

# Application of Phosphine–Oxazoline Ligands in Ir-Catalyzed Asymmetric Hydrogenation of Acyclic Aromatic *N*-Arylimines

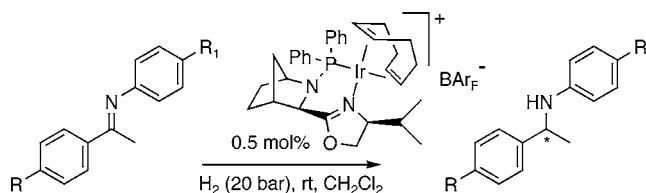
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## ABSTRACT



A new class of chiral phosphine–oxazoline ligands have been developed. Chiral Ir complexes prepared from these ligands induced high enantioselectivities (66–90% ee) when applied to the asymmetric hydrogenation of acyclic aromatic *N*-arylimines.

Chiral amines are useful synthetic intermediates in the preparation of many biologically active compounds, and development of an efficient method for their preparation is of great synthetic importance. One procedure which has received much attention in recent years is the enantioselective reduction of C–N double bonds.<sup>1</sup> The first investigations on Ru<sup>2a</sup> and Rh<sup>2b</sup> homogeneous catalysis were published in 1975; however, the enantioselectivities were low (15–22%). In recent years, a variety of chiral metal catalysts, including Rh,<sup>3</sup> Ru,<sup>4,5</sup> Ti,<sup>6</sup> Zr,<sup>6c</sup> and Ir<sup>7</sup> complexes, have been successfully applied to the asymmetric hydrogenation of imines.

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However, these procedures often require high catalyst loadings, elevated pressures, and long reaction times to obtain the desired amines in high yield. Although several useful methods have been described for hydrogenation of cyclic imines,<sup>5b,6c,7h,8</sup> the enantioselective hydrogenation of acyclic imines is more difficult to achieve.<sup>1</sup> The main reason for this problem is ease of interconversion between *E* and *Z* isomers of an acyclic imine in solution.<sup>6a,b</sup>

In 1979, Crabtree<sup>9</sup> reported (pyridine)(phosphane)iridium complexes displaying high catalytic activity as a homogeneous hydrogenation catalyst. Since that report, a number of research groups<sup>10</sup> have evaluated chiral analogues of the Crabtree catalyst in asymmetric hydrogenations,<sup>11</sup> including the hydrogenation of imines<sup>7d,f</sup> with varying success.

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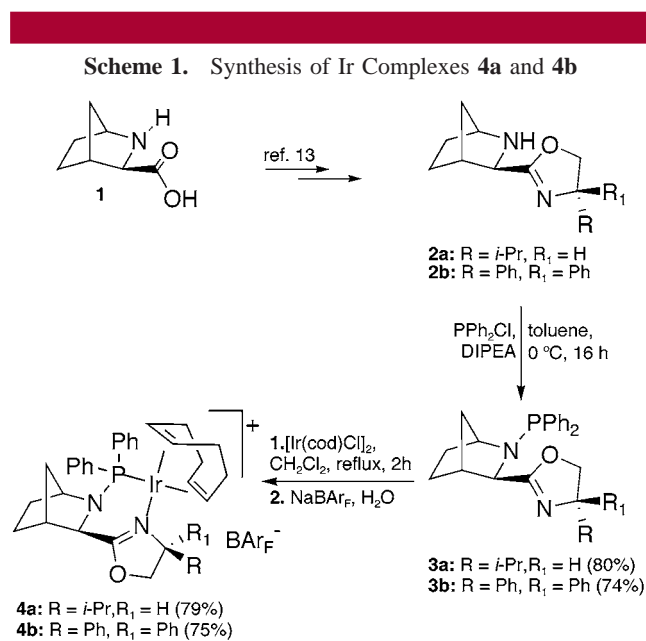
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Previously, 2-azanorbornan-3-ylmethanol and its derivatives have been used by our research group as efficient transition-metal ligands in different catalytic asymmetric reactions.<sup>12</sup> Recently, we have published the preparation of a new class of 2-azanorbornane-oxazoline ligands, which proved to be potent in the iridium-catalyzed transfer hydrogenation of acetophenone.<sup>13</sup>

Functionalization of 2-azanorbornane-oxazoline with phosphine leads to the novel class of phosphine-oxazoline ligands **3**. Herein, we report the synthesis of these new chiral phosphine-oxazolines and their efficient application as ligands in the iridium-catalyzed hydrogenation of acyclic *N*-arylimines.

The syntheses of complexes **4a** and **4b** are shown in Scheme 1. The (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-



carboxylic acid (**1**) is easily available from a stereoselective aza-Diels-Alder reaction.<sup>14</sup> 2-Azanorbornane-oxazolines **2a** and **2b** were prepared according to methods developed within our research group.<sup>13</sup> The phosphines **3a** and **3b** were obtained in high yield by treatment of compounds **2a** and

**2b** with diisopropylethylamine in CH<sub>2</sub>Cl<sub>2</sub> followed by addition of diphenylphosphine chloride. The use of triethylamine as a base resulted in the low yield of phosphine-oxazoline (20–30%). Iridium complexes **4a** and **4b** were prepared by heating to reflux the appropriate phosphine-oxazoline and [Ir(cod)Cl]<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> followed by anion exchange with NaBAR<sub>F</sub> in CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O solution.<sup>15</sup> The crude complexes were purified by column chromatography on silica gel to afford the desired complexes **4a** and **4b** as crystalline solids. Stored at low temperatures, no decomposition is detected by <sup>1</sup>H and <sup>31</sup>P NMR after several months.

