

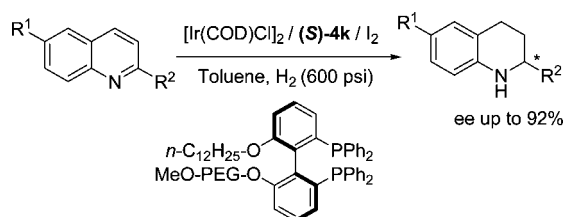
## Synthesis of Tunable Bisphosphine Ligands and Their Application in Asymmetric Hydrogenation of Quinolines

Xiao-Bing Wang and Yong-Gui Zhou\*

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, People's Republic of China

ygzhou@dicp.ac.cn

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A series of tunable axial chiral bisphosphine ligands have been synthesized from (*S*)-MeO-Biphep. The Ir complex of the MeO-PEG-supported ligand (*S*)-**4k** has been successfully applied in asymmetric hydrogenation of quinolines with up to 92% ee. The catalyst system is air-stable and recyclable.

Optically active compounds are very important for the synthesis of biologically active natural products and chiral drugs.<sup>1</sup> Transition metal-catalyzed asymmetric reactions are most often used for achieving high optical purity compounds.<sup>2</sup> Design and synthesis of chiral ligands are still a key issue for obtaining high activity and selectivity. In the past 30 years, thousands of chiral ligands have been synthesized and successfully applied in academic research and industrial production.<sup>3</sup> However, reactivities and enantioselectivities are generally substrate-dependent. There is no omnipotent ligand for every substrate, so developing easily prepared, tunable ligands is still necessary.

Atropisomeric C<sub>2</sub>-symmetric biaryl bisphosphines such as BINAP,<sup>4</sup> BIPHEP,<sup>5</sup> MeO-BIPHEP,<sup>6</sup> TunePhos,<sup>7</sup> P-Phos,<sup>8</sup> Seg-Phos,<sup>9</sup> Difluorophos,<sup>10</sup> and other important biaryl phosphine ligands<sup>11</sup> are very effective ligands for many asymmetric

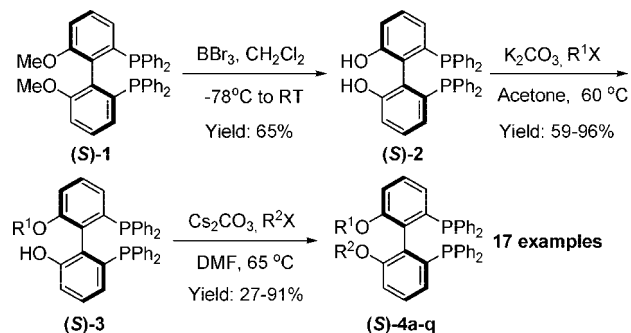
\* To whom correspondence should be addressed. Phone: +86-411-84379220. Fax: +86-411-84379220.

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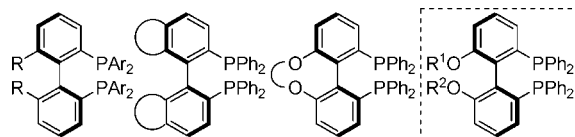
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## SCHEME 1. Synthesis of Bisphosphine Ligands (*S*)-4



reactions. At present, varying the dihedral angle of the chiral backbone, replacing P substitutes, and modification of the axial chiral backbone are effective strategies for divergent synthesis of biaryl bisphosphine ligands. Zhang and co-workers designed modular TunePhos by connecting the two aryl moieties with tunable chiral or achiral linkers.<sup>7</sup> Zhang and co-workers developed an effective method for the synthesis of bisphosphine ligands by changing the 5,6-substituents of every aryl moiety.<sup>11b</sup> In this note, we have developed a new method for a divergent synthesis of bisphosphine ligands by introduction of different substituents at the 6,6'-positions of the biaryl backbone, and these ligands have been successfully applied to asymmetric hydrogenations of quinolines.



(*S*)-MeO-Biphep was chosen as the starting material to make the chiral bisphosphine ligands (Scheme 1). (*S*)-**2** can be conveniently synthesized through demethylating according to

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the reported procedure.<sup>7</sup> Reaction of (*S*)-**2** with halides or sulfonate esters in the presence of excess anhydrous K<sub>2</sub>CO<sub>3</sub> in acetone gave (*S*)-**3** with 59–96% yields. (*S*)-**4** was prepared by the reaction of (*S*)-**2** or (*S*)-**3** with halides in the presence of Cs<sub>2</sub>CO<sub>3</sub> in DMF with 27–91% yields. Recently, separation and recycling of the expensive chiral catalyst has been developed by utilizing soluble PEG polymer supports. These catalysts have catalytic activities and enantioselectivities similar to those of the homogeneous parent systems. When the reaction is completed, the catalyst can be separated by either extraction or precipitation.<sup>12</sup> MeO-PEG-based ligands were also prepared by the reaction of MeO-PEG-OMs with (*S*)-**2** or (*S*)-**3** in the presence of Cs<sub>2</sub>CO<sub>3</sub> in DMF.

