Chiral Amino Amides for the Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation Reaction of Ketones in Water

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ABSTRACT The chiral amino amide **3** was derived from L-proline and used for the $[RuCl_2(p\text{-cymene})]_2$-catalyzed asymmetric transfer hydrogenation of prochiral ketones performed in water. Moderate to good chemical selectivities (up to 95% yield) and enantioselectivities (up to 90% ee) were obtained in the presence of 2 mol % of TBAB (n-Bu_4NBr) as the phase transfer catalyst. *Chirality 22:173–181, 2010.*

KEY WORDS: asymmetric transfer hydrogenation; ketones; water; enantioselectivity; ruthenium

INTRODUCTION

Asymmetric hydrogenation of prochiral ketones, imines, and activated alkenes has been considered as a direct route to get enantiomerically enriched chiral compounds in various manufactures of pharmaceuticals and advanced materials.[1–7] However, the use of molecular hydrogen and hence often expensive specialized high-pressure equipment reduced its accessibility and operability. Thus, asymmetric transfer hydrogenation (ATH) has emerged as an alternative because of its operational simplicity and the easy availability of hydrogen source.[8] In the past decades, two popular protocols have been developed by Noyori and coworkers, including KOH/^{i}PrOH and HCOOH/Et_3N systems.[9,10] Nowadays, a major concern for chemists is the development and employment of economical and environmentally friendly methodologies. Water is regarded as a "greener" solvent than most organic solvents as a medium for conducting reactions. Therefore, ATH performed in water using HCOONa gained great attention.[11–32] Various successful chiral ligands have been designed based on TsDPEN.[16–32] Recently, we have demonstrated that the low cost, commercially available (−)-ephedrine hydrochloride (**1**) was an efficient catalyst for Ru-catalyzed ATH of ketones performed in water and in air. And high conversions (up to 99%) and good enantioselectivities (up to 83% ee) were obtained.[14] Recently, we also found that the combination of commercially available (1*R*,2*S*)-cis-1-aminoindan-2-ol (**2**) with $[RuCl_2(p\text{-cymene})]_2$ is an effective catalyst for ATH of prochiral ketones in tap water and in open vessel, providing moderate to good conversions (up to 81%) and enantioselectivities (up to 70% ee; Fig. 1).[15]

Given the interest in conducting this reaction in water, the search for new efficient catalysts is still a challenging work till now. We convey here the use of chiral amino amides (**3–5**) derived from proline (**6**) as chiral ligands for Ru-catalyzed ATH of ketones in water, affording good yields (up to 95%) and good ee values (up to 90%) of the chiral secondary alcohols.

EXPERIMENTAL

All reactions were carried out in air and monitored by thin layer chromatography (TLC). All ketones were purchased from Aldrich or Acors. $[RuCl_2(p\text{-cymene})]_2$ was prepared following reported procedure. Sodium formate was purchased from Fluka. NMR spectra were measured in $CDCl_3$ on a Bruker DRX-400 NMR spectrometer (400 MHz) with TMS as an internal reference. Optical rotations were measured with a HORIBA SEPA-200 high sensitive polarimeter. Enantiomeric excess (ee) determination was carried out using HPLC with a Daicel Chiralcel OD-H or AD-H column on an Agilent HP-1100 HPLC instrument.

Synthesis of Chiral Ligands

A solution of proline (**6**) (50 mmol) in 200 ml of a H_2O/dioxane/NaOH (1 M, 1:2:1) mixture was added Boc_2O (55 mmol) at 0°C. After stirring the mixture at room temperature for overnight, the solvent was evaporated with the residue being adjusted pH = 9. The organic layer was extracted with AcOEt for three times, dried over $MgSO_4$, and concentrated under reduced pressure to yield the desired product (**7**). This unpurified Boc-proline and triethylamine (50 mmol) was dissolved in tetrahydrofuran and the solution was cooled down to 0°C. To the solution was added dropwise ethyl chloroformate (50 mmol) for 30 min and the pasty reaction mixture was stirred for an additional 30 min. Chiral amine (50 mmol) was added dropwise

