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SimplePHOX, a Readily Available Chiral Ligand System for Iridium-Catalyzed Asymmetric Hydrogenation

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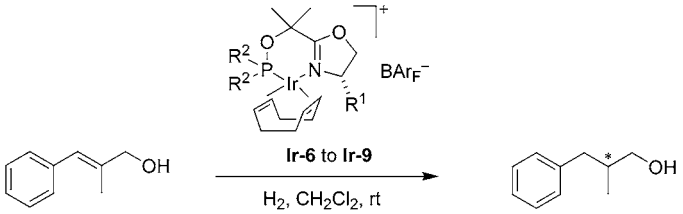
ABSTRACT



New Ir–SimplePHOX complexes Ir-6–Ir-9 catalyze the quantitative, highly enantioselective hydrogenation of a range of unfunctionalized and functionalized olefins. Synthesis, catalytic results, and X-ray crystal structures are presented here.

Iridium complexes with chiral P,N-ligands[1] have emerged as a new class of hydrogenation catalysts that are largely complementary to the well-known rhodium and ruthenium catalysts.[2] In contrast to their Rh and Ru counterparts, they do not require a coordinating group next to the C=C bond for efficient, highly enantioselective alkene hydrogenation. In addition to unfunctionalized alkenes, high enantiomeric excesses were also obtained with several classes of functionalized olefins for which no suitable catalysts were available. Originally, we used iridium(I)−COD complexes derived from chiral phosphinooxazoline (PHOX) ligands[3] as precatalysts. The choice of the counterion of these cationic complexes proved to be crucial. Coordinating anions, even very weak ligands such as triflate, almost completely inhibit the catalyst. The best results were obtained with tetrakis-[3,5-(trifluoromethyl)phenyl]borate (BAr_F^-), which became our standard anion for subsequent work. Iridium complexes with this anion are easy to handle as they are air and moisture stable and can be stored at ambient temperature for months without loss of activity.

The encouraging results obtained with Ir−PHOX catalysts prompted us as well as other groups to investigate new classes of chiral P,N-ligands containing a chiral oxazoline ring or, alternatively, a pyridine or quinoline system connected to a chiral backbone.[4] Some of these new ligands, especially phosphinite-oxazolines such as ThrePHOX, have considerably enhanced the application range of Ir-catalyzed hydrogenation. In connection with our work on Pd-catalyzed allylic substitution, we have developed phosphite and phosphoramidite ligands of type **A** derived from a readily accessible oxazolinyl alcohol and an additional chiral unit such as BINOL, TADDOL, or a chiral 1,2-diamine.[5] In view

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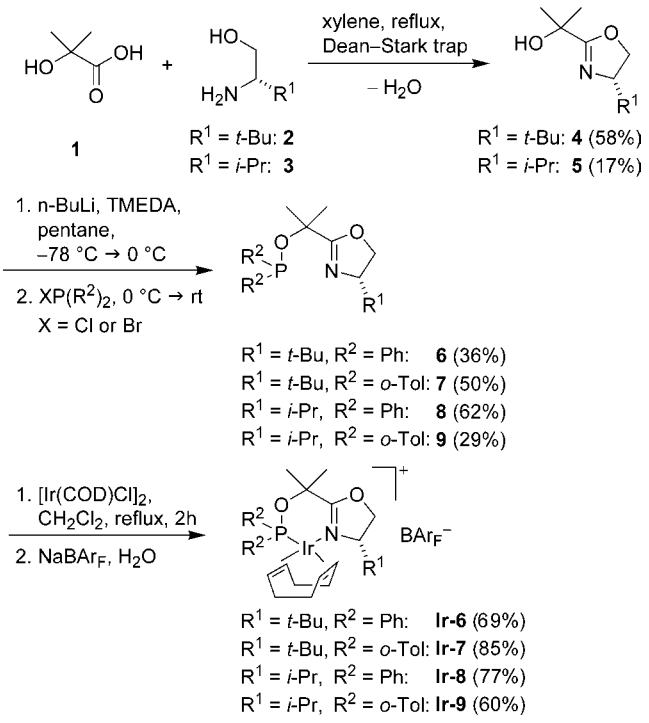
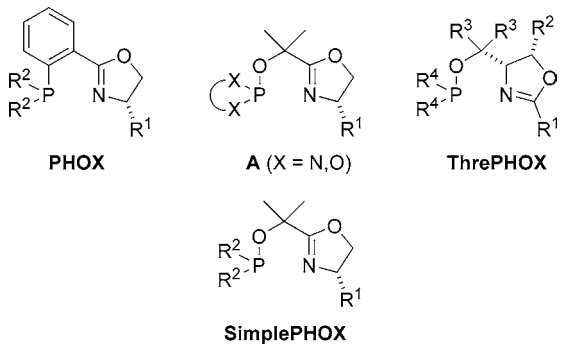
of the excellent results obtained with ThrePHOX ligands, we decided to prepare phosphinite analogues of ligands **A**, which we called SimplePHOX, because they are readily prepared in just two steps from simple precursors.