Asymmetric hydrogenation of easily accessible quinolines is doubtless the most direct and convenient access toward chiral tetrahydroquinoline derivatives, which are important synthetic intermediates and structural units of natural products and biologically active compounds. Recently, we discovered Ir complexes bearing the bisphosphines or N,P ligands performed effectively to give tetrahydroquinoline derivatives in the presence of iodine with high enantioselectivity and excellent yield.<sup>13</sup> Several groups reported the asymmetric hydrogenation of quinolines using other chiral phosphine ligands.<sup>14</sup> Asymmetric transfer hydrogenation of quinolines with organocatalysis has also been reported.<sup>15</sup>

With these chiral bisphosphine ligands in hand, Ir-catalyzed asymmetric hydrogenation of 2-methylquinoline as a model substrate was performed under the standard reaction (toluene as solvent, I<sub>2</sub> as additive, 600 psi of H<sub>2</sub>, rt). We first screened the effects that different ligands with alkyl and Bn group substitution had on the asymmetric hydrogenation of quinolines (entries 1–5, Table 1). The enantioselectivities varied from 87% to 93% ee. MeO-PEG-based ligands were also screened (entries 6–17), showing moderate enantioselectivity (74% ee, entry 15) when using (*S*)-**4o** with the same two MeO-PEG-(1600)

**TABLE 1.** Condition Optimization for Ir-Catalyzed Asymmetric Hydrogenation of 2-Methylquinoline<sup>a</sup>

entry	ligand	R <sup>1</sup>	R <sup>2</sup>	ee <sup>b</sup> (%)
1	( <i>S</i> )- <b>4a</b>	<i>n</i> -C <sub>16</sub> H <sub>33</sub> -	<i>n</i> -C <sub>16</sub> H <sub>33</sub> -	93
2	( <i>S</i> )- <b>4b</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub> -	<i>n</i> -C <sub>16</sub> H <sub>33</sub> -	89
3	( <i>S</i> )- <b>4c</b>	<i>n</i> -C <sub>16</sub> H <sub>33</sub> -	Bn	87
4	( <i>S</i> )- <b>4d</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub> -	Bn	91
5	( <i>S</i> )- <b>4e</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub> -	Bn	92
6	( <i>S</i> )- <b>4f</b>	Me	MeO-PEG-(1600)	83
7	( <i>S</i> )- <b>4g</b>	Et	MeO-PEG-(1600)	86
8	( <i>S</i> )- <b>4h</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub> -	MeO-PEG-(1600)	90
9	( <i>S</i> )- <b>4i</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub> -	MeO-PEG-(1600)	80
10	( <i>S</i> )- <b>4j</b>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> -	MeO-PEG-(1600)	81
11	( <i>S</i> )- <b>4k</b>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> -	MeO-PEG-(1600)	91
12	( <i>S</i> )- <b>4l</b>	<i>n</i> -C <sub>16</sub> H <sub>33</sub> -	MeO-PEG-(1600)	89
13	( <i>S</i> )- <b>4m</b>	Bn	MeO-PEG-(1600)	85
14	( <i>S</i> )- <b>4n</b>	CH <sub>2</sub> =CH-CH <sub>2</sub> -	MeO-PEG-(1600)	87
15	( <i>S</i> )- <b>4o</b>	MeO-PEG-(1600)	MeO-PEG-(1600)	74
16	( <i>S</i> )- <b>4p</b>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> -	MeO-PEG-(1100)	90
17	( <i>S</i> )- <b>4q</b>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> -	MeO-PEG-(5000)	89
18 <sup>c</sup>	( <i>S</i> )- <b>4k</b>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> -	MeO-PEG-(1600)	87
19 <sup>d</sup>	( <i>S</i> )- <b>4k</b>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> -	MeO-PEG-(1600)	86
20 <sup>e</sup>	( <i>S</i> )- <b>4k</b>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> -	MeO-PEG-(1600)	89

<sup>a</sup> All reactions were performed on a 0.5-mmol scale: [Ir(COD)Cl]<sub>2</sub> 0.5 mol %, ligand 1.1 mol %, I<sub>2</sub> 5 mol %, H<sub>2</sub> 600 psi, toluene 2 mL, 16 h, room temperature, >95% conversion. <sup>b</sup> Determined by HPLC analysis with OJ-H column. <sup>c</sup> CH<sub>2</sub>Cl<sub>2</sub> as solvent. <sup>d</sup> THF as solvent. <sup>e</sup> The reaction was carried out in air.

