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Chiral Phosphinopyrrolyl-Oxazolines: A New Class of Easily Prepared, Modular P,N-Ligands

Pier Giorgio Cozzi,[a,]* Nicole Zimmermann,[b] Robert Hilgraf,[b] Silvia Schaffner,[b]
Andreas Pfaltz[b,]*

[a] Dipartimento di Chimica "G.Ciamician", Via Selmi 2, 40126 Bologna, Italy
Fax: (+39) 51–209–9456, e-mail: pgcozzi@ciam.unibo.it
[b] Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland
Fax: (+41) 61–267–1103, e-mail: Andreas.Pfaltz@unibas.ch

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Abstract: Chiral 2-(*N*-phosphinopyrrol-2-yl)oxazolines (PyrPHOX ligands) are readily prepared from 2-cyanopyrrole by condensation with a chiral amino alcohol and subsequent reaction with dialkyl- or diaryl-chlorophosphines. Iridium complexes of these ligands proved to be highly efficient catalysts for the enantioselective hydrogenation of olefins. With unfunctionalized arylalkenes and ethyl cinnamate enantiomeric excesses of 70–99% were obtained.

Keywords: asymmetric catalysis; allylation; hydrogenation; iridium; palladium; phosphinooxazolines

Chiral P,N-ligands are used in a multitude of enantioselective catalytic reactions.[1] Among these, phosphinooxazolines (PHOX ligands, Figure 1)[2] represent a class of versatile and modular ligands, which have been successfully applied in many different transition metal-catalyzed processes.[3] PHOX ligands are readily accessible from chiral amino alcohols by several convenient routes[2,3] and, consequently, a wide variety of different derivatives has been prepared.

The electronic influence of the ligand on a coordinated metal strongly depends on the substituents at the phosphorus atom. For certain applications, PHOX ligands containing phosphorus units with electron-withdrawing substituents, such as bis(pentafluorophenyl)phosphine or phosphite groups, proved to be superior to the standard diarylphosphinooxazolines.[3] As *N*-pyrrolylphosphines are known to have strong π-acceptor properties,[4–6] we envisioned that incorporation of such a structural element into a phosphinooxazoline might result in useful new ligands. Herein, we report the synthesis of a series of pyrrole-derived phosphinooxazolines, PyrPHOX (Figure 1), and their application to palladium-catalyzed allylic alkylations, and iridium-catalyzed hydrogenations of olefins.

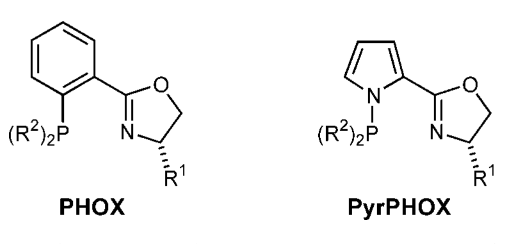
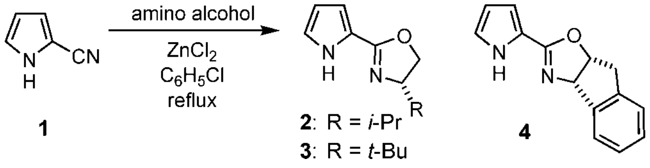
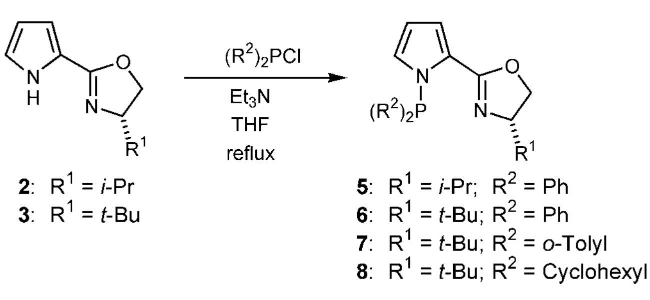


Figure 1. Structures of phosphinooxazoline (**PHOX**) and phosphinopyrrolyloxazoline (**PyrPHOX**) ligands.

