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Varying the ratio of formic acid to triethylamine impacts on asymmetric transfer hydrogenation of ketones

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ABSTRACT

Asymmetric transfer hydrogenation (ATH) is frequently carried out in the azeotropic mixture of formic acid (F) and triethylamine (T), where the F/T molar ratio is 2.5. This study shows that the F/T ratio affects both the reduction rate and enantioselectivity, with the optimum ratio being 0.2 in the ATH of ketones with the Ru-TsDPEN catalyst. Under such conditions, a range of substrates have been reduced, affording high yields and good to excellent enantioselectivities. In comparison with the common azeotropic F-T system, the reduction is faster. This protocol improves both the classic azeotropic and the aqueous-formate system when using water-insoluble ketones.

1. Introduction

ATH has emerged as a powerful and practical tool for reduction reactions in both academia and industry. It is simple to operate, requiring neither the hazardous hydrogen gas nor pressure vessels, and there are a number of chemicals that are easily available and can be used as hydrogen donors [1]. The first example of ATH appeared as enantioface discriminating reduction in the 1970s from the groups of Ohkubo and Sinou, who explored the catalysis with $[RuCl_2(PPh_3)_3]$ in the presence of a chiral monophosphine or chiral hydrogen donor [2]. However, the optical purity of products was generally low before the 1990s, with few ee values exceeding 90% [3]. Among the catalysts developed for ATH so far, the most notable and successful one is the TsDPEN-coordinated (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, **1**) Ru(II) complex (Ru-**1**) discovered by Noyori and co-workers in 1995 [4]. The application of the TsDPEN type ligand has led to the reduction of a wide range of substrates containing C=X (X=O, N, C) bonds with excellent ee's (up to 99%), including especially aromatic ketones and imines [5]. This significant breakthrough has inspired intense research into this field. As a result, a variety of related metal catalysts have been developed. Generally, the catalysts of choice are complexes based on the platinum metals rhodium [6] iridium [7] and ruthenium [8]. While other catalysts such as iron complexes and organocatalysts have been reported, their reduction rates and/or enantioselectivities are generally inferior [9–12].

The reaction medium and hydrogen sources employed are also important for the ATH reactions. Most often, the metal-catalyzed ATH reactions are performed in 2-propanol (IPA) or in the azeotropic mixture of formic acid (HCOOH) and triethylamine (NEt_3) (F-T), in which the F/T molar ratio is 2.5:1 [5d,h,i,8a,c,13]. A drawback regarding ATH in IPA is the reversibility of the reduction process. The equilibrium is regulated by the oxidation potentials of the relevant carbinol/ketone couples. The reaction gives a high stereoselectivity at low conversions, but the reverse reaction gets faster and the enantioselectivity declines as the conversion increases [14]. To optimize the conversion in IPA, the catalytic reaction is generally performed at a low substrate concentration. The azeotropic F-T, which acts as both the solvent and hydrogen donor, is a better hydrogen-donor than IPA because the resulting carbon dioxide is thermodynamically much more stable and can be removed, thus making the reaction irreversible. Furthermore, it gives a single phase at room temperature and is miscible with many organic compounds at 20–60 °C, allowing for high substrate concentrations without reverse reaction and racemization. The main drawback for ATH in the azeotropic F-T is that some catalysts undergo fast decomposition in it and some may lose completely the catalytic activity [14]. Another downside is that a long induction period may exist, necessitating a long reaction time to achieve good conversion [15].

Recently, we reported that water can be used as green solvent in ATH catalyzed by Ru(II), Rh(III) and Ir(III) complexes [5o,8d,15–20].

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The reduction affords fast reaction rate, excellent enantioselectivity and high chemoselectivity in a short reaction time for a wide range of substrates at substrate to catalyst ratios (S/C) ranging from 100:1 to 10,000:1. Moreover, it is easy to conduct, requiring no modification to the ligands, no organic solvents, and often no inert gas protection throughout. Additional advantage includes the use of HCO_2Na, a safe inexpensive reductant. This aqueous-phase reduction provides a new method that is simple, economical and eco-friendly, and can be readily adopted for laboratory synthesis and commercial scale production of chiral alcohols [16f,17]. However, not all ketones can be reduced in water with high conversion and good ee's, partly due to their limited solubility in water [1,5h,u,9c,14,16d,18]. Although surfactant can be used for ATH in water, [6b,18c,19] they obviously add further complication to the reaction.

During our study, we found that the pH of the reaction solution plays a crucial role in the catalyst performance in the aqueous-phase ATH [15,16a,c]. Both the reduction rate and enantioselectivity can be dependent on the solution pH. Further studies have revealed that this pH regulation is common for ATH of ketones and imines in water [5u,6b,l,8d,n,o,9e,j–l,n,10,12b,15,16,18d,20]. These observations prompted us to investigate the effect of the F/T molar ratios on ATH of ketones in F-T mixtures, in the hope to improve this powerful transformation. Surprisingly somehow, there are only two examples in the literature, where the F/T ratio was reduced to 1/1, and in each case, only one ketone substrate was examined [21].