The synthesis of four SimplePHOX derivatives is summarized in Scheme 1. Condensation of the enantiomerically pure amino alcohols **2** and **3** with hydroxy acid **1** in refluxing xylene under azeotropic removal of water led to oxazolinyl alcohols **4** and **5**.[5a,6] Deprotonation of the alcohol with butyllithium and subsequent reaction with the appropriate chloro- or bromophosphine afforded the desired phosphinites **6**−**9** in 30−60% yield. Weaker bases such as triethylamine/DMAP, which work well for phosphinite formation from less hindered alcohols, could not be used in this case.

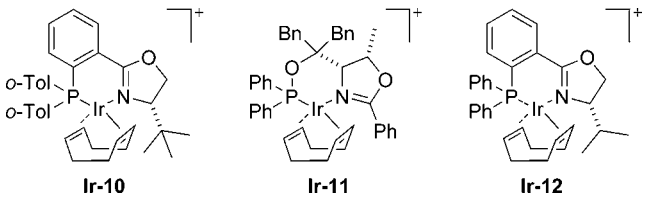
Scheme 1. Synthesis of SimplePHOX Ligands and Their Iridium−COD Complexes.





Following standard procedures, iridium complexes **Ir-6**−**Ir-9** were synthesized. Single crystals of compounds **Ir-6** and **Ir-8** suitable for X-ray crystallographic analysis could be grown from diethyl ether or dichloromethane solutions, respectively, that were layered with pentane.

Iridium complexes **Ir-6**−**Ir-9** were tested in the enantioselective hydrogenation of a series of unfunctionalized alkenes, an acrylic ester, and an allylic alcohol. The observed enantioselectivities were compared to those obtained with iridium−PHOX complexes **Ir-10** and **Ir-11**,[7] which are among the most selective catalysts developed so far. Unless stated otherwise, catalytic reactions were performed with 0.1 mmol of substrate and 1 mol % catalyst in 0.5 mL of CH_2Cl_2 at 50 bar H_2 for 2 h. Full conversion was routinely achieved.



(*E*)-1,2-Diphenyl-1-propene (**13**) is hydrogenated with high enantioselectivities by many iridium-P,N catalysts. With SimplePHOX catalyst **Ir-7**, too, a high ee of 98% ee was achieved, which is in the same range of selectivity as with the benchmark catalysts **Ir-10** and **Ir-11** (Table 1).

Table 1. Enantioselective Hydrogenation of Trisubstituted, Unfunctionalized Olefins with Catalysts **Ir-6**−**Ir-11**[a]

entry	substrate	complex	conv. [%][b]	ee [%][c]
1		**Ir-6**	>99	96 (*R*)
2		**Ir-7**	>99	98 (*R*)
3		**Ir-8**	>99	85 (*R*)
4		**Ir-9**	>99	90 (*R*)
5	**13**	**Ir-10**	>99	98 (*R*)[i]
6		**Ir-11**	>99	99 (*R*)[4e]
7		**Ir-6**	>99	90 (*R*)
8		**Ir-7**	>99	91 (*R*)
9		**Ir-8**	>99	88 (*R*)
10	MeO	**Ir-9**	>99	91 (*R*)
11	**14**	**Ir-10**	>99	81 (*R*)
12		**Ir-11**	>99	99 (*R*)[4e]
13		**Ir-6**	>99	78 (*R*)
14		**Ir-7**	>99	66 (*R*)
15		**Ir-8**	>99	**89 (*R*)**
16	MeO	**Ir-9**	>99	85 (*R*)
17	**15**	**Ir-10**	>99	63 (*R*)
18		**Ir-11**	>99	89 (*R*)[4e]
19		**Ir-6**	>99	85 (*S*)
20		**Ir-7**	>99	**95 (*S*)**
21		**Ir-8**	>99	82 (*S*)
22	MeO	**Ir-9**	>99	82 (*S*)
23	**16**	**Ir-10**	>99	72 (*S*)[i]
24		**Ir-11**	>99	71 (*S*)[4e]

[a] All reactions were performed using 0.1 mmol of alkene and 0.5 mL of dichloromethane at 50 bar of hydrogen pressure at room temperature (reaction time: 2 h). [b] Conversions were determined by GC. In all cases, a clean reaction was observed with a single product peak in the GC. [c] Determined by HPLC (see ref 4a,b).