The synthesis of PyrPHOX ligands starts from the known pyrrolyloxazolines, which are readily prepared from commercially available 2-cyanopyrrole in one step, as described by Brunner[7] (Scheme 1).[8] Reaction of **2** or **3** under the conditions reported by Moloy[4,5] (Scheme 2) with different chlorophosphines [diphenyl-, bis(*o*-tolyl)-, dicyclohexylchlorophosphine] afforded the PyrPHOX ligands **5 – 8** in 30 – 70% yield[9]. It is noteworthy that relatively mild,



Scheme 1. Synthesis of pyrrolyloxazolines **2** – **4** according to ref.[7].



Scheme 2. Synthesis of PyrPHOX ligands **5** – **8**.

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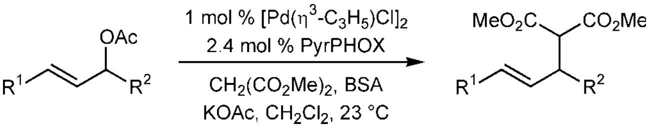
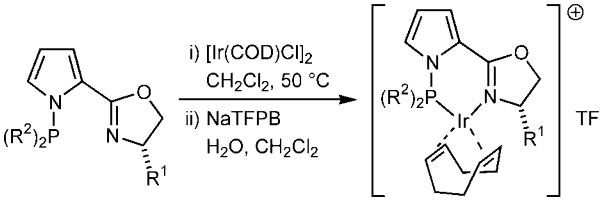
weakly basic conditions can be used to introduce the phosphine unit, in contrast to the synthesis of PHOX ligands, which involves metal phosphides or metalated aryl intermediates. Unfortunately, PyrPHOX ligands are sensitive to hydrolysis and attempts to purify them by chromatography resulted in cleavage of the P-N bond, giving back the starting pyrrolyloxazolines. However, ligands **5 – 8** could be isolated using standard Schlenk techniques by precipitation from a mixture of pentane/Et_2O.[10]

Ligands **5 – 8** were tested in palladium-catalyzed allylic alkylations[1–3,11–13] with dimethyl malonate (Scheme 3 and Table 1). With 3-phenylallyl acetate moderate to good enantioselectivities were obtained (Entries 5 – 8), while the enantiomeric excesses with the other two substrates were disappointing. A higher tendency towards formation of the branched regioisomer was observed than with PHOX ligands (Figure 1), which give almost exclusively the linear product.[12] In this respect, the PyrPHOX ligands resemble phosphite-oxazolines[12] and bis(*N*-tosylamino)phosphinooxazolines,[13] two classes of ligands which have been previously developed for the enantio- and regiocontrol in allylic alkylations of this type. As observed for other P,N-ligands,[12,13] the branched/linear ratio strongly depends on the substituents near the coordination sphere and is almost completely reversed when the two *P*-phenyl groups of ligand **6** are replaced by *o*-tolyl groups (Entries 6 and 7).

Much more promising results were obtained in the iridium-catalyzed hydrogenation of olefins, a reaction for which Ir-PHOX complexes have proven to be highly efficient catalysts.[14,15] In non-coordinating solvents such as dichloromethane or toluene, cationic iridium(I)-PHOX complexes with tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (BARF or TFPB) as the counterion react with unfunctionalized alkenes with high turnover frequencies and turnover numbers, in contrast to rhodium- and ruthenium-diphosphine catalysts which generally show very low catalytic activity toward such olefins. The choice of TFPB as counterion is crucial because it strongly enhances the lifetime of the catalyst, allowing the use of substrate/catalyst ratios of >1000. Analogous hexafluorophosphate or tetrafluoroborate salts lose catalytic activity during the reaction, resulting in incomplete conversion at low catalyst loadings. The best enantioselectivities (up to 99% ee) have been recorded for 1,2-diaryl-1-alkyl-substituted alkenes, while other olefins such as monoaryl-1,2-dimethyl-substituted alkenes afford only moderate enantiomeric excesses,



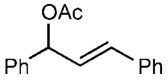
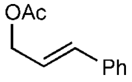
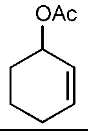
Scheme 3. Enantioselective palladium-catalyzed allylic alkylation using PyrPHOX complexes **5** and **6** (see Table 1).