2. Experimental

2.1. Instruments

^1H (400 MHz, 298 K) and ^{13}C (100 MHz, 298 K) NMR spectra were recorded on a 400 MHz Bruker spectrometer in $CDCl_3$ solution. Chemical shifts are reported as δ (in ppm) relative to the residual solvent ($CDCl_3$) peak for ^1H and ^{13}C. Gas chromatographic (GC) analyses for chiral alcohol products were performed on a Varian CP-3380 GC equipped with a Chrompack Chirasil-Dex CB column (25 m × 0.25 mm, 80 psi helium carrier gas, 60 psi hydrogen gas and 250 °C injector temperature) or a GILSON UV/VIS-151 HPLC equipped with a Chiral OD or OD-H column (ambient temperature, 254 nm detection). MS spectra were measured on Finnigan Mat TSQ 700 instrument. Analytical TLC was carried out utilizing 0.25 mm precoated plates (silica gel 60 UV_{254}) and spots were visualized by use of UV light and silica-I_2 revelation. Column chromatography was performed with silica gel 60 (70–230 mesh, Fluka).

2.2. Chemicals

$[RuCl_2(p\text{-cymene})]_2$, $[Cp^*RhCl_2]_2$, $[Cp^*IrCl_2]_2$, TsDPEN, ketones, HCOONa, HCOOH, NEt_3, and *N,N*-diisopropylethylamine were purchased from Johnson Matthey, Aldrich, Fluka, Strem, or Lancaster, and used without further purification unless otherwise noted. Water was deionized before use as solvent.

2.3. General procedure for preparation of catalysts

All the reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques, and all glassware was oven-dried for a minimum of two hours before use, unless otherwise stated.

The M-**1** catalysts were generated in situ by reacting M ($[RuCl_2(p\text{-cymene})]_2$, $[Cp^*RhCl_2]_2$, or $[Cp^*IrCl_2]_2$, 0.005 mmol) and 1 ((*R*,*R*)-TsDPEN, 0.012 mmol) in 2 mL of solvent. After stirring the mixture at 40 °C for 0.5 h, the suspension was directly used for the subsequent reduction reactions.

2.4. General procedure for ATH of ketones

A typical procedure for the ATH of acetophenone (acp) with Ru-**1** in a F-T mixture is as follows. The precatalyst was prepared by reacting $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol) and **1** (4.4 mg, 0,012 mmol) in degassed F-T (2 mL) with different F/T molar ratios (0.09/1 to 4.6/1) at 40 °C for 0.5 h under N_2. Then acp (0.11 mL, 1 mmol) was added and the reaction mixture was allowed to react at 40 °C for a certain period of time, and monitored by analytical TLC. The reaction mixture was then cooled to room temperature, followed by extraction with CH_2Cl_2 (DCM, 3 × 3 mL). The organic phase was then collected, a small amount of which was passed though a short silica gel column before being subjected to GC analysis. For isolation, the mixture was then dried over Na_2SO_4, filtered, concentrated and purified by silica gel column using hexane and ethyl acetate as eluent to give the expected product. The products were routinely analyzed by comparing their GC/HPLC and NMR (^1H and ^{13}C) data with the literature data, and additionally by mass spectroscopy and elemental analysis when it was necessary. The stereochemistry of products was assigned by comparing the GC/HPLC retention time with the literature data. The products under question have been reported in the literature [5,14–17].

(R)-1-Phenylethanol: [5j,16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injector temperature: 250 °C; column temperature: 120 °C; 8.17 min (*R*); 8.29 min (*S*). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.49 (d, *J* = 6.5 Hz, 3 H), 1.83 (bs, 1 H), 4.88 (q, *J* = 6.5 Hz, 1 H), 7.24–7.28 (m, 2 H), 7.32–7.38 ppm (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.5, 70.8, 125.8, 127.8, 128.9, 146.2 ppm. MS CI *m*/*z* (%): 140 ($[M+NH_4^+]$, 29), 122 (M^+, 100). Elemental analysis calcd (%) for $C_8H_{10}O$ (122.16): C, 78.65; H, 8.25. Found: C, 78.47; H, 8.35.

(R)-1-(4′-Nitrophenyl)ethanol, (Entry 1, Table 2):[16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injector temperature: 250 °C; column temperature: 175 °C; 8.36 min (*R*); 9.27 min (*S*). HPLC (Chiral OD); eluent: 2-propanol/hexane 5/95; tempt, r.t.; flow rate, 1.0 mL/min; detection, 254 nm light): 15.40 min (*S*), 16.41 min (*R*). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.52 (d, *J* = 6.5 Hz, 3 H), 2.10 (bs, 1 H), 5.03 (q, *J* = 6.5 Hz, 1 H), 7.52–7.58 (m, 2 H), 8.19–8.23 ppm (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.9, 69.9, 124.2, 126.5, 147.6, 153.4 ppm. Elemental analysis calcd (%) for $C_8H_9NO_3$ (167.16): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.30; H, 5.50; N, 8.44.

(R)-1-(4′-Chlorophenyl)ethanol (Entry 2, Table 2): [5j,16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 150 °C; 5.01 min (*R*); 5.17 min (*S*). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.45 (d, *J* = 6.0 Hz, 3 H), 2.04 (bs, 1 H), 4.85 (q, *J* = 6.0 Hz, 1 H), 7.26–7.32 ppm (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.7, 70.1, 127.4, 129.0, 133.5, 144.6 ppm. MS CI *m*/*z* (%):174 ($[M+NH_4^+]$, 100), 156 (M^+, 37). Elemental analysis calcd (%) for C_8H_9ClO (156.61): C, 61.35; H, 5.79. Found: C, 61.29; H, 5.58.

