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Ruthenium(II) complexes derived from C_2-symmetric ferrocene-based chiral bis (phosphinite) ligands: synthesis and catalytic activity towards the asymmetric reduction of acetophenones

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Chiral secondary alcohols are very important building blocks and valuable synthetic intermediates both in organic synthesis and in the pharmaceutical industry for producing biologically active complex molecules. A series of new chiral Ru–phosphinite complexes (1–8) were prepared from chiral C_2-symmetric ferrocenyl phosphinites and corresponding chloro complex, [Ru(η^6-*p*-cymene)(μ-Cl)Cl]$_2$. The complexes were characterized using conventional spectroscopic methods. The binuclear complexes were tested as pre-catalysts and were found to be good pre-catalysts for the asymmetric transfer hydrogenation of substituted acetophenones in basic 2-propanol at 82°C, providing the corresponding optically active alcohols with almost quantitative conversion and modest to high enantioselectivities (46–97%). Amongst the all complexes, complex 6 gave the highest *ee* of 97% in the reduction of 2-methoxyacetophenone to (*S*)-1-(2-methoxyphenyl)ethanol at 82°C. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: ferrocenyl bis(phosphinite); C_2 symmetry; asymmetric transfer hydrogenation; acetophenone; ruthenium

Introduction

Over the last few decades, much attention has been devoted to transition metal complexes with various types of ligands in the area of homogeneous catalysis.[1,2] There has been a growing interest in the development of new transition metal complexes of phosphorus- and nitrogen-based ligands for the catalytic asymmetric hydrogenation of prochiral ketones. Following the fascinating works of Noyori and co-workers, a broad range of transition metal complexes of phosphorus ligands have been developed, some of which have been shown to hydrogenate ketones with prominent catalytic activities.[3–5] Among phosphorus donor ligands, chiral bis(phosphine) ligands have played a dominant role in the development of efficient transition metal-catalysed asymmetric reactions.[6]

In recent years, much effort has been devoted to the use of rhodium, ruthenium and iridium catalysts containing phosphorus donor ligands in asymmetric hydrogenation.[7–10] The reduction of unsaturated molecules can be conducted either by direct hydrogenation with gaseous hydrogen, which is more widely applied, or by hydrogen obtained *in situ* from a suitable donor such as propan-2-ol or formic acid.[11,12] The latter has drawn great attention in the last decade due to its operational simplicity, use of inexpensive and benign reagents and there being no need for high-pressure hydrogen that can be potentially dangerous.[13] Asymmetric transfer hydrogenations of functionalized prochiral ketones and imines, as an efficient method for producing enantiopure alcohols and amines, have drawn great attention due to their potential for applications in the fine chemicals, pharmaceuticals and agrochemical industries and in new materials.[14,15]

While many studies have been reported concerning phosphine catalysts,[16–20] a notable underdeveloped area is the asymmetric transfer hydrogenation of unsaturated molecules catalysed by phosphinite ligands.

Numerous chiral ligands with ferrocenyl backbones have been prepared and used successfully in a variety of catalytic applications.[21–23] Enantiopure ferrocenyl phosphorus or nitrogen donor ligands have been reported as active catalysts in a variety of asymmetric catalytic reactions such as hydrogenation,[24] hydrosilylation,[25] allylic alkylation,[26] Grignard cross-coupling reactions,[27] cyclopropanation[28] and aldol-type condensation,[29] and further development of new ligands is still in progress.[30] Although some phosphines and aminoalcohols containing ferrocene skeletons have been employed successfully as ligands in ruthenium(II)-promoted transfer hydrogenation of ketones, a screening of catalytic activity of ferrocenyl phosphinites in this reaction is quite limited.[31–34]

Encouraged by these observations and the fact that C_2-symmetrical phosphines have wide potential in asymmetric synthesis, we

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have synthesized new ruthenium(II) complexes of C_2-symmetric ferrocenyl bis(phosphinite) ligands and used them as catalysts in ruthenium-catalysed asymmetric transfer hydrogenation of various ketones.

Experimental

Materials and methods

Unless otherwise stated, all reactions were performed under argon in flame-dried glassware using standard Schlenk techniques. All solvents were purified by distillation over drying agents using certain procedures prior to use and were transferred under argon. All reagents were purchased from Fluka and used as received. Analytical-grade and deuterated solvents were purchased from Merck.

