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Enantioselective Synthesis of (*S*)-γ-Amino Alcohols by Ru/Rh/Ir Catalyzed Asymmetric Transfer Hydrogenation (ATH) with Tunable Chiral Tetraaza Ligands in Water

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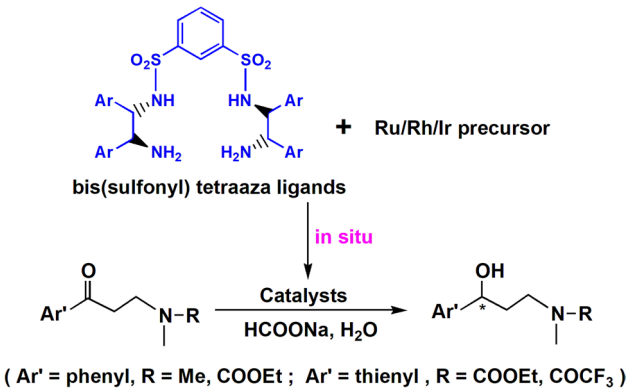
Abstract

(*R*/*S*)-γ-Amino alcohols are the key intermediates for the preparation of Fluoxetine, Atomoxetine, Nisoxetine and Duloxetine. In this paper, we describe an effective method to obtain (*S*)-γ-amino alcohols by Ru/Rh/Ir catalyzed asymmetric transfer hydrogenation with tunable chiral tetraaza ligands (**L1**–**L5**) in HCOONa/H_2O system. The asymmetric reduction of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$/**L1** was utilized as the model ATH reaction to achieve the optimum reaction conditions. The best results were obtained by [$RhCp^*Cl_2$]$_2$/**L5** affording the corresponding (*S*)-γ-amino alcohol with a good 97% conversion and an excellent > 99% ee in the reduction of 3-(*N*-methyl, *N*-carbethoxy)-1-phenylpropan-1-one. The influence of electronic and steric effects of the substituents in the ligands on the catalytic activities was also discussed.

Graphical Abstract

(*S*)-γ-Amino alcohols were prepared via asymmetric transfer hydrogenation of β-amino ketones catalyzed by Ru/Rh/Ir complexes in situ with tunable chiral tetraaza ligands in HCOONa/H_2O system. A moderate to excellent conversion (~ 99%) and enantioselectivity (~ 99%) were obtained with varied electronic and steric effects of the substituents on ligands and substrates.



Keywords Tetraaza ligand · Asymmetric transfer hydrogenation · β-Amino ketones · γ-Amino alcohols · HCOONa

1 Introduction

Fluoxetine, atomoxetine and duloxetine are the efficient serotonin (5-HT), norepinephrine (NE) and serotonin-norepinephrine re-uptake inhibitor, respectively. They are generally used as antidepressants for the treatment of several depression related disorders [1, 2]. Enantiomerically pure (*R*/*S*)-γ-amino alcohols, the key chiral precursor of these xetine's

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API, are obtained in the industrial production by chemical or enzymatic kinetic resolution [3, 4]. From the view of green chemistry, this approach has the disadvantage of low utilization rate of atom and serious environmental pollution.

Asymmetric transfer hydrogenation (ATH) have been developed to prepare the chiral secondary alcohols in excellent enantioselectivity and good yield by the reduction of simple or functionalized ketones with chiral Ru/Rh/Ir catalysts [5–8]. The ATH of *β*-amino ketones by Ru/Rh complexes with chiral monotosylated 1,2-diamines or amino alcohols, introduced by Noyori, is the efficient method to obtain the chiral *γ*-amino alcohol with mild reaction condition and operational simplicity [6, 9–11]. A highly enantioselective synthesis of (*R*)-*N*-Boc-*N*-methyl-3-hydroxy-3-phenyl-propylamine, a precursor of (*R*)-Fluoxetine, was achieved *via* ATH of 3-(*N*-Boc, *N*-methyl)-1-phenylpropan-1-one with combination of $[RhCp^*Cl_2]_2$ and a chiral amino alcohol ligand [12]. (*S*)-*N*-methyl-3-hydroxy-3-(2-thienyl) propylamine, a precursor of (*S*)-Duloxetine, was reported to be accomplished by aza-Michael addition-ATH of 1-(thiophen-2-yl)prop-2-enone and methylamine catalyzed by (*S,S*)-TsDPEN-Ru in HCOONa system with 92% yield and 99% ee [13]. Inspired by Noyori' (*S,S*)-TsDPEN-Ru, our group had developed some air-stable bis(sulfonyl) tetraaza ligands derived from (*1S, 2S*)-diphenylethylenediamine and paid attention to their catalytic activity in the $[Ru(p\text{-cymene})Cl_2]_2$-Catalyzed ATH of aromatic ketones [14–17]. In this work, we report the ATH of *β*-amino ketones catalyzed by Ru/Rh/Ir complexes in situ with tunable chiral tetraaza ligands (**L1–L5**) in HCOONa/H_2O system, giving the corresponding optically active *γ*-amino alcohols in moderate to excellent conversion and enantioselectivity.

2 Experimental

2.1 General

Unless otherwise stated, commercial reagents and solvents were used as received without further purification. 2-Acetylthiophene and 3-(dimethylamino)-1-phenylpropan-1-one were obtained from Zhejiang Liaoyuan Pharmaceutical Co., Ltd. (1*S*,2*S*)-1,2-diphenylethylenediamine and (1*R*,2*R*)-1,2-bis-(2-hydroxyphenyl)-1,2-diaminoethane were purchased from Sigma-Aldrich (Steinem, Germany). 1,3-Benzenedisulfonyl chloride and trifluoroacetic anhydride were purchased from TCI (Shanghai, China). Methylamine hydrochloride, *N*-methylbenzylamine, 2′-methyloxybenzaldehyde, 4′-methyloxybenzaldehyde, 4′-nitrobenzaldehyde and 4′-trifluoromethylbenzaldehyde were obtained from J&K chemicals (Shanghai, China). $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$, $[RhCp^*Cl_2]_2$ and $[IrCp^*Cl_2]_2$ were purchased from Alfa Aesar (Ward Hill, Massachusetts, UK). All ATH reactions were carried out under nitrogen atmosphere using oven-dried glassware in oil bath.

