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Asymmetric transfer hydrogenation of ketones catalyzed by nickel complex with new PNO-type ligands

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Abstract

The new polydentate mixed-N, P, O chiral ligands have been synthesized by the condensation of bis(*o*-formylphenyl)-phenylphosphane and *R*-phenylglycinol in $CHCl_3$, and fully characterized by IR, NMR and EIMS spectra. These ligands were employed with a simple Ni complex $Ni(PPh_s)_2Cl_2$ *in situ* as catalytic systems for asymmetric transfer hydrogenation of ketones, and the corresponding optical alcohols were obtained with up to 84% ee under mild conditions.

Keywords: Nickel complex; NPO-type ligand; Asymmetric transfer hydrogenation; Ketones

Among the most spectacular recent developments in catalytic asymmetric synthesis, asymmetric transfer hydrogenation (ATH) is an attractive method for the preparation of optically active alcohols [1,2] because of its operational simplicity and wide substrate scope. In this reaction, generally, chiral ligands are responsible for obtaining high enantioselectivity. Therefore, the design and synthesis of new chiral ligands are always a challenge for researchers. In the past decades, numerous different PP, NN, NO, NPN and PNNP-type ligands have been applied for this reaction [3], these mixed type ligands have attracted more and more attention because of their better ability to stabilize metal center and special chiral coordination environments surrounding the metal center. In previous studies of asymmetric transfer hydrogenation of ketones, however, most of research was focused on the expensive noble platinum metal-based complexes, such as Ru [4], Rh [5], and Ir [6] complexes. Compared with these precious metals, the first-row transition metals, which are more abundant and benign, attract more and more research interest because they are cost-effective and ''green'' catalysts. We reported the first example of iron catalyst used in the ATH reaction of ketones in 2004 [7], from then on, Morris and co-workers developed very excellent iron catalysts for the reaction in the recent years [8].

Although there have been some successful examples of iron complexes, as catalysts for ATH of ketones, other first-row transition metals, such as Ni or Co complexes, are still rarely reported [9].

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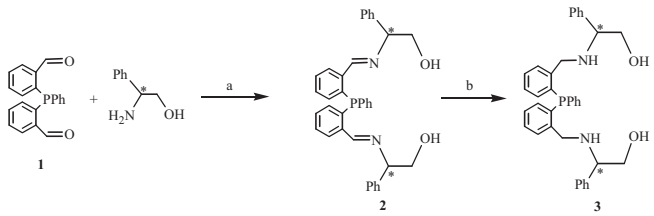


Scheme 1. Synthesis of the NPO-type ligands. Reagent and conditions: (a) $CHCl_3$, anhydrous Na_2SO_4, reflux, 26 h; (b) $NaBH_4$, C_2H_5OH, reflux, 2 days.

Recently, we synthesized the new PNO-type chiral ligands, which have been fully characterized by IR, NMR and EIMS spectra [10], and found that these chiral ligands coupled with a simple Ni complex $Ni(PPh_3)Cl_2$ *in situ* exhibited good catalytic activity and enantioselectivity as catalysts for asymmetric transfer hydrogenation of a series of aromatic ketones.

The Ni complex $Ni(PPh_3)Cl_2$ was synthesized according to literature [11].

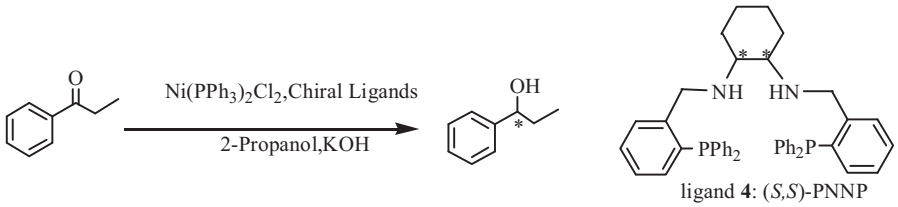
The NPO-type chiral ligands are synthesized as Scheme 1.