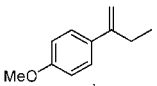
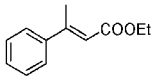
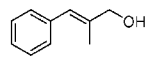
Hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene (**14**) with SimplePHOX complexes gives selectivities around 90%

ee, between the ee values obtained with **Ir-10** (81% ee) and **Ir-11** (99% ee).

(*Z*)-2-(4-Methoxyphenyl)-2-butene **15** is a more demanding substrate that normally reacts with lower enantioselectivity than the corresponding (*E*)-isomer. Hydrogenation of the (*E*)- and (*Z*)-isomers always leads to opposite enantiomers. Interestingly, catalyst **Ir-8** outperforms the other SimplePHOX complexes in this case. For this particular substrate, sterically less demanding substituents in the oxazoline ring and at the P atom seem better suited, whereas in most other reactions analogous complexes with *tert*-butyl- and *o*-tolyl-substituted ligands induce higher enantioselectivities than **Ir-8**. With 89% ee catalyst **Ir-8** induces respectable ee levels, close to the best value (95% ee) observed so far.[1] In the hydrogenation of the cyclic substrate 6-methoxy-1-methyl-3,4-dihydronaphthalene (**16**) complex **Ir-7** is clearly the most effective catalyst among the four SimplePHOX complexes. The observed ee of 95% is one of the best values recorded for this substrate.

Terminal alkenes are highly reactive substrates, giving full conversion with high rates even at the low hydrogen pressure of 1 bar. For this substrate class, the enantioselectivity drops significantly with increasing pressure, in contrast to the hydrogenation of trisubstituted alkenes, which shows little pressure dependence. With the Ir−PHOX complex **Ir-10**, e.g., the ee decreases from 61% to essentially 0% in the hydrogenation of 2-(4-methoxyphenyl)-1-butene, when the pressure is raised from 1 to 50 bar (Table 2). The SimplePHOX complexes perform significantly better at 50 bar; however, at 1 bar, they show only a modest increase in selectivity and cannot compete with the phosphinite complex **Ir-11** (90% ee).

Table 2. Enantioselective Hydrogenation of Terminal and Functionalized Olefins with Catalysts **Ir-6**−**Ir-11**[a]

entry	substrate	complex	conv. [%][b]	ee [%][c]
1	 **17** [d]	**Ir-6**	>99 / >99	36 / 78 (*S*)
2		**Ir-7**	>99 / >99	51 / 76 (*S*)
3		**Ir-8**	>99 / >99	49 / 54 (*S*)
4		**Ir-9**	>99 / >99	44 / 59 (*S*)
5		**Ir-10**	>99 / >99	*rac* / 61 (*S*)
6		**Ir-11**	>99 / >99	71 / 90 (*S*)[4e]
7	 **18**	**Ir-6**	>99	85 (*R*)
8		**Ir-7**	>99	**94 (*R*)**
9		**Ir-8**	>99	56 (*R*)
10		**Ir-9**	>99	61 (*R*)
11		**Ir-10**	>99	84 (*R*)[4b]
12		**Ir-11**	>99	92 (*R*)[4e]
13	 **19**	**Ir-6**	>99	93 (–)
14		**Ir-7**	>99	**97 (–)**
15		**Ir-8**	>99	95 (–)
16		**Ir-9**	>99	95 (–)
17		**Ir-10**	95	96 (–)[4b]
18		**Ir-11**	98	92 (–)[4e]

[a,b,c] See Table 1. [d] Second set of results was obtained in 2 mL of dichloromethane at 1 bar hydrogen pressure, 30 min reaction time.

The SimplePHOX complex **Ir-7** proved to be an excellent catalyst for the hydrogenation of the trisubstituted acrylic ester **18** and allylic alcohol **19**. The observed enantioselectivities of 94 and 97% ee, respectively, are among the highest values observed for these substrates.[4e,j] The same catalyst also gave high enantioselectivities for a range of trisubstituted alkenes bearing heteroaromatic rings at the C=C bond.[1,8]

Crystal structures of the two SimplePHOX complexes **Ir-6** and **Ir-8** are shown in Figure 1. The two structures are very similar with a characteristic boatlike conformation of the six-membered chelate ring. In both structures, the substituent in the oxazoline ring and the axial P-phenyl group point in the same direction. The only notable variation is the different rotational angle of the equatorial P-phenyl groups. However, in terms of energy, this difference is hardly significant. NMR studies of analogous P-(*o*-tolyl) derivatives show that the P-aryl groups rotate freely around the P−C bond, suggesting that the conformation of the phenyl groups is readily altered by minor effects such as crystal packing forces.

