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Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Aromatic Ketones in Water Using Novel Water-Soluble Chiral Monosulfonamide Ligands

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ABSTRACT: *Novel water-soluble analogues of Noyori's (R,R)-N-(p-tolylsulfonyl)-1,2-diphenylethylenediamine and Knochel's (R,R)-N-(p-tolylsulfonyl)-1,2-diaminocyclohexane, containing an additional quaternary ammonium group, have been synthesized. The ruthenium catalysts prepared in situ by reacting chiral monosulfonamides with $[RuCl_2(p\text{-cymene})]_2$ afforded high conversion rates and enantiomeric excess (ee) values in the asymmetric transfer hydrogenation of aromatic ketones in aqueous HCOONa. Furthermore, the catalyst could be easily recovered and reused at least five times without obvious loss of ee value.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:505–514, 2010; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20641

INTRODUCTION

Asymmetric transfer hydrogenation (ATH) of prochiral ketones has emerged as a very valuable synthetic tool to obtain optically pure secondary alcohols because of its operational simplicity, the easy availability of hydrogen sources, safety, and lower cost [1–6]. The use of aqueous media in organic reactions has attracted a great deal of interest because water is a desirable solvent with respect to environmental concerns, safety, and cost [7–9]. Rhyoo et al. [10] reported the first example of the Ru(II)-catalyzed asymmetric hydrogen-transfer reduction of aromatic ketones in an aqueous solution. Because there is an increasing demand for atom economy and environmentally friendly methods, the development of Ru(II)-catalyzed ATH reaction performed in water has expanded significantly [11–30]. However, it is worthwhile to develop new water-soluble catalysts that can simplify the purification step and be recycled and reused without significant loss of enantioselectivity and activity. Here, we would like to report the synthesis of novel water-soluble chiral monosulfonamides and their application in Ru(II)-catalyzed ATH of aromatic ketones in neat water.

RESULTS AND DISCUSSION

Xiao recently reported that the ATH of aromatic ketones with Knochel's Ru-TsCYDN [(*R,R*)-*N*-(*p*-toluenesulfonyl)-1,2-diaminocyclohexane] catalyst and Noyori's Ru-TsDPEN [(*R,R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] catalyst could be performed using water as solvent [24,25]. However, Ru-TsCYDN and Ru-TsDPEN cannot be easily separated from products because of the catalysts being soluble in common solvents, which renders catalysts separation by extraction impossible.

