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Synthesis of novel chiral tetraaza ligands and their application in enantioselective transfer hydrogenation of ketones

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Abstract

Novel chiral tetraaza ligands (*R*)-*N*, *N*′-bis[2-(piperidin-1-yl)benzylidene]propane-1, 2-diamine **6** and (*S*)-*N*-[2-(piperidin-1-yl)benzylidene]-3-{[2-(piperidin-1-yl)benzylidene]amino}-alanine sodium salt **7** have been synthesized and fully characterized by NMR, IR, MS and CD spectra. The catalytic property of the ligands was investigated in Ir-catalyzed enantioselective transfer hydrogenation of ketones. The corresponding optical active alcohols were obtained with high yields and moderate ees under mild reaction conditions.

Keywords: Asymmetric catalysis; Iridium; Ketones; Tetraaza ligand; Asymmetric transfer hydrogenation

Asymmetric catalysis with transition metal complexes is a research area which has grown enormously in the past twenty years. Chiral ligands containing N, P, O, S or their mixed moieties played a key role in the catalytic reaction [1–5]. Among the widely used chiral ligands, nitrogen-based ligands were particularly attractive due to their simple and inexpensive synthesis, more stability than phosphines ligands and versatile coordinated chemistry properties [6–8]. Chiral bisoxazolines (Box) **1** and pyridine bisoxazolines (Pybox) **2** represented a class of ligands which were successfully employed in metal-catalyzed asymmetric synthesis (Scheme 1) [9–13]. Another well known nitrogen-based ligand is TsDPEN **3** [14–18] which was first applied in Ru-catalyzed asymmetric transfer hydrogenation (ATH) of aromatic ketones developed by Noyori and co-workers.

In recent years, chiral tetraaza ligands have been studied as chiral auxiliaries for a wide range of reactions. Trost *et al*. applied ligand **4** and its analogues in Mo-catalyzed asymmetric allylic alkylation with extraordinary levels of regio- and enantioselectivity [19,20]. Luis and co-workers reported a series of bis(amino amide) ligands which showed excellent enantioselectivities (up to 99% ee) in asymmetric alkylation of dialkylzinc to aromatic aldehydes [21]. Feng *et al*. applied the C_2-symmetric chiral tetraaza-Ti(IV) complexes to asymmetric cyanosilylation of aldehydes and ketones with excellent activity [22]. In 2007, we reported the synthesis of a tetraaza ligand derived from (*R,R*)-1,2-diaminocyclohexane and its successful application in ATH of aromatic ketones [23]. To extend our study, we herein describe the synthesis of chiral ligands **6** and **7**, derived from the schiff-base condensation of

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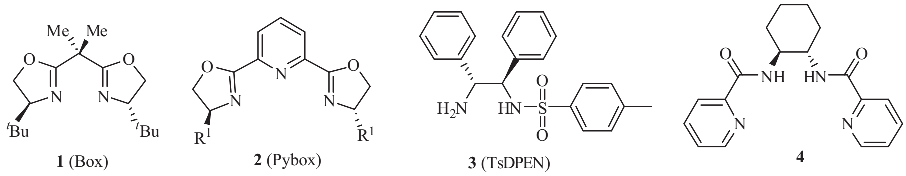


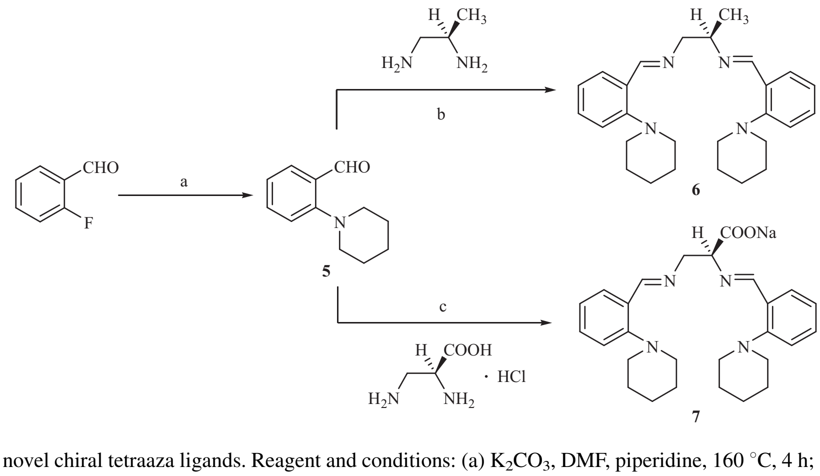
Scheme 1. Chiral nitrogen-based ligands.

2-(piperidin-1-yl)benzaldehyde **5** [24] and various chiral diamines and their further application in the Ir-catalyzed enantioselective transfer hydrogenation of ketones (Scheme 2).