(R)-1-(4′-Trifluoromethylphenyl)ethanol (Entry 3, Table 2): [15b,16c] GC (Chirasil Dex CB; carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 150 °C; 2.75 min (*R*), 3.02 min (*S*). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.50 (d, *J* = 6.0 Hz, 3 H), 2.11 (bs, 1 H), 4.95 (q, *J* = 6.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.60 ppm (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.8, 70.2, 124.6 (q, $^1J_{C\text{-}F}$ = 271.0 Hz), 125.8 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 126.0, 130.0 (q, $^2J_{C\text{-}F}$ = 32.0 Hz), 150.1 ppm. MS CI m/z (%): 190 (M^+, 100). Elemental analysis calcd (%) for $C_9H_9F_3O$ (190.16): C, 56.84; H, 4.77. Found: C, 56.75; H, 4.65.

(R)-4′-(1-Hydroxy-1-phenylethyl)benzonitrile (Entry 4, Table 2): [5j,16c] GC (Chirasil Dex CB): carrier gas: helium, 40 psi; injection temperature: 250 °C; column temperature: 150 °C; 19.77 min (*R*); 25.47 min (*S*). ^1H NMR (400 MHz, $CDCl_3$/TMS):

δ = 1.49 (d, J = 6.6 Hz, 3 H), 2.05 (d, J = 4.4 Hz, 1 H), 4.96 (q, J = 6.6 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 2 H), 7.36 ppm (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.42, 69.67, 111.09, 118.86, 126.07, 132.36, 151.09 ppm.

(R)-1-(Pyridin-2-yl)ethanol (Entry 5, Table 2): [15,16c] GC (Chirasil Dex CB): carrier gas: helium, 40 psi; injection temperature: 250 °C; column temperature: 100 °C; 22.50 min (*R*); 23.00 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.51 (d, J = 6.5 Hz, 3 H), 4.37 (bs, 1 H), 4.90 (q, J = 6.5 Hz, 1 H), 7.19 (dd, J = 7.5 Hz, 4.8 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.65–7.72 (m, 1 H), 8.52 ppm (d, J = 4.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 24.7, 68.9, 119.8, 122.2, 136.8, 148.1, 163.2 ppm. MS CI m/z (%): 123 (M^+, 100). Elemental analysis calcd (%) for C_7H_9NO (123.15): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.23; H, 7.38; N, 11.36.

(R)-1-(Pyridin-3-yl)ethanol (Entry 6, Table 2): [15,16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 130 °C; 8.51 min (*R*); 8.94 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.53 (d, J = 6.5 Hz, 3 H), 4.65 (bs, 1 H), 4.87 (q, J = 6.5 Hz, 1 H), 7.22 (dd, J = 7.8 Hz, 4.80 Hz, 1 H), 7.71–7.75 (m, 1 H), 8.32 (dd, J = 4.8 Hz, 1.8 Hz, 1 H), 8.42 ppm (d, J = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.1, 67.3, 123.6, 133.7, 142.0, 146.9, 147.8 ppm. MS CI m/z (%): 123 (M^+, 100). Elemental analysis calcd (%) for C_7H_9NO (123.15): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.28; H, 7.29; N, 11.33.

(R)-1-(3′-Bromophenyl)ethanol (Entry 7, Table 2): [16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 150 °C; 10.146 min (*R*), 11.140 min (S). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.53 (d, J = 6.5 Hz, 3 H), 2.58 (bs, 1 H), 4.95 (q, J = 6.5 Hz, 1 H), 7.10 (dd, J = 7.5 Hz, 1.50 Hz, 1H), 7.14–7.20 (m, 1 H), 7.32 (dd, J = 4.8 Hz, 1.50 Hz, 1 H), 7.32–7.38 ppm (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 24.4, 70.8, 122.4, 125.6, 128.9, 129.5, 133.8, 148.7 ppm. MS CI m/z (%): 201 (M^+, 100). Elemental analysis calcd (%) for C_8H_9BrO (201.06): C, 47.79; H, 4.51. Found: C, 47.65; H, 4.44.

(R)-1-(3′-Nitrophenyl)ethanol (Entry 8, Table 2): [15,16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 160 °C; 7.94 min (*R*); 8.40 min (*S*). HPLC (Chiral OD); eluent: 2-propanol/hexane 5/95; tempt, r.t.; flow rate, 1.0 mL/min; detection, 254 nm light): 14.80 min (*S*), 15.71 min (*R*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.54 (d, J = 6.5 Hz, 3 H), 1.99 (d, J = 3.3 Hz, 1 H), 5.03 (q, J = 6.5 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1 H), 7.72 (d, J = 6.8 Hz, 1 H), 8.13 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 8.27 ppm (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.56, 69.46, 120.47, 122.42, 129.48, 131.60 ppm.

(R)-1-(4′-Methylphenyl)ethanol (Entry 9, Table 2): [15j,16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 120 °C; 5.85 min (*R*); 6.28 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.47 (d, J = 6.0 Hz, 3 H), 1.91 (bs, 1 H), 2.35 (s, 3 H), 4.85 (q, J = 6.0 Hz, 1 H), 7.13–7.19 (m, 2 H), 7.24–7.28 ppm (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 21.5, 25.5, 70.7, 125.8, 129.6, 137.6, 143.3 ppm. MS CI m/z (%): 154 ([M+NH_4^+], 100), 136 (M^+, 80). Elemental analysis calcd (%) for $C_9H_{12}O$ (136.19): C, 79.37; H, 8.88. Found: C, 79.35; H, 8.85.