5	R^1 = *i*-Pr; R^2 = Ph	**9**
6	R^1 = *t*-Bu; R^2 = Ph	**10**
7	R^1 = *t*-Bu; R^2 = *o*-Tolyl	**11**
8	R^1 = *t*-Bu; R^2 = Cyclohexyl	**12**

Scheme 4. Preparation of iridium-PyrPHOX complexes **9 – 12**.

Table 1. Enantioselective allylic alkylation using PyrPHOX ligands **5–8**.[a]

Entry	Substrate	Ligand	Conv. [%][b]	ee [%][c]	Branched:Linear
1		5	100	72 (*S*)	
2		6	100	20 (*S*)	
3		7	100	19 (*S*)	
4		8	100	3 (*S*)	
5		5	100	71 (*S*)	16:84
6		6	100	75 (*S*)	20:80
7		7	100	81 (*S*)	69:31
8		8	100	92 (*S*)	56:44
9		5	49	21 (*R*)	
10		6	91	41 (*R*)	
11		7	100	37 (*R*)	
12		8	100	11 (*R*)	

[a] Experimental procedure and analysis of the products: see refs.[2,11,12].

[b] Determined by GC.

[c] Determined by GC or HPLC using chiral columns, see refs.[2,11,12].

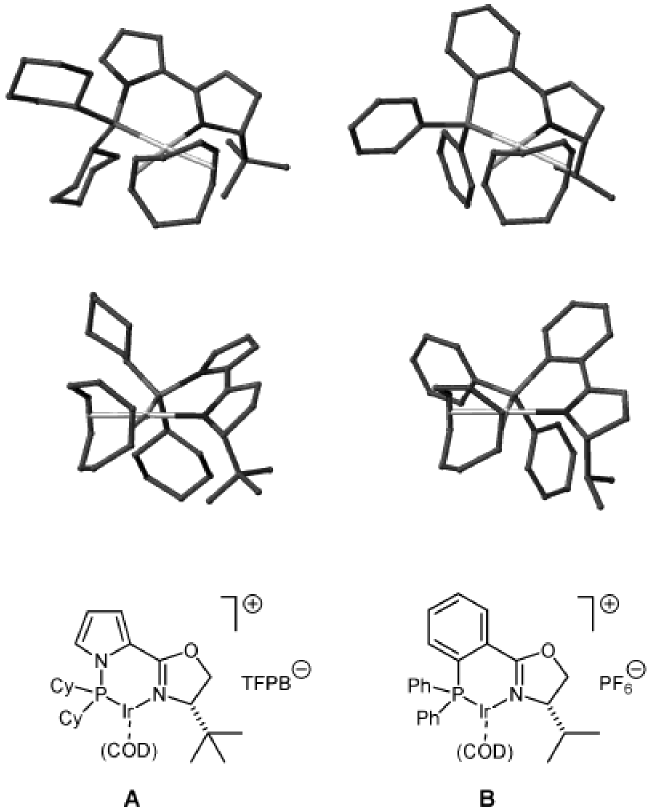
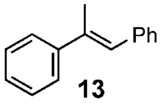
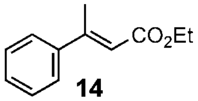
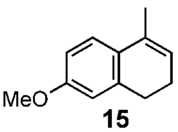
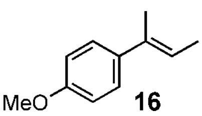
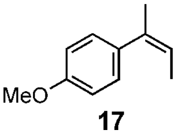


Figure 2. Crystal structures of the iridium-PyrPHOX complex **12** (**A**)[16] and an analogous PHOX complex (**B**)[17] (the anions have been omitted for clarity).

