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Asymmetric transfer hydrogenation catalyzed by a novel planar chiral *N*-heterocyclic carbene–rhodium(I) complex

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A novel chelated ferrocene-based planar chiral N-heterocyclic carbene-Rh(I) complex was synthesized by a simple method. It was applied to the asymmetric transfer hydrogenation of prochiral ketones. Enantioselectivities of up to 67% ee were observed.

Supporting information may be found in the online version of this article.

Keywords: chiral *N*-heterocyclic carbene; rhodium complex; ferrocene; asymmetric transfer hydrogenation; ketones

Introduction

Transition metal-catalyzed asymmetric transfer hydrogenation (ATH) of prochiral ketones has become one of the most important developments in organic synthesis chemistry.[1–3] In view of the low cost of reducing agents and operational simplicity, this reaction provides an efficient method for the preparation of optically active secondary alcohols. The common catalysts are rhodium, iridium and ruthenium complexes with chiral phosphine and chiral diamine ligands.[4–6]

Chiral *N*-heterocyclic carbenes (NHCs) as effective alternatives to chiral phosphine ligands in asymmetric catalytic processes are attracting increased attention due to their strong σ-donating and weak π-accepting properties.[7–10] However, the use of chiral NHCs in ATH has so far been limited and only a few examples have been reported. In 2003, Chung *et al*. applied a ferrocene-derived monodentate carbene–Ir(I) complex in ATH of 4′-methyl acetophenone and propiophenone giving corresponding secondary alcohols with 32%ee and 52.6%ee, respectively. However, towards other ketones, the products were obtained with very low ees or even racemic.[11] In 2005, Douthwaite reported the synthesis of a series of chiral NHC–phosphine ligands. Their complexes with iridium(I) exhibited poor asymmetric induction in ATH of acetophenone (11% ∼ 34% ee).[12] In 2006, Herrmann synthesized the reduced biisoquinoline-based chiral NHCs. Their complexes with rhodium and iridium were employed in ATH, but very low ees were obtained (<24% ee).[13] Therefore, the challenge remains to develop more efficient chiral NHC ligands for ATH. Herein, we report the synthesis of a chelated ferrocene-based planar chiral carbene–Rh (I) complex **1** and its application in ATH of ketones (Fig. 1).

Results and Discussion

Synthesis of Chiral Carbene–Rh(I) Complex 1

The planar chiral carbene–Rh(I) complex **1** was synthesized from ferrocene–carboxylic acid **2** (Scheme 1). Treatment of **2** with oxalyl chloride and (*S*)-valinol successively led to the formation of amide **3** in 86% yield, which was transformed into **4** in 84% yield by cyclization using Appel's method.[14] After a highly diastereoselective *ortho*-lithiation followed by treatment with 1,2-diiodoethane, **5** was obtained in 79% yield.[15] Then **5** was allowed to react with imidazole in the presence of $CsCO_3$, CuI and *trans*-1,2-cyclohexane diamine in dioxane at 110 °C. The resulting ferrocene imidazole **6** was treated with benzyl bromide followed by anion exchange with $TlPF_6$ to give ferrocene imidazolium salt **7** in 73% yield, which is the precursor of NHC. Deprotonation of **7** with *t*-BuOK followed by a reaction with $[Rh(COD)Cl]_2$ in THF yielded Rh(I)–carbene complex **1** as an orange air-stable crystal in 75% yield. The analytical and spectroscopic data for **1** are consistent with its proposed structures. The ^{13}C NMR spectra showed the expected signals for the carbene carbon linking with Rh at around 181 ppm. The mass spectra showed strong characteristic signals for the $[M^+ - PF_6]$ fragment.

ATH of Ketones Catalyzed by Carbene–Rh(I) Complex 1

ATH was carried out by reacting ketones with 2-propanol and base in the presence of carbene–Rh(I) complex **1**. To determine the optimal conditions for the catalytic reaction, acetophenone was chosen as the model substrate. The results are summarized in Table 1.