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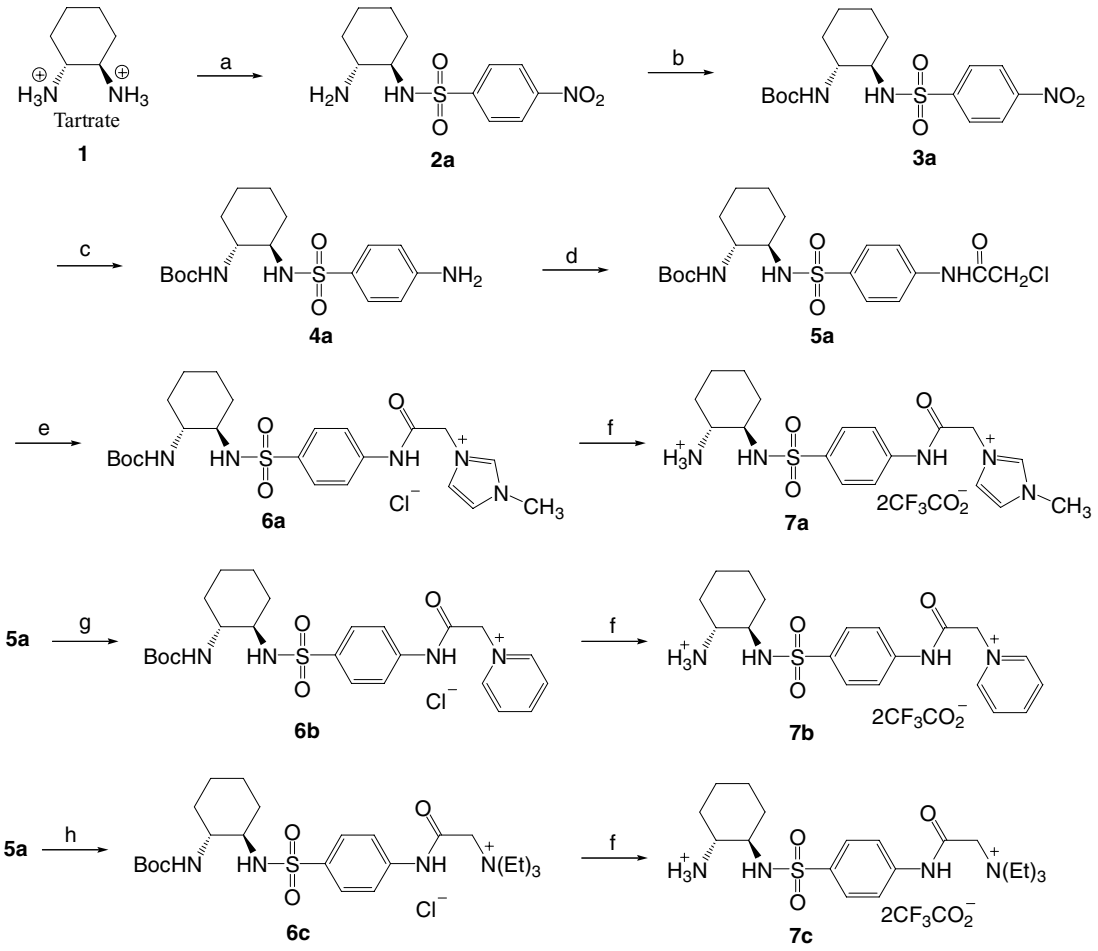
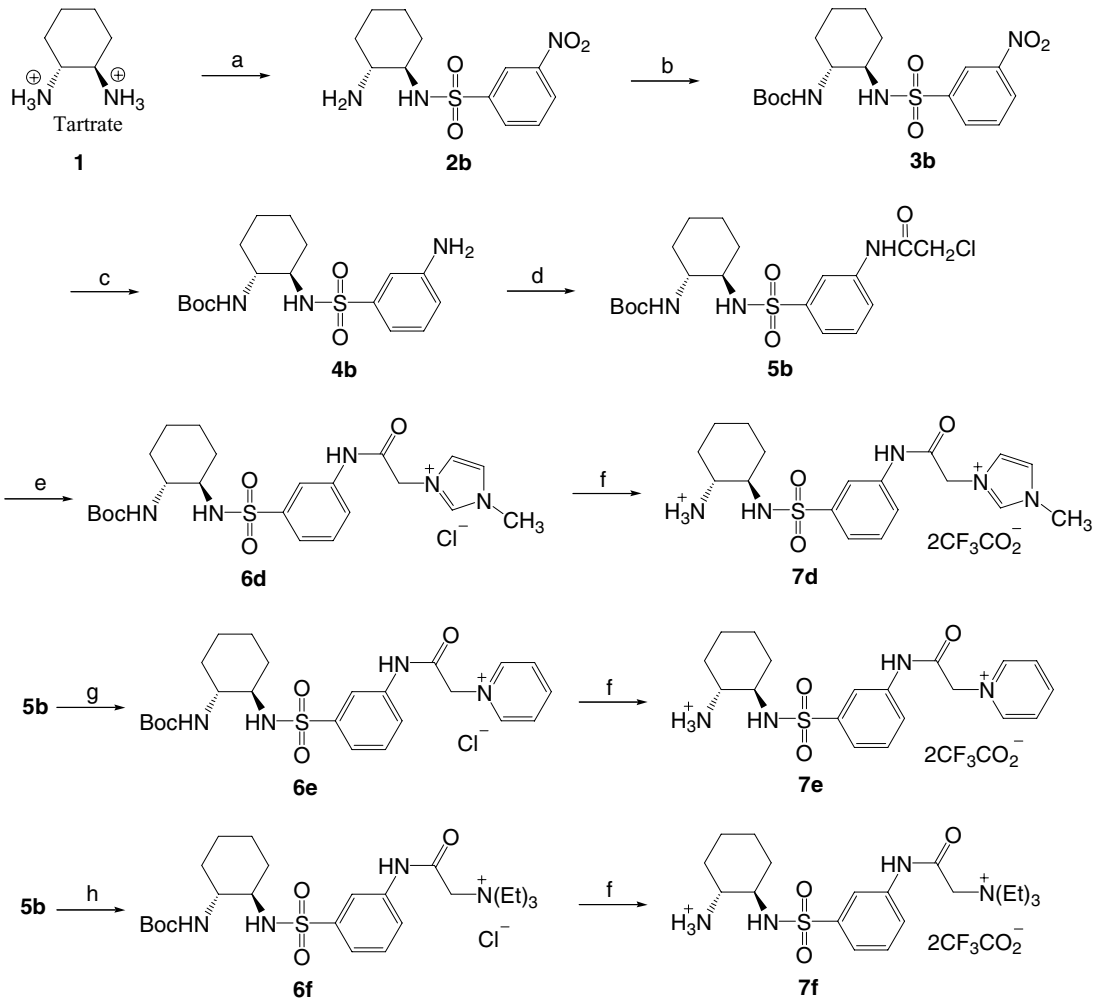
This prompted us to search for an improved and more efficient catalytic system for the ATH. To facilitate catalyst/product separation, we have successfully synthesized novel water-soluble chiral monosulfonamides by the introduction of imidazolium, triethylammonium, and pyridinium moiety to monosulfonylated-(*R*,*R*)-1,2-diaminocyclohexane or monosulfonylated-(*R*,*R*)-1,2-diphenylethylenediamine. The water-soluble ruthenium catalysts prepared from $[RuCl_2(p\text{-cymene})]_2$ and water-soluble chiral monosulfonamides could be easily separated from the reaction mixture because of its insolubility in common solvents and reused for the following reaction.

Water-soluble chiral monosulfonamides (*R*,*R*)-**7** can in general be readily prepared. (*R*,*R*)-*N*-Boc-*N*′-(4-aminophenylsulfonyl)-1,2-diaminocyclohexane (**4a**) was prepared according to the literature procedure [31]. The reaction of chloroacetyl chloride with (*R*,*R*)-**4a** in the presence of triethylamine provided monosulfonamide (*R*,*R*)-**5a**. The introduction of 1-methylimidazole to (*R*,*R*)-**5a** was achieved to give the quaternary salt (*R*,*R*)-**6a**. Then removal of the Boc group of (*R*,*R*)-**6a** by treatment with trifluoroacetic acid provided a novel ionic ligand (*R*,*R*)-**7a** in almost quantitative yield. The ligands (*R*,*R*)-**7b** and (*R*,*R*)-**7c** were similarly prepared using pyridine and triethylamine, respectively, instead of 1-methylimidazole (Scheme 1). The ligands **7d–7f** were similarly prepared using 3-nitrophenylsulfonyl chloride instead of 4-nitrophenylsulfonyl chloride (Scheme 2). The ligands (*R*,*R*)-**7g** and (*R*,*R*)-**7h** were similarly prepared using (*R*,*R*)-1,2-diphenylethylenediamine instead of (*R*,*R*)-1,2-diaminocyclohexane (Scheme 3).

