Practical Synthesis of Optically Active Amino Alcohols via Asymmetric Transfer Hydrogenation of Functionalized Aromatic Ketones

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Abstract: 2-Substituted acetophenones such as 2-cyano-, 2-azido-, or 2-nitroacetophenones were effectively reduced with a mixture of HCOOH/N(C_2H_5)$_3$ containing a chiral Ru(II) catalyst, RuCl[(*S*,*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine](*p*-cymene), giving the corresponding optically active alcohols, which can be converted to optically active amino alcohols with excellent ee's. Similarly, the reaction of 2-benzoylacetophenone with the same Ru catalyst gave a quantitative yield of the corresponding optically active 1,3-diol with 99% ee.

Coordinatively saturated 18-electron chiral Ru(II) complexes bearing optically active diamines, RuCl(Tsdpen)-(η^6-arene) (TsDPEN: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) have been extensively investigated as practical asymmetric reduction catalysts to produce optically active alcohols or amines.[1] Thanks to the characteristic properties of chiral Ru catalysts, functionalized aromatic ketones bearing neighboring functional groups at the α or *β* position of the carbonyl group could be readily reduced to optically active alcohols with extremely high ee's. The functional groups of these compounds are free from the metal center. In fact, reactions of benzils or benzoins,[1g] 2-amido-2-phenyl-acetophenone, acetylpyridines,[1h] or *β*-ketoesters[1e,2] proceeded smoothly under mild conditions to give optically active diols or alcohols with up to 99% ee in almost quantitative yields. We now describe a practical asymmetric transfer hydrogenation of 2-cyano-, 2-azido-, or 2-nitroacetophenone (**2a**−**c**) in a mixture of formic acid and triethylamine with chiral diamine-based Ru(II) catalysts, leading to optically active alcohols. These aromatic alcohols can be readily reduced with conventional reducing systems to the corresponding optically active amino alcohols with excellent enantiomeric purities.

Scheme 1

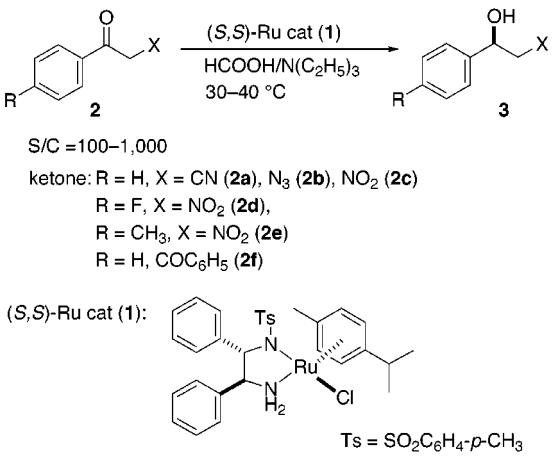

Table 1. Asymmetric Transfer Hydrogenation of 2-Substituted Acetophenones Catalyzed by Chiral Ru(II) Catalyst (1) with a Mixture of HCOOH/N(C_2H_5)$_3$[a]

ketone	S/C	HCOOH/N(C_2H_5)$_3$	*T*, °C	time, h	yield,[b] %	ee,[b] %	config[c]
2a	1000	3.1:2.6	30	24	100	98	*S*
2a	100	*d*	30	24	<1		
2b	100	3.1:2.6	30	24	33	91	*R*
2b	100	3.1:5.2	30	24	65	92	*R*
2c	100	3.1:2.6	30	16	18	96[f]	*R*[g]
2c[e]	100	6.0:2.4	30	16	87	97[f]	*R*[g]
2c[e]	200	6.0:2.4	30	16	90	98[f]	*R*[g]
2c[e]	500	6.0:2.4	30	16	58	98[f]	*R*[g]
2d[e]	200	6.0:2.4	30	16	95	96[f]	*h*
2e[e]	200	6.0:2.4	30	16	67	95[f]	*R*[g]
2f[e]	200	4.4:2.6	40	24	99	99[i]	*S*,*S*[j]

