

# New Chiral Ligand *N*-Toluenesulfonyl-2, 2'-dimethoxy-6, 6'-diaminobiphenyl for Catalytic Asymmetric Transfer Hydrogenation of Ketones

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A new chiral ligand *N*-*p*-toluenesulfonyl-2, 2'-dimethoxy-6, 6'-diaminobiphenyl (Ts-DMBDPPA) was prepared from 2, 2'-dimethoxy-6, 6'-diaminobiphenyl via *N*-tosylation. Its Ru(II) complex was effective catalysts for catalytic asymmetric transfer hydrogenation of aromatic ketones (with *ee*'s up to 69.3%).

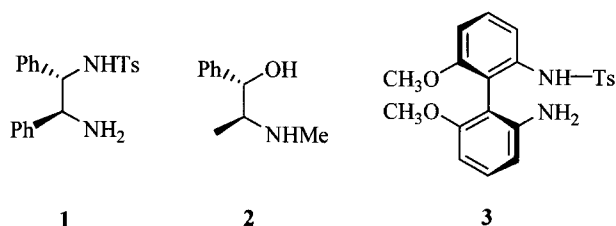
**Keywords** *N*-*p*-toluenesulfonyl-2, 2'-dimethoxy-6, 6'-diaminobiphenyl, chiral ligand, catalytic asymmetric transfer hydrogenation

## Introduction

Optically active secondary alcohols are useful building blocks for pharmaceuticals, agrochemicals as well as other materials.<sup>1</sup> A variety of asymmetric catalytic reactions have been developed for preparing such important secondary alcohols.<sup>2</sup> In addition to straightforward asymmetric hydrogenation of ketone, ruthenium-catalyzed hydrogen transfer using 2-propanol as hydrogen source has proven in recent years to be a valuable method for the same purpose.<sup>3</sup> This method has been extensively studied because of the low cost, favorable properties of the hydrogen donor as well as the ease of operation. Efficient catalytic systems developed by Lemaire, Noyori, Helmchen and others consist of Rh, Ir, or Ru precursor in combination with simple chiral bidentate ligand bearing

NH moiety such as diamine (1) or an aminoalcohol (2). Other types of chiral phosphorus and nitrogen ligands have also been used, however, with rather lower levels of yield and enantioselectivity.<sup>4</sup>

Despite the efforts recently being made on this catalytic enantioselective process, there are only a few successful examples of using simple diamines as chiral ligands for asymmetric transfer hydrogenation of ketone.<sup>5</sup> Recently, the use of biquinoline<sup>6</sup> and diamine derivatives<sup>7</sup> as chiral ligands in asymmetric catalysis has been reported, and the promising results obtained prompted us to further design another new chiral ligand, *N*-*p*-toluenesulfonyl-2, 2'-dimethoxy-6, 6'-diaminobiphenyl (Ts-DMBDPP, 3), for asymmetric transfer hydrogenation of ketones (Fig. 1).



**Fig. 1** Examples of the chiral bidentate ligands bearing NH moiety.

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## Results and discussion

Preparation of Ts-DMBDPPA (**3**) started from previously synthesized chiral diamine **4**.<sup>7</sup> Using triethylamine as a base, compound **4** can be easily converted to its *N*-tosylated product (*S*)-Ts-DMBDPPA (**3**), and the chiral ligand was produced by column chromatography in 67% isolated yield (Fig. 2).

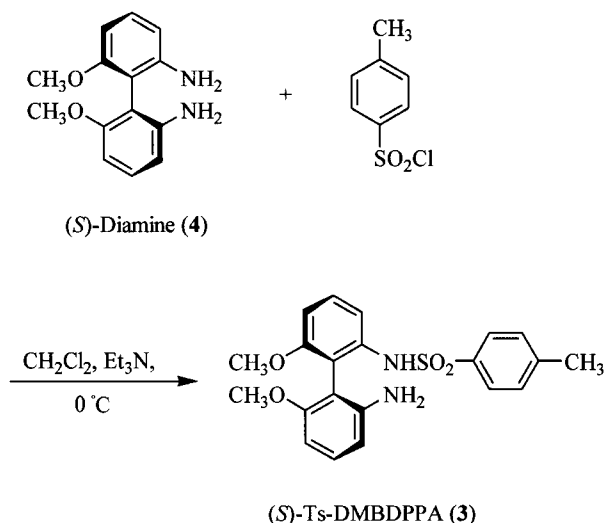


Fig. 2 Synthetic route of chiral ligand Ts-DMBDPPA.

