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New chiral ferrocenyldiphosphine ligand for catalytic asymmetric transfer hydrogenation

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Abstract

New chiral ferrocenyldiphosphine ligands (*R*)-(*S*)-**3** and (*R*)-(*S*)-**4** were prepared. The ligands were employed in Ru(II) catalyzed asymmetric transfer hydrogenation of ketones to give corresponding secondary alcohols. Up to 99% conversion with 90% e.e. was obtained on $Ru(DMSO)_4Cl_2$/**4** in transfer hydrogenation of acetophenones with propan-2-ol.
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Keywords: Ferrocenyldiphosphine; Transfer hydrogenation; (*R*)-*N*-(2-(Diphenylphosphino)benzylidene)-1-((*S*)-2-(diphenylphosphino)ferrocenyl)ethylamine

1. Introduction

Because of its great success in catalytic asymmetric reactions [1], chiral ferrocenylphosphine ligands have attracted considerable attentions in recent years [2]. These ligands are very effective for a wide range of reactions, such as hydrogenation [3], hydrosilylation [4], allylic alkylation [5], Grignard cross-coupling reactions [6], and cyclopropanation [7]. As a long-term project in developing new chiral ferrocenyliminodiphosphine ligands for catalytic asymmetric reactions, we have developed ligand **1** (Scheme 1), which is an efficient ligand in asymmetric allylic alkylation [8]. Recently, C_2-symmetrical P,N,P-type ligand **2** (Scheme 1) was used in asymmetric transfer hydrogenation of ketones, however, only moderate e.e. was obtained [9]. As far as we know, there are no reports of asymmetric transfer hydrogenation of ketones by using chiral ferrocenyliminodiphosphine as ligand.

With an effort to design an efficient chiral ferrocenyliminodiphosphine ligand for asymmetric transfer hydrogenation of ketones, herein, we described the synthesis of novel ferrocenyldiphosphine ligands **3** and **4** (Scheme 1) and their application in asymmetric transfer hydrogenation of ketones.

2. Experiment

2.1. General

Unless otherwise mentioned, all reactions were carried out under argon atmosphere. (*R*)-1-((*S*)-2-(diphenylphosphino)-ferrocenyl)ethylamine ((*R*)-(*S*)-**PPFNH**$_2$) was synthesized according to the literature method [10].

Optical rotations were measured on a HORIBA SEPA-200 high sensitive polarimeter. ^{1}H NMR spectra were recorded on Bruker DRX-400 NMR spectrometer with TMS as an internal standard. ^{31}P NMR spectra were referenced to external 85% H_3PO_4. The conversions and e.e. values were determined by GC with a chiral capillary column (cyclodex-β,2,3,6-methylated, 30 m × 0.25 mm (i.d.)). Elemental analysis was carried out on a Fisous EA 1110. Racemic samples of alcohols were obtained by reduction of the corresponding ketones with $NaBH_4$ and used as the authentic samples for e.e. determination. Column chromatography was carried out on silica gel (200–300 mesh) using ethyl acetate/petroleum ether as eluent.

2.2. Synthesis of (R)-(S)-3

A mixture of 2-(diphenylphoshino)benzaldehyde (319 mg, 1.1 mmol), (*R*)-(*S*)-**PPFNH**$_2$ (413 mg, 1.0 mmol) and $MgSO_4$ (500 mg, 4.2 mmol) in absolute ethanol was stirred under refluxing for 2 h. The solid was filtered off and the resulting yellow solution was evaporated to dryness under

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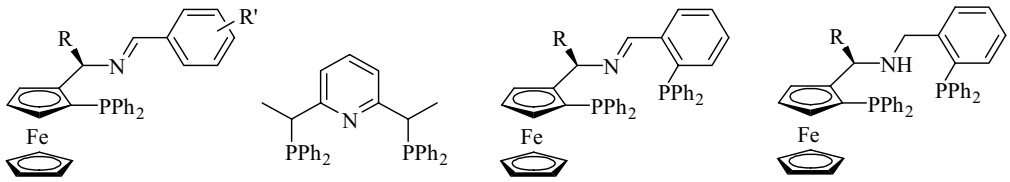


Scheme 1.

reduced pressure. The residue was recrystallized from *n*-hexane to afford **3 (**588 mg, 86% yield) as yellow powder. The mp 102–103 °C; $[\alpha]_D^{20}$ −320 (c 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, $J = 6.6$ Hz, 3H), 3.76 (s, 1H), 3.99 (s, 5H), 4.28 (m, 1H), 4.47 (s, 1H), 4.68–4.73 (m, 1H), 6.66–7.49 (m, 24H), and 8.65 (s, 1H). ^{31}P NMR ($CDCl_3$) δ −13.30, −24.44; Anal. Calcd. for $C_{43}H_{37}FeNP_2$: C, 75.34; H, 5.44; N, 2.04. Found: C, 75.22; H, 5.57; N, 2.11.