The ruthenium catalysts were prepared by reacting water-soluble monosulfonamide ligands with $[RuCl_2(p\text{-cymene})]_2$ in neat water at 40°C for 1 h



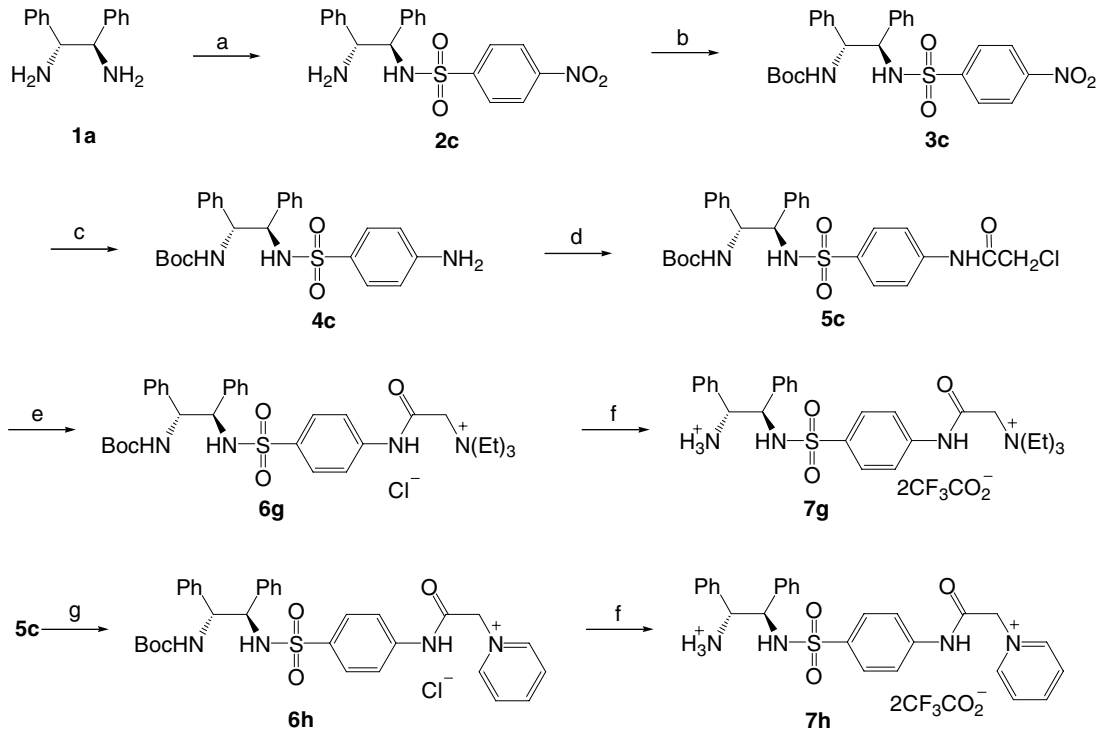
SCHEME 1 Synthesis of ligands **7a–7c**. Reagents and conditions: (a) 4-O_2N-$PhSO_2Cl$, triethylamine, CH_2Cl_2; (b) $(Boc)_2O$, triethylamine, CH_2Cl_2, room temperature (rt); (c) Pd/C, $HCOONH_4$, MeOH, rt; (d) $ClCH_2COCl$, triethylamine, CH_2Cl_2; (e) 1-methylimidazole, CH_3CN, 80°C; (f) CF_3COOH, 0°C; (g) pyridine, CH_3CN, 80°C; and (h) triethylamine, CH_3CN, 80°C.



SCHEME 2 Synthesis of ligands **7d–7f**. Reagents and conditions: (a) 3-O_2N-$PhSO_2Cl$, triethylamine, CH_2Cl_2; (b) $(Boc)_2O$, triethylamine, CH_2Cl_2, room temperature (rt); (c) Pd/C, $HCOONH_4$, MeOH, rt; (d) $ClCH_2COCl$, triethylamine, CH_2Cl_2; (e) 1-methylimidazole, CH_3CN, 80°C; (f) CF_3COOH, 0°C; (g) pyridine, CH_3CN, 80°C; and (h) triethylamine,CH_3CN, 80°C.

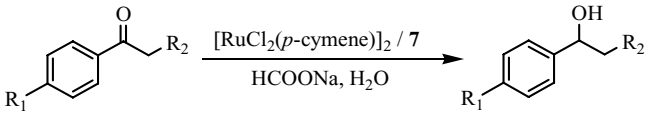
under argon atmosphere. The resulting precatalysts were used for the ATH without purification. On the basis of Xiao's work [24,25], the amount of HCOONa and the reaction temperature were not screened. All these catalytic reactions were carried out using 5 equiv of HCOONa at 40°C. The ATH of acetophenone in water has been examined using **7a–7f** derived from (*R,R*)-1,2-diaminocyclohexane as ligands and the results are summarized in Table 1. The catalyst prepared from (*R,R*)-**7b** showed the best catalytic activity. When monosulfonamide (*R,R*)-**7b** was used as the ligand, the reduction of acetophenone proceeded to give almost quantitative conversion with a substrate/catalyst (S/C) ratio of 100 at 40°C in 2-h reaction time, furnishing (*R*)-1-phenylethanol in 84% enantiomeric excess (ee) (entry 2, Table 1). The ATH of acetophenone derivatives was investigated using the Ru-**7b** catalyst. As can be seen from Table 1, various ketones tested, including 2-substituted, electron-deficient, and electron-rich variants, were reduced with quantitative conversion and good ee values, using HCOONa as a hydrogen source and neat water as the solvent, for several hours.

The ATH of acetophenone in water has also been examined using **7g–7h** derived from (*R,R*)-1,2-diphenylethylenediamine as ligands and the results are summarized in Table 2. The Ru-**7g** catalyst gave slightly higher ee than the Ru-**7h** catalyst in the case of reduction of acetophenone. The ATH of acetophenone derivatives was investigated using the Ru-**7g** catalyst. As shown in Table 2, the Ru-**7g** catalyst delivered high conversion for most of the ketones in 2-h reaction time, with ee value reaching up to 96%. An exception was encountered for propiophenone; the reduction of propiophenone led to a 100% conversion in 90% ee in 4 h (entry 3, Table 2).



SCHEME 3 Synthesis of ligands **7g–7h**. Reagents and conditions: (a) *p*-O_2N-$PhSO_2Cl$, triethylamine, CH_2Cl_2; (b) $(Boc)_2O$, triethylamine, CH_2Cl_2, room temperature (rt); (c) Pd/C, $HCOONH_4$, MeOH, rt; (d) $ClCH_2COCl$, triethylamine, CH_2Cl_2; (e) triethylamine, CH_3CN, 80°C; (f) CF_3COOH, 0°C; (g) pyridine, CH_3CN, 80°C.