substituents. MeO-PEG-(1600)-based chiral ligands bearing different alkyl substituents gave 80–91% ee. The different enantioselectivities may be due to the varying of the dihedral angle of the chiral backbone. The introduction of the different molecular weight of MeO-PEG- on the ligands had no significant effect on the ee values (entries 11, 16, and 17). The best enantioselectivity was achieved by using ligand (*S*)-**4k** (entry 11). The effect of solvents on the reactivity and enantioselectivity was also studied with (*S*)-**4k** as ligand. Full conversions were achieved in CH<sub>2</sub>Cl<sub>2</sub> and THF with slightly lower enantioselectivities (entries 18 and 19). It is coming to light that the existence of trace air in the reaction can lead to deactivation of the catalyst and irreproducible results because the transition metal catalyst is air sensitive. Hence it is highly desirable to develop a catalyst with high activity and good air-stability. It is notable that our catalyst displayed the same activity with slightly lower enantioselectivity when it was prepared in air (entry 20).

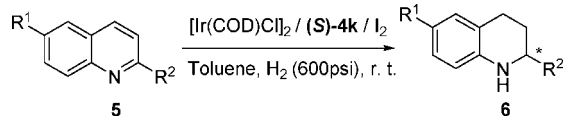
On the basis of the optimized reaction conditions, asymmetric hydrogenation of a variety of 2-substituted quinoline derivatives were also carried out. The results are summarized in Table 2. Good to excellent enantioselectivities were achieved in the hydrogenation of 2-alkyl-substituted quinolines. The length of the alkyl chain has no significant effect on the ee values (entries 1–4). When the alkyl group at the 2-position was replaced by the phenyl group, a lower enantioselectivity was observed (entry 8). However, 2-phenylethyl-substituted quinolines can afford excellent enantioselectivity (92% ee). With 6-substituted quinolines, the strong electro-donating methoxy group afforded lower enantioselectivity (78% ee, entry 13). The hydrogenation of quinolines with hydroxyl groups also proceeded smoothly, affording excellent enantioselectivities (entries 9 and 10).

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TABLE 2. Ir-Catalyzed Asymmetric Hydrogenation of Quinolines<sup>a</sup>


entry	R <sup>1</sup> /R <sup>2</sup>	yield (%)	ee <sup>b</sup> (%)
1	H/Me ( <b>5a</b> )	91 ( <b>6a</b> )	91 (S)
2	H/Et ( <b>5b</b> )	93 ( <b>6b</b> )	91 (S)
3	H/ <i>n</i> -Bu ( <b>5c</b> )	91 ( <b>6c</b> )	89 (S)
4	H/ <i>n</i> -pentyl ( <b>5d</b> )	93 ( <b>6d</b> )	91 (S)
5	H/phenethyl ( <b>5e</b> )	92 ( <b>6e</b> )	92 (S)
6	H/3,4-methylenedioxy-phenethyl ( <b>5f</b> )	92 ( <b>6f</b> )	92 (S)
7	H/3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> - ( <b>5g</b> )	90 ( <b>6g</b> )	92 (S)
8	H/Ph ( <b>5h</b> )	96 ( <b>6h</b> )	72 (R)
9	H/ <i>c</i> -C <sub>6</sub> H <sub>10</sub> (OH)CH <sub>2</sub> - ( <b>5i</b> )	85 ( <b>6i</b> )	91 (R)
10	H/Ph <sub>2</sub> CH(OH)CH <sub>2</sub> - ( <b>5j</b> )	97 ( <b>6j</b> )	91 (R)
11	Me/Me ( <b>5k</b> )	98 ( <b>6k</b> )	90 (S)
12	F/Me ( <b>5l</b> )	91 ( <b>6l</b> )	91 (S)
13	MeO/Me ( <b>5m</b> )	91 ( <b>6m</b> )	78 (S)

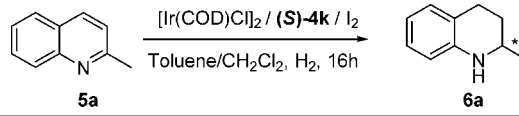
<sup>a</sup> Reaction conditions: 0.5 mmol quinolines, [Ir(COD)Cl]<sub>2</sub> (0.5 mol %), (S)-**4k** (1.1 mol %), I<sub>2</sub> (5 mol %), 2 mL of toluene, 600 psi H<sub>2</sub>, rt, 16 h. <sup>b</sup> Determined by HPLC analysis with OJ-H, OD-H, and AS-H columns.