The ^1H NMR and ^{13}C NMR spectra were recorded on a 500 MHz Bruker spectrometer. Mass spectra were measured with Agilent (Santa Clara, CA, USA) 5979 spectrometer. LC-MS was measured with Agilent (Santa Clara, CA, USA) Infinity 1290 LC and 6530 Accurate-Mass Q-TOF MS. Chiral GC analysis was carried out using Agilent GC 7890A with CP-Chiralsil-Dex-CB Chiral column (Santa Clara, CA, USA).

2.2 Synthesis of the Ligands

L1–L5 were prepared as per the procedure reported in our previous work [16]. The synthetic route in outlined in Scheme 1.

2.2.1 (*S,S,S,S*)-*N,N*-Bis(1,2-Diphenylethylenediamino)-1,3-Benzenedisulfonyl Amine L1

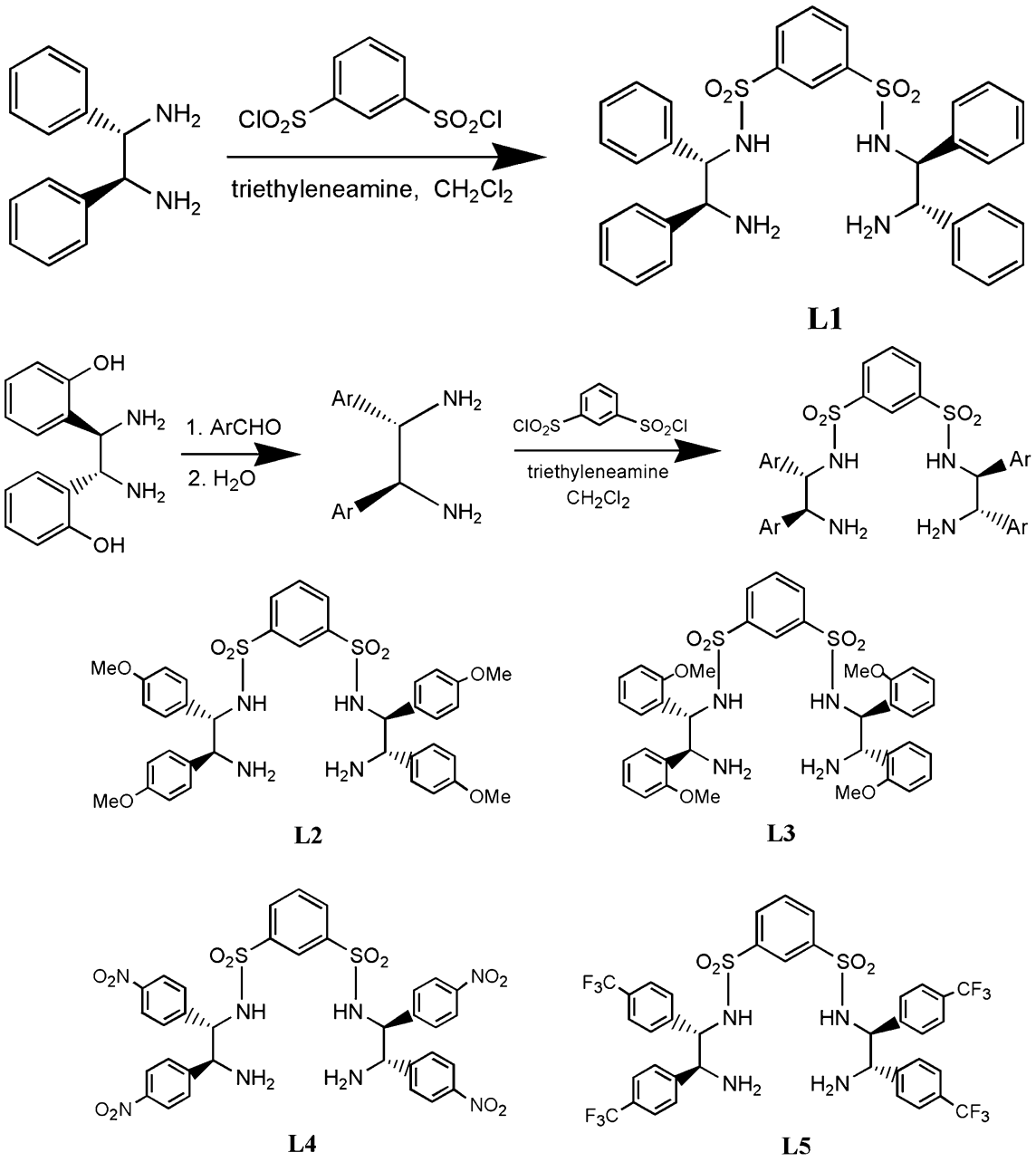
Light yellow powder, $[\alpha]_D^{20}$: +88.4°(c 0.1, $CHCl_3$). ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 3.38 (br singlet, 6H), 3.99-4.00 (d, J = 7.5 Hz, 2H), 4.31–4.33 (d, J = 7.5 Hz, 2H), 6.87–6.92 (m, 10H), 7.08–7.09 (m, 10H), 7.19 (m, 1H), 7.28–7.30 (dd, J = 1.5 Hz, 8.0 Hz, 2H), 7.70 (singlet, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 60.22(*C*HNH), 64.23(*C*HNH), 124.71, 127.31, 127.82, 127.98, 128.09, 128.14, 128.29, 128.58, 129.50, 138.41, 140.72, 140.09, 141.09. HRMS (ESI) calcd for $C_{34}H_{35}N_4O_4S_2$ $[M+H]^+$ 627.2100, found 627.2088.

