628, 1510, 1246, 1218, 1179; MS [ESI] m/z for $[C_{19}H_{18}O_3+Na]^+$ found (exceped): 317.1140 (317.1157).

(S)-2-(naphthalen-2-yloxy)-1-phenylethanol (2i)

$[\alpha]_D^{25}$ = + 26.1 ^{o} (*c* 0.93, CH_2Cl_2); 90% yield. 92% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 15 : 85). Retention time: t_{minor} = 11.31 min, t_{major} =16.21 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.76 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.45–7.41 (m, 3H), 7.38–7.33 (m, 2H), 7.22–7.19 (m, 1H), 7.13 (d, J = 2.4 Hz, 1H), 5.21 (td, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 1H), 4.24 (dd, J_1 = 2.8 Hz, J_2 = 9.2 Hz, 1H), 4.14 (t, J = 9.2 Hz, 1H), 2.81 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 155.3, 138.6, 133.4, 128.6, 127.6, 127.3, 126.7, 125.8, 125.5, 125.3, 122.9, 117.6, 106.0, 72.4, 71.6, 57.2; IR (cm^{-1}) : 3229, 1630, 1601, 1456, 1258, 1218, 1183; MS [ESI] m/z for $[C_{18}H_{16}O_2+Na]^+$ found (exceped): 287.1027 (287.1048).

(S)-2-phenoxy-1-(thiophen-2-yl)ethanol (2j)

$[\alpha]_D^{25}$ = − 1.98 ° (*c* 0.66, acetone); 86% yield. 98% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 10 : 90). Retention time: t_{minor} = 11.72 min, t_{major} = 19.22 min. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.30 (t, *J* = 8.0 Hz, 3H), 7.10 (d, *J* = 3.2 Hz, 1H), 7.04–7.94 (m, 4H), 5.38 (dd, J_1 = 3.2 Hz, J_2 = 8.0 Hz, 1H), 4.21 (dd, J_1 = 3.6 Hz, J_2 = 9.6 Hz, 1H), 4.14 (t, *J* = 8.8 Hz, 1H), 2.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.1, 143.1, 129.6, 126.8, 125.3, 124.7, 121.5, 114.7, 72.9, 68.9; IR (cm^{-1}) : 3496, 1599, 1498, 1243; MS [ESI] m/z for $[C_{12}H_{12}O_2$ S+Na$]^+$ found (exceped): 243.0432 (243.0456).

(S)-1-phenyl-2-(phenylthio)ethanol (4a)

$[\alpha]_D^{25}$ = − 8.69 ° (*c* 2.14, acetone); 93% yield. 100% *ee* determined by HPLC analysis (Chiralcel IA column, IPA : hexane = 3 : 97). Retention time: t_{major} = 19.54 min, t_{minor} =20.61 min. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.44−7.41 (m, 2H), 7.36−7.29 (m, 7H), 7.24−7.22 (m, 1H), 4.73 (dd, J_1 = 3.2 Hz, J_2 = 9.2 Hz, 1H), 3.33 (dd, J_1 = 3.6 Hz, J_2 = 13.8 Hz, 1H), 3.10 (dd, J_1 = 9.6 Hz, J_2 = 14.0 Hz, 1H), 2.83 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 136.9, 129.5, 125.0, 123.9, 123.3, 122.8, 121.6, 120.6, 66.4, 38.9; IR (cm^{-1}) : 3405, 1583, 1480, 1195, 1055; MS [ESI] m/z for $[C_{14}H_{14}OS+Na]^+$ found (exceped): 253.0681 (253.0663).

(S)- 1-(4-methoxyphenyl)-2-(phenylthio)ethanol (4b)

$[\alpha]_D^{25}$ = − 21.69 ° (*c* 0.83, acetone); 90% yield. 79% ee determined by HPLC analysis (Chiralcel AD-H column, IPA : hexane = 10 : 90). Retention time: t_{minor} = 16.70 min, t_{major} = 15.10 min. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.41 (d, *J* = 7.2 Hz, 2H), 7.33 − 7.21 (m, 5H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.68 (dd, J_1 = 3.6 Hz, J_2 = 9.4, 1H), 3.80 (s, 3H), 3.31 (dd, J_1 = 3.6 Hz, J_2 = 13.8 Hz, 1H), 3.10 (dd, J_1 = 9.6 Hz, J_2 = 14.0 Hz, 1H), 2.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 154.1, 129.1, 125.0, 123.9, 121.9, 121.5, 112.7, 108.7, 66.1, 50.1, 38.7; IR (cm^{-1}) : 3396, 2912, 1583, 1574, 1480, 1439, 1179, 1058; MS [ESI] m/z for $[C_{15}H_{16}O_2S+Na]^+$ found (exceped): 283.0749 (283.0769).