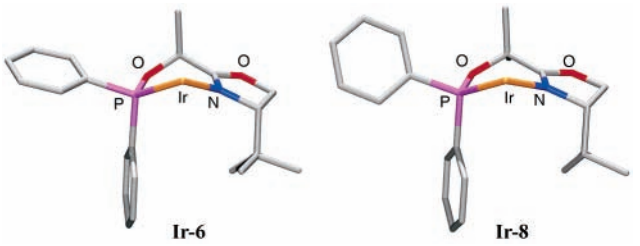


Figure 1. Comparison of the crystal structures of the cations of **Ir-6** (left) and **Ir-8** (right). COD and hydrogen atoms have been omitted for clarity.

The coordination geometry as well as the chiral pocket formed by the P,N-ligand are very similar in the two SimplePHOX complexes **Ir-6** and **Ir-8** and the PHOX complex **Ir-12** (see Table 3 and Supporting Information). However, compared to PHOX complexes, which form a rather rigid chelate ring due to the geometric constraint of the bridging phenyl group, the chelate ring in analogous phosphinite ligand complexes such as **Ir-6**, **Ir-8**, or **Ir-11** is more flexible. NMR and X-ray studies of complex **Ir-11** and related derivatives show that the energetic differences between different boat- and chairlike conformations are small. In some phosphinite complexes, a chairlike conformation of the chelate ring is actually preferred in the solid state.[4c] Therefore, it seems dangerous to draw conclusions concerning the enantioselectivity induced by a particular precatalyst on the basis of crystal structure data.

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(7) Complex **Ir-11** is commercially available from Strem, Inc.

(8) Wüstenberg, B. Ph.D. Dissertation, University of Basel, Basel, Switzerland, 2003.

Table 3. Comparison of Structural Parameters in Crystal Structures of Ir Complexes[a]

complex	**Ir-6**	**Ir-8**	**Ir-12**
R/R_w [%]	4.3/4.8	3.1/3.6	6.0/6.8
Ir−N [pm]	208.8(4)	208.7(3)	211.9(7)
Ir−P [pm]	224.9(1)	223.9(1)	226.6(3)
P−O/P−C [pm][b]	161.1(4)	160.7(4)	182.0(9)
∠P−Ir−N [deg]	85.6(1)	85.1(1)	85.0(2)
Ir−(C═C) trans to P [pm][c]	212	211	211
Ir−(C═C) trans to N [pm][c]	201	202	202

[a] Parameters are averaged for independent crystallographic moieties present in the unit cell. Crystallographic estimated standard deviations are given in parentheses. [b] P−C bond in the chelate ring of **Ir-12**. [c] Distances between iridium and the C═C bonds.

The Ir−P and Ir−N bonds, as well as the distances between Ir and the C═C bonds of the COD ligand, are remarkably similar in length in the two SimplePHOX complexes **Ir-6** and **Ir-8** and the PHOX complex **Ir-12** (Table 2), suggesting that the electronic properties of the phosphine and phosphinite ligands are comparable.

In summary, we have developed a readily accessible class of chiral modular P,N-ligands consisting of a chiral oxazoline ring tethered to a phosphinite group. These ligands, which are prepared in just two steps from simple starting materials, induce high enantioselectivities in the iridium-catalyzed hydrogenation of olefins. Particularly high ee values of 94−97% were obtained in the hydrogenation of a cyclic unfunctionalized alkene, an acrylic ester, and an allylic alcohol. Our results indicate a considerable potential of this ligand class in asymmetric catalysis.[9]

Acknowledgment. We thank Markus Neuburger and Dr. Silvia Schaffner, University of Basel, for X-ray crystallographic analyses. Financial support by the Swiss National Science Foundation, the Federal Commission for Technology and Innovation (KTI Project No. 5189.2 KTS), and Solvias AG (Basel) is gratefully acknowledged. S.P.S. thanks the Gottlieb Daimler and Carl Benz Foundation and the German Academic Exchange Service (DAAD) for Ph.D. fellowships. F.M. thanks the Fonds der Chemischen Industrie (Frankfurt) and the German Federal Ministry for Science and Technology (BMBF) for a Kekulé Fellowship.

Supporting Information Available: Experimental procedures, characterization of unknown compounds, references to known compounds, tables, and additional figures for the X-ray crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Ligand **7** and catalyst **Ir-7** will be soon available from Strem, Inc.