^{1}H NMR (at 400.1 MHz), ^{13}C NMR (at 100.6 MHz) and ^{31}P-{^{1}H} NMR (at 162.0 MHz) spectra were recorded using a Bruker AV400 spectrometer, with tetramethylsilane as an internal standard for ^{1}H NMR and ^{13}C NMR or 85% H_3PO_4 as the external reference for ^{31}P-{^{1}H} NMR. Infrared (IR) spectra were recorded with a Mattson 1000 ATI UNICAM FT-IR spectrometer as KBr pellets. Elemental analysis was carried out using a Fision EA 1108 CHNS-O instrument. Melting points were recorded with Gallenkamp apparatus with open capillaries. GC analyses were performed using a Shimadzu GC 2010 Plus gas chromatograph equipped with a Cyclodex B (Agilent) capillary column (30 m × 0.32 mm inner diameter × 0.25 μm film thickness). Racemic samples of alcohols were obtained by reduction of the corresponding ketones with $NaBH_4$ and used as authentic samples for *ee* determination. The GC parameters for asymmetric transfer hydrogenation of ketones were as follows: initial temperature, 50°C; initial time, 1.1 min; solvent delay, 4.48 min; temperature ramp, 1.3°C min^{-1}; final temperature, 150°C; initial time, 2.2 min; temperature ramp, 2.15°C min^{-1}; final temperature, 250°C; initial time, 3.3 min; final time, 44.33 min; injector port temperature, 200°C; detector temperature, 200°C; injection volume, 2.0 μl.

General procedure for synthesis of ferrocene-based bis (phosphinite) ruthenium(II) complexes (1–8)

To a solution of ferrocene-based phosphinite ligand[35] (1 equiv.) in dry toluene (20 ml), the metal precursor [Ru(η^6-*p*-cymene)(μ-Cl)Cl]$_2$ (1 equiv.) was added at room temperature. The mixture was stirred until the resonance of free ligand disappeared in the ^{31}P NMR spectrum (1 to 14 h). The solvent was evaporated to *ca* 1–2 ml and petroleum ether (20 ml) was added to yield a tile-red powder which was washed with diethylether–*n*-hexane (1:1) and then dried in vacuum.

(S)-Bis[[N-(2-diphenylphosphinite-1-benzyl)ethyl]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (1)

Yield 180 mg, 88%; m.p. 136–138°C. ^{1}H NMR (400.1 MHz, $CDCl_3$, δ, ppm): 7.82–7.88 (m, 8H, *o*-C_6H_5P), 7.05–7.44 (m, 10H, C_6H_5 +12H, *m*- and *p*-C_6H_5P), 5.13–5.22 (m, 8H, C_6H_4 of *p*-cymene), 3.68–4.17 (m, 8H, C_5H_4 + 4H, (CH_2OP) + 4H, CH_2NH), 3.06 (br, 2H, *CH*NH), 2.84–2.93 (m, 4H, CH_2Ph), 2.60–2.53 (m, 2H, *CH*(CH_3)$_2$ of *p*-cymene), 1.80 (s, 6H, CH_3 of *p*-cymene), 1.06 (d, 6H, J = 6.9 Hz, CH(CH_3)$_2$ of *p*-cymene (a)), 1.01 (d, 6H, J = 6.6 Hz, CH(CH_3)$_2$ of *p*-cymene (b)). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 127.97, 128.07, 129.03, 131.00, 131.43, 132.39 (C_6H_5 + C_6H_5OP), 97.34, 111.41 (quaternary carbons of *p*-cymene), 87.33, 87.89, 89.97, 91.14 (C_6H_4 of *p*-cymene), 68.71, 68.90, 69.11, 69.89 (br, C_5H_4 + CH_2OP), 58.25 (*CH*N), 46.11 (CH_2NH), 36.07 (CH_2Ph), 30.09 (*CH*(CH_3)$_2$ of *p*-cymene), 21.79, 22.02 (CH(CH_3)$_2$ of *p*-cymene), 17.50 (CH_3 of *p*-cymene). ^{31}P-{^{1}H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 113.8 (s, O-*P*Ph$_2$). IR (KBr pellet, cm^{-1}): ν(NH): 3332; ν(CH): 2860, 2925, 3028, 3060; ν(C=C–Cp): 1447; ν(O–P): 1021. Anal. Calcd for [$C_{74}H_{82}N_2O_2P_2FeRu_2Cl_4$] (1493.3 g mol^{-1}) (%): C, 59.52; N, 1.88; H, 5.55. Found (%): C, 59.48, N, 1.80, H, 5.51%. $[\alpha]_D^{20}$ +66.44 (C 1.2, MeOH).