(S)-2-(p-tolylthio)-1-p-tolylethanol (4c)

$[\alpha]_D^{25}$ = − 50.20 ° (*c* 1.02, acetone); 91% yield. 95% *ee* determined by HPLC analysis (Chiralcel IA column, IPA : hexane = 3 : 97). Retention time: t_{major} = 20.44 min, t_{minor} =21.81 min. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.34 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 4H), 4.65 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 3.26 (d, *J* = 13.6 Hz, 1H), 3.06−3.00 (m, 1H), 2.84 (s, 1H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 139.2, 137.7, 137.0, 131.0, 129.9, 129.2, 125.8, 71.3, 44.7, 21.1, 21.0; IR (cm^{-1}) : 3418, 1514, 1493, 1056, 1018, 805; MS [ESI] m/z for $[C_{16}H_{17}OS-H]^-$ found (exceped): 257.1003 (257.1000).

(S)-2-(phenylthio)-1-p-tolylethanol (4d)

$[\alpha]_D^{25}$ = − 8.90 ° (*c* 3.15, acetone); 99% yield. 95% *ee* determined by HPLC analysis (Chiralcel IA column, IPA : hexane = 3 : 97). Retention time: t_{major} = 17.71 min, t_{major} =18.75 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.33−7.29 (m, 2H), 7.24 (s, 2H), 7.16 (d, *J* = 7.6 Hz, 3H), 4.71 (dd, J_1 = 3.6 Hz, J_2 = 9.2 Hz, 1H), 3.31 (dd, J_1 = 3.6 Hz, J_2 = 13.6 Hz, 1H), 3.10 (dd, J_1 = 9.6 Hz, J_2 = 14.0 Hz, 1H), 2.76 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 134.0, 132.5, 129.8, 124.9, 124.0, 123.9, 121.5, 120.6, 66.4, 38.7, 15.9; IR (cm^{-1}) : 3396, 2921, 1583, 1514, 1480, 1439, 1179, 1058, 1025, 739; MS [ESI] m/z for $[C_{15}H_{16}OS+Na]^+$ found (exceped): 283.0983 (267.0820).

(S)-1-(4-chlorophenyl)-2-(phenylthio)ethanol (4e)

$[\alpha]_D^{25}$ = −10.83 ° (*c* 2.16, acetone); 92% yield. 91% *ee* determined by HPLC analysis (Chiralcel IA column, IPA : hexane = 3 : 97). Retention time: t_{major} = 28.47 min, t_{minor} = 31.67 min. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.47(d, *J* = 1.6 Hz, 1H), 7.46(d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 1.2 Hz, 1H), 7.41 (t, *J* = 1.2 Hz, 1H), 7.34−7.30 (m, 2H), 7.25−7.22 (m, 3H), 4.67 (dd, J_1 = 3.6 Hz, J_2 = 9.2 Hz, 1H), 3.29 (dd, J_1 = 3.2 Hz, J_2 = 13.8, 1H), 3.04 (dd, J_1 = 9.6 Hz, J_2 = 14.0 Hz, 1H), 2.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.9, 129.2, 126.4, 125.3, 124.0, 122.3, 121.8, 116.5, 65.7, 38.9; IR (cm^{-1}) : 3395, 1585, 1481, 1403, 1189, 1070, 1010, 740; MS [ESI] m/z for $[C_{14}H_{13}OS+Na]^+$ found (exceped): 287.0294 (287.0273).

(S)-2-(p-tolylthio)-1-(4-chlorophenyl)ethanol (4f)

$[\alpha]_D^{25}$ = − 107.06 ° (*c* 0.17, acetone); 90% yield. 98% *ee* determined by HPLC analysis (Chiralcel IA column, IPA : hexane = 3 : 97). Retention time: t_{major} = 5.19 min, t_{minor} = 6.18 min. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.45 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* =8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.62 (dd, J_1 = 3.4 Hz, J_2 = 9.4 Hz, 1H), 3.23 (dd, J_1 = 3.6 Hz, J_2 = 14.0 Hz, 1H), 2.96 (dd, J_1 = 9.6 Hz, J_2 = 14.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 140.6, 137.4, 133.6, 131.3, 130.5, 130.0, 128.6, 127.2, 70.8, 44.9, 21.1; IR (cm^{-1}) : 3300, 1433, 1416, 1182, 1128, 1078, 753; MS [ESI] m/z for $[C_{15}H_{15}OS-H]^-$ found (exceped): 278.0513 (278.0532).

(S)-2-(p-tolylthio)-1-(4-methoxyphenyl)ethanol (4g)

$[\alpha]_D^{25}$ = − 52.60 ° (*c* 1.04, acetone); 88% yield. 95% *ee* determined by HPLC analysis (Chiralcel IA column, IPA : hexane = 3 : 97). Retention time: t_{major} = 30.75 min, t_{minor} = 34.74 min. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.34 (d, *J* = 8.0 Hz, 2H), 7.27 (s, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.63 (dd, J_1 = 2.6 Hz, J_2 = 9.4 Hz, 1H), 3.80 (s, 3H), 3.24 (d, *J* = 9.6 Hz, 1H), 3.03 (dd, J_1 = 9.6 Hz, J_2 = 14.0 Hz, 1H), 2.86 (d, *J* = 14.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.0, 137.8, 135.0, 131.7, 130.6, 127.8, 114.6, 77.8, 55.9, 45.4, 21.7;

IR (cm^{-1}) : 3457, 2835, 1586, 1513, 1248, 1091, 1033; MS [ESI] m/z for $[C_{16}H_{18}O_2S-H]^-$ found (exceped): 273.0982 (273.0949).

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