Iridium complex **4a** was tested in asymmetric hydrogenation of various aromatic *N*-arylimines; the results of this study are presented in the Table 1. Hydrogenation of the model substrate *N*-(1-phenylethylidene)aniline (**5**)<sup>7d</sup> revealed that optimal results were obtained when the reaction was performed in dichloromethane under a pressure of 20 bar (H<sub>2</sub>), with a catalyst loading of 0.5 mol %. Under these conditions, the corresponding (*R*)-*N*-phenyl-*N*-(1-phenylethyl)amine was obtained with 90% ee and 98% conversion in 2 h. Although it was possible to carry on the reaction at reduced pressures (5 bar) and lower catalyst loadings (0.05 mol %) without loss of enantioselectivity, the reaction rate is decreased. The same standard conditions were applied to the hydrogenation of imines **6–13**.

For substrates **6** and **7** (entries 2 and 3), having *o*-methyl substituents on the aromatic rings, a decrease in the reaction rate together with a slight decrease of enantioselectivity (80–83% ee) was observed. The imines **8–12** bearing electron-withdrawing and electron-donating groups at the *para*-positions in aromatic rings (entries 2–8) were reduced in similar enantiomeric excess to imine **5** (86–89% ee). Full conversion was achieved for all compounds **8–12** after 1.5–3 h. A correlation between the electronic nature of the *para*-substituent of the substrate and ee of the product was not observed. *N*-(1-Phenylethylidene)benzylamine (**13**)<sup>7d</sup> (entry 9) which exists as a mixture of *E/Z* isomers in a 13:1 ratio in CDCl<sub>3</sub>, was reduced to (*R*)-*N*-benzyl-*N*-(1-phenylethyl)amine with 66% ee; however, a catalyst loading of 1 mol % was required to obtain 63% conversion in 12 h.

Iridium complex **4b** prepared from bulky ligand **3b** did not show catalytic activity in the reduction of imines (Table 2, entries 1 and 2) under the standard conditions. However, it was efficient in the hydrogenation of olefins **14** and **15**. (*R*)-1,2-Diphenylpropane<sup>15a</sup> was obtained in 96% ee and 81%

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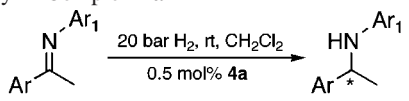
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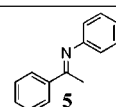
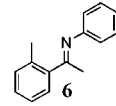
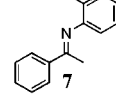
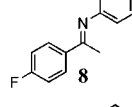
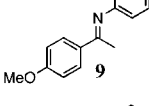
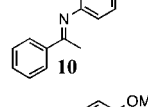
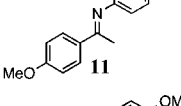
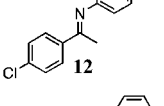
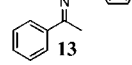
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**Table 1.** Asymmetric Hydrogenation of Acyclic *N*-Arylimines Catalyzed by Ir Complex **4a**

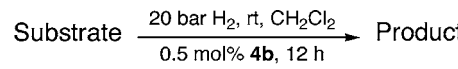


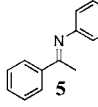
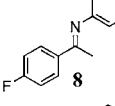
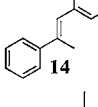
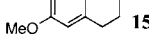
entry	substrate	time, h	conv., % <sup>a</sup>	ee, % <sup>b</sup>
1		2	98	90 ( <i>R</i> )
2		12	52	83 (-)
3		3	99	80 (-)
4		2	99	89 (-)
5		3	99	86 (+)
6		1.5	99	89 (+)
7		2	99	86 (+)
8		1.5	99	89 (+)
9 <sup>c</sup>		12	63	66 ( <i>R</i> )

<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Determined by chiral HPLC, absolute configuration assigned by comparison of retention times with literature values<sup>7d</sup> or the sign of optical rotation is reported. <sup>c</sup> 1 mol % of catalyst was used (see the Supporting Information for details).

conversion (entry 3), and 6-methoxy-1-(*S*)-methyl-1,2,3,4-tetrahydronaphthalene<sup>15b</sup> was produced in 77% ee with full conversion (entry 4) in 12 h.

**Table 2.** Asymmetric Hydrogenation Catalyzed by Ir Complex **4b**



entry	substrate	conv., % <sup>a</sup>	ee, % <sup>b</sup>
1		0	n.d.
2		0	n.d.
3		81	96 ( <i>R</i> )
4		99	77 ( <i>S</i> )

<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Determined by chiral HPLC or chiral GC MS, absolute configuration assigned by comparison of retention times with literature values<sup>15</sup> (see the Supporting Information for details).

In conclusion, we have developed a new class of chiral phosphine–oxazoline ligands. These ligands were used for preparation of chiral iridium complexes for asymmetric hydrogenation. Complex **4a** was applied to enantioselective acyclic aromatic *N*-arylimines to induce high enantioselectivities (66–90% ee). Complex **4b** was efficient in hydrogenation of olefins. Our current effort is concentrated on improving enantioselectivity and broadening the scope of these hydrogenation reactions.

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**Supporting Information Available:** Experimental procedures, characterization data, and NMR spectra for unknown compounds, references to known compounds, and chiral separation data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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