The condensation of bis(*o*-formylphenyl)phenylphosphane **1** [12] with *R*-phenylglycinol in $CHCl_3$ was refluxed for 26 h in the presence of anhydrous Na_2SO_4 under a nitrogen atmosphere. After cooling down to room temperature, the mixture was filtrated and the solvent was removed *in vacuo* to afford a light yellow solid **2** in 80% yield, featuring the MS signals at 557.2 (M+1). The ^1H NMR spectrum of **2** presented two doublets at δ 8.61 and δ 8.55 for the imino protons. The ^{31}P NMR spectrum exhibited a singlet at δ −10.83.

A suspension of **2** and $NaBH_4$ in absolute ethanol was refluxed with stirring for 2 days. The solution was then cooled to room temperature and H_2O was introduced to destroy the excess $NaBH_4$. The mixture was extracted with CH_2Cl_2 and washed successively with saturated NH_4Cl solution and H_2O. The organic fraction was dried over anhydrous Na_2SO_4, followed by filtering, concentrating to afford the corresponding NPO-type ligand **3** as a white solid in 60% yield, featuring the MS signals at 561.3 (M+1). The disappearance of the peaks at δ 8.61 and δ 8.55 in the ^1H NMR spectrum of **3** indicated that the two imino groups were reduced to the corresponding amino groups, and a broad peak (4H) at δ 2.68 for the –NH– and –OH protons was also observed. The ^{31}P NMR spectrum exhibited a singlet at δ −26.07.

To examine the catalytic activity of the Ni-based system, several catalytic systems, which was generated *in situ* from the new NPO-type ligands **2**, **3** and our earlier PNNP ligand **4** [13a] with $Ni(PPh_3)_2Cl_2$ respectively, have been investigated for the ATH of propiophenone. The typical results were listed in Table 1.

Table 1
Asymmetric transfer hydrogenation of propiophenone catalyzed by Ni-NPO system.[a]

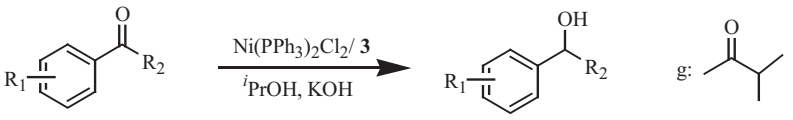


ligand **4**: (*S,S*)-PNNP

Entry	Ligand	Time (h)	Temp. (°C)	Yield[b] (%)	Ee[b] (%)
1	2	22	70	5	–
2	3	21	70	93	84
3	4	20	70	16	67.5
4[c]	3	20	70	81	66
5	3	26	25	–	–

[a] Unless otherwise stated, the reaction was carried out with $S/C/OH^- = 100/1/6$.
[b] Yields and enantiomeric excesses were determined by GC analysis using a CP-Chirasil-Dex column.
[c] $S/C/OH^- = 100/1/4$.

Table 2
Asymmetric transfer hydrogenation of various ketones catalyzed by Ni-NPO system.[a]



Entry	Ketone		Cat/OH$^-$	Time (h)	Temp. (°C)	Yield[b] (%)	ee[b] (%)
	R_1	R_2					
1	H	CH_3	1/4	20	70	81	66
2	H	CH_2CH_3	1/6	21	70	93	84
3	H	$(CH_2)_2CH_3$	1/8	56	70	51	60
4	H	$(CH_2)_3CH_3$	1/8	21	70	90	80
5	H	$CH(CH_3)_2$	1/6	56	70	72	76
6	*m*-CH_3	CH_3	1/6	48	70	98	75
7	*p*-CH_3	CH_3	1/6	53	70	96	60
8	g		1/4	24	70	>99	10

[a] The reaction was carried out with S/C = 100.
[b] Yields and enantiomeric excesses were determined by GC analysis using a CP-Chirasil-Dex column.

We found that the catalyst system generated from $Ni(PPh_3)Cl_2$ with ligand **3** efficiently catalyzed the reaction (Table 1, entry 2) at 70 °C. The similar PNO ligand **2** was ineffective for the reduction of ketones, however, and the enantioselectivity of chiral alcohol remarkably decreased (Table 1, entry 1). These results indicated that the structure of the NH group was a crucial factor for ligand acceleration, and the NH functions in the ligand **3** and its structure are responsible for the good enantioselectivity [13a]. In addition, our earlier ligand **4**, which exhibited very excellent catalytic results in ATH of aromatic ketones [13], was not so good together with Ni complex as with Ru or Ir complexes (Table 1, entry 3). If the base was reduced, the ee value will slightly decrease (Table 1, entry 4). The temperature was also important for the Ni-based catalytic system, the reaction will not proceed if the reaction temperature is too low (Table 1, entry 5).