[a] The reaction of aromatic ketones (1.0−3.0 mmol) was carried out in a mixture of HCOOH and N(C_2H_5)$_3$ containing (*S*,*S*)-Ru catalyst (**1**). [b] Unless otherwise noted, yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard, and ee values were determined by HPLC analysis using Daicel Chiralcel OB, OD, and OJ, Chiralpak AD column. [c] Unless otherwise noted, determined from the sign of rotation of the isolated product. [d] Reaction in 2-propanol, conditions: (*S*,*S*)-Ru amide complex, 0.1 M in 2-propanol. [e] Reaction in 1.0 M DMF. [f] Determined after reduction to the corresponding amino alcohol with H_2−Pd/C and subsequent monobenzoylation. [g] Absolute configration was determined from the sign of rotation after reduction to the corresponding amino alcohol with H_2−Pd/C. [h] Not determined. [i] Determined after derivatization to acetal. [j] *dl*/*meso* = 94/6.

A well-defined chiral Ru catalyst, RuCl[(*S*,*S*)-Tsdpen]-(*p*-cymene) (**1**) effected asymmetric transfer hydrogenation of 2-cyanoacetophenone (**2a**) with HCOOH as a hydrogen source, giving (*S*)-1-phenyl-2-cyano-1-ethanol (**3a**) with excellent enantioselectivity (Scheme 1). As shown in Table 1, the reaction with a substrate to catalyst molar ratio (S/C) of 1,000:1 in a mixture of HCOOH/N(C_2H_5)$_3$ (ketone/HCOOH/N(C_2H_5)$_3$ molar ratio = 1:3.1:2.6) proceeded smoothly at 30 °C to give the corresponding reduction product in an almost quantitative yield and with up to 98% ee.[3] The sense of enantio-

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(3) Enantioselective biochemical reduction of 2-cyanoketone, **2a** to (*S*)-**3a**: Dehli, J. R.; Gotor, V. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3693−3700.

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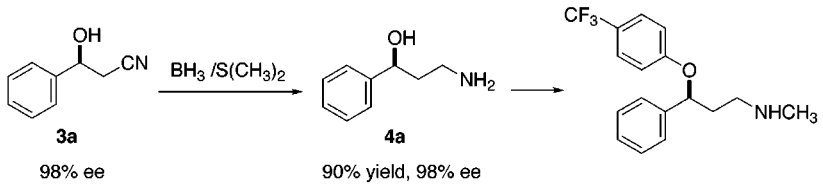
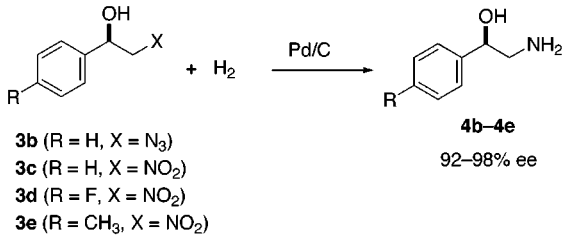
Scheme 2



face selection in this reaction was the same as that attained in the reaction of acetophenone.[1a] The neighboring cyano group did not affect seriously the outcome of the reaction. Formic acid is the best choice for hydrogen sources. Attempted transfer hydrogenation of **2a** with 2-propanol and a Ru amide catalyst, Ru[(*S*,*S*)-Tsdpen]-(*p*-cymene)[1b] or **1**/KO*t*-Bu catalyst system, gave less than 1% of the reduction product. Asymmetric hydrogenation of **2a** in 2-propanol with the practical stereoselective hydrogenation catalyst, $RuCl_2$[(*S*)-binap][(*S*,*S*)-dpen][4] and KO*t*-Bu, (S/C = 200, H_2 10 atm, 30 °C, 24 h), did not proceed. The alcohol product (*S*)-**3a** was readily reduced with conventional reducing agents, $BH_3/S(CH_3)_2$ in THF to give optically active 1-phenyl-3-amino-1-propanol (*S*)-**4a**, which is an intermediate of (*S*)-fluoxetin,[5] in 90% yield and with 98% ee as shown in Scheme 2.