2.3. Synthesis of (R)-(S)-4

A solution of compound (*R*)-(*S*)-**3** (1.37 g, 2 mmol) and $NaBH_4$ (0.57 g, 15 mmol) in absolute ethanol (30 ml) was refluxed with stirring for 8 h. The solution was cooled to room temperature, H_2O (10 ml) was added to destroy the excess $NaBH_4$. The mixture solution was extracted with CH_2Cl_2 (3×30 ml). The combined extract was washed with 10% aqueous NH_4Cl (2×10 ml), H_2O (2×10 ml) and the organic layer was dried over anhydrous Na_2SO_4. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from *n*-hexane to afford **4** (1.91 g, 72%) as orange crystal. The mp 106–108 °C; $[\alpha]_D^{20}$ −356 (c 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.21–1.25 (m, 1H), 1.38–1.40 (d, $J = 6.0$ Hz, 3H), 3.57–3.61 (m, 1H), 3.69–3.77 (m, 2H), 3.97 (s, 5H), 4.08 (s, 1H), 4.25 (s, 1H), 4.41 (s, 1H), and 6.52–7.52 (m, 24H). ^{31}P NMR (DMSO-d_6) δ −15.00, −24.60; Anal. Calcd. for $C_{43}H_{39}FeNP_2$: C, 75.11; H, 5.72; N, 2.04. Found: C, 71.75; H, 5.45; N, 2.08.

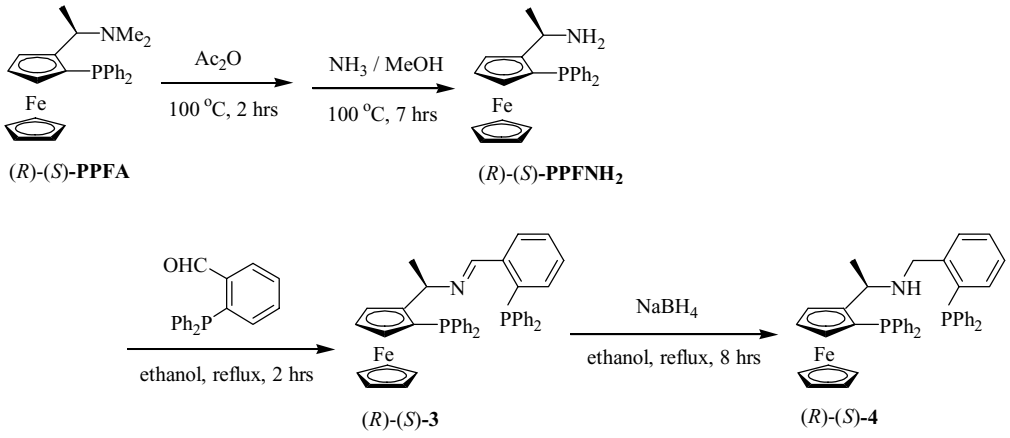
2.4. General procedure for ruthenium catalyzed transfer hydrogenation of ketone

The catalyst was generated in situ by refluxing ligand **3** or **4** (2.0 mol%) with $Ru(DMSO)_4Cl_2$ (1.0 mol%) in 2-propanol at 80 °C under argon for 1 h. After cooling down to room temperature, ketone (2.0 mmol) was added, followed by *tert*-BuOK (34 mg, 0.3 mmol) under argon. The transfer hydrogenation was conducted at desired temperature under argon for a given time. The resulting solution was quenched with 1M HCl and the organic phase was concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column eluted by petroleum ether/ethyl acetate (9/1) and the product was analyzed by GC.