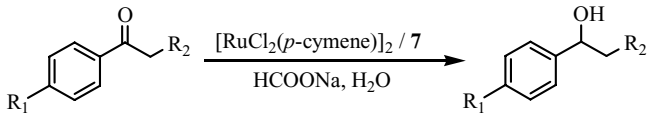
TABLE 1 Asymmetric Transfer Hydrogenation of Aromatic Ketones Promoted by **7a–7f** in Water[a]



Entry	R_1	R_2	*Ligand*	*Time (h)*	*Conversion (%)*[b]	*ee (%)*[c]	*Configuration*[d]
1	H	H	**7a**	9	>99	87	*R*
2	H	H	**7b**	2	>99	84	*R*
3	H	H	**7c**	3.5	99	85	*R*
4	H	H	**7d**	7	90	87	*R*
5	H	H	**7e**	8	81	84	*R*
6	H	H	**7f**	6	95	87	*R*
7	H	CH_3	**7b**	4	100	67	*R*
8	H	Cl	**7b**	4	100	87	*S*
9	CH_3	Cl	**7b**	4.5	100	87	*S*
10	Cl	H	**7b**	4	100	80	*R*
11	Br	H	**7b**	4	100	87	*R*
12	CH_3	H	**7b**	4	100	74	*R*
13	CH_3O	H	**7b**	3.5	100	70	*R*
14	Cl	Cl	**7b**	4	100	82	*S*
15	H	Br	**7b**	4.5	100	89	*S*

[a]Reactions were carried out using 1 mmol of ketone, 5 equiv of HCOONa, and an S/C ratio of 100 in 2 mL of water under argon atmosphere at 40°C.
[b]Determined by GC–MS analysis on an HP-5ms column.
[c]Determined by GC, using a chiral column (Chirasil-Dex CP 7502).
[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported [32,33].

TABLE 2 Asymmetric Transfer Hydrogenation of Aromatic Ketones Promoted by **7g–7h** in Water[a]



Entry	R_1	R_2	*Ligand*	*Conversion (%)*[b]	*ee (%)*[c]	*Configuration*[d]
1	H	H	**7g**	100	94	*R*
2	H	H	**7h**	100	92	*R*
3[e]	H	CH_3	**7g**	100	90	*R*
4	H	Cl	**7g**	100	95	*S*
5	CH_3	Cl	**7g**	100	94	*S*
6	Cl	H	**7g**	99	94	*R*
7	Br	H	**7g**	100	95	*R*
8	CH_3	H	**7g**	92	94	*R*
9	H	Br	**7g**	100	95	*S*
10	CH_3O	H	**7g**	100	96	*R*
11	Cl	Cl	**7g**	100	93	*S*

[a]Unless otherwise indicated, reactions were carried out using 1 mmol of ketone, 5 equiv of HCOONa, and an S/C ratio of 100 in 2 mL of water under argon atmosphere at 40°C for 2 h.
[b]Determined by GC–MS analysis on an HP-5ms column.
[c]Determined by GC, using a chiral column (Chirasil-Dex CP 7502).
[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported [32,33].
[e]The reaction was carried out using 1 mmol of ketone, 5 equiv of HCOONa, and an S/C ratio of 100 in 2 mL of water under argon atmosphere at 40°C for 4 h.

From the standpoint of green chemistry, it is highly desirable that the catalyst can be recovered and reused. To investigate the catalyst recyclability and reusability in neat water, we chose HCOONa as the reductant and acetophenone as a model substrate. On completion of the reaction, the catalyst was easily recovered after extraction of the reduced products with hexane. The aqueous solution containing the catalyst was used for the subsequent transfer hydrogenation run by adding 1 equiv of formic acid to regenerate sodium formate. As shown in Tables 3 and 4, catalysts Ru-**7b** and Ru-**7g** could be used for five runs with completely maintained yields and enantioselectivity, although there was gradual decrease in the reaction rates. Catalyst recycle led to the loss of reaction rates, presumably because of some decomposition of active Ru-**7** complexes.

In conclusion, novel water-soluble chiral monosulfonamides containing quaternary ammonium group have been successfully synthesized in good yields by the introduction of imidazolium, pyridinium, and triethylammonium moieties to monosulfonylated-(*R,R*)-1,2-diaminocyclohexane or monosulfonylated-(*R,R*)-1,2-diphenylethylenediamine. Water-soluble ruthenium catalysts prepared in situ from ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ and monosulfonamide ligands were used in the ATH of aromatic ketones and high conversion rates and ee values were achieved using HCOONa as

TABLE 3 Recycling of Catalyst Ru-**7b** in Asymmetric Transfer Hydrogenation of Acetophenone in Water[a]

Run	*Ligand*	*Time (h)*	*Conversion (%)*[b]	*ee (%)*[c]	*Configuration*[d]
1	**7b**	2	>99	83	*R*
2	**7b**	2	>99	83	*R*
3	**7b**	2.5	>99	82	*R*
4	**7b**	3.5	>99	82	*R*
5	**7b**	6.5	>99	81	*R*

[a]Reactions were carried out using 1 mmol of acetophenone, 5 equiv of HCOONa, and an S/C ratio of 100 in 2 mL of water under argon atmosphere at 40°C in the first run. Since the second run, 1 mmol of HCOOH was added to regenerate sodium formate in every recycling run.
[b]Determined by GC–MS analysis on an HP-5ms column.
[c]Determined by GC, using a chiral column (Chirasil-Dex CP 7502).
[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported [32,33].