(S)-Bis[[N-(2-diphenylphosphinite-1-phenyl)ethyl]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (2)

Yield 195 mg, 92%; m.p. 168–170°C. ^{1}H NMR (400.1 MHz, $CDCl_3$, δ, ppm): 7.76–7.85 (m, 8H, *o*-C_6H_5OP), 7.28, 7.37 (m, 10H, C_6H_5 + 12H, C_6H_5OP), 5.15 (br, 8H, C_6H_4 of *p*-cymene), 3.86–4.03 (br, 8H, C_5H_4 + 2H, *CH*NH+ 4H, CH_2OP), 3.26 (br, 4H, CH_2NH), 2.60 (br, 2H, *CH*(CH_3)$_2$ of *p*-cymene), 1.83 (br, 6H, CH_3 of *p*-cymene), 1.06 (m, 12H, CH(CH_3)$_2$ of *p*-cymene). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 127.97, 128.06, 128.74, 129.45, 130.96, 131.22 (C_6H_5 + C_6H_5OP), 97.10, 111.36 (quaternary carbons of *p*-cymene), 87.55, 87.70, 90.49, 91.15 (C_6H_4 of *p*-cymene), 67.18, 67.83, 68.14, 68.74, 71.03 (C_5H_4 + CH_2OP), 62.33 (CHN), 46.05 (CH_2NH), 30.10 (*CH*(CH_3)$_2$ of *p*-cymene), 21.74–21.92 (CH(CH_3)$_2$ of *p*-cymene), 17.55 (CH_3 of *p*-cymene). ^{31}P-{^{1}H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 109.5 (s, O-*P*Ph$_2$). IR (KBr pellet, cm^{-1}): ν(NH): 3323; ν(CH): 2865, 2917, 3025, 3064; ν(C=C–Cp): 1436; ν(O–P): 1018. Anal. Calcd for [$C_{72}H_{78}N_2O_2P_2FeRu_2Cl_4$] (1465.2 g mol^{-1}) (%): C, 59.02; N, 1.91; H, 5.38. Found (%): C, 58.92; N, 1.80; H, 5.22. $[\alpha]_D^{20}$ +77.8 (C 1.2, MeOH).

(S)-Bis[[N-(2-diphenylphosphinite-1-isobutyl)ethyl]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (3)

Yield 198 mg, 88%; m.p. 126–128°C. ^{1}H NMR (400.1 MHz, $CDCl_3$, δ, ppm): 7.80–7.49 (m, 8H, *o*-C_6H_5OP), 7.40–7.42 (b, 12H, *m*- and *p*-C_6H_5OP), 5.20–5.29 (m, 8H, C_6H_4 of *p*-cymene), 4.25 (s, 4H, C_5H_4), 4.08 (s, H C_5H_4), 3.61–3.70 (b, 4H, CH_2NH + 2H, CH_2OP (a)), 3.91 (b, 2H, CH_2OP (b)), 2.79 (b, 2H, NHC*H*), 2.59–2.63 (m, 2H, *CH*(CH_3)$_2$ of *p*-cymene), 1.88 (s, 6H, CH_3 of *p*-cymene), 1.33–1.35 (b, 4H, $CHCH_2$ + 2H, *CH*(CH_3)$_2$), 1.03–1.09 (m, 12H, CH(CH_3)$_2$ of *p*-cymene), 0.72–0.77 (m, 12H, CH(CH_3)$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 127.95, 128.04, 132.11, (C_6H_5OP), 97.24, 111.30 (quaternary carbons of p-cymene), 87.42, 87.87, 90.32, 91.22 (*p*-cymene C_6H_4), 67.68, 68.13, 68.85, 69.03, 69.79 (C_5H_4 + CH_2OP), 55.01 (*CH*N), 45.81 (CH_2NH), 40.46 ($CHCH_2$), 30.11 (*CH* of *p*-cymene), 24.63 ($CHCH_3$), 21.69, 21.98, 22.36, 23.03 (CH(CH_3)$_2$ + CH(CH_3)$_2$ of *p*-cymene), 17.58 (CH_3 of *p*-cymene). ^{31}P-{^{1}H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 109.5 (s, O-*P*Ph$_2$). IR (KBr pellet, cm^{-1}): ν(NH): 3330; ν(CH): 2867, 2955, 2961, 3070; ν(C=C–Cp): 1436; ν(O–P): 1021. Anal. Calcd for [$C_{68}H_{86}N_2O_2P_2FeRu_2Cl_4$] (1425.2 g mol^{-1}) (%): C, 57.30; N, 1.97; H, 6.08. Found (%): C, 57.23; N, 1.94; H, 6.01. $[\alpha]_D^{20}$ +47.3 (C 1.2, MeOH).

(S)-Bis[[N-(2-diphenylphosphinite-1-sec-butyl)ethyl]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (4)

Yield 180 mg, 80%; m.p. 129–131°C. ^{1}H NMR (400.1 MHz, $CDCl_3$, δ, ppm): 7.84–7.95 (m, 8H, *o*-C_6H_5P), 7.42 (b, 12H, *m*- and *p*-C_6H_5P), 5.21–5.33 (m, 8H, C_6H_4 of *p*-cymene), 4.07–4.16 (br, 8H, C_5H_4), 3.91 (br, 2H, CH_2OP (a)), 3.69 (br, 2H, CH_2OP (b)), 3.48 (br, 4H, CH_2NH), 2.61–2.65 (b, 2H, *CH*NH + 2H, *CH* of *p*-cymene), 1.60 (b, 2H, CH_3CH), 1.28–1.33 (m, 4H, CH_2CH_3), 1.88 (s, 6H, CH_3 of *p*-cymene), 1.10 (d, 6H, J = 7.0 Hz, CH(CH_3)$_2$ of *p*-cymene), 1.06 (d, 6H, J = 6.7 Hz, CH(CH_3)$_2$ of *p*-cymene), 0.80–0.92 (m, 6H, $CHCH_3$ + 6H, CH_2CH_3). ^{13}C NMR (100.6