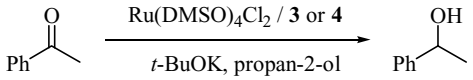
3. Results and discussion

3.1. Preparation and characterization of (R)-(S)-3 and (R)-(S)-4

(*R*)-(*S*)-**3** was prepared by Schiff base condensation of 2-(diphenylphosphino)benzaldehyde with (*R*)-1-((*S*)-2-(diphenylphosphino)ferrocenyl)ethylamine ((*R*)-(*S*)-**PPFNH$_2$**) in ethanol with anhydrous $MgSO_4$ as dehydrating agent. The yellow solid of (*R*)-*N*-(2-(diphenylphosphino)benzylidene)-1-((*S*)-2-(diphenylphosphino)ferrocenyl)ethylamine (*R*)-(*S*)-**3** was obtained with 86% yield (Scheme 2). The ^{1}H NMR



Scheme 2.



Scheme 3.

spectrum exhibits a singlet at δ 8.65 ppm for the imino protons and ^{31}P NMR spectrum presents two singlets at δ −13.30 and −24.44 ppm, which could be assigned to PPh_2 connected with benzene ring and ferrocene ring, respectively. The spectroscopic results and elemental analysis indicate that (*R*)-(*S*)-**3** contains one imino group and two unidentical diphosphino groups, which is consistent with the given formula.

Reduction of the iminophosphine (*R*)-(*S*)-**3** with excess $NaBH_4$ was carried out in refluxing ethanol to afford the corresponding (*R*)-*N*-(2-(diphenylphosphino)benzyl)-1-((*S*)-2-(diphenylphosphino)ferrocenyl)ethylamine (*R*)-(*S*)-**4** with 72% yield. ^{1}H NMR spectrum of (*R*)-(*S*)-**4** shows the emergence of –NH– proton at δ 1.25 ppm and $–CH_2–$ proton at δ 3.75 ppm together with the disappearance of doublet at δ 8.65 ppm confirmed the reduction of imino group to corresponding amino group. Two singlets at δ −15.00 and −24.60 ppm were observed in ^{31}P NMR spectrum of (*R*)-(*S*)-**4**, which was in accordance with two different phosphino groups.

3.2. Asymmetric transfer hydrogenation of acetophenone with propan-2-ol

The Ru(II) catalyst was generated in situ by refluxing ligand (2 mol%) (ligand: (*R*)-(*S*)-**3**, and (*R*)-(*S*)-**4**) with $Ru(DMSO)_4Cl_2$ (1 mol%) in propan-2-ol at 80 °C under argon for 1 h. After the solution containing catalyst was cooled down to desired temperature, the acetophenone and *tert*-BuOK was added. Transfer hydrogenation occurred immediately (Scheme 3). 1-Phenylethanol was the only product formed. The (*R*)-(*S*) type ligands favor 1-phenylethanol with (*R*) configuration (Table 1). Ligand **3** with imino group showed comparatively low conversion and enantioselectivity (entries 1 and 2, Table 1). Ligand **4** with amino group shows much higher activity and enantioselectivity than ligand **3**. Up to 90% conversion with 80% e.e. was obtained (entry 3, Table 1). Similar tendency was reported from earlier studies [11–13], indicating that the NH functional moiety in ligand plays an important role in Ru(II)-ligand catalytic system. Higher activity and enantioselectivity of amino containing ligand may be duo to the fact that NH moiety can stabilize the catalytic transition state [14,15]. Prolonging reaction time (2 h) led to slight decreasing of enantioselectivity (entries 2 and 4, Table 1).

Choosing (*R*)-(*S*)-**4** as model ligand, the reaction was conducted at different temperature. With reaction temperature decreasing from 80 to 0 °C, the conversion decreased from 98 to 30%. In the mean time, e.e. value remained almost the same (entries 4–6, Table 1). These results indicated that the reaction temperature plays an important role on the catalytic activity.

Different ruthenium precursors were also investigated for the transfer hydrogenation. Under identical reaction conditions, $Ru(PPh_3)_3Cl_2$-**4** and $Ru(cymene)_2Cl_2$-**4** exhibited almost the same enantioselectivities (entries 7 and 8, Table 1).

It could be concluded from the above results that in Ru(II)-**3** or -**4** catalytic system, NH moiety is the main factor for the high activity and enantioselctivity in asymmetric transfer hydrogenation of acetophenone.