TABLE 4 Recycling of Catalyst Ru-**7g** in Asymmetric Transfer Hydrogenation of Acetophenone in Water[a]

Run	*Ligand*	*Time (h)*	*Conversion (%)*[b]	*ee (%)*[c]	*Configuration*[d]
1	**7g**	2	100	94	*R*
2	**7g**	2	100	93	*R*
3	**7g**	2	100	93	*R*
4	**7g**	2.5	100	93	*R*
5	**7g**	3	100	93	*R*

[a]Reactions were carried out using 1 mmol of acetophenone, 5 equiv of HCOONa, and an S/C ratio of 100 in 2 mL of water under argon atmosphere at 40°C in the first run. Since the second run, 1 mmol of HCOOH was added to regenerate sodium formate in every recycling run.
[b]Determined by GC–MS analysis on an HP-5ms column.
[c]Determined by GC, using a chiral column (Chirasil-Dex CP 7502).
[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported [32,33].

the reductant in neat water. The catalysts could be easily recovered and reused at least five times without obvious loss of ee value, though a prolonged reaction time was needed. The organic solvent-free reaction conditions, simple experimental procedure, ease of catalyst recovery, and efficient reusability make this method very advantageous.

EXPERIMENTAL

Material and Instruments

Melting points were determined on a melting point apparatus and were uncorrected. Specific rotations were measured on a WZZ-3 digital polarimeter. Infrared (IR) spectra were recorded on a Nicolet Nexus 470 FTIR spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance III 400 spectrometer, with tetramethylsilane as the internal standard. Elemental analysis was performed using a Vario EL Series III apparatus. The conversions were measured by gas chromatography–mass spectrometry (GC–MS) on an Agilent 5973N system (HP-5ms capillary column). The ee values were determined by GC (Agilent 6890N), using a chiral column (Chirasil-Dex CP 7502). The chemicals used in this work were purchased from the Alfa Aesar (Tianjin, China) and Sinopharm Chemcial Reagent Co., Ltd., (Shanghai, China).

*(R,R)-N-(4-Nitrophenylsulfonyl)-1,2-diaminocyclohexane (***2a***)*

Dichloromethane (10 mL) was added to a stirred solution of the L-tartrate salt of (*R,R*)-1,2-diaminocyclohexane (1.32 g, 5 mmol) in 5.3 mL of 2N NaOH solution. The mixture was cooled to 0°C, and a solution of 4-nitrophenylsulfonyl chloride (554 mg, 2.5 mmol) in 10 mL of dichloromethane was added dropwise over 20 min. After the addition was completed, the mixture was allowed to warm to room temperature and stirred overnight. The resulting solution was washed with water (3 × 50 mL) and dried over anhydrous $MgSO_4$. After concentration, the residue was dried to afford **2a** as a pale yellow powder (632 mg, 84.5%). m.p. 180°C (lit. [31], m.p. 177.5–178°C). $[\alpha]_D = +26.7$ ($c = 0.49$, C_2H_5OH). IR (KBr), ν: 3429, 3359, 3297, 1528, 1349, 1162, 1092 cm^{-1}.

*(R,R)-N-Boc-N′-(4-nitrophenylsulfonyl)-1,2-diaminocyclohexane (***3a***)*

(*R,R*)-*N*-Boc-*N′*-(4-nitrophenylsulfonyl)-1,2-diaminocyclohexane (**3a**) was prepared according to the literature procedure [31]. Yield 75.5%, m.p. 159–162°C, $[\alpha]_D = +42.8$ ($c = 0.42$, C_2H_5OH).

*(R,R)-N-Boc-N′-(4-aminophenylsulfonyl)-1,2-diaminocyclohexane (***4a***)*

(*R,R*)-*N*-Boc-*N′*-(4-aminophenylsulfonyl)-1,2-diaminocyclohexane (**4a**) was prepared according to the literature procedure [31]. Yield 95.7%, m.p. 187°C, $[\alpha]_D = +69.6$ ($c = 0.39$, C_2H_5OH).

*Preparation of (R,R)-***6a**

To a solution of (*R,R*)-**4a** (369 mg, 1 mmol) and triethylamine (0.18 mL, 1.25 mmol) in CH_2Cl_2 (12 mL) cooled in an ice bath, a solution of chloroacetyl chloride (0.1 mL, 1.3 mmol) in CH_2Cl_2 (12 mL) was added dropwise. At the end of the addition, the mixture was stirred for further 8 h at the same temperature and then stirred for 32 h at room temperature. The mixture was washed successfully with 0.5 M citric acid, water, saturated sodium bicarbonate, and brine and dried over anhydrous $MgSO_4$. After concentration, the crude product of **5a** was obtained (434 mg, 97.4%), m.p. 183–186°C. A mixture of **5a** (223 mg, 0.5 mmol), 1-methylimidazole (0.2 mL, 15 mmol), and acetonitrile (3 mL) was stirred for 24 h at 80°C under argon. The solvent and excess

of 1-methylimidazole were removed under reduced pressure, and the residue was dried in vacuo to give **6a** as a pale yellow solid (214 mg, 81.2%). m.p. 159–161°C. $[\alpha]_D = +50$ ($c = 0.3$, C_2H_5OH). IR (KBr), ν: 3550, 3478, 3423, 3105, 2936, 1689, 1597, 1544, 1318, 1161 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.98–1.76 (m, 8H), 1.38 (s, 9H), 2.86 (br s, 1H), 3.14 (br s, 1H), 3.93 (s, 3H), 5.28 (s, 2H), 6.37 (d, $J = 8$ Hz, 1H), 7.44 (d, $J = 8$ Hz, 1H), 7.74 (d, $J = 7.2$ Hz, 2H), 7.76 (d, $J = 6.8$ Hz, 2H), 9.12 (s, 1H), 11.13 (s, 1H). Anal. Calcd for $C_{23}H_{34}ClN_5O_5S$: C, 52.31; H, 6.49; N, 13.26; Found: C, 52.01; H, 6.71; N, 13.01.