Ligand **6** was synthesized by the condensation of (*R*)-propane-1, 2-diamine with 2-(piperidin-1-yl)benzaldehyde in refluxing ethanol for 48 h. It was obtained as white solid in 49% yield, featuring the MS signals at 417.3 (M+1) [25]. The ^{1}H NMR spectrum presented two singlets at δ 8.56 and 8.60 for the imino protons. The CD spectra of the two enantiomers of chiral ligand **6** have been measured in methanol as solvent and exhibited the mirror-image relationship with $\Delta\varepsilon_{max} = 62.27\ mol^{-1}\ Lcm^{-1}$ at $\lambda = 248$ nm (Fig. 1).

The interaction of (*S*)-2,3-diaminopropionic acid hydrogen chloride with two equivalents of sodium hydroxide gave (*S*)-2,3-diaminopropionate sodium salt in quantitative, which was further reacted with 2-(piperidin-1-yl)benzaldehyde **5** in refluxing methanol for 48 h. After crystallization of methanol, ligand **7** was obtained as yellowish solid, featuring the MS signals at 468.9 (M+Na). The ligand was stable in solid state but unstable in its methanol solution with the color turned dark, which was also confirmed by mass spectra analysis. The ligand was slightly soluble in water but hard to dissolve in chlorinated solvents and toluene. The ^{1}H NMR spectrum presented two singlets at δ 8.51 and 8.54 for the imino protons.

In order to examine the chiral induction abilities of chiral tetraaza ligands **6** and **7**, we explored the enantioselective transfer hydrogenation of various ketones in the presence of Ir-based catalyst. The results were summarized in Table 1. Obviously, no enantioselectivity was observed without chiral ligand (Table 1, entry 1). Coupled with $IrCl(CO)(PPh_3)_2$, chiral tetraaza ligand **6** exhibited high activity (99% conv.) and 34% ee in the ATH of propiophenone (Table 1, entry 10). Under the same conditions, the tetraaza ligand **7** derived from (*S*)-2,3-diaminopropionic acid, showed low enantioselectivity (Table 1, entry 11), which might attributed to the carboxyl group next to the chiral center. Next, we investigated the ATH of ketones with ligand **6** as chiral auxiliary. Various aromatic ketones were reduced smoothly with high yields and moderate enantioselectivities. Acetophenone derivatives with substituents on the aromatic rings at *ortho* position were reduced smoothly with improved enantioselectivities (Table 1, entries 3, 6 and 9). And reaction activities were obviously impacted by electronic properties of the substituents. Substrates with electron-donating substituent on the aromatic rings displayed inferior activities (Table 1, entries 3–9). Furthermore, the substituents on the aromatic rings at different positions had observable effects on the enantioselectivity of the products. The *ortho* position substituents showed much higher enantioselectivity than *meta* or *para* position ones (Table 1, entries 3 *vs.* 4



Scheme 2. Synthesis of novel chiral tetraaza ligands. Reagent and conditions: (a) K_2CO_3, DMF, piperidine, 160 °C, 4 h; (b) C_2H_5OH, reflux, 48 h; (c) NaOH (2 eq.), MeOH, reflux, 48 h.

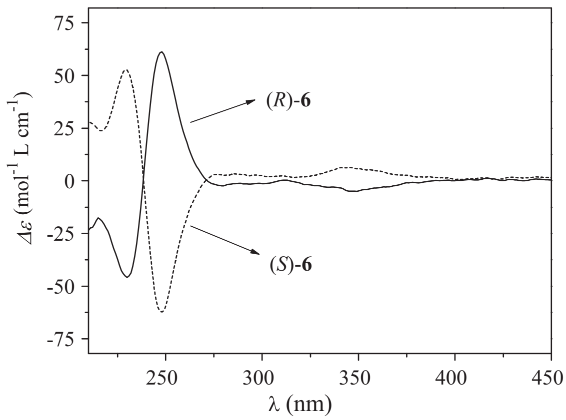
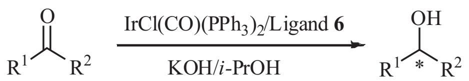


Fig. 1. The CD spectra of chiral ligand **6**.

and 5, 6 *vs.* 7 and 8), probably because the *ortho* substituted substrates are more likely to coordinate with the ligand. These results are in accordant with our previous investigations [23]. More rigid and hindered ketones, however, would need much longer reaction time than acetophenone and its derivatives (Table 1, entries 10 and 12–14). For the reduction of 1,1-diphenylacetone, the corresponding optical active alcohol was obtained with 97% yield and 50% ee at 75 °C for 5 h (Table 1, entry 15).