2.2.2 (*S,S,S,S*)-*N,N*-Bis(1,2-Bis(4′-Methyloxybenzene) Ethylenediamino)-1,3-Benzenedisulfonyl Amine L2

Bright yellow powder, $[\alpha]_D^{20}$: -109° (c 0.1, $CHCl_3$). ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 3.58 (s, 6H), 3.648 (s, 6H), 3.98-4.00 (d, J = 8.0 Hz, 2H), 4.28–4.29 (d, J = 8.0 Hz, 2H), 6.43–6.45 (d, J = 8.5 Hz, 4H), 6.65–6.67 (d, J = 9.0 Hz, 4H), 6.75–6.77 (d, J = 8.5 Hz, 4H), 7.01–7.02 (d, J = 9.0 Hz, 4H), 7.04–7.07 (t, J = 8.0 Hz, 1H), 7.29–7.30 (d, J = 1.5 Hz, 1H), 7.31–7.32 (d, J = 2.0 Hz, 1H), 7.66 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 55.21(O*C*H_3), 55.32(O*C*H_3), 59.85(*C*HNH), 64.26(*C*HNH), 113.41, 113.58, 124.82, 128.91, 129.06, 129.40, 131.00, 133.25, 142.01, 158.25, 158.56. HRMS (ESI) calcd for $C_{38}H_{43}N_4O_8S_2$ $[M+H]^+$ 747.2522, found 747.2480.

2.2.3 (*S,S,S,S*)-*N,N*-Bis(1,2-Bis(2′-Methyloxybenzene) Ethylenediamino)-1,3-Benzenedisulfonyl Amine L3

Yellow powder, $[\alpha]_D^{20}$: +125° (c 0.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.42 (s, 6H), 3.55 (s, 6H),



Scheme 1 Synthesis of ligands **L1–L5**

4.81 (s, 2H), 5.10 (s, 2H), 6.27–6.28 (d, $J = 8.0$ Hz, 2H), 6.40–6.43 (d, $J = 7.5$ Hz, 2H), 6.71–6.80 (m, 7H), 6.91–6.95 (t, $J = 7.5$ Hz, 8.0 Hz, 2H), 7.10–7.14 (td, $J = 1.0$ Hz, 8.0 Hz, 2H), 7.19–7.21 (dd, $J = 1.5$ Hz, 8.0 Hz, 2H), 7.30 (s, 2H), 7.43 (s, 1H). ^{13}C NMR (125 MHz, CDCl3): δ (ppm) 55.37(*C*HNH), 55.91(*C*HNH), 110.22, 111.29, 119.87, 120.30, 129.10, 129.34, 129.56, 130.44, 140.80, 155.82, 156.84. HRMS (ESI) calcd for $C_{38}H_{43}N_4O_8S_2$ $[M + H]^+$ 747.2522, found 747.2480.

2.2.4 (*S,S,S,S*)-*N,N*-Bis(1,2-Bis(4′-Nitrobenzene) Ethylenediamino)-1,3-Benzenedisulfonylnyl Amine L4

Brownish red powder, $[\alpha]_D^{20}$: − 107° (c 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.20 (s, 4H), 6.80–6.83 (t, $J = 7.5$ Hz, 1H), 6.93–6.95 (d, $J = 8.0$ Hz, 1H), 6.97–6.99 (d, $J = 7.5$ Hz, 1H), 7.19–7.22 (t, $J = 7.0$ Hz, 8.0 Hz, 1H), 7.41–7.43 (d, $J = 8.5$ Hz, 8H), 8.13–8.15 (d, $J = 8.5$ Hz, 8H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm)

45.99(*C*HNH), 82.89, 89.18, 123.77, 123.85, 123.90, 124.17, 128.90, 128.93, 129.39, 129.67. HRMS (ESI) calcd for $C_{34}H_{31}N_8O_{12}S_2$ $[M+H]^+$ 807.1503, found 807.1454.

2.2.5 (*S,S,S,S*)-*N,N*-Bis(1,2-Bis(4′-Trifluoromethylbenzene) Ethylenediamino)-1,3-Benzenedisulfo-nyl Amine L5

Pinkish purple solid, $[\alpha]_D^{20}$: −95.6° (c 0.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.20–4.21 (d, $J=4.5$ Hz, 2H), 4.49–4.50 (d, $J=5.0$ Hz, 2H), 6.80–6.83 (t, $J=7.5$ Hz, 8.0 Hz, 1H), 7.29–7.31 (d, $J=8.0$ Hz, 4H), 7.35–7.37 (d, $J=8.0$ Hz, 4H), 7.37–7.39 d, $J=8.5$ Hz, (4H), 7.44–7.46 (d, $J=8.5$ Hz, 4H), 7.54–7.55 (d, $J=8.0$ Hz, 3H), 7.95 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 59.69(*C*F_3), 61.64(*C*HNH), 62.74(*C*HNH), 125.29, 125.32, 125.51, 125.58, 125.62, 126.70, 126.96, 137.31, 129.46, 129.56, 129.96, 130.21, 140.85, 142.57, 144.512, 147.04. HRMS (ESI) calcd for $C_{38}H_{31}F_{12}N_4O_4S_2$ $[M+H]^+$ 899.1595, found 899.1587.