*Preparation of (R,R)-***6b**

Compound **6b** was prepared using the same procedure as **6a**, yield 77.2% (two steps). m.p. 215–218°C. $[\alpha]_D = +69.3$ ($c = 0.3$, C_2H_5OH). IR (KBr), ν: 3338, 2937, 1685, 1598, 1550, 1524, 1319, 1259, 1157, 1090 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.97–1.75 (m, 8 H), 1.38 (s, 9 H), 2.83–2.85 (m, 1H), 3.12–3.14 (m, 1H), 5.75 (s, 2H), 6.37 (d, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 1H), 7.77 (d, $J = 8.8$ Hz, 2H), 7.80 (d, $J = 9.2$ Hz, 2H), 8.24 (t, $J = 6.8$ Hz, 2H), 8.71 (t, $J = 7.6$ Hz, 1H), 9.08 (d, $J = 5.6$ Hz, 2H), 11.51 (s, 1H). Anal. Calcd for $C_{24}H_{33}ClN_4O_5S$: C, 54.90; H, 6.33; N, 10.67; Found: C, 54.57; H, 6.61; N, 10.34.

*Preparation of (R,R)-***6c**

Compound **6c** was prepared using the same procedure as **6a**, yield 88.4% (two steps). m.p. 152–155°C. $[\alpha]_D = +45.3$ ($c = 0.3$, C_2H_5OH). IR (KBr), ν: 3411, 2933, 1697, 1598, 1547, 1318, 1255, 1159, 1090 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.97–1.74 (m, 8 H), 1.29 (s, 9 H), 1.37 (s, 9 H), 2.86–2.88 (m, 1H), 3.06–3.12 (m, 1H), 3.53 (d, $J = 6$ Hz, 6H), 4.37 (s, 2H), 6.37 (d, $J = 5.6$ Hz, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.84 (d, $J = 7.6$ Hz, 2H), 11.51 (s, 1H). Anal. Calcd for $C_{25}H_{43}ClN_4O_5S$: C, 54.88; H, 7.92; N, 10.24; Found: C, 54.51; H, 8.21; N, 10.03.

*Preparation of (R,R)-***7a**

Trifluoroacetic acid (4.5 mL) was added to (*R,R*)-**6a** (264 mg, 0.5 mmol) at 0°C under argon. After stirring for 4 h at 0°C, toluene (12 mL) was added to the mixture and the volatile was removed under reduced pressure to give **7a** as a pale yellow solid (99%). m.p. 88–90°C. $[\alpha]_D = +35.8$ ($c = 0.5$, CH_3OH). IR (KBr), ν: 3418, 3114, 2947, 1680, 1598, 1549, 1323, 1201 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.95–1.96 (m, 8 H), 2.67–2.82 (m, 1H), 2.94 (br s, 1H), 3.87 (s, 3H), 5.27 (s, 2H), 6.62 (d, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 1H), 7.74–7.81 (m, 4H), 9.05 (s, 1H), 11.09 (s, 1H). Anal. Calcd for $C_{22}H_{27}F_6N_5O_7S$: C, 42.65; H, 4.39; N, 11.30; Found: C, 42.23; H, 4.17; N, 11.02.

*Preparation of (R,R)-***7b**

Compound **7b** was prepared using the same procedure as **7a**, yield 99%. m.p. 132–134°C. $[\alpha]_D = +69.8$ ($c = 0.32$, CH_3OH). IR (KBr), ν: 3418, 3068, 2947, 1680, 1598, 1549, 1497, 1321, 1263, 1200 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.96–1.97 (m, 8 H), 2.76 (br s, 1H), 2.96 (br s, 1H), 5.73 (s, 2H), 7.82 (s, 4H), 8.24 (s, 2H), 8.71 (t, $J = 7.2$ Hz, 1H), 9.07 (s, 2H), 11.34 (s, 1H). Anal. Calcd for $C_{23}H_{26}F_6N_4O_7S$: C, 44.81; H, 4.25; N, 9.09; Found: C, 44.31; H, 4.47; N, 8.62.

*Preparation of (R,R)-***7c**

Compound **7c** was prepared using the same procedure as **7a**, yield 99%. m.p. 84–86°C. $[\alpha]_D = +47.7$ ($c = 0.35$, CH_3OH). IR (KBr), ν: 3419, 2947, 1680, 1599, 1548, 1467, 1323, 1201 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.85–1.96 (m, 8 H), 1.29 (s, 9 H), 2.76 (br s, 1H), 2.96 (br s, 1H), 3.55 (d, $J = 6.8$ Hz, 6H), 4.29 (s, 2H), 7.84 (d, $J = 9.2$ Hz, 4H), 11.32 (s, 1H). Anal. Calcd for $C_{24}H_{36}F_6N_4O_7S$: C, 45.14; H, 5.68; N, 8.77; Found: C, 44.91; H, 5.92; N, 8.33.

*(R,R)-N-(3-Nitrophenylsulfonyl)-1,2-diaminocyclohexane (***2b***)*

Compound **2b** was prepared using the same procedure as **2a**, using 3-nitrophenylsulfonyl chloride instead of 4-nitrophenylsulfonyl chloride, yield 84.5%. m.p. 110–112°C. $[\alpha]_D = -34.0$ ($c = 0.5$, $CHCl_3$). IR (KBr), ν: 3570, 3375, 3302, 1670, 1534, 1352, 1324, 1164, 1099, 1082 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.17–1.68 (m, 8H), 1.91–1.97 (m, 3H), 2.38–2.41 (m, 1H), 2.68–2.73 (m, 1H), 7.74 (t, $J = 8$ Hz, 1H), 8.23 (d, $J = 8$ Hz, 1H), 8.41–8.42 (m, 1H), 8.77 (s, 1H). Anal. Calcd for $C_{12}H_{17}N_3O_4S$: C, 48.15; H, 5.72; N, 14.04; Found: C, 48.27; H, 5.61; N, 14.19.