(R)-1-(4′-Methoxyphenyl)ethanol (Entry 10, Table 2): [15j,16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 130 °C; 12.10 min (*R*); 13.10 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.5 (d, J = 6.4 Hz, 3 H), 2.39 (bs, 1 H), 3.79 (s, 3 H), 4.83 (q, J = 6.4 Hz, 1 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.28 ppm (d, J = 8.7 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 24.8, 55.2, 69.8, 113.8, 126.5, 137.8, 159.0 ppm. MS CI m/z (%): 152 (M^+, 100). Elemental analysis calcd (%) for $C_9H_{12}O_2$ (152.19): C, 71.03; H, 7.95. Found: C, 70.95; H, 7.88.

(R)-1-(2′-Nitrophenyl)ethanol: [15,16c] GC (Chirasil Dex CB): carrier gas: helium, 80 psi; injection temperature: 250 °C; column temperature: 150 °C; 8.84 min (*R*), 10.25 min(*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.58 (d, J = 6.3 Hz, 3 H), 2.36 (bs, 1 H), 5.42 (q, J = 6.3 Hz, 1 H), 7.24 (t, J = 8.0 Hz, 1 H), 7.65 (t, J = 8.0 Hz, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.90 ppm (d, J = 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 24.19, 65.59, 124.33, 127.58, 128.13,133.63, 140.89, 147.88 ppm.

(1R,1′R)-1,1′-(1,3-Phenylene)diethanol (Entries 1–2, Table 3): [5l,24] GC (Chirasil Dex CB, 80 psi helium as carrier gas, 250 °C injection temperature, 160 °C column temperature): (meso) 11.00 min; (*S*, *S*) 11.20 min; (*R*, *R*) 11.35 min. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.48 (d, J = 6.8 Hz, 6 H), 2.17 (bs, 2 H), 4.87 (q, J = 6.8 Hz, 2 H), 7.24–7.27(m, 2 H), 7.30–7.34 (m, 1 H), 7.37 ppm (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.16, 70.36, 122.44, 124.53, 128.65, 146.10 ppm. MS CI m/z (%): 166.2 (M^+, 100).

(1R,1′R)-1,1′-(1,4-Phenylene)diethanol (Entries 3–4, Table 3): [5l,24] GC (Chirasil Dex CB, 80 psi helium as carrier gas, 250 °C injection temperature, 160 °C column temperature): 160 °C, (*R*, *R*) 15.99 min; (meso) 17.50 min; (*S*, *S*) 17.92 min. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.50 (d, J = 1.6 Hz, 6 H), 4.85-4.93 (m, 2 H), 1.82 (s, 2 H), 7.36 ppm (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.1, 25., 70.2, 125.6, 145.1 ppm. MS CI m/z (%): 166.1 (M^+, 6), 131.0 [(M−(OH) × 2)$^+$, 100].

(1R,1′R)-1,1′-(Biphenyl-4,4′-diyl)diethanol (Entries 5–6, Table 3): [24] GC (Chirasil Dex CB, 80 psi helium as carrier gas, 250 °C injection temperature, 168 °C column temperature): 168 °C, (*R*, *R*) 36.02 min; (*S*, *S*) 38.50 min. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.54 (d, J = 6.6 Hz, 6 H), 1.84 (d, J = 2.6 Hz, 2 H), 4.93–4.99 (m, 2H), 7.45 (d, J = 8.0 Hz, 4 H), 7.58 ppm (d, J = 8.0 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.2, 70.2, 125.9, 127.2 ppm. MS CI m/z (%): 242.2 (M^+, 6), 207.1 [(M-(OH) × 2)$^+$, 100].

(*R*)-1-(9′-Phenanthryl)ethanol (1st, Scheme 2): [16c] HPLC (Chiral OD-H); eluent: 2-propanol/hexane 5/95; tempt, r.t.; flow rate, 1.0 mL/min; detection, 254 nm light): 22.49 min (*R*); 26.99 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.72 (d, J = 6.5 Hz, 3 H), 2.0 (bs, 1 H), 5.67 (q, J = 6.5 Hz, 1 H), 7.57–7.68 (m, 4 H), 7.89 (d, J = 6.5 Hz, 1 H), 7.93 (s, 1 H), 8.15 (d, J = 8.0 Hz, 1 H), 8.65 (d, J = 8.0 Hz, 1H), 8.74 ppm (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 24.15, 67.24, 122.46, 122.75, 123.37, 123.90, 126.31, 126.64, 126.78, 128.79, 129.59, 130.04, 130.79, 131.53, 139.50 ppm. MS CI m/z (%): 222.3 (M^+, 11), 205.3 [(M-OH)$^+$, 100].

(*R*)-1,2-Diphenylethan-1-ol (2nd, Scheme 2): [16c,g] HPLC (Chiral OD-H); eluent: 2-propanol/hexane 5/95; tempt, r.t.; flow rate, 1.0 mL/min; detection, 254 nm light): 12.99 min (*R*); 16.47 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.96 (bs, 1 H), 2.99 (dd, J = 14.0 Hz, 8.0 Hz, 1H), 3.05 (dd, J = 14.0 Hz, 5.2 Hz, 1H), 4.90 (dd, J = 8.0 Hz, J = 4.8 Hz, 1 H), 7.19–7.38 ppm (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 47.0, 76.2, 126.8, 127.5, 128.5, 129.3, 129.4, 130.4, 138.9, 144.7 ppm; MS CI m/z (%): 198 (M^+, 100), 181 (32). Elemental analysis calcd (%) for $C_{14}H_{14}O$ (198.26): C, 84.81; H, 7.12. Found: C, 84.70; H, 7.18.