2.3 Synthesis of the Substrates

3-(*N*-Carbethoxy, *N*-methyl)-1-phenylpropan-1-one (**II**) and 3-(*N*-carbethoxy, *N*-methyl)-1-(thiophen-2-yl)propan-1-one (**IV**) were prepared by a modified literature procedure [18, 19] with improved yield (Scheme 2)

N-Benzylmethylamine (9.09 g, 75 mmol), paraformaldehyde (2.26 g, 75 mmol), and 37% HCl (2 mL) were added to isopropanol (16 mL). The mixture was heated to reflux at 78 °C till the full dissolution of paraformaldehyde. Acetophenone (6.6 g, 60 mmol) or 2-Acetylthiophene (7.56 g, 60 mmol) was added to the reaction mixture with stirring, and the mixture was refluxed for a further 8 h. After the removal of the solvent, 20 mL of acetone was added. White crystalline powder **I** (11.5 g, 58% yield) or **III** (9.8 g, 52% yield) was formed, which was filtered off, washed with cooled acetone (3 × 10 mL), and dried in air.

I (1.737 g, 6 mmol) or **III** (1.773 g, 6 mmol), $NaHCO_3$ (1.2629 g, 15 mmol), KI (0.0499 g, 0.3 mmol), and ethyl chloroacetate (0.9609 g, 9 mmol) were mixed in dichloromethane (20 mL). The mixture was heated to reflux at 50 °C. After completion of the reaction tracing by TLC, the solvent was removed under reduced pressure. The crude product was purified by column chromatogram on silica using ethyl acetate/petroleum ether (1:4) as the eluent (R_f = 0.29). Product **II** and **IV** were obtained as pale yellow oily liquid (**II**: 0.79 g, 56%; **IV** (0.74 g, 51%).

II: ^1H NMR (500 MHz, $CDCl_3$): δ(ppm) 1.25 (t, $J=6.5$ Hz, 3H), 2.96 (s, 3H), 3.25 (m, 2H), 3.68 (t, $J=7.5$ Hz, 2H), 4.13 (t, $J=4.5$ Hz, 2.5 Hz, 2H), 7.45–7.48 (m, 2H), 7.55–7.58 (m, 1H), 7.98–7.97 (m, 2H).

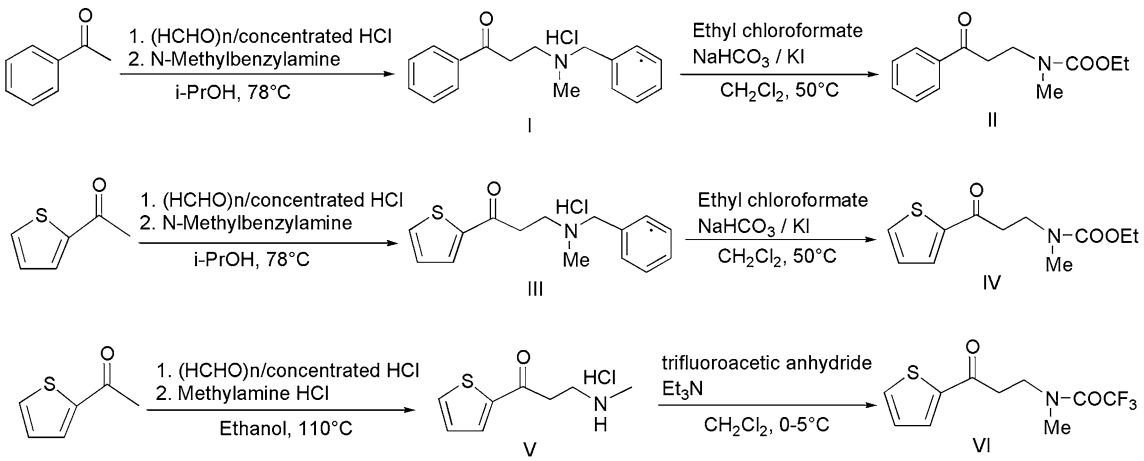
IV: ^1H NMR (500 MHz, $CDCl_3$): δ(ppm) 1.22–1.26 (m, 3H), 2.83 (s, 3H), 4.09–4.13 (m, 2H), 4.15–4.20 (m, 2H), 4.46 (s, 2H), 7.24–7.73 (m, 3H).

3-(*N*-Methyl, *N*-trifluoroacetyl)amino-1-(thiophen-2-yl) propan-1-one (**VI**) was synthesized according to the reported method [20] as a yellow crystalline solid.

VI: Mp: 44–45 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.06 (s, 3H), 3.28 (t, 2H), 3.82–3.89 (t, $J=6.5$ Hz, 2H), 7.13–7.18 (m, 1H), 7.66–7.77 (m, 2H).

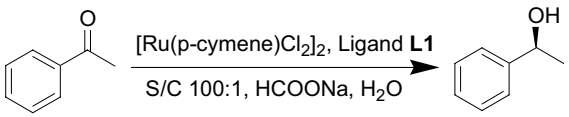
2.4 General Procedure for the Asymmetric Transfer Hydrogenation in Water

The metal precursor $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$, $[Cp^*RhCl_2]_2$ or $[Cp^*IrCl_2]_2$ (0.005 mmol) and the ligands **L1–L5** (0.011 mmol) were mixed in degassed water (2 mL) and stirred at 28 °C for 1 h, subsequently, anhydrous sodium formate (0.6801 g, 10 mmol) and the substrate (1.0 mmol) were added. If applicable, cetyl trimethylammonium bromide