MHz, $CDCl_3$, δ, ppm): 127.84, 130.90, 132.64 (C_6H_5P), 97.34, 11.28 (quaternary carbons of *p*-cymene), 87.55, 87.65, 87.71, 90.36 (C_6H_4 of *p*-cymene), 67.10, 67.90, 68.12, 68.64, 69.33 (C_5H_4 + CH_2OP), 61.10 (*C*HNH), 46.79 (CH_2NH), 36.01 ($CHCH_3$), 30.01 (*C*H of *p*-cymene), 25.72 (CH_2CH_3), 21.73, 22.01 ($CH(CH_3)_2$ of *p*-cymene), 17.55 (–CH_3 of *p*-cymene), 11.98, 14.71 ($CHCH_3$ + CH_2CH_3). ^{31}P-{^1H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 110.80 (s, O-*P*Ph_2). IR (KBr pellet, cm^{-1}): ν(NH): 3325; ν(CH): 2872, 2921, 2959, 3063; ν(C=C–Cp): 1460; ν(O–P): 1015. Anal. Calcd for [$C_{68}H_{86}N_2O_2P_2FeRu_2Cl_4$] (1425.2 g mol^{-1}) (%): C, 57.30; N, 1.97; H, 6.08. Found (%): C, 57.20; N, 1.82; H, 5.91. $[\alpha]_D^{20}$ +64.2 (C 1.2, MeOH).

(R)-Bis[[N-(2-diphenylphosphinite-1-ethyl)ethyl]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (5)

Yield 175 mg, 91%; m.p. 130–132°C. ^1H NMR (400.1 MHz, $CDCl_3$, δ, ppm): 7.26–7.80 (m, 20H, C_6H_5P), 5.20–5.28 (m, 8H, C_6H_4 of *p*-cymene), 4.10–4.24 (m, 8H, C_5H_4), 3.85–3.93 (m, 4H, CH_2OP), 3.62–3.67 (m, 4H, CH_2NH), 2.78–2.85 (m, 2H, *C*HN), 1.31–1.52 (m, 4H, CH_2CH_3), 2.64 (m, 2H $CH(CH_3)_2$ of *p*-cymene), 1.80 (s, 6H, CH_3 of *p*-cymene), 1.04–1.10 (m, 12H, $CH(CH_3)_2$ of *p*-cymene), 0.91–0.95 (m, 6H, CH_2CH_3). ^{13}C-NMR (100.6 MHz, $CDCl_3$, δ, ppm): 141.76 (d, J = 9.0 Hz, i-C_6H_5P), 128.03, 130.95, 132.14 (*o*-, *m*-, *p*-C_6H_5), 97.32, 111,27 (quaternary carbons of *p*-cymene), 87.47, 87.88, 90.32, 91.09 (C_6H_4 of *p*-cymene), 86.59 (i-C_5H_4), 71.24 (d, J = 18.1 Hz, CH_2OP), 68.46, 68.88, 69.51, 69.65 (C_5H_4), 58.37 (*C*HN), 46.05 (CH_2NH), 23.41 (CH_2CH_3), 21.96, 21.71 ($CH(CH_3)_2$ of *p*-cymene), 30.10 ($CH(CH_3)_2$ of *p*-cymene), 17.57 (CH_3 of *p*-cymene), 10.22 (CH_2CH_3). ^{31}P-{^1H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 110.9 (s, O-*P*Ph_2). IR (KBr pellet, cm^{-1}): ν(NH): 3342; ν(CH): 2868, 2920, 3038, 3101; ν(C=C–Cp): 1457; ν(O–P): 1011. Anal. Calcd for [$C_{64}H_{78}N_2O_2P_2FeRu_2Cl_4$] (1369.1 g mol^{-1}) (%): C, 56.14; N, 2.05; H, 5.75. Found (%): C, 56.02; N, 1.99; H, 5.71. $[\alpha]_D^{20}$ −63.2 (C 1.2, MeOH).