The reaction did not proceed below 40 °C, but when the temperature was elevated to 75 °C, the reaction proceeded smoothly to yield (*S*)-1-phenylethanol with 88% chemical yield (Table 1, entry 1 vs 2).

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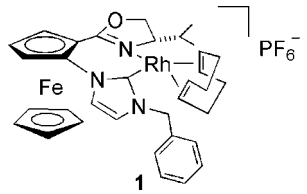
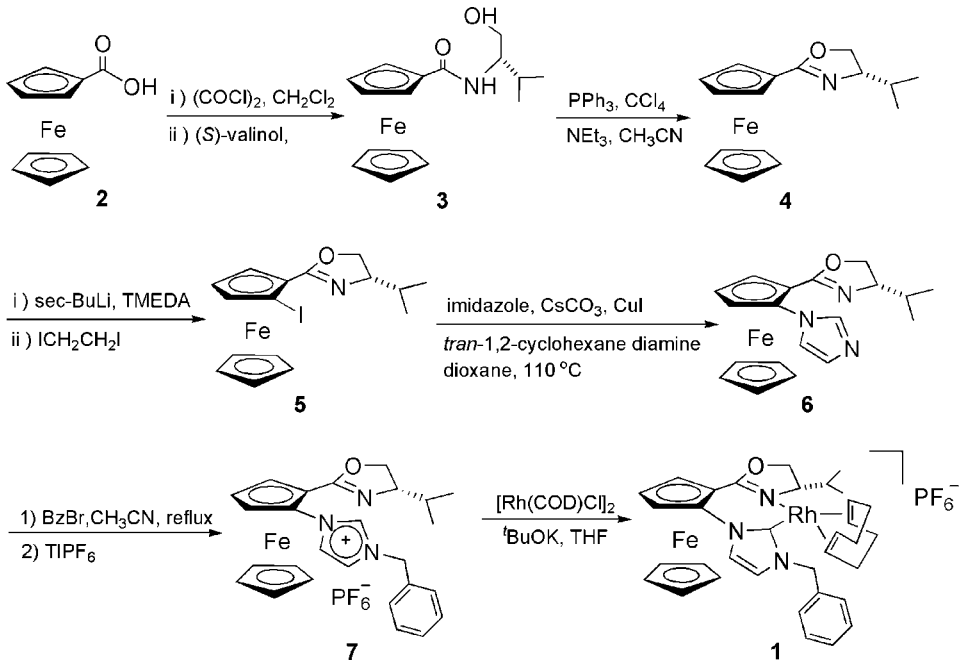


Figure 1. Planar chiral carbene–Rh(I) complex 1.

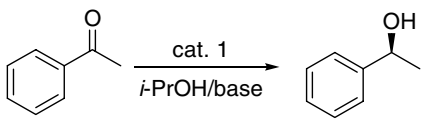
It is well known that the base co-catalyst can activate the catalyst markedly in ATH.[16] As in previous reports, base was used to deprotonate *i*-PrOH, allowing the complexation of the metal with isopropoxide ion, followed by formation of the nonracemic metal hydride and elimination of acetone. We also studied the effect of base on the reduction of acetophenone. NaOH, KOH, *i*-PrONa and *t*-BuOK were tested in the reaction (entries 2–5). The highest enantioselectivity was obtained by using KOH (entry 2), and the optimal molar ratio of KOH–substrate was 4 mol% (entries 2, 6–8).

We subsequently looked into the effect of the amount of catalyst on the catalytic activity and enantioselectivity. As shown in Table 1, the yield and enantioselectivity increased with the rise of catalyst amount from 0.5 to 10 mol% (entries 2 and 9–11). Extension of the catalyst amount from 10 to 20 mol% increased the yield, but



Scheme 1. Synthesis of carbene–Rh(I) complex 1.