(*R*)-1-(4′-Biphenylyl)-1-ethanol (3rd, Scheme 2): [22,23] HPLC (Chiral OD-H); eluent: 2-propanol/hexane 5/95; tempt, r.t.; flow rate, 1.0 mL/min; detection, 254 nm light): 15.80 min (*S*), 16.68 min (*R*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.54 (d, J = 6.0 Hz, 3 H), 1.85 (bs, 1H), 4.95 (q, J = 6.0 Hz, 1 H), 7.32–7.38 (m, 1 H), 7.41–7.47 (m, 4 H), 7.58 ppm (d, J = 8.0 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.2, 70.2, 125.9, 127.1, 127.3, 128.8, 140.5, 140.9, 144.8 ppm. MS CI m/z (%): 198.2 (M^+, 13), 181.2 [(M-OH)$^+$, 100].

3. Results and discussion

The experiment was conducted initially using acp as a model substrate. The M-**1** catalyst was prepared in situ from a metal precursor (M, 0.005 mmol; see Section 2.3) and ligand **1** (TsDPEN, 0.012 mmol) in 2 mL of a solvent to be used for the ATH. After stirring at 40 °C for 1 h, the suspension was used directly for the

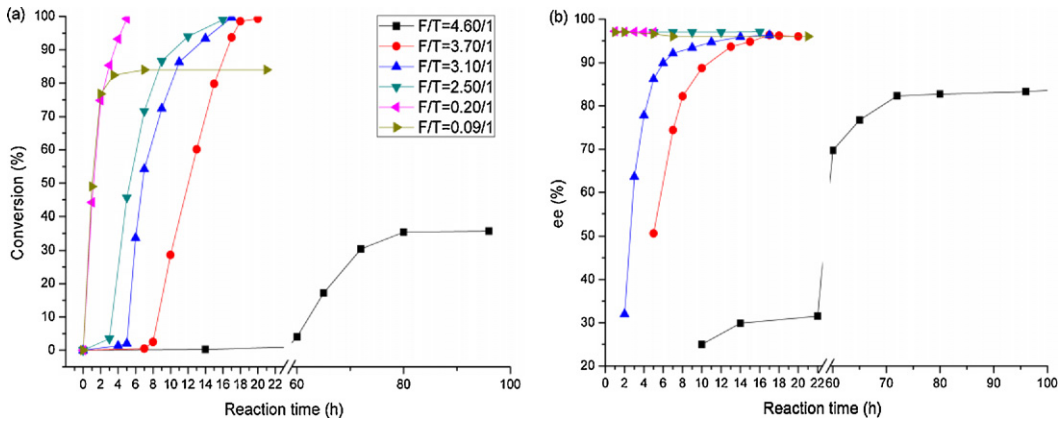
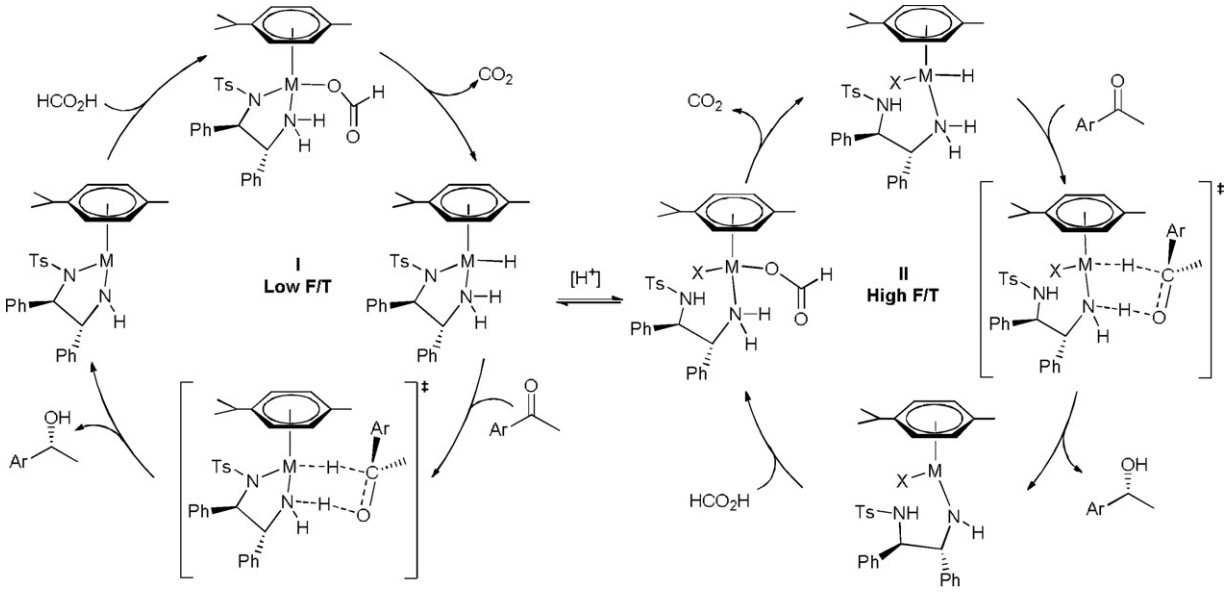


Fig. 1. Conversion (a) and ee (b) versus reaction time for ATH of acp with Ru-**1** in F-T mixtures at different initial F/T ratios at 40 °C.

subsequent reduction reactions without any further purification. The precatalyst can be isolated with high yield [15,16a,c].