(R)-Bis[[N-(2-diphenylphosphinite-2-phenyl)ethyl]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (6)

Yield 218 mg, 93%; m.p. 156–158°C. ^{31}P-{^1H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 111.2 (s, O-*P*Ph_2). IR (KBr pellet, cm^{-1}): ν(NH): 3310; ν(CH): 2861, 2926, 3029, 3056; ν(C=C–Cp): 1437; ν(O–P): 1026. Anal. Calcd for [$C_{72}H_{78}N_2O_2P_2FeRu_2Cl_4$] (1465.2 g mol^{-1}) (%): C, 59.02; N, 1.91; H, 5.38. Found (%): C, 58.89; N, 1.96; H, 5.32. $[\alpha]_D^{20}$ −73.3 (C 1.2, MeOH).

(1S,2R)-Bis[[N-(2-diphenylphosphinite-1,2-diphenyl)ethyl]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (7)

Yield 218 mg, 93%; m.p. 160–162°C. ^{31}P-{^1H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 113.6 (s, O-*P*Ph_2). IR (KBr pellet, cm^{-1}): ν(NH): 3342; ν(CH): 2865, 2935, 3040, 3057; ν(C=C–Cp): 1460; ν(O–P): 1018. Anal. Calcd for [$C_{84}H_{86}N_2O_2P_2FeRu_2Cl_4$] (1617.4 g mol^{-1}) (%): C, 62.37; N, 1.73; H, 5.37. Found (%): C, 58.86; N, 1.60; H, 5.17. $[\alpha]_D^{20}$ +55.2 (c 1.2, MeOH).

(S)-Bis[[N-(2-diphenylphosphinitepropyl)]-1,1′-ferrocenylmethyldiamine (dichloro η^6-p-cymene ruthenium(II))] (8)

Yield 181 mg, 90%; m.p. 126–128°C. ^{31}P-{^1H} NMR (162.0 MHz, $CDCl_3$, δ, ppm): 110.0 (s, O-*P*Ph_2). IR (KBr pellet, cm^{-1}): ν(NH): 3372; ν(CH): 2850, 2915, 3018, 3066; ν(C=C–Cp): 1442; ν(O–P): 1031. Anal. Calcd for [$C_{62}H_{74}N_2O_2P_2FeRu_2Cl_4$] (1341.1 g mol^{-1}) (%): C, 55.52; N, 2.09; H, 5.57. Found (%): C, 55.42; N, 2.01; H, 5.49. $[\alpha]_D^{20}$ +43.2 (C 1.2, MeOH).

General procedure for asymmetric transfer hydrogenation of ketones

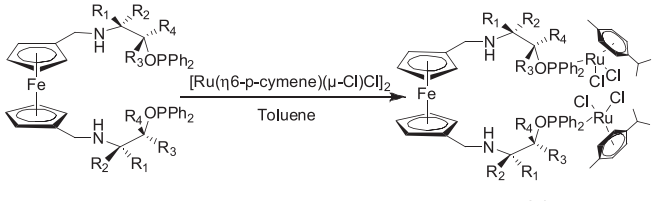
The ruthenium catalyst (0.005 mmol) and anhydrous 2-propanol (5 ml) were placed in a flame-dried Schlenk tube under inert atmosphere. Then, the corresponding ketone (0.5 mmol) and NaOH (0.025 mmol) were added and the mixture was heated at the required temperature with stirring until the reaction was complete. Subsequently, a sample of reaction mixture was taken off and diluted with acetone. The product distribution was determined immediately using GC. Conversions obtained are related to unreacted ketone.

Results and discussion

The complexes [Ru_2Cl_4L], where L is **L_1–L_8**, were prepared by the addition of an equivalent of [Ru(η^6-*p*-cymene)(μ-Cl)Cl]$_2$ to a dry solution of ferrocene-based bis(phosphinite) ligands (Fig. 1). After 1–14 h stirring at room temperature, the ^{31}P NMR spectrum of the reaction mixture displays the complete disappearance of the signal corresponding to the free bisphosphinites and the appearance of a new signal for the expected complexes. All complexes are obtained as tile-red powders in high yields. A single resonance ranging from 109.5 to 113.8 ppm is obtained for all complexes in the ^{31}P-{^1H} NMR spectra. The ^1H NMR and ^{13}C NMR data for complexes **1–5** are consistent with the formulation of [Ru_2Cl_4L] and in line with the values previously observed for similar complexes. However, ^1H NMR and ^{13}C NMR spectra were not recorded for complexes **6–8** due to the low solubility of these complexes in common NMR solvents.

We have recently reported the synthesis of several chiral ferrocenyl phosphinite ligands and their applications in Ru(II)(arene)-catalysed transfer hydrogenation of ketones.[27–29] As part of our continuing interest in ferrocene-based chiral ligands and their applications in asymmetric catalysis, we herein report the results obtained for the asymmetric transfer hydrogenation of various ketones using ruthenium(II) complexes of C_2-symmetric chiral phosphinite ligands containing ferrocenyl moiety.