Similarly, 2-azidoacetophenone (**2b**) and 2-nitroacetophenone (**2c**) were reducible with the same catalyst **1** in a mixture of formic acid and $N(C_2H_5)_3$ to the corresponding optically active alcohol **3b** and **3c**, respectively, with an excellent enantioselectivity.[6,7] The outcome of these reactions was greatly influenced by the reaction conditions. The reaction of **2b** with a mixture of HCOOH and $N(C_2H_5)_3$ = 3.1:2.6 proceeded sluggishly because the reactant is labile under the reaction conditions and there is a serious product inhibition effect. In fact, an addition of the product alcohol **3b** (**2b**/*rac*-**3b** = 1:1) to the reaction mixture caused a significant decrease in the product yield to ca. 10%.[8] Increasing the amount of $N(C_2H_5)_3$ from HCOOH/$N(C_2H_5)_3$ = 3.1:2.6 to 3.1:5.2 resulted in an improvement of the yield from 33 to 65% without any change in the ee value. The azido group in the product

Scheme 3



3b (R = H, X = N_3)
3c (R = H, X = NO_2)
3d (R = F, X = NO_2)
3e (R = CH_3, X = NO_2)

is easily hydrogenated over Pd/C to give the optically active 2-amino alcohol **4b** with 92% ee (Scheme 3).[9,10]

The reaction of the nitro group substituted acetophenone **2c** with a mixture of HCOOH and $N(C_2H_5)_3$ in a 3.1:2.6 molar ratio did not give a satisfactory yield albeit with an excellent enantioselectivity (**3c**, 18% yield, 96% ee). However, the use of DMF or CH_2Cl_2 as a solvent as well as an increase in the molar ratio of HCOOH to $N(C_2H_5)_3$ to 6.0:2.4 resulted in a significant increase in the product yield of up to 90%. The enantiomeric excess of the reduction product was determined to be 98% ee after the nitro alcohol was reduced to 2-amino alcohol **4b** by H_2−Pd/C. Para-substituted 2-nitroacetophenones are consistently convertible to the alcohols with excellent ee's. For example, an electron-withdrawing fluoro group on the aromatic ring in **2d** increases the yield of **3d** up to 96%, as expected. 2-Nitroacetophenone with an electron-donating methyl group, **2e**, is also reducible to the corresponding optically active alcohol with a high ee and a moderate yield (Table 1).

Among the notable features of this asymmetric transfer hydrogenation promoted by chiral Ru catalyst is the carbonyl group selectivity. The neighboring groups at the α or *β* position of the carbonyl group do not interact with the metal center because of the coordinatively saturated nature of the diamine-based Ru(II)-arene complexes, leading to excellent enantioselectivity. Such unique catalyst properties were also demonstrated by the reaction of 2-benzoylacetophenone (1,3-diphenyl-1,3-propanedione **2f**) under reaction conditions similar to those described in Table 1. The reaction of 1,3-diketone in a mixture of HCOOH/$N(C_2H_5)_3$ (4.4/2.6) containing catalyst **1** gave a quantitative yield of the corresponding optically active 1,3-diol (**3f**) with 99% ee and in 99% yield (*dl*:*meso* = 94:6).[11] However, 1,3-pentanedione did not give the reduction product under the same conditions.

This work presents the successful reductive transformation of 2-cyano-, 2-azido-, or 2-nitroacetophenone via asymmetric transfer hydrogenation to optically active

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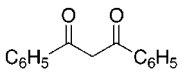
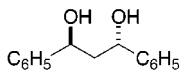


2f



3f 99% yield
dl:*meso* = 94:6
99% ee

primary amino alcohols. Optically active amino alcohols as well as optically active diols obtained here are useful building blocks for the synthesis of various biologically active compounds or chiral auxiliaries and have been prepared by stoichiometric or catalytic asymmetric synthetic methods.[12] The present asymmetric transfer hydrogenation procedure serves as a useful practical method for these important class of compounds.