Encouraged by the results, the catalytic system $Ni(PPh_3)_2Cl_2$/ligand **3** was then further investigated for the ATH of a diverse range of ketones in 2-propanol (Table 2).

The catalytic system catalyzed asymmetric reduction of various ketones to the secondary alcohols with a satisfied chemical yield and a moderate to good enantioselectivity, the best result is up to 84% ee. Generally, the enantioselectivity was improved with increase of the bulkiness of the alkyl substituents (Table 2, entries 1–4), but *n*-butyrophonone is not a good substrate for this catalytic system, the conversion of *n*-butyrophonone is only 51%. The introduction of a group to the aromatic ring will make it more difficult to reduce the ketones (Table 2, entries 6 and 7). Notably, the catalyst can promote the reduction of alkyl ketone smoothly (Table 2, entry 8), although the ee value is low.

In conclusion, we have disclosed a useful Ni-based catalyst system for the asymmetric transfer hydrogenation of ketones, high conversions and good enantioselectivities were obtained. The further work will concentrate on confirming the structure of the real catalyst and improving the enantioselectivity of the catalytic system.

Acknowledgments

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[10] Compound **2**: mp 64–66 °C; $[\alpha]_D^{20}$ +123.0 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) *ν*: 3386, 3057, 3024, 2923, 2856, 1643, 1490, 1436, 1384, 1164, 1128, 1055, 902, 829, 757, 700, 638, 544, 485; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* −10.83; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.59 (m, 3H), 3.80 (t, 1H, *J* = 9.6 Hz), 4.01 (s, 1H), 4.20 (s, 1H), 4.38 (m, 2H), 6.55 (d, 2H, *J* = 6.8 Hz), 6.65 (d, 2H, *J* = 6.8 Hz), 7.01–7.53 (m, 19H), 8.55 (d, 1H, *J* = 2.8 Hz), 8.61 (d, 1H, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 161.9, 161.4, 140.8, 140.5, 140.2, 140.0, 139.0, 138.9, 138.8, 138.1, 136.0, 134.9, 134.1, 133.9, 132.0, 131.2, 130.1, 129.9, 129.7, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.3, 127.2, 127.0, 126.9, 126.8, 78.3, 76.5, 68.1, 68.0; HRMS (ESI) calcd. for $C_{36}H_{34}N_2O_2P$: 557.2352 $(M+H)^+$, found: 557.2360. Compound **3**: mp 66–68 °C; $[\alpha]_D^{20}$ −52.7 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) *ν*: 3417, 3056, 2923, 2854, 1649, 1560, 1541, 1491, 1455, 1436, 1384, 1198, 1162, 1050, 1027, 755, 700, 628, 538, 469; ^{31}P NMR (202.5 MHz, $CDCl_3$): *δ* −26.07; ^1H NMR (500 MHz, $CDCl_3$): *δ* 2.68 (br, 4H), 3.35 (m, 1H), 3.41–3.46 (m, 2H), 3.59 (q, 1H, *J* = 4 Hz), 3.64 (m, 1H), 3.71 (t, 2H, *J* = 9.75 Hz), 3.78 (q, 1H, *J* = 4 Hz), 3.93 (dd, 1H, *J* = 2.5 Hz and 12 Hz), 4.02 (d, 1H, *J* = 12.5 Hz), 6.91–6.95 (m, 2H), 7.18–7.37 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.2, 144.0, 140.5, 140.0, 136.6, 136.5, 136.0, 135.9, 135.8, 135.7, 134.7, 134.6, 134.4, 134.3, 134.0, 133.9, 133.8, 133.7, 130.4, 130.3, 129.2, 129.1, 128.7, 128.6, 128.5, 127.8, 127.7, 127.6, 127.5, 127.4, 66.7, 64.6, 64.5, 63.5, 50.6, 50.4; HRMS (ESI) calcd. for $C_{36}H_{38}N_2O_2P$: 561.2665 $(M+H)^+$, found: 561.2667.
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