At first, the asymmetric transfer hydrogenation of acetophenone was chosen as the model reaction. Under argon atmosphere, heating a mixture of  $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$

and (*S*)-**3** in 2-propanol at 80 °C for 20 min yielded an orange solution. This *in situ* prepared catalyst (**5**) can be used for asymmetric transfer hydrogenation of ketones (Fig. 3).

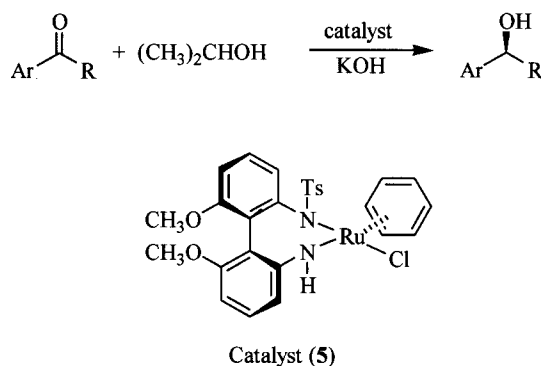


Fig. 3 Asymmetric transfer hydrogenation for aromatic ketones catalyzed by Ru-[Ts-DMBDPPA].

Thus, when a solution of acetophenone (0.1 mol/L) in 2-propanol containing prepared Ru catalyst (S/C = 200) and KOH (0.1 mol/L) was stirred at room temperature for 8 h, (*S*)-1-phenylethanol was obtained in 64.2% *ee* at 93% conversion. Without Ts-DMBDPPA under otherwise identical conditions the ketone was reduced with less than 10% conversion. The function of the chiral ligand can thus be easily seen. Results for the asymmetric transfer hydrogenation of aromatic ketones are shown in Table 1.

Table 1 [Ts-DMBDPPA]-Ru(II) catalyzed asymmetric transfer hydrogenation of aromatic ketones<sup>a</sup>

Entry	Ar	R	Temp. (°C)	Time (h)	Conv. (%) <sup>b</sup>	<i>ee</i> (%) <sup>b</sup>	Config. <sup>b</sup>
1	Ph	Me	25	8	93.0	64.2	<i>S</i>
3	Ph	Me	50	8	92.1	25.8	<i>S</i>
4	Ph	<i>t</i> -Butyl	25	8	27.6	12	<i>S</i>
5	<i>o</i> -CH <sub>3</sub> -Ph	Me	25	8	92.0	43.9	<i>S</i>
6	<i>p</i> -CH <sub>3</sub> -Ph	Me	25	8	96.0	57.1	<i>S</i>
7	<i>o</i> -OMe-Ph	Me	25	8	91.6	55.4	<i>S</i>
8	<i>p</i> -OMe-Ph	Et	25	8	95.7	57.2	<i>S</i>
9	<i>o</i> -Br-Ph	Me	25	8	90.8	66.0	<i>S</i>
10	<i>p</i> -Br-Ph	Me	25	8	92.2	69.3	<i>S</i>
11	1-Np	Me	25	8	83.4	29.5	<i>S</i>

<sup>a</sup> The reaction was carried out with a solution of ketone (0.1 mol/L) in propan-2-ol; ketone: Ru(II): (*S*)-Ts-DMBDPPA: KOH = 200:1:2:5 (molar ratio); <sup>b</sup> *ee* and yield were determined by GC analysis with a Chrompack CP-Chirasil-DEX CB capillary column (50 m); absolute configurations were determined by comparing optical rotations with literature.<sup>2(b)</sup>

As shown in Entries 1–3, Ru(II) catalyst (**5**) bearing chiral ligand Ts-DMBDPPA are highly active, and the ketones can be reduced with over 90% conversion. The enantioselectivity and reaction rate depended strongly on the reaction temperature. Lower temperature gave higher enantioselectivity at the expense of the reaction rate, and higher reaction temperature gave poor enantioselectivity.

The optimized conditions were then applied to the transfer hydrogenation of a variety of substituted aryl alkyl ketones. As shown in Table 1, the reactivity and stereoselectivity are also affected by bulkiness of the alkyl group of the ketone and the electronic properties of the substituents on the benzene ring. Acetophenone was reduced smoothly with 66% *ee*, while phenyl *t*-butyl ketone gave very low *ee* (12%). *Ortho*-substituted acetophenones (Entries 5, 7 and 9) reacted slowly as expected. Substrate containing methyl or methoxyl group at *para*- or *ortho*-position gave significantly lower enantioselectivity comparing with that containing *para*- or *ortho*-bromo group (Entries 9 and 10) which gave the highest *ee* value among the others. 1-Acetonaphthalene can also be reduced to corresponding alcohol with low *ee* but somehow moderate conversion (Entry 11).