Experimental Section

2-Cyanoacetophenone, 1,3-diphenyl-1,3-propanedione, triethylamine, formic acid (>98%), and dry DMF were purchased from Kanto Chemical Co., Inc. 2-Nitroacetophenone was purchased from Aldrich. 2-Azidoacetophenone was synthesized according to the published procedure.[13] 4′-Fluoro-2-nitroacetophenone, and 4′-methyl-2-nitroacetophenone were synthesized from the reaction of substituted benzaldehyde and nitromethane in the presence of K_2CO_3 and Jones oxidation.[14] Asymmetric reduction of ketones with chiral Ru catalysts was conducted in an atmosphere of dry Argon. The typical experimental procedures including analytical and spectroscopic data are as follows.

Asymmetric Transfer Hydrogenation of 2-Cyanoacetophenone (2a) Catalyzed by RuCl[(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine](η⁶-*p*-cymene) (1) Leading to (*S*)-1-Phenyl-2-cyano-1-ethanol (3a). A mixture of triethylamine (1.09 mL, 7.8 mmol) and formic acid (0.35 mL, 9.3 mmol) was added to 2-cyanoacetophenone (**2a**) (435 mg, 3.0 mmol) and (*S*,*S*)-Ru (**1**) (1.9 mg, 0.003 mmol), and the mixture was then stirred at 30 °C for 24 h. After the reaction, the reaction mixture was neutralized with $NaHCO_3$ (aq) and diluted with ethyl acetate, and the organic layer was washed with water. The organic layer was dried over Na_2SO_4, passed through a silica gel pad, and concentrated under reduced pressure to give (*S*)-1-phenyl-2-cyano-1-ethanol (**3a**) with 98% ee in almost quantitative yield.

(*S*)-**3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (brs, 1H, O*H*), 2.76 (m, 2H, CH_2CN), 5.04 (t, J = 6.0 Hz, 1H, C*H*OH), 7.35−7.50 (m, 5H, aromatic protons); $[\alpha]^{20}_D$ −52.5 (*c* 2.60, C_2H_5OH) (lit.[3] $[\alpha]^{20}_D$ −57.7 (*c* 2.6, C_2H_5OH, >96% ee (*S*))).

According to a literature procedure, the alcohol product (*S*)-**3a** was reduced with BH_3/S$(CH_3)_2$ in THF to give optically active 1-phenyl-3-amino-1-propanol, (*S*)-**4a** in 90% yield and with 98% ee.[3] **4a**: $[\alpha]^{25}_D$ −46.3 (*c* 1.46, CH_3OH) (lit.[15] $[\alpha]^{25}_D$ −43.65 (*c* 1, CH_3OH, 100% ee (*S*))); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70−1.90 (m, 2H, CH_2NH$_2$), 2.90−3.10 (m, 2H, CH_2CH(OH)), 4.95 (dd, J = 3.0, 8.6 Hz, 1H, C*H*OH), 7.20−7.40 (m, 5H, aromatic protons).