Scheme 2 Synthesis of the substrates

Table 1 ATH reaction of acetophenone



Entry[a]	S/M/L/base	T/°C	T/h	Conv.[b] (%)	ee (%)
1	100:1:1.1:100	28	11	24	95(S)
2	100:1:1.1:500	28	11	58	94(S)
3	100:1:1.1:1000	28	11	71	96(S)
4	100:1:1.1:1500	28	11	96	93(S)
5	100:1:1.1:2000	28	11	75	94(S)
6	100:1:1.1:100	40	11	52	93(S)
7	100:1:1.1:500	40	11	75	93(S)
8	100:1:1.1:1000	40	11	86	93(S)
9	100:1:1.1:1500	40	11	95	93(S)
10	100:1:1.1:2000	40	11	98	92(S)
11	100:1:1.1:100	60	11	76	85(S)
12	100:1:1.1:500	60	11	98	90(S)
13	100:1:1.1:1000	60	4	48	90(S)
14	100:1:1.1:1000	60	6	61	90(S)
15	100:1:1.1:1000	60	8	72	90(S)
16	100:1:1.1:1000	60	11	>99	90(S)
17	100:1:1.1:1000	60	13	98	90(S)
18	100:1:1.1:1500	60	11	98	89(S)
19	100:1:1.1:2000	60	11	98	90(S)

S/M/L/base: mole proportion of substrate, metal, ligand and base

[a]Reaction conditions: acetophenone: 1.0×10^{-3} mol; ligand: 1.1×10^{-5} mol; $[Ru(p\text{-cymene})Cl_2]_2$: 5.0×10^{-6} mol; HCOONa: 1–20 mmol; water: 2 cm^3; temperature: 28, 40 and 60 °C; reaction time: 4, 6, 8, 11 and 13 h; nitrogen protection

[b]Conversion and ee were determined by chiral GC (CP-Chiralsil-Dex-CB Chiral column)

(CTMAB, 0.0365 g, 0.1 mmol) was added. At 28 °C, 40 °C or 60 °C the mixture was heated for another 11 h. The suspension was extracted with dichloromethane (3×5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure, and then passed through a short silica gel column. The enantiomeric excess (ee) was measured by Chiral GC analysis along with the conversion.

3 Results and Discussion

Tetraaza ligands **L2–L5** were designed to explore the electronic and steric effects on the catalytic activity by introducing either an electron donating or an electron withdrawing substituent at 2- or 4-position of the phenyl rings.

The asymmetric reduction of acetophenone catalyzed by $[Ru(p\text{-cymene})Cl_2]_2$ complexed with **L1** in situ was utilized as the model ATH reaction to gain the optimum reaction conditions in $HCOONa/H_2O$ system. Screening was carried out for the base amount, reaction temperature and reaction time. The results were reported in Table 1.

The reaction temperature had an important effect on conversion and ee value. By comparing the data of the same base amount and reaction time at 28, 40 and 60 °C in Table 1, the conversion increased significantly, but the ee value decreased slowly as the reaction temperature increased. The conversion and ee value of the reduction reaction at 60 °C under different reaction time were determined, respectively. As shown in Fig. 1a, the highest conversion was more than 99% at 11 h. However, the ee value was comparatively stable with the extending of reaction time. The influence of HCOONa amount on catalysis activities was also investigated when the reduction reaction was performed. As shown in Fig. 1b, the conversion increased obviously, and

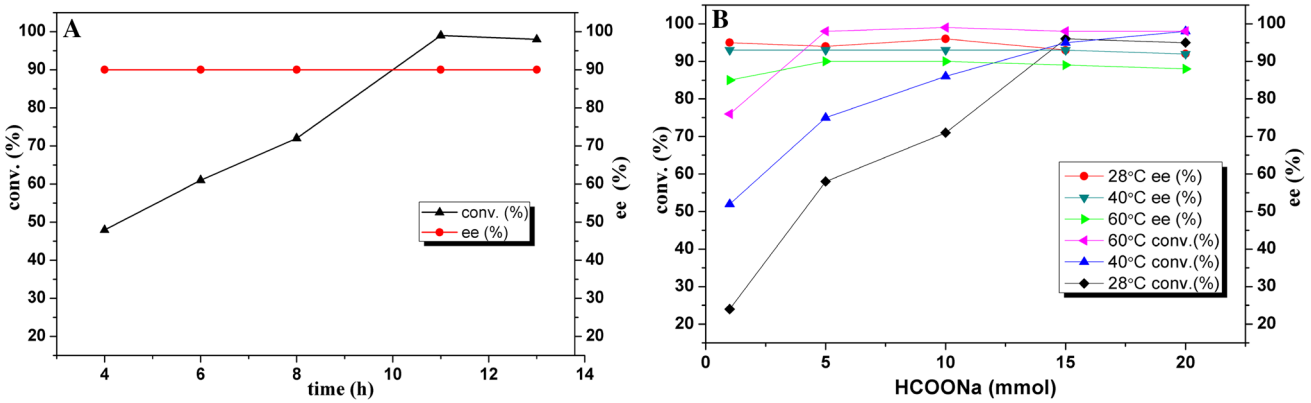
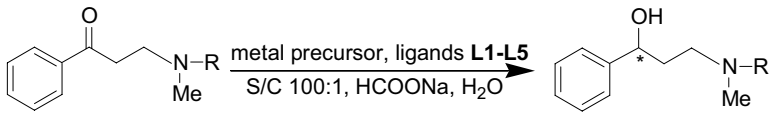


Fig. 1 **a** The effect of reaction time on conversion and ee value (temperature of 60 °C, HCOONa of 10 mmol). **b** The effect of HCOONa on catalysis activities (reaction time of 11 h)

Table 2 ATH reaction of 3-(*N,N*-dimethyl)amino-1-phenylpropan-1-one and 3-(*N*-carbethoxy, *N*-methyl) amino-1-phenylpropan-1-one