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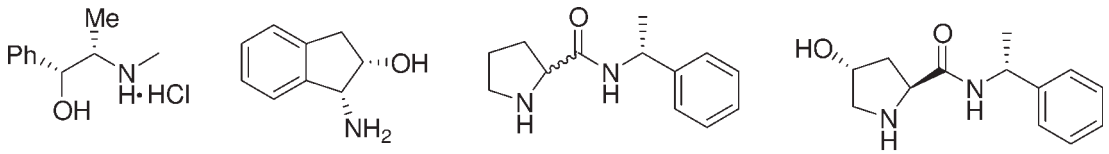


(*1R,2S*) **1** (*1R,2S*) **2** (*S, R*) **3** (*R, R*) **4** (*S, R*) **5**

Fig. 1. The chiral ligands were studied in the article.

to the mixture for 30 min. The resulting solution was stirred at 0°C for 1 h, at r.t. for another 16 h, and then refluxed for 3 h. After cooling down to r.t., the mixture was filtered and the solid was thoroughly washed with AcOEt. After the filtrate and wash liquids were evaporated at reduced pressure, the residue was redissolved in ethyl acetate and successively washed with water, an aqueous Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give products (**8** and **9**). Then to a solution of **8** (7.54 mmol) in CH_2Cl_2 (15 ml) was added trifluoroacetic acid (201 mmol) solution in CH_2Cl_2 (15 ml) dropwise at 0°C. The mixture was stirred for 1 h at 0°C. Water (10 ml) was added and aqueous layer was extracted with CH_2Cl_2. The combined organic solvents were dried and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica to afford the desired pure products (**3–5**).

Characterization of the Representative Chiral Ligands

(2*S*)-*N*-((*R*)-1-phenylethyl)pyrrolidine-2-carboxamide (3). $[\alpha]_{25}^{D} = -5.5$ (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (d, J = 6.8 Hz, 3H), 1.64–1.71 (m, 1H), 1.87–1.91 (m, 2H), 2.07–2.17 (m, 1H), 2.84–2.90 (m, 1H), 2.98–3.04 (m, 1H), 3.76 (dd, J = 5.2, 8.8 Hz, 1H), 5.05–5.13 (m, 1H), 7.23–7.35 (m, 5H), 7.94 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 26.5, 31.1, 47.6, 48.2, 60.9, 126.2, 127.4, 128.9, 144.1, 174.5; HRMS: calcd [M+H] for $C_{13}H_{18}N_2O$ 218.1419, found 218.1419.

(2*R*)-*N*-((*R*)-1-phenylethyl)pyrrolidine-2-carboxamide (4). $[\alpha]_{25}^{D} = -25.9$ (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (d, J = 6.8 Hz, 3H), 1.68–1.78 (m, 2H), 1.90–1.98 (m, 1H), 2.01–2.19 (m, 1H), 2.87–2.93 (m, 1H), 2.98–3.03 (m, 1H), 3.71 (dd, J = 5.6, 9.2 Hz, 1H), 5.05–5.13 (m, 1H), 7.25–7.36 (m, 5H), 7.92 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.4, 26.4, 31.0, 47.4, 48.2, 60.8, 126.3, 127.3, 128.8, 143.7, 174.5; HRMS: calcd [M + H] for $C_{13}H_{18}N_2O$ 218.1419, found 218.1428.

(2*S*,4*R*)-4-Hydroxy-*N*-((*R*)-1-phenylethyl)pyrrolidine-2-carboxamide (5). $[\alpha]_{25}^{D} = +1.4$ (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (d, J = 7.2 Hz, 3H), 1.84–1.91 (m, 1H), 2.20–2.23 (m, 3H), 2.73 (dd, J = 3.2, 12.4 Hz, 1H), 2.99 (dd, J = 1.2, 12.4 Hz, 1H), 4.00 (t, J = 8.4 Hz, 1H), 4.37 (t, J = 3.6 Hz, 1H), 5.02–5.10 (m, 1H), 7.22–7.34 (m, 5H), 8.04 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 40.3, 48.5, 55.7, 60.0, 73.1, 126.2, 127.5, 129.0, 143.9, 174.7; HRMS: calcd [M–H_2O + H] for $C_{13}H_{16}N_2O$ 216.1263, found 216.1267.