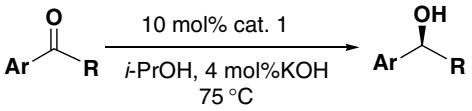
Table 1. ATH of acetophenone catalyzed by **1**



Entry	Catalyst : substrate (mol%)	Base	Base/substrate (mol%)	Temperature (°C)	Yield (%)	Ee (%)[a]
1	10	KOH	4	<40	–	–
2	10	KOH	4	75	88	60
3	10	NaOH	4	75	79	52
4	10	*i*-PrONa	4	75	71	22
5	10	*t*-BuOK	4	75	63	17
6	10	KOH	2	75	45	43
7	10	KOH	1	75	38	29
8	10	KOH	6	75	85	58
9	0.5	KOH	4	75	59	16
10	1	KOH	4	75	65	17
11	5	KOH	4	75	82	54
12	20	KOH	4	75	93	57

[a] Determind by HPLC using Chiracel OD-H.

Table 2. ATH of aryl alkyl ketones catalyzed by **1**



Entry	Substrate	Yield (%)	ee (%)[a]
1	Acetophenone	88	60
2	*p*-Methyl acetophenon	89	60
3	*p* -Methoxy -acetophenon	87	59
4	*p* -Chloroacetophenon	93	43
5	*p* -Triflumethylacetophenon	91	39
6	Propiophenone	83	64
7	2-Methyl propiophenone	75	63
8	Butyrophenone	81	64
9	Cyclohexyl phenyl ketone	72	67
10	2-Acetonaphthone	86	61

[a] Determined by HPLC using Chiracel OD-H or by GC using chiral CP-Cyclodex-β-236 M-19 column. All products had *S* configuration. Entry 1 (1-phenylethanol): Daicel Chiralcel OD-H, hexane : *i*-PrOH = 96 : 4, flow rate 0.5 ml min^{-1}, t_R (min) = 17.1 (minor), t_S (min) = 19.9 (major); entry 2 (1-*p*-methylphenylethanol): Daicel Chiralcel OD-H, hexane : *i*-PrOH = 99 : 1, flow rate 0.5 ml min^{-1}, t_R (min) = 16.3 (minor), t_S (min) = 17.5 (major); entry 3 (1-*p*-methoxyphenylethanol): Daicel Chiralcel OD-H, hexane : *i*-PrOH = 98 : 2, flow rate 0.5 ml min^{-1}, t_R (min) = 34.3 (minor), t_S (min) = 36.6 (major); entry 4 (1-*p*-chlorophenylethanol): chiral CP-Cyclodex-β-236 M-19 column, 0.25 mm × 50 m, T = 130 °C, p = 15 psi, t_R (min) = 25.2 (minor), t_S (min) = 27.6 (major); entry 5 (1-*p*-trifluoromethylphenylethanol): chiral CP-Cyclodex-β-236 M-19 column, 0.25 mm × 50 m, T = 120 °C, p = 15 psi, t_R (min) = 9.9 (minor), t_S (min) = 10.3 (major); entry 6 (1-phenyl-1-propanol): Daicel Chiralcel OD-H, hexane : *i*-PrOH = 96 : 4, flow rate 0.5 ml min^{-1}, t_R (min) = 17.4 (minor), t_S (min) = 20.4 (major); entry 7 (2-methyl-1-phenyl -1-propanol): chiral CP-Cyclodex-β-236 M-19 column, 0.25 mm × 50 m, T = 115 °C, p = 15 psi, t_R (min) = 28.2 (minor), t_S (min) = 28.6 (major); entry 8 (1-phenyl-1-butanol): Daicel Chiralcel OD-H, hexane : *i*-PrOH = 96 : 4, flow rate 0.5 ml min^{-1}, t_R (min) = 16.3 (minor), t_S (min) = 17.5 (major); entry 9 (cyclohexylphenylmethanol): chiral CP-Cyclodex-β-236 M-19 column, 0.25 mm × 50 m, T = 160 °C, p = 10 psi, t_R (min) = 35.9 (minor), t_S (min) = 36.5 (major); entry 10 [1-(2′-naphthyl)ethanol]: Daicel Chiralcel OD-H, hexane : *i*-PrOH = 98 : 2, flow rate 1.0 ml min^{-1}, t_S (min) = 21.7 (major), t_R (min) = 23.6 (minor).