3.3. Asymmetric transfer hydrogenation of different ketone substrates

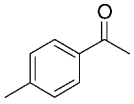
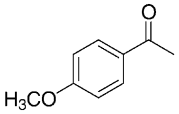
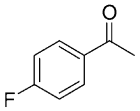
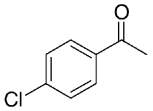
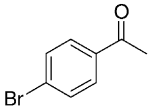
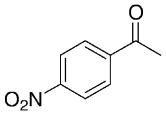
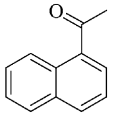
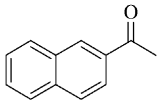
Due to its efficiency in the transfer hydrogenation of acetophenone, ligand **4** was further investigated in transfer hydrogenation of various methyl aryl ketones. The results were summarized in Table 2. Ligand **4** showed high activity with good enatioselectivity for most of ketones listed in Table 2. The highest enantioselectivity was found for transfer hydrogenation of 1-acetonaphtone (90% e.e.). The introduction of electron-withdrawing substituents, such as F, Cl, Br, and NO_2, to the para position of the aryl ring of the ketone, resulted in improved activity with good enantio-

Table 1
Asymmetric transfer hydrogenation of acetophenone catalyzed by chiral Ru(II) complexes

Entry	Catalyst	*T* (°C)	Reaction time (h)	Conversion (%)[a]	e.e. (%, configuration)[a,b]
1	Ru/(*R*)-(*S*)-**3**	80	0.5	61	40 (*R*)
2	Ru/(*R*)-(*S*)-**3**	80	2	59	39 (*R*)
3	Ru/(*R*)-(*S*)-**4**	80	0.5	90	80 (*R*)
4	Ru/(*R*)-(*S*)-**4**	80	2	98	75 (*R*)
5	Ru/(*R*)-(*S*)-**4**	25	2	96	76 (*R*)
6	Ru/(*R*)-(*S*)-**4**	0	24	30	77 (*R*)
7[c]	Ru/(*R*)-(*S*)-**4**	80	1	85	70 (*R*)
8[d]	Ru/(*R*)-(*S*)-**4**	80	1	96	72 (*R*)

[a] Conversion and enantiometric excesses were determined by GC using a capillary chiral column (cyclodex-β,2,3,6-methylated, 30 m × 0.25 mm (i.d.)).
[b] The absolute configuration was determined by comparison of the retention time of the enantiomers on the GC analysis with literature values.
[c] $Ru(PPh_3)_3Cl_2$ was used as Ru(II) precursor, and after catalyst was formed, free PPh_3 and **4** were washed away with diethyl ether before adding acetophenone and *tert*-BuOK.
[d] $(Ru(p\text{-cymene})Cl_2)_2$ used as Ru(II) precursor.

Table 2
Catalytic asymmetric transfer hydrogenation with $Ru(DMSO)_4Cl_2$/**4** for acetophenones with propan-2-ol[a]

Entry	Ketone	Reaction time (h)	Conversion (%)[b]	e.e. (%)[b,c]
1		1	99	82
2		2	82	52
3		0.5	98	83
4		0.5	99	85
5		0.5	96	86
6		0.5	99	88
7		1.5	99	90
8		1.5	98	82

[a] Reactions were carried out at 80 °C in the presence of 2.0 mmol ketone, 1 mol% $Ru(DMSO)_4Cl_2$, 2 mol% **4**, and 15 mol% *tert*-BuOK.

[b] The conversion and enantiomeric excesses were determined by GC using capillary chiral column (cyclodex-β,2,3,6-methylated, 30 m × 0.25 mm (i.d.)).

[c] The absolute configuration was not determined.

selectivity (entries 3–6, Table 2). The conversion of ketones with electron-donating substituents on aromatic ring slightly decreased, but enantioselectivity remained almost the same. The lowest activity and enantioselectivity was found in transfer hydrogenation of *p*-methoxyacetophenone (entry 2, Table 2), this is probably because of the strong electron-donating effect of methoxy group on the aryl ring of the ketone.

4. Summary

In summary, we have synthesized a new type of P,N,P ferrocenyliminodiphosphine ligands, the catalyst generated in situ by mixing the ligands together with $Ru(DMSO)_4Cl_2$ is effective for the asymmetric transfer hydrogenation of methyl aryl ketones. Up to 99% conversion with 90% e.e. was obtained using (*R*)-(*S*)-**4** as ligand for the asymmetric transfer hydrogenation of 1-acetonaphtone. The ligand **4** with amino moiety exhibits much higher activity and enantioselectivity than ligand **3** with imino moiety. The result suggests that the NH moiety in the ligand plays an important role for the improved reactivity and enantioselectivity in the transfer hydrogenation of ketones. Further studies of these ligands in other catalytic reactions are underway and good activity and enantioselectivity is anticipated.

Acknowledgements

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