The Representative Procedure of Asymmetric Transfer Hydrogenation of Ketones

A suspension of $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol) and ligand (0.03 mmol) in H_2O (2 ml) and stirred at room temperature for 2 h. HCOONa (5.0 mmol) was then added to the solution. After the solution was stirred for 10 min, acetophenone (1.0 mmol) was then introduced. The resulting mixture was stirred for the predetermined reaction time. After the reaction time, the reaction products were extracted by the mixed solvents of hexane and diethyl ether. The extracted solvent was dried over Na_2SO_4 and enantiomeric excess (ee) determination was carried out using HPLC with a Daicel Chiralcel OD-H or AD-H column on an Agilent HP-1100 HPLC instrument (solvent, 98:2 hexane/isopropanol; flow rate 1 ml/min; 254 nm UV detection). The configuration was assigned by comparison with the sign of specific rotation of the known compounds.

Characterization of the Chiral Secondary Alcohols

1-Phenylethanol. Yield: 70%. Fifty-five percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 8:92). Retention time: t_{minor} = 6.80 min, t_{major} = 6.12 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (d, J = 6.8 Hz, 3H), 1.82 (br, 1H), 4.91 (q, J = 6.4 Hz, 1H), 7.28–7.30 (m, 1H), 7.34–7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 70.7, 125.8, 127.8, 128.9, 146.2.

1-(2-Fluorophenyl)ethanol. Yield: 83%. Forty-three percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 1:99). Retention time: t_{minor} = 22.16 min, t_{major} = 20.45 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (d, J = 6.4 Hz, 3H), 2.04 (br, 1H), 5.19 (q, J = 6.4 Hz, 1H), 6.99–7.04 (m, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.21–7.26 (m, 1H), 7.48 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.4, 64.7, 115.5–115.7 (d, J = 21.7 Hz), 124.7, 127.0–127.1 (d, J = 4.3 Hz), 129.0–129.1 (d, J = 8.1 Hz).

1-(2-Chlorophenyl)ethanol. Yield: 62%. Eighty-three percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 1:99). Retention time: t_{minor} = 26.30 min, t_{major} = 23.74 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (d, J = 6.4 Hz, 3H), 2.13 (br, 1H), 5.28 (q, J = 6.4 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.26–7.33 (m, 2H), 7.58 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 67.3, 126.8, 127.6, 128.8, 129.8, 132.0, 143.5.

1-(4-Bromophenyl)ethanol. Yield: 89%. Forty-four percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 1:99). Retention time: t_{minor} = 42.13 min, t_{major} = 45.33 min. ^{1}H NMR (400 MHz, $CDCl_3$)

δ: 1.47 (d, J = 6.4 Hz, 3H), 1.80 (br, 1H), 4.87 (q, J = 6.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 69.9, 121.4, 127.5, 131.8, 145.1.

1-*o*-Tolylethanol. Yield: 60%. Forty-seven percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 10:90). Retention time: t_{minor} = 6.66 min, t_{major} = 6.12 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (d, J = 6.4 Hz, 3H), 1.77 (br, 1H), 2.35 (s, 3H), 5.14 (q, J = 6.4 Hz, 1H), 7.12–7.24 (m, 3H), 7.52 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.3, 24.3, 67.2, 127.9, 126.8, 127.5, 130.8, 134.6, 144.3.

1-*m*-Tolylethanol. Yield: 60%. Forty-three percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 10:90). Retention time: t_{minor} = 5.81 min, t_{major} = 5.28 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (d, J = 6.8 Hz, 3H), 1.76 (br, 1H), 2.36 (s, 3H), 4.86 (q, J = 6.4 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.15–7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 25.5, 70.6, 122.8, 126.5, 128.5, 128.7, 138.4, 146.2.