Table 2: Enantioselective hydrogenation of olefins with iridium catalysts **9–12**.[a]

Entry	Olefin	Catalyst	Conv. [%][b]	ee [%][c]
1	 **13**	**9**	100	81 (*R*)
2		**10**	100	91 (*R*)
3		**11**	100	99 (*R*)
4		**12**	100	99 (*R*)
5		PHOX[d]	100	99 (*R*)
6	 **14**	**9**	99	91 (*R*)
7		**10**	90	91 (*R*)
8		**11**	99	92 (*R*)
9		**12**	99	90 (*R*)
10		PHOX[e]	86	84 (*R*)
11	 **15**	**9**	84	52 (*S*)
12		**10**	73	37 (*S*)
13		**11**	100	92 (*S*)
14		**12**	100	90 (*S*)
15		PHOX[e]	100	61 (*S*)
16	 **16**	**9**	100	64 (*R*)
17		**10**	100	72 (*R*)
18		**11**	100	56 (*R*)
19		**12**	100	75 (*R*)
20		PHOX[e]	100	61 (*R*)
21	 **17**	**9**	100	44 (*S*)
22		**10**	100	27 (*S*)
23		**11**	100	59 (*S*)
24		**12**	100	70 (*S*)
25		PHOX[e]	100	42 (*S*)

[a] All reactions were performed using 0.2 mmol of substrate, 1 mol % of catalyst, 0.5 mL of dichloromethane at 50 bar of hydrogen pressure at rt. (reaction time: 2 h).

[b] Determined by GC.

[c] Determined by HPLC using chiral columns (see refs.[14,15]).

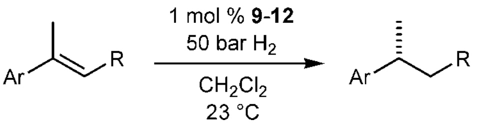
[d] Result from ref.[15]; catalyst: [Ir(PHOX)(COD][TFPB] (R^1 = *t*-Bu, R^2 = cyclohexyl).

[e] Results from refs.[14,15]; catalyst: [Ir(PHOX)(COD][TFPB] (R^1 = *t*-Bu, R^2 = *o*-tolyl).

making the search for other P,N-ligands highly pertinent.

Iridium-PyrPHOX complexes are readily prepared by the standard procedure shown in Scheme 4.[14,15] Unlike the free ligands, the complexes **9** – **12** are stable to air and moisture. We were able to obtain crystals of the iridium-PyrPHOX complex **12**, which were suitable for an X-ray analysis (Figure 2).[16]

Comparison of the crystal structures of the Ir-PyrPHOX and an analogous PHOX complex[17] reveals some distinct differences. The angle constraints imposed by the pyrrole ring result in a flattening of the chelate ring. The plane defined by the pyrrole ring forms a smaller angle with the (P-Ir-N) coordination plane than the corresponding plane defined by the phenyl backbone in the PHOX complex (20° vs. 42°). As a consequence, the geometries of the phosphine groups differ substantially. The P-C bond to the equatorial phenyl group in the PHOX complex, which is thought to play a crucial role in chirality transfer,[3] is located approximately in the coordination plane, while the corresponding P-C bond to the cyclohexyl group in the PyrPHOX complex sticks out of the coordination plane. These geometrical dissimilarities suggest that the steric properties of PyrPHOX and PHOX ligands are quite different even when the substituents at the oxazoline ring and the phosphorous atom are identical.



Scheme 5. Enantioselective hydrogenation of olefins catalyzed by iridium-PyrPHOX complexes **9** – **12** (see Table 2).

Iridium-PyrPHOX complexes **9–12** were tested in the enantioselective hydrogenation of five different olefins (Scheme 5).[18] All complexes exhibited high catalytic activity comparable to the analogous PHOX complexes. In the reaction of (*E*)-1,2-diphenylpropene (**13**) excellent enantioselectivities (up to 99% ee) were obtained, as with the best PHOX ligands (Table 2; Entries 3 – 5). With all other substrates the enantiomeric excesses surpassed those previously obtained with PHOX ligands.[14,15] For methyl cinnamate (**14**) the enantiomeric excess could be improved from 84% to 92% (Entries 7 – 10), and for the cyclic substrate **15** from 61% to 92% (Entries 13 – 15). Substantially higher enantioselectivities were also obtained with the (*E*)- and (*Z*)-alkenes **16** and **17** (Entries 19 and 24). In general, complexes **11** and **12**, containing a *tert*-butyl group on the oxazoline ring and *o*-tolyl or cyclohexyl substituents on the phosphorus atom, were the most selective catalysts, in line with the findings for analogous PHOX complexes.