*(R,R)-N-Boc-N′-(3-nitrophenylsulfonyl)-1,2-diaminocyclohexane (***3b***)*

Compound **3b** was prepared using the same procedure as **3a**, yield 87.3%. m.p. 115–118°C. $[\alpha]_D = +11.9$ ($c = 0.42$, C_2H_5OH). IR (KBr), ν: 3364, 3221, 1690, 1611, 1533, 1352, 1324, 1167, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.17–2.05 (m, 8H), 1.43 (s, 9H), 3.02–3.04 (m, 1H), 3.37–3.39 (m, 1H), 4.45 (d, J = 7.2 Hz, 1H), 6.18 (d, $J = 4.8$ Hz, 1H), 7.72 (t, $J = 8$ Hz, 1 H), 8.20 (d, $J = 8$ Hz, 1H), 8.41–8.43 (m, 1H), 8.72 (t, $J = 2$ Hz, 1H). Anal. Calcd for $C_{17}H_{25}N_3O_6S$:

C, 51.11; H, 6.31; N, 10.52; Found: C, 51.32; H, 6.13; N, 10.39.

*(R,R)-N-Boc-N′-(3-aminophenylsulfonyl)-1,2-diaminocyclohexane (**4b**)*

Compound **4b** was prepared using the same procedure as **4a**, yield 71.8%. m.p. 134–137°C. $[\alpha]_D$ = +44.1 (c = 0.3, $CHCl_3$). IR (KBr), ν: 3374, 2935, 1692, 1630, 1517, 1451, 1387, 1313, 1159, 1084 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.09–2.01 (m, 8H), 1.47 (s, 9H), 2.92 (br s, 1H), 3.32–3.34 (m, 1H), 4.50 (d, J = 6.4 Hz, 1H), 5.52 (s, 1H), 6.85 (d, J = 6.8 Hz, 1H), 7.19 (s, 1H), 7.23 (t, J = 8 Hz, 1H), 7.28 (d, J = 4.4 Hz, 1H). Anal. Calcd for $C_{17}H_{27}N_3O_4S$: C, 55.26; H, 7.37; N, 11.37; Found: C, 55.03; H, 7.12; N, 11.15.

*(R,R)-N-Boc-N′-(3-chloroacetylaminophenylsulfonyl)-1,2-diaminocyclohexane (**5b**)*

To a solution of (*R,R*)-**4b** (900 mg, 2.44 mmol) and triethylamine (0.44 mL, 3.05 mmol) in CH_2Cl_2 (12 mL) cooled in an ice bath a solution of chloroacetyl chloride (0.25 mL, 3.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise. At the end of the addition, the mixture was stirred for further 8 h at the same temperature and then stirred for 32 h at room temperature. The mixture was washed successfully with 0.5 M citric acid, water, saturated sodium bicarbonate, and brine and dried over anhydrous $MgSO_4$. After concentration, the crude product was purified by silica gel column chromatography (petroleum ether/AcOEt = 1:1) to afford **5b** (993 mg, 91.4%). m.p. 143–145°C. $[\alpha]_D$ = +45 (c = 0.30, $CHCl_3$). IR (KBr), ν: 3395, 2934, 1685, 1629, 1601, 1524, 1452, 1368, 1315, 1160 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.20–2.07 (m, 8H), 1.39 (s, 9H), 3.07 (br s, 1H), 3.36 (br s, 1H), 4.24 (s, 2H), 4.75 (d, J = 5.2 Hz, 1H), 5.71 (s, 1H), 7.51 (t, J = 8 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 8.02 (s, 1H), 8.44 (s, 1H). Anal. Calcd for $C_{19}H_{28}ClN_3O_5S$: C, 51.17; H, 6.33; N, 9.42; Found: C, 51.01; H, 6.16; N, 9.54.

*Preparation of (R,R)-**7d***

A mixture of (*R,R*)-**5b** (223 mg, 0.5 mmol), 1-methylimidazole (0.2 mL, 15 mmol) and acetonitrile (3 mL) was stirred for 24 h at 80°C under argon. The solvent and excess of 1-methylimidazole were removed under reduced pressure, and the residue was dried in vacuo to give **6d** as a pale yellow powder (203 mg, 77%). Trifluoroacetic acid (3 mL) was added to (*R,R*)-**6d** (180 mg, 0.34 mmol) at 0°C under argon. After stirring for 4 h at 0°C, toluene (9 mL) was added to the mixture and the volatile was removed under reduced pressure to give **7d** as a pale yellow solid (99%). m.p. 80–81°C. $[\alpha]_D$ = +21.1 (c = 0.5, CH_3OH). IR (KBr), ν: 3425, 3061, 2960, 1690, 1633, 1554, 1485, 1386, 1169 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.91–1.91 (m, 8H), 2.75 (br s, 1H), 2.96 (br s, 1H), 3.94 (s, 3H), 4.62 (s, 2H), 5.28 (s, 1H), 7.58–8.26 (m, 6H), 8.62 (s, 1H), 9.11 (s, 3H). Anal. Calcd for $C_{22}H_{27}F_6N_5O_7S$: C, 42.65; H, 4.39; N, 11.30; Found: C, 42.37; H, 4.21; N, 11.15.

*Preparation of (R,R)-**7e***

Compound **7e** was prepared using the same procedure as **7d**, yield 82% (two steps). m.p. 70–72°C. $[\alpha]_D$ = +20.7 (c = 0.5, CH_3OH). IR (KBr), ν: 3426, 3058, 2960, 1698, 1634, 1552, 1487, 1385, 1160, 1089 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.90–1.92 (m, 8H), 2.73 (br s, 1H), 2.95 (br s, 1H), 4.61(t, J = 6.8 Hz, 2H), 5.72 (s, 1H), 7.57–7.64 (m, 1H), 7.91 (s, 1H), 8.17 (s, 2H), 8.25–8.28 (m, 1H), 8.61 (t, J = 8 Hz, 1H), 9.11 (m, 3H), 11.12 (s, 1H). Anal. Calcd for $C_{23}H_{26}F_6N_4O_7S$: C, 44.81; H, 4.25; N, 9.09; Found: C, 44.43; H, 4.41; N, 8.73.