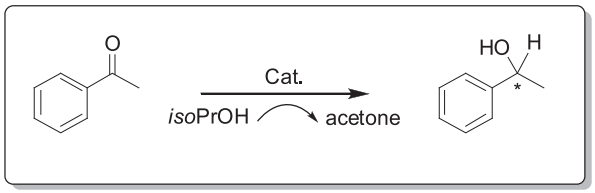
To evaluate the effectiveness of our ruthenium(II) complexes (**1–8**) as catalysts in asymmetric transfer hydrogenation reaction of ketones, we prefer starting with the reduction of acetophenone as a standard test reaction. For screening the activity and enantioselectivity for the reaction, the optimal conditions were investigated, such as reaction temperature and molar ratio of substrate to catalyst. The results presented in Table 1 clearly show that the catalysts are active and selective for asymmetric transfer



R_1: benzyl,	R_2: H,	R_3: H,	R_4: H	1
R_1: phenyl,	R_2: H,	R_3: H,	R_4: H	2
R_1: *iso*butyl,	R_2: H,	R_3: H,	R_4: H	3
R_1: *sec*butyl,	R_2: H,	R_3: H,	R_4: H	4
R_1: H,	R_2: ethyl,	R_3: H,	R_4: H	5
R_1: H,	R_2: H,	R_3: phenyl,	R_4: H	6
R_1: phenyl,	R_2: H,	R_3: phenyl,	R_4: H	7
R_1: H,	R_2: H,	R_3: H,	R_4: CH_3	8

Figure 1. Synthetic route for the preparation of C_2-symmetric ferrocene-based chiral bis(phosphinite) ruthenium(II) complexes **1–8**.

Table 1. Asymmetric transfer hydrogenation of acetophenone with iso-PrOH catalysed by C_2-symmetric bisphosphinite ruthenium(II) complexes (**1–8**)

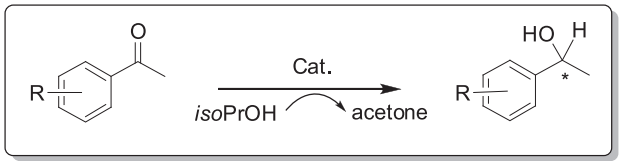


Entry	Complex	Substrate/catalyst/base	Time (h)	Conv. (%)[a]	*ee* (%)[b]	Config.[c]	TOF (h^{-1})[d]
1	**1**[e]	100:1:5	1	99	90	*R*	99
2	**2**[e]	100:1:5	1	98	92	*S*	98
3	**3**[e]	100:1:5	12	97	64	*R*	8
4	**4**[e]	100:1:5	12	98	78	*S*	8
5	**5**[e]	100:1:5	12	98	62	*R*	8
6	**6**[e]	100:1:5	12	99	98	*R*	8
7	**7**[e]	100:1:5	12	98	95	*R*	8
8	**8**[e]	100:1:5	12	99	96	*S*	8
9	**1**[f]	100:1	24	<10	—	—	—
10	**2**[f]	100:1	24	<10	—	—	—
11	**3**[f]	100:1	24	<10	—	—	—
12	**4**[f]	100:1	24	<10	—	—	—
13	**5**[f]	100:1	24	<10	—	—	—
14	**6**[f]	100:1	24	<10	—	—	—
15	**7**[f]	100:1	24	<10	—	—	—
16	**8**[f]	100:1	24	<10	—	—	—
17	**1**[g]	100:1:5	0.5	98	84	*R*	196
18	**2**[g]	100:1:5	0.5	99	87	*S*	198
19	**3**[g]	100:1:5	0.5	98	59	*R*	196
20	**4**[g]	100:1:5	0.5	98	64	*S*	196
21	**5**[g]	100:1:5	0.5	98	55	*R*	196
22	**6**[g]	100:1:5	2 (2)[h]	98 (96)[h]	95 (92)[h]	*R*	49 (48)
23	**7**[g]	100:1:5	0.5	98	84	*R*	196
24	**8**[g]	100:1:5	1	98	89	*S*	98
25	**6**[g]	100:1:3	2	96	92	*R*	48
26	**6**[g]	100:1:5	2	98	95	*R*	49
27	**6**[g]	100:1:7	2	96	93	*R*	48
28	**6**[g]	100:1:9	2	93	89	*R*	47
29	**6**[g]	250:1:5	2	96	89	*R*	48
30	**7**[g]	250:1:5	2	93	79	*R*	47
31	**8**[g]	250:1:5	2	94	83	*S*	47
32	**6**[g]	500:1:5	3	93	82	*R*	31
33	**7**[g]	500:1:5	3	90	71	*R*	30
34	**8**[g]	500:1:5	3	91	76	*S*	30
35	**6**[g]	1000:1:5	5	87	77	*R*	17
36	**7**[g]	1000:1:5	5	80	64	*R*	16
37	**8**[g]	1000:1:5	5	82	68	*S*	16