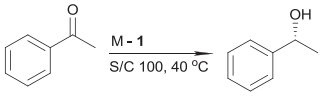
Using a simply mixed F-T solution at different initial F/T molar ratios, ATH of acp catalyzed by Ru-**1** was carried out to examine the effects of the F/T ratio on the performance of this catalyst. Representative results are shown in Fig. 1. As can be seen, the reduction of acp requires a very long time to achieve a high conversion under acidic conditions. The higher the F/T ratios, the longer the reaction takes. For example, ATH of acp gave 39% conversion in 150 h at a initial F/T molar ratio of 4.6/1 (Fig. 1a). It is noteworthy that there exists a very long induction period for the reduction under these conditions. Thus, the reaction afforded less than 1% conversion in the first 48 h and 4% conversion in 60 h. Thereafter, the reaction speeded up, achieving over 30% conversion in 12 h. The reaction was sluggish again after 70 h, possibly due to insufficient hydrogen source. It has been revealed that formic acid can be decomposed by the catalyst to produce CO_2 and H_2 during the reaction, which would result in a decrease in the F/T ratio with time and thereby initiate the reaction [15,16c]. Similar induction periods were also observed from the reduction carried out at initial F/T molar ratio of 3.7/1 and 3.1/1 (Fig. 1a). When the initial F/T ratios were lowered, meaning that the reaction media became more basic, the reaction rate increased significantly. The average reaction rate increased 4 times when the initial molar ratio of F/T varied from 3.7/1 to 0.2/1. In particular, when the F/T ratio was lowered to 0.9/1–0.2/1, the reduction started immediately and completed in a short reaction time (Fig. 1a). However, the reaction was incomplete at the F/T ratio of 0.09/1 after 2 h, possibly due to the hydrogen source being exhausted; the total quantity of HCOOH was only 1.2 equivalents relative to the substrate in this case.

Interestingly, as shown in Fig. 1b, the ee's of the product varied dramatically as well when the initial F/T ratio was higher (From 4.6/1 to 3.1/1, Fig. 1b), whilst it remained high in the cases of lower F/T ratios (F/T < 2.5/1, Fig. 1b). This finding resembles that made in aqueous ATH [15,16] but is the first one revealed for ATH in a F-T mixture. On the basis of previous studies of ATH in water, [15,16a,c] we propose that two different catalytic cycles are likely to operate in this reduction, depending on the F/T molar ratios (Scheme 1). ATH of acp at low F/T ratios is more efficient, affording faster rates and higher enantioselectivities (Cycle I, Scheme 1). At higher F/T ratios, protonation occurs at both the hydride and TsDPEN ligands, driving the catalyst into a less active and less enantioselective cycle (Cycle II, Scheme 1). Our results thus show that the catalysis in F-T mixtures is similar to that in water, where both the reaction rates and enantioselectivities are pH-regulated [8,15,16d]. Taken together, the screening suggests that in terms of reaction rate and enantioselectivity, the optimum F/T molar ratio is 0.2/1. Hereafter, this mixture will be referred to as 0.2 F/T.



Scheme 1. Proposed catalytic cycles for ATH of acp under near neutral (I) and acidic (II) conditions in a F-T solution.

Table 1
Comparison of ATH of acp with M-**1** under various conditions.[a]



Entry	Catalysts	Solvent	Time (h)	Conv. (%)[b]	Ee (%)[b]
1	Ru-**1**	IPA[c]	24	81	89
2	Ru-**1**	2.5 F/T[d]	16	98	97
3	Ru-**1**	H_2O-HCOONa[e]	1	>99	94
4	Ru-**1**	H_2O-2.5 F/T[f]	12	98	97
5	Ru-**1**	0.2 F/T[g]	5	>99	97
6	Ru-**1**	0.2 F/D[h]	5	98	97
7	Rh-**1**	0.2 F/T	80	>99	86
8	Ir-**1**	0.2 F/T	23	74	82

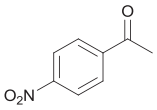
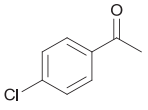
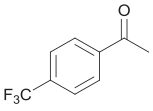
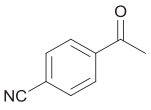
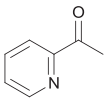
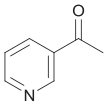
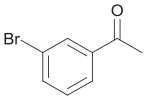
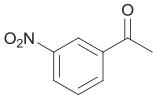
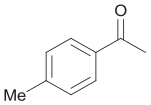
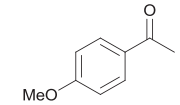
[a] Reaction conditions: 1 mmol acp, 0.01 mmol M-**1**, 2 mL solution, 40 °C.
[b] Determined by GC equipped with a chiral column. The alcohol configuration was *R*.
[c] 0.01 equiv. KOH was added.
[d] Azeotropic F/T solution.
[e] 5 equiv. HCOONa.
[f] $V_{azeotrope} = V_{H_2O} = 1$ mL.
[g] HCOOH/Et_3N = 0.2/1.
[h] HCOOH/*N,N*-diisopropylethylamine = 0.2/1.