Asymmetric Transfer Hydrogenation of 2-Azidoacetophenone (2b) Catalyzed by Chiral Ru(II) (1) Leading to (*R*)-1-Phenyl-2-azido-1-ethanol (3a). A mixture of triethylamine (0.72 mL, 5.2 mmol) and formic acid (0.12 mL, 3.1 mmol) was added to 2-azidoacetophenone (**2b**) (161 mg, 1.0 mmol) and (*S*,*S*)-Ru (**1**) (6.4 mg, 0.010 mmol), and the mixture was then stirred at 30 °C for 24 h. After the reaction, the reaction mixture was neutralized with $NaHCO_3$ (aq) and diluted with ethyl acetate, and the organic layer was washed with water. The organic layer was dried over Na_2SO_4, passed through a silica gel pad, and concentrated under reduced pressure to give (*R*)-1-phenyl-2-azido-1-ethanol (**3b**) with 92% ee in 65% yield. (*R*)-**3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (brs, 1H, O*H*), 3.45 (m, 2H, CH_2N$_3$), 4.87 (dd, J = 4.0, 7.9 Hz, 1H, C*H*OH), 7.25−7.50 (m, 5H, aromatic protons); $[\alpha]^{25}_D$ −89.3 (*c* 0.80, $CHCl_3$) (lit.[9] $[\alpha]^{25}_D$ −80.1 (*c* 0.78, $CHCl_3$, (*R*))).

According to a literature procedure,[9] (*R*)-**3b** was hydrogenated with H_2−Pd/C in methanol to give 1-phenyl-3-amino-1-ethanol, (*R*)-**4b** with 92% ee, quantitatively: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (brs, 3H, O*H*, NH_2), 2.80 (dd, J = 7.6, 13.0 Hz, 1H, C*H*HNH$_2$), 2.97 (dd, J = 3.9, 13.0 Hz, 1H, CH*H*NH$_2$), 4.61 (dd, J = 3.9, 7.6 Hz, 1H, C*H*OH), 7.20−7.45 (m, 5H, aromatic protons); $[\alpha]^{20}_D$ −39.1 (*c* 1.30, C_2H_5OH) (lit.[16] $[\alpha]^{20}_D$ −42.2 (*c* 1, C_2H_5OH, 95% ee (*R*))).

Asymmetric Transfer Hydrogenation of 2-Nitroacetophenone (2c) to (*R*)-1-Phenyl-2-nitro-1-ethanol (3c) Catalyzed by Chiral Ru(II) (1) Leading to (*R*)-1-Phenyl-2-nitro-1-ethanol (3c). A mixture of triethylamine (0.33 mL, 2.4 mmol) and formic acid (0.23 mL, 6.0 mmol) was added to 2-nitroacetophenone (**2c**) (165 mg, 1.0 mmol) and (*S*,*S*)-Ru (**1**) (3.2 mg, 0.005 mmol) in 1.0 mL of DMF, and the mixture was stirred at 30 °C for 16 h, neutralized with $NaHCO_3$ (aq), and diluted with ethyl acetate, and the organic layer was washed with water. The organic layer was dried over Na_2SO_4, passed through a silica gel pad, and concentrated under reduced pressure to give (*R*)-1-phenyl-2-nitro-1-ethanol (**3c**) with 98% ee in 90% yield. (*R*)-**3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (d, J = 3.4 Hz, 1H, O*H*), 4.52 (dd, J = 3.0, 13.4 Hz, 1H, C*H*HNO$_2$), 4.61 (dd, J = 9.5, 13.4 Hz, 1H, CH*H*NO$_2$), 5.46 (m, 1H, C*H*OH), 7.30−7.55 (m, 5H, aromatic protons);[7a,17] $[\alpha]^{20}_D$ −20.2 (*c* 1.0, C_2H_5OH). absolute configuration was determined from the sign of rotation after reduction to amino alcohol with H_2−Pd/C.

According the literature method,[10b] the alcohol product (*R*)-**3c** was readily reduced with H_2−Pd/C in methanol to give (*R*)-1-phenyl-2-amino-1-ethanol, (*R*)-**4b**, in an almost quantitative yield and with 98% ee.[16]

Similarly, the alcoholic products **3d** and **3e** were obtained by asymmetric reduction of **2d** and **2c** and were hydrogenated with H_2−Pd/C in methanol to give quantitatively **4d** and **4e**, respectively.