[a]Determined by GC (three independent catalytic experiments).
[b]Determined by capillary GC analysis using a chiral Cyclodex B (Agilent) capillary column.
[c]Determined by comparison of retention times of enantiomers on the GC traces with literature values; (*S*) or (*R*) configuration was obtained in all experiments.
[d]TOF = (mol product/mol catalyst) × h^{-1}.
[e]At room temperature, in the presence of NaOH.
[f]Refluxing in iso-PrOH, in absence of base.
[g]Refluxing in iso-PrOH, in presence of NaOH.
[h]Refluxing in iso-PrOH; acetophenone/Ru/KOH, 100:1:5.

hydrogenation of acetophenone. The transfer hydrogenation of acetophenone using complexes **1–8** as catalysts at a molar substrate-to-catalyst ratio of 100 in 2-propanol with NaOH at room temperature gives almost quantitative conversion and moderate to high enantioselectivities (62–98%, entries 1–8). As evident from Table 1, the reaction rate is markedly increased on increasing the

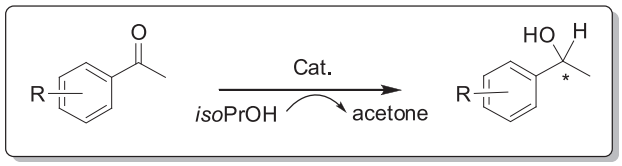
Table 2. Transfer hydrogenation of substituted acetophenones catalysed by **1–8**[a]



Entry	Catalyst	R	Time (h)	Conv. (%)[b]	*ee* (%)[c]	TOF (h^{-1})[d]	Config.[e]
1	**1**	H	0.5	98	84	196	*R*
2	**2**		0.5	99	87	198	*S*
3	**3**		0.5	98	59	196	*R*
4	**4**		0.5	98	64	196	*S*
5	**5**		0.5	98	55	196	*R*
6	**6**		2	98	95	49	*R*
7	**7**		0.5	98	86	196	*R*
8	**8**		1	98	89	98	*S*
9	**1**	2-F	0.5	98	78	196	*R*
10	**2**		0.5	99	79	198	*S*
11	**3**		0.5	99	49	198	*R*
12	**4**		0.5	98	55	196	*S*
13	**5**		0.5	99	47	196	*R*
14	**6**		1	98	88	98	*R*
15	**7**		0.5	98	78	196	*R*
16	**8**		1	98	82	98	*S*
17	**1**	4-F	0.25	97	80	388	*R*
18	**2**		0.25	98	82	392	*S*
19	**3**		0.25	98	53	392	*R*
20	**4**		0.33	98	60	294	*S*
21	**5**		0.33	98	51	294	*R*
22	**6**		0.75	99	92	132	*R*
23	**7**		0.25	99	83	396	*R*
24	**8**		0.5	99	86	198	*S*
25	**1**	2-Br	0.75	98	81	131	*R*
26	**2**		0.75	98	83	131	*S*
27	**3**		0.75	98	56	131	*R*
28	**4**		0.75	97	62	129	*S*
29	**5**		1	98	50	98	*R*
30	**6**		3	98	91	33	*R*
31	**7**		0.75	98	84	131	*R*
32	**8**		1	98	87	98	*S*
33	**1**	4-Br	0.5	98	82	196	*R*
34	**2**		0.5	98	83	196	*S*
35	**3**		0.5	97	55	194	*R*
36	**4**		0.5	98	63	196	*S*
37	**5**		0.75	98	53	131	*R*
38	**6**		2	97	94	49	*R*
39	**7**		0.5	99	85	198	*R*
40	**8**		0.5	98	89	198	*S*
41	**1**	2-OCH_3	2	96	85	48	*S*
42	**2**		2	98	90	49	*R*
43	**3**		2	96	61	48	*S*
44	**4**		2	97	65	49	*R*
45	**5**		2	98	57	49	*S*
46	**6**		4	98	97	25	*S*
47	**7**		2	98	90	49	*S*
48	**8**		3	98	94	33	*R*
49	**1**	4-OCH_3	1	96	72	96	*R*
50	**2**		1	95	79	95	*S*

(Continues)

Table 2. (Continued)



Entry	Catalyst	R	Time (h)	Conv. (%)[b]	*ee* (%)[c]	TOF (h^{-1})[d]	Config.[e]
51	**3**		1	94	52	94	*R*
52	**4**		1	96	56	96	*S*
53	**5**		1	96	51	96	*R*
54	**6**		3	97	88	32	*R*
55	**7**		1	97	79	97	*R*
56	**8**		2	96	82	48	*S*
57	**1**	4-NO_2	1	97	81	97	*R*
58	**2**		1	99	84	99	*S*
59	**3**		1	98	55	98	*R*
60	**4**		1	97	60	97	*S*
61	**5**		4	98	51	25	*R*
62	**6**		6	98	92	16	*R*
63	**7**		1	98	83	98	*R*
64	**8**		3	99	88	33	*S*
65	**1**	4-CF_3	0.33	98	78	294	*R*
66	**2**		0.33	99	81	297	*S*
67	**3**		0.33	99	49	297	*R*
68	**4**		0.33	97	55	291	*S*
69	**5**		0.33	99	46	297	*R*
70	**6**		0.5	99	89	198	*R*
71	**7**		0.33	99	81	297	*R*
72	**8**		0.33	99	84	297	*S*