resulted in slight erosion of the enantioselectivity (entry 12). The highest ee value was achieved by reacting acetophenone with 2-propanol in the presence of 10 mol% catalyst and 4 mol% KOH at 75 °C (entry 2).

To extend the scope of the carbene–Rh(I) complex **1** as a chiral catalyst in this reaction, various aryl alkyl ketones were screened. As shown in the Table 2, these ketones can be transformed to the corresponding secondary alcohols under the optimized conditions. The chemical yield and enantioselectivity were affected by the steric and electronic properties of the ketones. Electron-donating groups on the phenyl ring of acetophenone did not significantly affect activity and enantioselectivity (entries 2 and 3). Introduction of an electron-drawing group, however, led to much lower enantioselectivities but higher yields (entries 4 and 5). The bulk of the R group in the ketone demonstrated a positive effect on enantioselectivity, but a negative effect on yields (entries 6, 7 and 8 vs 1). Furthermore, cyclohexyl phenyl ketone was converted to the corresponding optically active alcohol at the highest ee value of 67% (entry 9). Replacement of the phenyl group of acetophenone by a naphthyl group showed no significant difference in enantioselectivity and yield (entry 10 vs 1).

According to previous work, iridium and ruthenium complexes with chiral ligands were efficient catalysts for ATH of ketones. We also synthesized iridium and ruthenium complexes with carbene ligand **7** and attempted to apply them in the ATH of acetophenone. Unfortunately, they delivered very low activity and enantioselectivity.

Conclusions

A chelated ferrocene-based planar chiral N-heterocyclic carbene–Rh(I) complex was synthesized and applied to the ATH of ketones. High catalytic activity and moderate enantioselectivity were observed. Compared with previous results, a significant improvement has been made. Further investigations into reactivity and application are underway.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer. High-performance liquid chromatography (HPLC) was performed by an Agilent 1100 interfaced to a HP 71 series computer workstation with a Daicel Chiralcel OD-H chiral column. Gas chromatography analyses were performed on a chiral CP-Cyclodex-β-236 M-19 column (25 m × 0.32 mm) on a Varian CP-3800. Optical rotations were measured on a Perkin-Elmer 343 Polarimeter. Commercial reagents were used as received, unless otherwise stated. THF and toluene were dried over sodium and freshly distilled before use. Compounds **3**–**5** were prepared according to published procedures.[14,15]

Preparation of 6

To a well-dried Schlenk tube, CuI (48 mg, 0.25 mmol), imidazole (0.51 g, 6 mmol) and $CsCO_3$ (3.42 g, 10.5 mmol) were added, evacuated twice and back-filled with nitrogen. Dioxane (5 ml), **5** (2.12 g, 5 mmol) and *trans*-1,2-cyclohexane diamine (0.11 g, 1 mmol) were then successively added under nitrogen. The Schlenk tube was sealed and the reaction mixture was stirred with heating at 110 °C for 24 h. The reaction mixture was cooled to ambient temperature, diluted with 250 ml ethyl acetate and filtered through a plug of silica gel followed by eluting with 500 ml of ethyl acetate. The filtrate was concentrated and the resulting residue was purified by column chromatography (hexane–ethyl acetate 1 : 5) to provide **6** in 51% yield. $[\alpha]_D$ = +26.3 (*c* 0.135, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.93 (m, 6H), 1.70 (m, 1H), 3.8–3.9 (m, 2H), 4.2–4.7 (m, 9H), 7.0 (s, 1H), 7.2 (s, 1H), 7.8 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 18.8, 32.6, 61.3, 65.7, 66.9, 67.9, 68.5, 69.6, 70.4, 71.2, 72.0, 72.6, 93.9, 122.6, 128.3, 139.8, 163.0 ppm. HRMS (ESI): calcd for [M + H$^+$]: 364.1112, found 364.1091.