Optically active 1-(4′-fluorophenyl)-2-nitro-1-ethanol (3d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (d, J = 3.6 Hz, 1H, O*H*), 4.49 (dd, J = 3.0, 13.4 Hz, 1H, C*H*HNO$_2$), 4.58 (dd, J = 9.5, 13.4 Hz, 1H, CH*H*NO$_2$), 5.45 (m, 1H, C*H*OH), 7.00−7.25, 7.30−7.50 (m, 4H, aromatic protons); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.3, 116.0 (d, J_{CF} = 21.5 Hz), 127.7 (d, J_{CF} = 8.2 Hz), (*C*H$_2$), 81.1 (*C*H), 133.9, 162.9 (d, J_{CF} = 247.8 Hz), (*C*); MS (EI, 70 eV) 185 (M^+), 167 (−F), 140, 138, 125, 123, 121, 109, 101; $[\alpha]^{25}_D$ −19.1 (*c* 1.04, C_2H_5OH).

Optically active 1-(4′-fluorophenyl)-2-amino-1-ethanol (4d):[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (brs, 3H, O*H*, NH_2), 2.76 (dd, J = 7.8, 12.7 Hz, 1H, C*H*HNH$_2$), 2.98 (dd, J = 3.9, 12.7 Hz, 1H, CH*H*NH$_2$), 4.61 (dd, J = 3.9, 7.8 Hz, 1H, C*H*OH), 6.90−7.15, 7.20−7.45 (m, 4H, aromatic protons); $[\alpha]^{20}_D$ −40.8 (*c* 1.68, C_2H_5OH).

(11) Part of the results were reported at the 2000 International Chemical Congress of Pacific Basin Societies at Honolulu (ORGN 1064, 2000), and full details of the reaction will be published separately. During the preparation of this manuscript, similar results on the asymmetric transfer hydrogenation of 1,3-diketones were reported. Cossy, J.; Eustache, F.; Daiko, P. I. *Tetrahedron Lett*. **2001**, *42*, 5005−5007.

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Optically active 1-(4′-methylphenyl)-2-nitro-1-ethanol (3e):[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3), 2.72 (brs, 1H, O*H*), 4.49 (dd, J = 2.9, 13.2 Hz, 1H, C*H*HNO_2), 4.60 (dd, J = 9.5, 13.2 Hz, 1H, CH*H*NO_2), 5.42 (dd, J = 2.9, 9.5 Hz, 1H, C*H*OH), 7.15−7.40 (m, 4H, aromatic protons); $[\alpha]^{25}_D$ −23.0 (*c* 0.95, C_2H_5OH).

Optically active 1-(4′-methylphenyl)-2-amino-1-ethanol (4e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (brs, 3H, O*H*, NH_2), 2.34 (s, 3H, CH_3), 2.80 (dd, J = 7.6, 12.9 Hz, 1H, C*H*HNH_2), 2.96 (dd, J = 3.9, 12.9 Hz, 1H, CH*H*NH_2), 4.59 (dd, J = 3.9, 7.6 Hz, 1H, C*H*OH), 7.05−7.40 (m, 4H, aromatic protons); $[\alpha]^{20}_D$ −42.5 (*c* 1.48, C_2H_5OH) (lit.[20] $[\alpha]^{20}_D$ −42.5 (*c* 0.6, $(C_2H_5)_2O$, (*R*))).

(*S*,*S*)-1,3-Diphenyl-1,3-propanediol (3f): ^{1}H NMR (400 MHz, $CDCl_3$); δ 2.18 (t, J = 5.8 Hz, 2H, CH_2), 2.87 (brs, 2H, O*H*), 4.98 (t, J = 5.8 Hz, 2H, C*H*OH), 7.30−7.40 (m, 10H, aromatic protons); $[\alpha]^{28}_D$ −68.2 (*c* 1.12, CH_3OH) (lit.[21] $[\alpha]^{23}_D$ +52 (*c* 0.5, $CHCl_3$), >99% ee (*R*,*R*))).

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