1 R= Me
2 R= COOEt

Entry[a]	Sub.	Metal precursor	Ligand	CTMAB (mg)	Conv.[b](%) (Reduction by-product[c])	ee (%)
1	1	$[Ru(p\text{-cymene})Cl_2]_2$	L1	–	0.0(71)	N(N)
2	2		L1	–	93	82(S)
3	2		L2	–	80	79(S)
4	2		L3	–	61	83(S)
5	2		L4	–	16	47(R)
6	2		L5	–	81	87(S)
7	2		L1	36.5	99	92(S)
8	2		L2	36.5	> 99	93(S)
9	2		L3	36.5	95	90(S)
10	2		L4	36.5	80	40(R)
11	2		L5	36.5	95	94(S)
12	2	$[RhCp^*Cl_2]_2$	L1	36.5	55	> 99(S)
13	2		L2	36.5	98	90(S)
14	2		L3	36.5	96	90(S)
15	2		L4	36.5	97	59(R)
16	2		L5	36.5	97	> 99(S)
17	2	$[IrCp^*Cl_2]_2$	L1	36.5	68	98(S)
18	2		L2	36.5	94	96(S)
19	2		L3	36.5	90	89(S)
20	2		L4	36.5	88	27(R)
21	2		L5	36.5	88	96(S)

"–": no surfactant; "N": no detected

[a]Reaction conditions: substrate: 1.0×10^{-3} mol; ligand: 1.1×10^{-5} mol; catalyst: 5.0×10^{-6} mol; HCOONa: 1.0×10^{-2} mol; water: 2 cm^3; temperature 60 °C; reaction time 11 h; nitrogen protection

[b]Conversion and ee were determined by chiral GC (CP-Chiralsil-Dex-CB Chiral column)

[c]Reduction by-product: 1-phenylpropan-1-ol

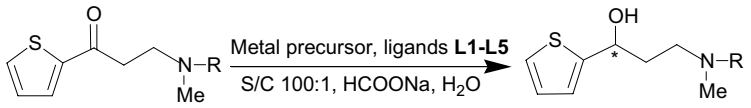
ee value declined gently on the whole when the amount of HCOONa increased from 1 to 20 mmol.

After preliminary optimization, it was established that 60 °C of reaction temperature, 10 mmol of HCOONa and 11 h of reaction time were the optimum reaction conditions taking both conversion and ee value into account.

Comparing entries 2–6 with entries 7–11 in Table 2 when $[Ru(p\text{-cymene})Cl_2]_2$ was used as the catalysis precursor, cetyl tri methyl ammonium bromide (CTMAB), a surfactant, was significantly helpful for both conversion and ee value [21]. Therefore, this surfactant was applied in the ATH of β-amino ketones in $HCOONa/H_2O$ system.

As shown surprisingly on entry 1 in Table 2, the reduction reaction did not afford the expected 3-(*N,N*-dimethyl) amino-1-phenylpropan-1-ol, but instead 1-phenylpropanol, the deamination by-product, was available with the conversion of 71% when the substrate was 3-(*N,N*-dimethyl) amino-1-phenylpropan-1-one. Due to the strong alkalinity of N atom of substrate resulting from two electron-donating groups of methyl, the N atom was apt to coordinate with Ru(II), resulting in the activation of C–N bond. It may benefit the side reaction of deamination. Similar results was found in Qu's experiments when the ATH reduction was executed under formic acid/triethylamine system [22]. In order to avoiding the side reaction, carbethoxy or trifluoroacetyl,

Table 3 ATH reaction of 3-(*N*-carbethoxy, *N*-methyl)amino-1-(thiophen-2-yl)propan-1-one and 3-(*N*-methyl, *N*-trifluoroacetyl)amino-1-(thiophen-2-yl)propan-1-one



Entry[a]	Sub.	Metal precursor	Ligand	Conv. [b](%)	ee (%)
1	1	$[Ru(p\text{-cymene})Cl_2]_2$	L1	92	74(S)
2	1		L2	91	81(S)
3	1		L3	85	76(S)
4	1		L4	71	40(R)
5	1		L5	95	84(S)
6	2		L1	92	76(S)
7	2		L2	93	81(S)
8	2		L3	88	80(S)
9	2		L4	67	59(S)
10	2		L5	94	87(S)
11	1	$[RhCp^*Cl_2]_2$	L1	42	81(S)
12	1		L2	51	47(S)
13	1		L3	22	40(S)
14	1		L4	26	81(R)
15	1		L5	56	57(S)
16	1	$[IrCp^*Cl_2]_2$	L1	80	56(S)
17	1		L2	78	48(S)
18	1		L3	12	32(S)
19	1		L4	54	56(R)
20	1		L5	78	56(S)

[a]Reaction conditions: substrate: 1.0×10^{-3} mol; ligand: 1.1×10^{-5} mol; catalyst: 5.0×10^{-6} mol; HCOONa: 1.0×10^{-2} mol; water: 2 cm^3; surfactant: 36.5 mg; temperature 60 °C; reaction time 11 h

[b]Conversion and ee were determined by chiral GC (CP-Chiralsil-Dex-CB Chiral column)

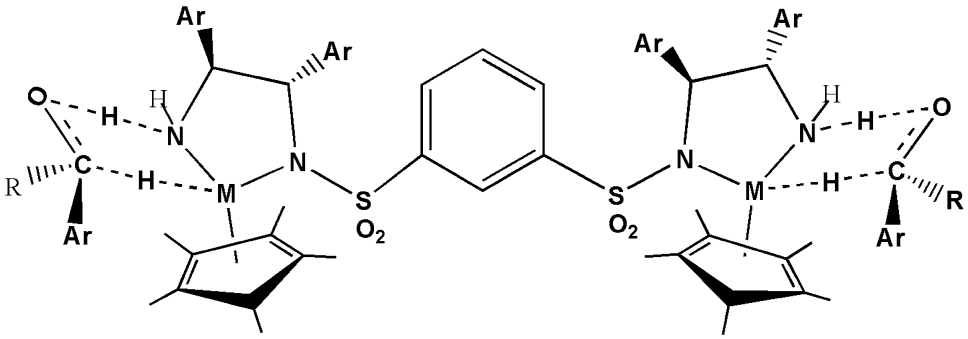


Fig. 2 The proposed six-membered metal–ligand-substrate transition state (M: Rh or Ir)

an electron-withdrawing group, was introduced to the N atom of two *β*-amino ketones as described in Sect. 2.3.