1-(Naphthalen-4-yl)ethanol. Yield: 62%. Eighty-six percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 10:90). Retention time: t_{minor} = 9.29 min, t_{major} = 13.74 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.68 (d, J = 6.4 Hz, 3H), 1.96 (br, 1H), 5.69 (q, J = 6.4 Hz, 1H), 7.47–7.55 (m, 3H), 7.68 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.87–7.89 (m, 1H), 8.12 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 67.2, 122.4, 123.5, 125.8, 125.9, 126.3, 128.1, 129.2, 130.6, 134.1, 141.8.

1-(2-Chlorophenyl)propan-1-ol. Yield: 56%. Sixty-six percent ee determined by HPLC analysis (Chiralcel AD-H column, IPA:hexane = 1:99). Retention time: t_{minor} = 24.38 min, t_{major} = 23.24 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (t, J = 7.8 Hz, 3H), 1.71–1.87 (m, 2H), 1.96 (br, 1H), 5.07 (dd, J = 4.8, 7.6 Hz, 1H), 7.12–7.22 (m, 1H), 7.28–7.34 (m, 2H), 7.55 (dd, J = 1.6, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.5, 30.9, 72.3, 127.4, 127.6, 128.7, 129.7, 132.4, 142.4.

1-(4-Chlorophenyl)propan-1-ol. Yield: 95%. Twenty-three percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 5:95). Retention time: t_{minor} = 29.35 min, t_{major} = 31.46 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.4 Hz, 1H), 1.68–1.83 (m, 2H), 1.90 (br, 1H), 4.58 (t, J = 6.6 Hz, 1H) 7.26–7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.3, 32.2, 75.5, 127.7, 128.8, 133.3, 143.4.

1-(2,4-Dichlorophenyl)propan-1-ol. Yield: 94%. Forty-eight percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 5:95). Retention time: t_{minor} = 6.04 min, t_{major} = 6.47 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98 (t, J = 7.2 Hz, 3H), 1.67–1.83 (m, 2H), 2.01 (br, 1H), 5.02 (dd, J = 4.8, 7.6 Hz, 1H), 7.26–7.28 (m, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.3, 30.9, 71.7, 127.7, 128.5, 129.4, 132.8, 133.7, 150.0.

1-(Naphthalen-6-yl)ethanol. Yield: 87%. Sixty percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 5:95). Retention time: t_{minor} = 16.07 min, t_{major} = 16.85 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57 (d, J = 6.4 Hz, 3H), 1.85 (br, 1H), 5.07 (q, J = 6.4 Hz, 1H), 7.44–7.51 (m, 3H), 7.80–7.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 70.8, 124.2, 124.3, 126.2, 126.5, 128.1, 128.3, 128.7, 133.3, 133.7, 143.6.

1,2,3,4-Tetrahydronaphthalen-1-ol. Yield: 78%. Ninety percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 4:96). Retention time: t_{minor} = 9.47 min, t_{major} = 10.31 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76–1.80 (m, 1H), 1.90–2.00 (m, 3H), 4.78–4.80 (m, 1H), 7.09–7.12 (m, 1H), 7.18–7.23 (m, 2H), 7.42–7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.2, 29.6, 32.5, 68.2, 126.4, 127.7, 129.0, 129.2, 137.4, 139.1.