In conclusion, the novel chiral tetraaza ligands **6** and **7** were successfully synthesized and fully characterized by physical and chemical methods. And the ligands were easily prepared from commercially available materials. Furthermore, they were firstly applied in the iridium-catalyzed asymmetric transfer hydrogenation of aromatic ketones. High activities (up to >99%) and moderate ees have been achieved with catalytic system generated *in situ* from $IrCl(CO)(PPh_3)_2$ and ligand **6** in the presence of base. Further mechanism study is underway in our laboratory.

Table 1
Ir-catalyzed asymmetric transfer hydrogenation of various ketones with chiral tetraaza ligands.[a] .



Entry	R^1	R^2	Time/h	Conv.[b] (%)	ee[b] (%)	Config.[c]
1[d]	Ph	Me	5	85	0	–
2	Ph	Me	5	93	21	*R*
3	*o*-Cl-Ph	Me	5	>99	48	*R*
4	*m*-Cl-Ph	Me	5	>99	16	*R*
5	*p*-Cl-Ph	Me	5	>99	11	*R*
6	*o*-Me-Ph	Me	5	95	52	*R*
7	*m*-Me-Ph	Me	5	80	20	*R*
8	*p*-Me-Ph	Me	5	67	13	*R*
9	*o*-OMe-Ph	Me	5	>99	27	*R*
10	Ph	Et	10	99	34	*R*
11[e]	Ph	Et	10	98	3	*S*
12	Ph	*n*-Pr	10	96	32	*R*
13	Ph	*n*-Bu	10	98	30	*R*
14	Ph	Cy	10	99	25	*R*
15	$(Ph)_2CH$	Me	5	97	50	*R*

[a] Reaction conditions: ketone, 0.5 mmol; *i*-PrOH, 10 mL; propiophenone:ligand **6**:$IrCl(CO)(PPh_3)_2$:KOH = 100:1.5:1:2, molar ratio; 75 °C.
[b] Conversions and enantiomeric excesses were determined by GC analysis using a CP-Chirasil-Dex CB column.
[c] The configurations were determined by comparison of the retention times of the enantiomers on the GC traces with literature values.
[d] Without ligand.
[e] Ligand **7** was used instead of ligand **6**.

Acknowledgments

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[25] Compound **6**: mp 104–105 °C; $[\alpha]_D^{20}$ −56.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, 3H, *J* = 6.4 Hz), 1.46–1.58 (m, 4 H), 1.58–1.74 (m, 8 H), 2.75–2.90 (m, 8 H), 3.75–3.95 (m, 3 H), 6.92–7.02 (m, 4 H), 7.26–7.34 (m, 2 H), 7.81–7.88 (m, 2 H), 8.56 (s, 1 H), 8.60 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.63, 24.19, 26.29, 54.53, 54.63, 66.91, 68.80, 118.46, 118.63, 122.32, 122.36, 127.71, 127.91, 129.48, 129.58, 130.82, 130.93, 154.05, 154.20, 159.16, 161.03; IR (KBr) ν: 3451, 2969, 2948, 2926, 2853, 2832, 2802, 2735, 1634, 1597, 1481, 1448, 1378, 1363, 1326, 1280, 1231, 1158, 1140, 1100, 1024, 927, 777, 762, 750, 652 cm^{-1}; EIMS (*m/z*): 417.3 (M+1). Compound **7**: mp 216 °C (dec.); $[\alpha]_D^{20}$ + 9.5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 1.46–1.70 (m, 12 H), 2.65–2.81 (m, 8 H), 3.93 (t, 1H, *J* = 10.8 Hz,), 4.25 (dd, 1H, *J* = 10.8 Hz and 3.2 Hz), 4.38–4.47 (m, 1 H), 6.91–7.04 (m, 4 H), 7.26–7.34 (m, 2 H), 7.72 (dd, 1H, *J* = 7.6 Hz and 1.6 Hz), 7.91 (dd, 1H, *J* = 7.6 Hz and 1.6 Hz), 8.51 (s, 1 H), 8.54 (s, 1 H); ^{13}C NMR (100 MHz, CD_3OD): δ 25.19, 25.20, 27.33, 27.38, 55.79, 55.83, 65.69, 78.68, 119.74, 120.02, 123.34, 123.43, 128.66, 129.19, 130.14, 130.42, 132.36, 132.63, 155.86, 155.91, 163.27, 164.11, 178.14; IR (KBr) ν: 3424, 2936, 2847, 2786, 2738, 1628, 1591, 1481, 1448, 1372, 1286, 1222, 1158, 1024, 927, 756, 747 cm^{-1}; MS (ESI) *m/z*: $[M+Na]^+$ 468.9.