Preparation of 7

Benzyl bromide (0.85 g, 5 mmol) in dry acetonitrile (3 ml) was added dropwise into a solution of **6** (1.82 g, 5 mmol) in dry

acetonitrile (5 ml) under reflux. The mixture was further refluxed for 1.5 h. TLC showed that **6** disappeared from the mixture. $TlPF_6$ (1.75 g, 5 mmol) in acetonitrile (10 ml) was added dropwise into the reaction solution under vigorous stirring. The deposition formed promptly, and the mixture was further stirred for 20 min. After filtration, the solvent was removed *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to give **7** as a brown oil in 73% yield. $[\alpha]_D = -43.2$ (*c* 0.09, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 0.69–0.76 (m, 6H), 1.46–1.55 (m, 1H), 3.70–3.72 (m, 2H), 3.80–3.85 (m, 1H), 4.07–4.79 (m, 1H), 5.26–5.27 (m, 2H), 7.11 (s, 1H), 7.27 (s, 5H), 7.51 (s, 1H), 8.92 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 18.9, 32.4, 53.6, 64.4, 65.7, 68.4, 68.5, 69.5, 69.6, 72.2, 72.5, 72.7, 92.2, 121.5, 125.9, 129.1, 129.4, 129.5, 132.6, 137.8, 162.5 ppm. HRMS (ESI): calcd for [M-PF_6]: 454.1582, found 454.1539.

Preparation of 1

t-BuOK (0.11 g, 0.95 mmol), $[Rh(COD)Cl]_2$ (0.22 g, 0.45 mmol) and **7** (0.54 g, 0.90 mmol) were added into dry THF (8 ml) under nitrogen. The mixture was refluxed for 12 h. After the solvent was removed *in vacuo*, the residue was purified by column chromatography (CH_2Cl_2) to provided **1** as an orange air stable solid in 75% yield. $[\alpha]_D = -541.0$ (*c* 0.083, acetone); ^1H NMR (400 MHz, $CDCl_3$): δ 0.85–0.87 (m, 6H), 1.69–1.94 (m, 9H), 3.35 (m, 1H), 3.75–3.76 (m, 2H), 3.78 (m, 1H), 4.37–4.91 (m, 11H), 5.52 (d, 1H, $J = 15.2$ Hz), 5.69 (d, 1H, $J = 15.1$ Hz), 7.01–7.69 (m, 7H) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ 17.4, 17.6, 27.9, 32.3, 34.3, 55.1, 67.3, 69.3, 69.4, 70.3, 70.4, 71.0, 71.3, 71.7, 73.0, 80.0, 97.6, 97.7, 98.9, 123.7, 126.7, 128.4, 129.2, 129.3, 129.8, 137.5, 166.9, 167.0, 181.42 (d, $^1J_{C-Rh} = 51.1$ Hz, C-Rh) ppm. HRMS (ESI): calcd for [$M^+ - PF_6$]: 664.1498; found 664.1400.

General Procedure for the ATH of Ketones

The ketone (1 mmol), KOH (2.24 mg, 0.04 mmol) and catalyst **1** (0.08 g, 0.10 mmol) were added to 2-propanol (5 ml). The mixture was heated at 75 °C for 19 h. After the solvent was evaporated, the product was purified by column chromatography with petroleum ether–diethyl ether (6 : 1 to 2 : 1). Enantiomeric excesses were determined by HPLC with a Chiralcel OD-H or by GC using a chiral CP-Cyclodex-β-236 M-19 column.

Supporting information

Supporting information may be found in the online version of this article.

Acknowledgments

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