*Preparation of (R,R)-**7f***

Compound **7f** was prepared using the same procedure as **7d**, yield 99% (two steps). m.p. 77–79°C. $[\alpha]_D$ = +27.4 (c = 0.5, CH_3OH). IR (KBr), ν: 3260, 2936, 1683, 1596, 1550, 1478, 1427, 1316, 1200, 1156, 1086 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.01–2.37 (m, 8H), 1.02 (t, J = 6.4 Hz, 9H), 2.60 (d, J = 6.4 Hz, 6H), 2.76 (br s, 1H), 3.13 (br s, 1H), 3.54 (s, 2H), 7.17 (d, J = 7.2 Hz, 1H), 7.24 (d, J = 6.8 Hz, 1H), 7.47–7.59 (m, 1H), 7.70–7.81 (m, 1H), 9.98 (s, 1H). Anal. Calcd for $C_{24}H_{36}F_6N_4O_7S$: C, 45.14; H, 5.68; N, 8.77; Found: C, 44.71; H, 5.85; N, 8.34.

*(R,R)-N-Boc-N′-(4-chloroacetylaminophenylsulfonyl)-1,2-diphenylethylenediamine (**5c**)*

(*R,R*)-*N*-Boc-*N′*-(4-aminophenylsulfonyl)-1,2-diphenylethylenediamine (**4c**) was prepared according to the literature procedure [34]. Compound **5c** was prepared from **4c**, using the similar procedure as that of **5b**, yield 84.7%. m.p. 235°C. $[\alpha]_D$ = +21.24 (c = 0.32, acetone). IR (KBr), ν: 3371, 3301, 1685, 1523, 1324, 1159 cm^{-1}.^1H NMR (acetone-d_6, 300 MHz): δ 1.35 (s, 9H), 4.25 (s, 2H), 4.69 (t, J = 4.2 Hz, 1H), 4.92 (t, J = 4.2 Hz, 1H), 6.61 (d, J = 3.3 Hz, 1H), 7.01–7.18 (m, 10H), 7.45 (d, J = 3.9 Hz, 2H), 7.57 (d, J = 4.2 Hz, 2H), 9.62 (s, 1H). Anal. Calcd for $C_{27}H_{30}ClN_3O_5S$: C, 59.61; H, 5.56; N, 7.72; Found: C, 59.32; H, 5.41; N, 7.85.

*Preparation of (R,R)-***7g**

A mixture of (*R,R*)-**5c** (270 mg, 0.496 mmol), triethylamine (0.72 mL, 5 mmol), and acetonitrile (5 mL) was stirred for 50 h at 80°C under argon. The solvent and excess of triethylamine were removed under reduced pressure, and the residue was dried in vacuo to give **6g**. Trifluoroacetic acid (4 mL) was added to **6g** at 0°C under argon. After stirring for 7 h at 0°C, toluene (10 mL) was added to the mixture and the volatile was removed under reduced pressure to give **7g** as a pale yellow solid (99%). m.p. 124°C. $[\alpha]_D = +46.7$ ($c = 0.27$, MeOH). IR (KBr), ν: 3426, 3059, 2882, 1678, 1598, 1547, 1326, 1200, 1154, 837 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.25 (s, 9H), 3.52 (m, 6H), 4.21 (s, 2H), 4.40 (d, $J = 8.0$ Hz, 1H), 4.62 (d, $J = 8.4$ Hz, 1H), 6.82–7.40 (m, 14H), 10.97 (s, 1H). Anal. Calcd for $C_{32}H_{38}F_6N_4O_7S$: C, 52.17; H, 5.20; N, 7.60; Found: C, 51.95; H, 4.83; N, 7.41.

*Preparation of (R,R)-***7h**

A mixture of (*R,R*)-**5c** (280 mg, 0.515 mmol), pyridine (0.40 mL, 5 mmol), and acetonitrile (5 mL) was stirred for 50 h at 80°C under argon. The solvent and excess of pyridine were removed under reduced pressure, and the residue was dried in vacuo to give **6h**. Trifluoroacetic acid (4 mL) was added to **6h** at 0°C under argon. After stirring for 7 h at 0°C, toluene (10 mL) was added to the mixture and the volatile was removed under reduced pressure to give **7h** as a pale yellow solid (99%). m.p. 147°C. $[\alpha]_D = +55.0$ ($c = 0.30$, MeOH). IR (KBr), ν: 3425, 3066, 2882, 1678, 1598, 1548, 1496, 1458, 1325, 1200, 1154, 837 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 4.43 (d, $J =$ 10 Hz, 1H), 4.66 (d, $J = 10$ Hz, 1H), 5.65 (s, 2H), 6.82–7.39 (m, 14H), 8,23 (t, $J = 7.2$ Hz, 2H), 8.70 (t, $J = 7.6$ Hz, 1H), 9.03 (d, $J = 6$ Hz, 2H), 10.98 (s, 1H). Anal. Calcd for $C_{31}H_{28}F_6N_4O_7S$: C, 52.10; H, 3.95; N, 7.84; Found: C, 51.83; H, 3.66; N, 7.62.

General procedure for ATH

(*R,R*)-**7** (0.012 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol) were dissolved in degassed water (2 mL). The resulting solution was stirred at 40°C for 1 h under an argon atmosphere. $HCO_2Na{\cdot}2H_2O$ (520 mg, 5 mmol) and ketone (1.0 mmol) were then added. The mixture was stirred at 40°C for a certain period of time. After cooling to room temperature, the organic compounds were extracted with hexane (3×5 mL) with a syringe. The conversions were determined by GC–MS analysis. The ee values were determined by GC (Agilent 6890N) equipped with a chiral column (Chirasil-Dex CP 7502).

Recycle experiment for the ATH of acetophenone in water

After the organic compounds were extracted, the residual aqueous phase containing the catalyst was reused by adding formic acid (0.039 mL, 1.0 mmol) to regenerate sodium formate and then acetophenone (120 mg, 1.0 mmol) was added into the aqueous solution for a new reaction cycle and the second cycle of the reaction was started under the same conditions.

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