Other reaction conditions were also compared. As shown in Table 1, the performance of the Ru-**1** catalyst is much better than that of Rh-**1** and Ir-**1** under the optimized conditions (0.2 F/T). Ru-**1** delivered >99% conversion with 97% ee in 5 h (Entry 5, Table 1) while Rh-**1** and Ir-**1** afforded >99% conversion with 86% ee in 80 h (Entry 7, Table 1) and 74% conversion with 82% ee in 23 h (Entry 8, Table 1), respectively. The poor performance of Rh-**1** and Ir-**1** may be due to there being different optimum pH windows for them. These results are again reminiscent of the ATH of ketones in water with these catalysts [8d,15,16]. Comparison of the Ru-**1** catalyzed ATH of acp in different reaction media show that the reaction run in IPA gave the poorest performance (entry 1, Table 1), while the reduction in water afforded the fastest rate (entry 3, Table 1). The reaction in the azeotropic F-T (2.5 F/T) was markedly slower (entry 2, Table 1) than in the 0.2 F/T, while adding water to the 2.5 F/T shortened the reaction time by 4 h. The ATH of acp in a HCOOH and *N,N*-diisopropylethylamine mixture with a molar ratio of 0.2 gave a faster reaction as well, affording 98% conversion and 97% ee in 5 h.

The comparison above shows that the 0.2 F/T affords faster reduction than the azeotropic 2.5 F/T without compromising the ee. In the previous two studies, the F/T ratio was set at 1:1 and the reduction was also shown to be faster than in 2.5 F/T [21]. These results clearly establish that the ATH could be made faster with a smaller amount of HCO_2H. Although the M-**1** (M = Ru, Rh, Ir) catalyzed ATH of ketones in water has proved to be successful as aforementioned, not all ketones can be reduced efficiently in aqueous solution to give high conversion and ee values. Combining M-**1** with 0.2 F/T could provide a new option, however.

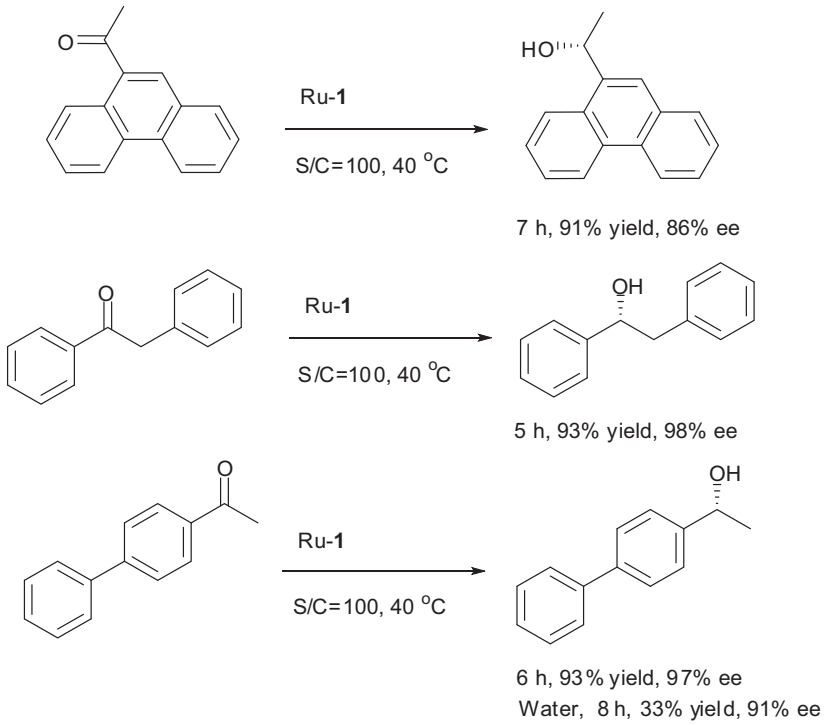
Aiming to determine the potential applicability of the protocol, the reduction was then extended to a range of aromatic ketones, using the simply mixed 0.2 F/T as reductant and solvent. The results of the ATH are summarized in Table 2 and Scheme 2. As shown in Table 2, for the simple ketones, the Ru-**1** catalyzed reduction furnished high conversions within 5 h and the enantioselectivities were excellent in most cases. For instance, 4′-nitro-acp, 4′-chloro-acp, 4′-(trifluoromethyl)-acp and 4′-acetylbenzonitrile were all converted into the corresponding alcohols in 99% conversion and up to 99% ee in 5 h (Entries 1–4, Table 2). In contrast, it took 24 h to achieve 99% conversion and 88% ee for the reduction of 4′-CF_3-acp in the azeotropic 2.5 F/T solution (2.5 F/T) [13e]. The reduction of 4′-chloro-acp and 4′-acetylbenzonitrile afforded full conversion and 95% ee in 24 h, and >99% conversion and 90% ee in 21 h in the 2.5 F/T, respectively [5,13,j,b]. When it comes to the *meta*-substituted acp,

Table 2
ATH of simple ketones with Ru-**1** in 0.2 F/T.[a]

Entry	Ketones	Time (h)	Conv. (%)[b]	Ee (%)[c]
		5	>99 (96)	99
		5	99 (95)	94[d]
		5	>99 (87)	95[d]
		5	>99 (95)	88[d]
		5	93 (89)	>99
		5	98 (93)	88[d]
		5	>99 (93)	94[d]
		5	>99 (94)	75
		50	97(91)	93[d]
		50	(86)	95

[a] Reaction condition: 1 mmol acp,1% mmol Ru-**1**, 2 mL 0.2 F/T at 40 °C.
[b] Determined by GC or NMR. The number in bracket refers to the isolated yield.
[c] Determined by GC with a chiral column. The alcohol configuration was *R* and was determined by comparison of GC retention time or sign of optical rotation with literature data.
[d] Determined by HPLC with a chiral OD-H or OD column.