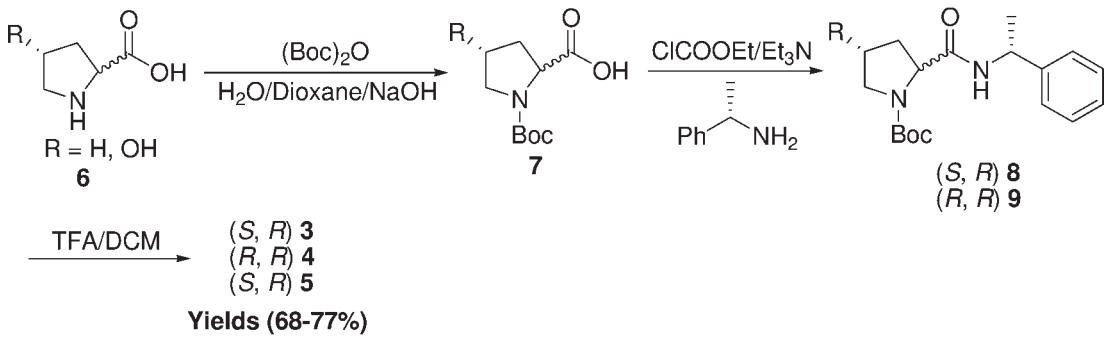
1-(Thiophen-2-yl)ethanol. Yield: 79%. Thirty-two percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 1:99). Retention time: t_{minor} = 40.04 min, t_{major} = 38.17 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.61 (d, J = 6.0 Hz, 3H), 1.98 (br, 1H), 5.15 (q, J = 6.0 Hz, 1H), 6.96–6.99 (m, 2H), 7.24–7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 66.7, 123.7, 124.9, 127.1.

1-*p*-Tolylethanol. Yield: 60%. Forty-nine percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 1:99). Retention time: t_{minor} = 28.77 min, t_{major} = 25.41 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (d, J = 6.8 Hz, 3H), 2.34 (s, 3H), 4.86 (q, J = 6.4 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 25.5, 70.5, 125.8, 129.5, 137.4, 143.3.

1-(3-(Trifluoromethyl)phenyl)ethanol. Yield: 60%. Forty-nine percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 1:99). Retention time: t_{minor} = 28.77 min, t_{major} = 25.41 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (d, J = 6.4 Hz, 3H), 1.94 (br, 1H), 4.98 (q, J = 6.4 Hz, 1H), 7.45–7.49 (m, 1H), 7.53–7.58 (m, 2H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 70.2, 122.6–122.7 (d, J = 3.6 Hz), 124.6–124.7 (d, J = 3.6 Hz), 129.3–129.4 (d, J = 13.8 Hz), 147.2.

4-Phenylbutan-2-ol. Yield: 65%. Thirty-one percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 10:90). Retention time: t_{minor} = 7.91 min, t_{major} = 7.03 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, J = 6.0 Hz, 3H), 1.72-1.78 (m, 2H), 2.60–2.75 (m, 2H), 3.78–3.86 (m, 1H), 7.09–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 32.1, 41.4, 67.9, 128.7, 129.5, 135.6, 139.4.

3,4-Dihydro-2H-thiochromen-4-ol. Yield: 81%. Eighty-nine percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 10:90). Retention time: t_{minor} = 8.87 min, t_{major} = 7.61 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86 (br, 1H), 2.00–2.09 (m, 1H), 2.31–2.38 (m, 1H), 2.83–2.89 (m, 1H), 3.28–3.35 (m, 1H), 4.80 (t, J = 4.0 Hz, 1H), 7.05–7.15 (m, 3H), 7.26–7.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 30.3, 66.6, 124.6, 127.0, 128.7, 130.9, 133.5, 134.9.



Scheme 1. Synthesis of chiral amide amine ligands.

2,3-Dihydro-1H-inden-1-ol. Yield: 83%. Thirty-one percent ee determined by HPLC analysis (Chiralcel OD-H column, IPA:hexane = 8:92). Retention time: t_{minor} = 7.25 min, t_{major} = 6.70 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.89–2.05 (m, 2H), 2.44–2.52 (m, 1H), 2.77–2.85 (m, 1H), 3.01–3.09 (m, 1H), 5.24 (t, J = 6.0 Hz, 1H), 7.23–7.25 (m, 3H), 7.40–7.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.1, 36.0, 76.5, 124.6, 125.1, 126.9, 128.5, 143.6, 145.3.