We then examined recyclability of the Ir complex of the MeO-PEG-(1600)-supported ligand (S)-**4k** in asymmetric hydrogenation of quinolines. After the first run of the reaction, hexane was added to the reaction mixture, precipitating out the catalyst, which was then filtered off and washed with hexane three times. Because the recovered catalyst cannot be entirely redissolved in toluene, we chose CH<sub>2</sub>Cl<sub>2</sub>/toluene (1/3) as solvent to test the recyclability of the catalyst. The recovered catalyst could be recycled with only a slight loss in the activity and enantioselectivity for asymmetric hydrogenation of quinolines (from 91% ee in the first run to 84% ee in the fifth run, Table 3). These results demonstrate further advantages of the type of ligands, which can be reused in asymmetric hydrogenation of quinolines.

In conclusion, a series of tunable chiral bisphosphine ligands were conveniently synthesized and successfully applied in asymmetric hydrogenation of quinolines. [Ir(CODCl)<sub>2</sub>]/(S)-**4k**/I<sub>2</sub> catalyst has the advantage of air-stability and easy reutilization. Future work on the application of these ligands will focus on extension of other transition metal-catalyzed enantioselective reactions.

## Experimental Section

**General Procedure for the Synthesis of (S)-**4f–q**.** A solution of (S)-**2** or (S)-**3** in DMF was bubbled with N<sub>2</sub>. To this solution

TABLE 3. Recyclability of the Ir Complex in Asymmetric Hydrogenation of Quinolines<sup>a</sup>


cycle	run 1	run 2	run 3	run 4	run 5
conv <sup>b</sup> (%)	>95	>95	>95	>95	95
ee <sup>c</sup> (%)	91	90	88	85	84

<sup>a</sup> Reaction conditions: 1 mmol of **5a** in toluene/CH<sub>2</sub>Cl<sub>2</sub> (3/1) 4 mL, [Ir(COD)Cl]<sub>2</sub> 0.5 mol %, (S)-**4k** 1.1 mol %, I<sub>2</sub> 5 mol %, 600 psi H<sub>2</sub>, room temperature, 16 h. <sup>b</sup> Conversions were determined by <sup>1</sup>H NMR analysis of the crude products. <sup>c</sup> Determined by HPLC analysis with an OJ-H column.

was added Cs<sub>2</sub>CO<sub>3</sub> (4 equiv) and MeO-PEG-OMs (2.0 equiv for (S)-**2** or 1.0 equiv for (S)-**3**). The mixture was heated at 65 °C for 16 h. After removal of Cs<sub>2</sub>CO<sub>3</sub>, the residue was evaporated and dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). Hexane (25 mL) was added slowly to the solution with vigorous stirring at -20 °C. The precipitate formed was isolated by filtration and then dried in vacuo to give the MeO-PEG derivatives (S)-**4f–q**. (S)-**4k**: [α]<sub>D</sub><sup>25</sup> -5.1 (*c* 2.00, CHCl<sub>3</sub>); 73%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77 (t, *J* = 6.4 Hz, 3H), 0.93–1.22 (m, 20H), 3.10–3.16 (m, 1H), 3.42–3.48 (m, 1H), 3.19–3.81 (polyethylene glycol peaks), 6.59–7.08 (m, 4H), 7.08–7.19 (m, 22H); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ -13.91.

**Procedure for Asymmetric Hydrogenation of Quinoline Derivatives.** A mixture of [Ir(COD)Cl]<sub>2</sub> (1.7 mg, 0.0025 mmol) and (S)-**4k** (14.4 mg, 0.0055 mmol) in toluene (2 mL) was stirred at room temperature for 10 min in a glovebox, then the mixture was transferred by syringe to an autoclave in which I<sub>2</sub> (6.4 mg, 0.025 mmol) and substrate (0.5 mmol) were placed beforehand. The hydrogenation was performed at room temperature under H<sub>2</sub> (600 psi) for 16 h. After the hydrogen was carefully released, the reaction mixture was concentrated to afford the crude product. Purification was performed by a silica gel column eluted with hexane/EtOAc to give pure product. (S)-**2-Methyl-1,2,3,4-tetrahydroquinoline (6a)**: Yield 91%, [α]<sub>D</sub><sup>25</sup> -78.3 (*c* 0.76, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.24 (t, *J* = 6.5 Hz, 3H), 1.62 (m, 1H), 1.96 (m, 1H), 2.81 (m, 2H), 3.42 (m, 1H), 3.50 (br, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 6.63 (m 1H), 6.98 (m, 2H).

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**Supporting Information Available:** Spectroscopic date, HPLC spectra, and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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