for example, 3′-Br-acp and 3′-NO_2-acp, the ketones were almost fully converted with ee's of 94% and 75% in 5 h, respectively (Entries 7 and 8, Table 2). The heterocyclic 2′-acetylpyridine gave a 93% conversion and >99% ee in 5 h (Entry 5, Table 2), while 3′-acetylpyridine afforded 98% conversion and 88% ee at the same reaction time (Entry 6, Table 2). However, 4′-Me-acp and 4′-MeO-acp, which are often problematic in ATH, required 50 h to achieve a conversion of >90% (Entries 9 and 10, Table 2). For comparison, when using the 2.5 F/T, ATH of the 4′-OMe-acp took 65 h to arrive at a similar conversion [4]. There appeared to be strong correlation between the electronic properties of the substitutes with the reaction rate but none with enantioselectivity. Thus with electron withdrawing substituted group, such as NO_2-, CF_3- and CN-, the reaction gave fast reaction rate while with electron donating group, such as Me-

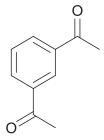
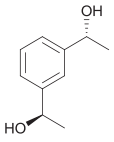
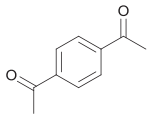
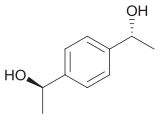
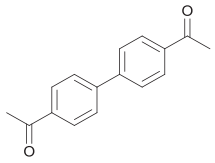
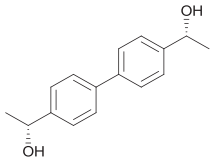


Scheme 2. ATH of water-insoluble ketones in 0.2 F/T.

and MeO-, the reaction rate decreased dramatically (*e.g.* Entries 1–4 *vs* 9 and 10). Steric bulk inhibits the reduction as well. The reduction of isobutyrophenone afforded only 2% conversion and 87% ee in 5 h and it took 80 h to complete the ATH of 2′-NO_2-acp, affording 78% ee. Furthermore, there was no reaction observed for ketones with very bulky substitutions at either the α methyl position or the phenyl ring. For instance, 2′-benzoyl-5-norbornene and 4′-*tert*-butyl-2,6-dimethyl-3,5-dinitro-acp could not be reduced at all under these conditions.

Comparing ATH of 4′-acetylbiphenyl in different reaction media showed that the aqueous reduction by HCOONa afforded (*R*)-1-(4′-biphenylyl)-1-ethanol with a lower yield 33% and an ee value of 91% in 8 h, demonstrating that not all the ketones are suitable for reduction in water. In contrast, an isolated yield of 93% and an ee

Table 3
ATH of diketones with Ru-**1** in F-T mixture.[a]

Entry	Diketones	Products	F/T ratio	Time (h)	Yield[b] (%)	Ee[c] (%)	de[c]
1			0.2	25	90	>99	90/10
2			2.5[d]	95	63	>99	90/10
3			0.2	25	91	>99	94/6
4			2.5[d]	95	44	>99	94/6
5			0.2	25	94	>99	>99
6			2.5[d]	25	30	>99	>99

[a] Reaction Conditions: 1 mmol diketone, 1% mmol Ru-**1**, in a 4 mL of F/T solution at 40 °C.
[b] Isolated yield.
[c] Determined by GC or HPLC equipped with chiral column.
[d] Azeotropic F/T mixture.

value of 97% were achieved within 6 h in the 0.2 F/T. Scale up is also possible, as demonstrated by the ATH of 4′-acetylbiphenyl. The reduction of 2 g of this ketone afforded 93% isolated yield and 96% ee in 11 h under the conditions shown in Table 2. Matsumura et al. reported the same reduction with trichlorosilane as reductant in $CHCl_3$ at room temperature, furnishing 93% yield and 95% ee in 6 h [22]. Furthermore, this result compares favorably to that obtained with the enzyme *C. laurentii*, which afforded 34% isolated yield and 99% ee at 35 °C in 36 h [23].

Diketones can also be reduced efficiently to chiral diols with excellent ee and de values under the current conditions (Table 3). There are few example of ATH of diketones in the literature [5,24l]. Hence a comparison was made with the ATH of diketones run in the 2.5 F/T. As shown in Table 3, whilst there is no difference in the de and ee, the reduction in the 0.2 F/T proceeded at significantly faster rates as compared with the same transformation in the azeotrope. For instance, (1*R*,1′*R*)-1,1′-(1,3-phenylene)diethanol and (1*R*,1′*R*)-1,1′-(1,4-phenylene)diethanol were produced with isolated yields of 90% and 91% in 25 h in the 0.2 F/T solution (Entries 1 and 3, Table 3). In contrast, the reduction in the 2.5 F/T afforded much lower isolated yields in a longer reaction time (Entries 2 and 4, Table 3).

4. Conclusion

A simple, easy-to-operate reduction system for the ATH of ketones has been developed. The Ru-**1**/0.2 F/T system is particularly suited to those ketones that are insoluble in water or are slow to be reduced in or sensitive to the azeotropic 2.5 F/T. In comparison with the commonly-used azeotropic 2.5 F/T system, this new protocol is more efficient and easy to scale-up. Whilst ATH in azeotropic 2.5 F/T has been widely exploited, the effect of the F/T molar ratios on the efficacy of the reduction has seldom been subjected to scrutiny. This study shows that the F/T ratio has a significant effect on both the ATH rate and enantioselectivity, a finding reminiscent of the pH-dependence of ATH in aqueous media and of value to laboratory or commercial applications of ATH.

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