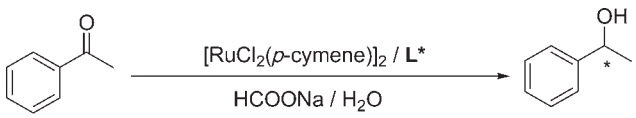
1-(Ferrocenyl)ethanol. Yield: 78%. Fifty-seven percent ee determined by HPLC analysis (Chiralcel AD-H column, IPA:hexane = 5:95). Retention time: t_{minor} = 17.06 min, t_{major} = 17.91 min.

RESULTS AND DISCUSSIONS

The amide amine ligands were prepared from chiral L(D)-proline or *trans*-4-hydroxyl-*L*-proline in three steps.[33–35] The synthetic route was shown in Scheme 1. To study the matching between the stereogenic centers, ligands (**3** and **4**) were destined to synthesize in good yields (73% and 77%). Considering that additional hydroxyl group in the ligand will possibly enhance its solubility in water, we synthesized ligand **5** from *trans*-4-hydroxyl-L-proline in 68% yield (see Supporting Information).

Then these chiral amide amine ligands (**3–5**) and the intermediates (**6–9**) were investigated into the ATH performed in water and the results were listed in Table 1. To our astonishment, we did not get desired secondary alcohol for all of the chiral ligands (**3–9**) (entry 1, Table 1). Enhanced temperature (40°C) was beneficial for the reaction catalyzed by ligands (**3–5**) (entries 2–4, Table 1), whereas it was unfavorable for ligands (**6–9**) (entry 5, Table 1). Although ligand **3** could afford the highest enantioselectivity among them, the yield of the desired product

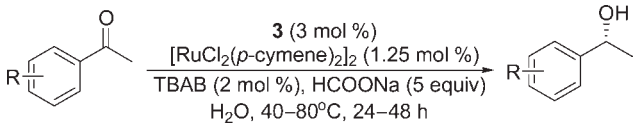
TABLE 1. Screening various chiral ligands (3–9) in the ATH of acetophenone in water[a]



Entry	**L*** (mol %)	PTC (mol %)	Temperature (°C)	Yield (%)[b]	ee (%)[c]	Configuration[d]
1	**3–9** (3)	–	r.t.	Trace	–	–
2	**3** (3)	–	40	32	49	*R*
3	**4** (3)	–	40	75	47	*S*
4	**5** (3)	–	40	35	48	*R*
5	**6–9** (3)	–	40	Trace	–	–
6	**3** (3)	CTAB (2)	40	71	53	*R*
7	**3** (3)	CTAB (2)	r.t.	63	53	*R*
8	**3** (6)	CTAB (2)	40	80	53	*R*
9	**3** (12)	CTAB (2)	40	90	49	*R*
10	**3** (1.5)	CTAB (2)	40	Trace	–	–
11	**3** (3)	SDBS (2)	40	Trace	–	–
12	**3** (3)	DDAC (2)	40	82	51	*R*
13	**3** (3)	TBAB (2)	40	70	55	*R*
14	**3** (3)	TBAB (1)	40	63	52	*R*
15	**3** (3)	TBAB (5)	40	44	49	*R*
16	**3** (3)	TBAB (10)	40	41	54	*R*

[a]All the reactions were performed in 2 ml of water at room temperature for 24 h. A total of 1 mmol of acetophenone, 5 equiv of HCOONa, L*/Ru ratio of 1.2 and S/C ratio of 40.
[b]Isolated yield.
[c]The enantiomeric excess was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column.
[d]Absolute configuration determined by comparison with reported optical rotations.

TABLE 2. Asymmetric transfer hydrogenation of prochiral ketones performed in water using 3[a]