Comparing to ligand **L2** and **L3** carrying an electron-donating group on the phenyl, the ligand **L5** bearing a strong electron-withdrawing group displayed higher catalytic enantioselectivity (94–99% (*S*)-enantiomer), but did not exhibit advantage on conversion when the substrate is 3-(*N*-carbethoxy, *N*-methyl)amino-1-phenylpropan-1-one (entries 8, 9 and 11; entries 13, 14 and 16; entries 18, 19 and 21 in Table 2). The same trend was also observed

when substrates are 3-(*N*-carbethoxy, *N*-methyl)amino-1-(thiophen-2-yl)propan-1-one and 3-(*N*-methyl, *N*-trifluoroacetyl)amino-1-(thiophen-2-yl)propan-1-one (entries 2, 3 and 5; entries 7, 8 and 10; entries 12, 13 and 15; entries 17, 18 and 20 in Table 3). We had proposed a six-membered metal–ligand substrate transition state (TS) in the previous work based on the experimental results and Noyori's calculated mechanism [9] when mixing 1:1 ratio of Ru to ligand **L1** in water at 60 °C [16]. The component of [(Cp*)ClRh**L1**RhCl(Cp*)] was confirmed by elemental analysis of the isolated precatalyst when 1:1 ratio of $[Cp^*RhCl_2]_2$ to **L1** was mixed in $HCOONa/H_2O$ at 60 °C with the same reaction conditions as in transfer hydrogenation. It was reasonable to presume the similar double metals TS as indicated in Fig. 2 when $[Cp^*RhCl_2]_2$ or $[Cp^*IrCl_2]_2$ was the precursor under the same reaction conditions. The electron withdrawing effect may promote the formation of six-membered hydrogen bonds ring in TS via increasing the nucleophilicity of ligands to Ru/Rh/Ir. However, the electron donating effect restrains the stability of the six-membered metal–ligand substrate TS [9, 23–25]. Moreover, comparing to **L2, L3** with steric hindrance effect besides electron-donating effect exerted a more negative influence on conversion and enantioselectivity (entries 8 and 9, entries 13 and 14, entries 18 and 19 in Table 2; entries 2 and 3, entries 7 and 8, entries 17 and 18 in Table 3).

When (*S,S,S,S*)-tetraaza ligand and *p*-cymene or pentamethylcyclopentadiene (Cp*) were used as ancillaries, two (*R*)-configured metal centers were obtained, in which two N atoms of tetraaza ligand chelated one metal independently. The transfer hydrogenation via this (*R*)-configured TS with *S* conformation of carbonyl carbon atom, resulting perhaps from the attractive CH/π interaction between *p*-cymene or pentamethylcyclopentadiene of the Ru/Rh/Ir complexes and the aryl substituent in the substrate, afforded (*S*)-enantiomer.

Astonishingly, a reversion of enantioselectivity was observed when nitro was imported in para-position (**L4**) (entries 10, 15, 20 in Table 2 and entries 4, 9, 14,19 in Table 3). (*R*)-enantiomer was found to be the predominant product. The reversion phenomenon was also found in our previous work when nitro-tetraaza ligand was applied in the ATH reduction of simple or functionalized ketones [16]. It is speculated that the delocalized π-bond of nitro causes this distinctness of enantioselectivity by dragging strongly the hydrogen attached upon the prochiral carbon.

4 Conclusions

On the basis of our efforts in asymmetric transfer hydrogenation, we report herein the asymmetric synthesis of (*S*)-γ-amino alcohols via ATH reduction catalyzed by Ru/Rh/Ir precursor complexing with tunable chiral tetraaza ligands in an environmentally friendly medium with a moderate to excellent conversions and enantioselectivities. A good 97% conversion and an excellent > 99% ee value of (*S*)-3-(*N*-methyl, *N*-carbethoxy)amino-1-phenylpropan-1-ol were obtained by $[RhCp^*Cl_2]_2$/**L5** under the optimal reaction conditions. This makes it particularly attractive for the practical synthesis of antidepressants through a sequential de-esterification and etherification reaction.