[a]Catalyst (0.005 mmol), substrate (0.5 mmol), iso-PrOH (5 ml), NaOH (0.025 mmol%), 82°C, concentration of acetophenone derivatives 0.1 M.
[b]Purity of compounds checked by ^{1}H NMR and GC (three independent catalytic experiments); yields are based on aryl ketone.
[c]Determined by capillary GC analysis using a chiral Cyclodex B (Agilent) capillary column (30 m × 0.32 mm inner diameter × 0.25 μm film thickness).
[d]TOF = (mol product/mol catalyst) × h^{-1}.
[e]Determined by comparison of the retention times of the enantiomers on the GC traces with literature.

reaction temperature from 25 to 82°C, whereas the reactivity decreases on increasing the substrate concentration 10-fold. The enantioselectivity also decreases markedly on increasing both reaction temperature and substrate concentration. Among the catalysts screened, complex **6** proves to be the best catalyst, yielding (*R*)-1-phenylethanol with 99% conversion and 98% *ee* after 12 h at room temperature (Table 1, entry 6). At reflux temperature of 82°C, the reaction takes less time to complete than at room temperature but gives lower enantiomeric excess. As evident from Table 1, changing the base does not affect the product conversion (entry 22). It is worth mentioning that the opposite absolute configuration of 1-phenylethanol is obtained compared to the configuration of the complexes (**1** and **3**) used as catalysts, while for all other complexes the product configurations do not change.

Following investigation of the optimal conditions, these complexes were also evaluated for catalytic activity towards transfer hydrogenation of substituted acetophenones using 2-propanol both as the hydrogen source and solvent in the presence of NaOH as the base. The results clearly indicate that all the substituted acetophenones are transformed into the corresponding secondary alcohols in high yields. The results also show that the electronic properties of the substituent on the phenyl ring of the acetophenone change the reduction rate but have only little effect on the enantioselectivity. As observed in many studies, the presence of an electron-withdrawing group on the phenyl ring generally facilitates the hydrogenation reaction, which is attributed to the hydridic nature of the reducing species involved.[36] Table 2 shows that the *ortho*-substituted acetophenone is reduced more slowly than *para*-substituted ones and shows a slightly lower selectivity probably due to an undesirable steric clash.

4-Methoxyacetophenone is known to be a tough substituent probably because of its rather low redox potential, and it gives lower conversion and enantioselectivity.[37] However, in the present work, the reduction of 2- or 4-methoxyacetophenone occurs with 98 or 97% conversion and 97 or 88% *ee*, respectively, at 82°C. Compared to our previous report[29] in which Ru(II) complexes were derived from chiral monophosphinite ligands containing a ferrocenyl moiety, using **1** or **2** as catalyst under identical conditions the hydrogenation of acetophenone or its derivatives is accomplished with similar conversion but with slightly higher enantiolesectivity. It is well known that structural differences considerably affect catalytic activity. Experimental results obtained from the catalytic evaluation reveal that complexes **6**, **7** and **8** are efficient catalysts for the reduction of

acetophenones to the corresponding secondary alcohols. It is observed that changing the substituent on the asymmetric carbon atom in the ligands of complexes **1–8** results in a significant difference in both catalyst reactivity and enantioselectivity. The results clearly indicate that when the chiral centre is present near the metal atom, high enantioselectivity is observed. Moreover, the aryl moiety on the carbon atom having a chiral centre is more responsible for both higher activity and selectivity than the alkyl moiety. Among the eight new catalysts described herein, catalyst **6** gives almost quantitative conversions (97–99%) for all ketones screened. The enantioselectivities obtained using this catalyst range from 88 to 97% *ee* at 82°C. Reduction of 2-methoxyacetophenone to (*S*)-1-(2-methoxyphenyl)ethanol is achieved with both high conversion and enantioselectivity of 98 and 97%, respectively, at 82°C.

Conclusions

A series of C_2-symmetric bis(phosphinite) ruthenium(II) complexes bearing ferrocenyl moiety were developed and evaluated for catalytic activity towards asymmetric transfer hydrogenation of acetophenone derivatives using 2-propanol in the presence of NaOH. Almost complete conversion and moderate to excellent enantioselectivity were obtained using all complexes as catalysts. Complex **6** is the most efficient catalyst among the eight complexes. The most efficient conversion and enantioselectivity were found in the case of 2-methoxyacetphenone with catalyst **6**.

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