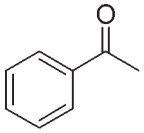
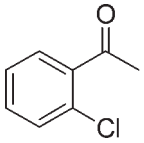
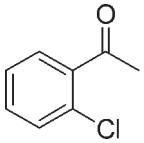
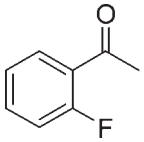
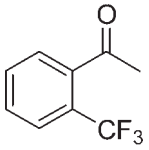
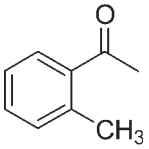
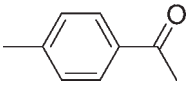
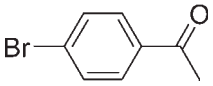
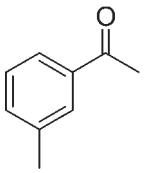
Entry	Ketone	Time/Temperature (°C)	Yield (%)[b]	e.e. (%)[c]	Configuration[d]
1		24 (40)	70	55	*R*
2		24 (40)	62	83	*R*
3[e]		24 (40)	56	82	*R*
4		24 (40)	83	43	*R*
5		24 (40)	93	53	*R*
6		48 (80)	60	47	*R*
7		48 (80)	60	49	*R*
8		24 (40)	89	44	*R*
9		48 (80)	60	43	*R*

TABLE 2. Continued

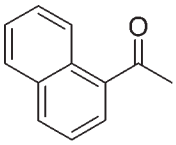
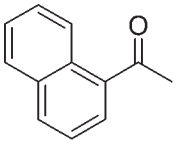
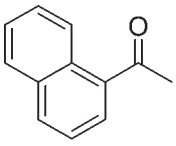
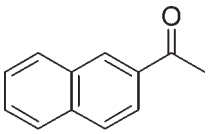
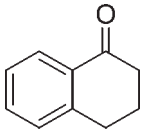
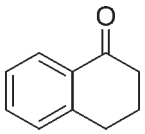
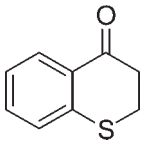
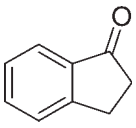
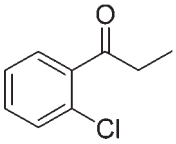
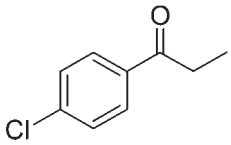
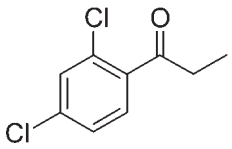
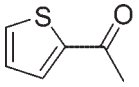
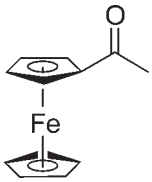
Entry	Ketone	Time/Temperature (°C)	Yield (%)[b]	e.e. (%)[c]	Configuration[d]
10		24 (40)	62	86	*R*
11[f]		24 (40)	41	74	*S*
12[e]		24 (40)	65	90	*R*
13		36 (40)	87	60	*R*
14		36 (80)	78	80	*R*
15[e]		36 (80)	85	82	*R*
16		36 (80)	81	89	*R*
17		36 (80)	83	31	*R*
18		24 (40)	56	66	*R*
19		36 (80)	95	23	*R*

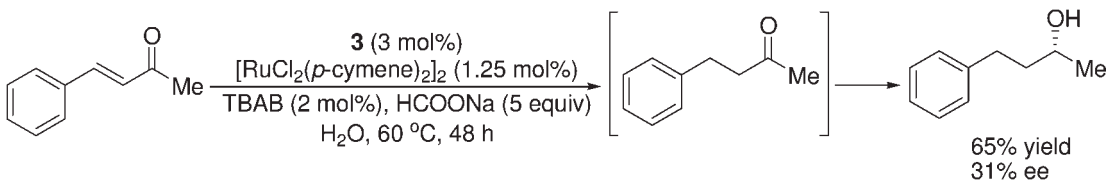
TABLE 2. Continued

Entry	Ketone	Time/Temperature (°C)	Yield (%)[b]	e.e. (%)[c]	Configuration[d]
20		36 (80)	94	48	*R*
21		36 (40)	79	32	*R*
22		36 (80)	78	57	*R*

[a]All the reactions were performed in 2 ml of water in the presence of 2 mol % of TBAB at room temperature for 24–48 h. A total of 1 mmol of ketone, 5 equiv of HCOONa, ligand **3**/Ru ratio of 1.2 and S/C ratio of 40.
[b]Isolated yield.
[c]The enantiomeric excess was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column.
[d]Absolute configuration determined by comparison with reported optical rotations.
[e]Ligand **5** was used instead of ligand **3**.
[f]Ligand **4** was used instead of ligand **3**.