In conclusion, we have designed and synthesized a new chiral ligand Ts-DMBDPPA which is effective for asymmetric transfer hydrogenation of aromatic ketones. This result may provide some useful information for designing further efficient catalyst systems.

## Experimental

### General information

All reactions were carried out under inert atmosphere, and the commercial reagents were used as received without further purification. All solvents were dried using standard methods and were distilled before use. NMR spectra were recorded on a Bruker Dpx-400 spectrometer. Mass analyses were performed on a Model Mat 95 ST. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter. Melting points were determined using an Electrothermal 9100 apparatus in capillaries sealed under nitrogen. GLC and HPLC analyses were performed using a Hewlett-Packard Model HP5890 series II GC and a Waters 600E, respectively.

(*S*)-*N*-Toluenesulfonyl-2,2'-dimethoxy-6,6'-diaminobiphenyl [(*S*)-Ts-DMBDPPA] (**3**)

A dried 50 mL flask with a magnetic stirring bar was charged with (*S*)-2,2'-dimethoxy-6,6'-diaminobiphenyl (230 mg, 0.9 mmol), *p*-toluenesulfonyl chloride (180 mg, 0.9 mmol), 30 mL of dichloromethane and 2 mL of triethylamine. The mixture was stirred for 24 h at room temperature. After the complete consumption of the starting diamine as indicated by TLC, the reaction mixture was poured into ice-water and extracted with dichloromethane (20 mL × 2). The combined organic layers were washed with brine, dried, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (*V*: *V* = 1:1) to afford pure (*S*)-*N*-toluenesulfonyl-2,2'-dimethoxy-6,6'-diaminobiphenyl [(*S*)-Ts-DMBDPPA] (**3**) (240 mg, 67% of theoretical yield). M. p. 143–146 °C,  $[\alpha]_D^{20} - 20.18$  (*c* 1.14, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (DMSO, 400 MHz) δ: 2.40 (s, 3H), 3.51 (s, 3H), 3.65 (s, 3H), 6.32 (d, *J* = 8.24 Hz, 1H), 6.49 (d, *J* = 7.98 Hz, 1H), 6.86 (d, *J* = 8.28 Hz, 1H), 6.98 (d, *J* = 8.08 Hz, 1H), 7.15–7.11 (m, 1H), 7.29–7.26 (m, 1H), 7.34 (d, *J* = 8.06 Hz, 2H), 7.55 (d, *J* = 8.16 Hz, 2H). Anal. calcd for C<sub>21</sub>H<sub>22</sub>SN<sub>2</sub>O<sub>4</sub>: C 63.30, H 5.56, N 7.03; found C 63.31, H 5.62, N 7.14 (HRMS calcd for C<sub>21</sub>H<sub>22</sub>SN<sub>2</sub>O<sub>4</sub> 398.13003, found 398.12994).

[RuCl<sub>2</sub>(η<sup>6</sup>-C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>-(*S*)-Ts-DMBDPPA catalyst (**5**)

A mixture of [RuCl<sub>2</sub>(η<sup>6</sup>-C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>] (2.5 mg, 0.005 mmol) and (*S*)-Ts-DMBDPPA (3.98 mg, 0.01 mmol) in 2-propanol (8 mL) were heated at 80 °C for 20 min under argon atmosphere to give an orange solution of [RuCl<sub>2</sub>(η<sup>6</sup>-C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>-(*S*)-Ts-DMBDPPA (**5**).

*A typical procedure for the transfer hydrogenation of acetophenone with catalyst 5*

To the prepared orange solution of [RuCl<sub>2</sub>(η<sup>6</sup>-C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>-(*S*)-Ts-DMBDPPA catalyst (0.005 mmol in 1.5 mL of 2-propanol) were added a degassed solution of acetophenone (120 mg, 1.0 mmol in 10 mL of 2-propanol, 0.1 mol/L) and a solution of KOH (0.1 mol/L) in 2-propanol (0.5 mL). After reacting at room temperature for 8 h, the reaction was quenched by addition of dilute

hydrochloric acid and the reaction mixture was concentrated *in vacuo* to dryness. The residue was suspended in ethyl acetate and the organic solution was washed with brine. The organic layer was dried over  $\text{MgSO}_4$  and a portion of the reaction mixture was analyzed by GLC with a Chrompack CP-Chirasil-DEX-CB capillary column.

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