The influence of electronic and steric effects of the substituents in the ligands on the catalytic activities was preliminary explored. The experiment results reveal that the electron withdrawing effect strengthens the enantioselectivity by way of consolidating the sixed-membered transition state but the electron donating effect and steric effect discourage the catalytic activity of the ligands.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

References

1. Dugan SE, Fuller MA (2004) Duloxetine: a dual reuptake inhibitor. Ann Pharmacother 38:2078–2082
2. Fournier JC, DeRubeis RJ, Hollon SD, Sona Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J (2010) Antidepressant drug effects and depress severity. J Am Med Assoc 303:47–53
3. Sakai K, Sakurai R, Yuzawa A, Kobayashi Y, Saigo K (2003) Resolution of 3-(methylamino)-1-(2-thienyl)propan-1-ol, a new key intermediate for duloxetine, with (S)-mandelic acid. Tetrahedron: Asymmetry 14:1631–1636
4. Liu HL, Hoff BH, Anthonsen T (2000) Chemo-enzymatic synthesis of the antidepressant duloxetine and its enantiomer. Chirality 12:26–29
5. Fujii A, Hashiguchi S, Uematsu N, Ikariya T, Noyori R (1996) Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones using a formic acid—triethylamine mixture. J Am Chem Soc 118:2521–2522
6. Noyori R, Hashiguchi S (1997) Asymmetric transfer hydrogenation catalyzed by chiral ruthenium complexes. Acc Chem Res 30:97–102
7. Noyori R, Yamakawa M, Hashiguchi S (2001) Metal–ligand bifunctional catalysis: a nonclassical mechanism for asymmetric hydrogen transfer between alcohols and carbonyl compounds. J Org Chem 66:7931–7944
8. Hashiguchi S, Fujii A, Takehara J, Ikariya T, Noyori R (1995) Asymmetric transfer hydrogenation of aromatic ketones catalyzed by chiral ruthenium(II) complexes. J Am Chem Soc 117:7562–7563
9. Hamada T, Torii T, Izawa K, Noyori R, Ikariya T (2002) Practical synthesis of optically active styrene oxides via reductive transformation of 2-chloroacetophenones with chiral rhodium catalysts. Org Lett 4:4373–4376

10. He SZ, Li XM, Dai J, Yan M (2008) Synthesis of antidepressant duloxetine *via* asymmetric transfer hydrogenation. Chin Chem Lett 19:23–25
11. Cortez NA, Aguirre G, Parra-Hake M, Somanathan R (2013) Synthesis of (*R*)-tembamide and (*R*)-aegeline via asymmetric transfer hydrogenation in water. Tetrahedron: Asymmetry 24:1297–1302
12. Buitrago E, Lundberg H, Andersson H, Ryberg P, Adolfsson H (2012) High throughput screening of a catalyst library for the asymmetric transfer hydrogenation of heteroaromatic ketones: formal syntheses of (*R*)-fluoxetine and (*S*)-duloxetine. ChemCatChem 4:2082–2089
13. Wu L, Jin RH, Li L, Hu XY, Cheng TY, Liu GH (2017) A michael addition–asymmetric transfer hydrogenation one-pot enantioselective tandem process for syntheses of chiral γ-secondary amino alcohols. Org Lett 19:3047–3050
14. Hong YL, Tan HJ, Qiu J, Shen L (2012) New C2-symmetric chiral tetraaza ligands and their application for $[Ru(p\text{-}cymene)Cl_2]_2$-catalyzed asymmetric transfer hydrogenation. Synth React Inorg Met-Org Nano-Met Chem 42:502–506
15. Liu XG, Zhang T, Hu YY, Shen L (2013) Synthesis and crystal structure of (*S,S,S,S*)-*N,N'*-bis[*N*-(*P*-toluenesulfonamido)-1,2-diphenylethyl]ethylenediamine. Crystallogr Rep 58:1091–1095
16. Liu XG, Zhang T, Hu YY, Shen L (2014) Asymmetric transfer hydrogenation of aromatic ketones catalyzed by new chiral C2-symmetric bis(sulfonyl) tetraaza ligands complexed with $[Ru(\eta^6\text{-}p\text{-}cymene)Cl_2]_2$ in water. Catal Lett 144:1289–1295
17. Yu HQ, Liu XG, Shen L (2015) Synthesis and structure of C2-symmetric chiral tetraaza liangds and asymmetric transfer hydrogenation of acetophenone. J Hangzhou Norm Univ 14:378–384
18. Kenny JA, Palmer MJ, Wills M (1999) Asymmetric transfer hydrogenation of α-amino and α-alkoxy substituted ketones. Synth Lett 10:1615–1617
19. Li AJ, Liu DZ, Zhou XQ, Yin CX, Cao H Process for preparing of duloxetine and its isomer. CN 101012219 2007-08-08
20. Barbara M, Rok Z, Michel SM, Miha S, Jaroslav T Process for preparation of duloxetine via asymmetric transfer hydrogenation of β-ketoamines. WO 2010003942 A2 2010-01-14
21. Yamakawa M, Ito H, Noyori R (2000) The metal-ligand bifunctional catalysis: a theoretical study on the ruthenium(II)-catalyzed hydrogen transfer between alcohols and carbonyl compounds. J Am Chem Soc 122:1466–1478
22. Zhao JF, Dou HJ, Zhou YH, Qu JP (2011) Asymmetric transfer hydrogenation of β-amino ketone catalyzed by (*S,S*)-TsDPEN-Ru complex and its application in the synthesis of duloxetine. Chem J Chin Univ 32:2331–2334
23. Cortez NA, Rodrıguez-Apodaca R, Aguirre G, Parra-Hake M, Cole T, Somanathan R (2006) New C2-symmetric bis(sulfonamide)-cyclohexane1,2-diamine-RhCp* complex and its application in the asymmetric transfer hydrogenation (ATH) of ketones in water. Tetrahedron Lett 47:8515–8518
24. Cortez NA, Aguirre G, Parra-Hake M, Somanathan R (2009) New heterogenized C2-symmetric bis(sulfonamide)-cyclohexane1,2-diamine-RhIIICp* complexes and their application in the asymmetric transfer hydrogenation (ATH) of ketones in water. Tetrahedron Lett 50:2228–2231
25. Soni R, Cheung FK, Clarkson GC, Martins JED, Grahamb MA, Wills M (2011) The importance of the N–H bond in Ru/TsDPEN complexes for asymmetric transfer hydrogenation of ketones and imines. Org Biomol Chem 9:3290–3294