was not good (entry 2, Table 1). Thus, 2 mol % of cetyltimethylammonium bromide (CTAB) was used as the phase transfer catalyst (PTC). It obviously resulted in the development of the catalytic efficiency of ligand **3** (entry 6, Table 1). The catalytic reaction performed at room temperature afforded slightly decreased yield (entry 7, Table 1). Although higher loading of the catalyst led to increased yield, the enantioselectivity was not raised (entries 8–9, Table 1). Reduced loading of the catalyst could not promote the reaction (entry 10, Table 1). In addition, other PTCs, such as SDBS (sodium dodecyl benzene sulfonate), DDAC (dimethyl dioctadecylammonium chloride), and TBAB, were also employed under the same conditions (entries 11–13, Table 1). The results showed that TBAB gave the best enantioselectivity (55% ee) (entry 13, Table 1). Changing the amount of TBAB could not get enhanced results (entries 14–16, Table 1).

To assess the practical usefulness of the catalytic system, we evaluated a number of substrates in ATH in water using ligand **3** and the results obtained were shown in Table 2. It can be seen that the reaction rate and enantioselectivity are greatly influenced by the steric and electronic properties of prochiral ketones. For the ortho-substituted substrates (Table 2, enties 2–6), comparing with electron-donating group (such as methyl), electron-withdrawing groups, including Cl, F, and CF_3 gave the better results. Among them, the catalytic reaction of 2-chloroacetophenone gave the good enantioselectivity (83% ee) (entry 2, Table 2). Under the same conditions, ligand **5** afforded similar ee value (82% ee) (entry 3, Table 2). Meta- and para-substituted substrates gave similar results (entries 7–9, Table 2). To our delight, satisfactory results were acquired when the bulky substrates were used (entries 10–16, Table 2). For 1-acetonaphtone, as expected, ligand **3** gave better result than ligand **4** (entries 10 and 11, Table 2). However, for the same substrate, ligand **5** gave the higher enantioselectivity (90% ee) than ligand **3** (86% ee) (entry 12 vs. entry 10, Table 2). In contrast, 2-acetonaphtone afforded inferior result (60% ee) (entry 13, Table 2). Aromatic cyclic ketones afforded the corresponding alco-



Scheme 2. ATH of (*E*)-4-phenylbut-3-en-2-one using our catalytic system.

hol with good enantioselectivities (entries 14–16, Table 2). However, to our surprise, 1-indanone gave poor result (entry 17, Table 2). In addition, several propiophenones were employed as the substrates in ATH (entries 18–20, Table 2). 2-Chloro-substituted ketone afforded the desired product with 66% ee (entry 18, Table 2). In addition, heterocyclic aromatic ketone has also been investigated in the reaction and promising result was obtained (entry 21, Table 2). When 1-acetylferrocene was used as the substrate, the desired alcohol was obtained in 78% yield and 57% ee (entry 22, Table 2).

The interesting reduction of a ketone with both C=O and C=C bonds was performed using our catalytic system.[36] The question is whether carbonyl or imine group could be reduced. GC-MS showed that the C=C bond was first saturated followed by the C=O bond. The chiral alcohol was obtained with 65% yield and 31% ee (Scheme 2).

CONCLUSION

In summary, we have demonstrated that the combination of the readily available chiral amide amines with $[RuCl_2(p\text{-cymene})]_2$ is an effective catalytic system for ATH in water. The desired chiral secondary alcohols were obtained in moderate to good yields (up to 95%) and enantioselectivities (up to 90% ee). To keep better conversions of substrates, 2 mol % of TBAB as PTC was necessary. The discovery of these new chiral ligands provides an efficient method for the catalytic transfer hydrogenation using aqueous sodium formate as the hydrogen source. The search for more active and enantioselective ligands is ongoing in our laboratories.

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