Our results show that PyrPHOX ligands are a useful new variant of the phosphinooxazolines, with different electronic and steric properties. In the iridium-catalyzed hydrogenation of a number of olefins, PyrPHOX ligands induced significantly higher enantioselectivities than analogous phosphinooxazolines. Application of these new ligands to other transition metal-catalyzed processes is currently under investigation.

Experimental Section

Synthesis of (4*S*)-2-[(*N*-(Diphenylphosphino)-pyrrol-2-yl]-4-isopropyl-4,5-dihydrooxazole (5)

(4*S*)-2-(Pyrrol-2-yl)-4-isopropyl-4,5-dihydrooxazole[7] (1.13 g, 6.46 mmol) was dissolved in THF (30 mL) and distilled Et_3N (0.95 mL, 6.46 mmol) followed by Ph_2PCl (1.2 mL, 6.65 mmol) were added at room temperature. The reaction mixture was heated at reflux for two hours and, after cooling to rt., filtered under nitrogen. The solvent was evaporated under reduced pressure to give a crude oil. After addition of pentane (20 mL) and Et_2O (2 mL) crystallization of the oil was induced by scraping with a spatula. Further 10 mL of pentane were added and the suspension was stirred for 30 minutes. The product was obtained as a white solid by filtration under nitrogen; yield: 65%; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.65 [d, *J* = 6.6 Hz, 3H, $CH(CH_3)_2$], 0.66 [d, *J* = 6.4 Hz, 3H, $CH(CH_3)_2$], 1.51 – 1.68 [sept, *J* = 6.5 Hz, 1H, $CH(CH_3)_2$], 3.91 (t, *J* = 7.65, 1H, H_2C), 4.06 – 3.95 (m, 1H, *H*C), 4.44 (dd, *J* = 7.8, 9.1 Hz, 1H, H_2C), 6.15 (br. s, 1H, H_{py}), 6.28 (br s, 1H, H_{py}), 6.9 (br s, 1H, H_{py}), 7.1 – 7.4 (m, 8H, H_{Ar}), 7.58 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.78 (dd, *J* = 7.8, 8.5 Hz, 1H, H_{Ar}); ^{31}P NMR (121 MHz, $CDCl_3$): δ = 50 (s).

Synthesis of {(4*S*)-2-[(*N*-(Diphenylphosphino)-pyrrol-2-yl]-4-isopropyl-4,5-dihydrooxazole}(η^4–1,5-cyclooctadiene)iridium(I) Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (9)

To an ampoule with a Young® valve was added under argon PyrPHOX-ligand **5** (77 mg, 0.21 mmol), $[Ir(COD)Cl]_2$ (72 mg, 0.11 mmol) and CH_2Cl_2 (2 mL). The valve was closed and the deep red solution was stirred at 50 °C for two hours. After cooling to rt. sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (282 mg, 0.32 mmol) was added, followed by 2 mL of water and the resulting two-phase mixture was stirred vigorously for 10 min. The layers were separated, the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts evaporated under reduced pressure. The orange solid was purified by chromatography (silica gel; CH_2Cl_2) to give complex **9** as a crystalline solid; yield: 209 mg (65%); $C_{62}H_{47}BF_{24}IrN_2OP$ (1526.07); mp 132 °C (dec.); $[\alpha]_D^{25}$: –99.3 (*c* 1.10, $CHCl_3$); R_f = 0.95 (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.16 [d, *J* = 6.6 Hz, 3H, $CH(CH_3)_2$], 0.85 [d, *J* = 7.1 Hz, 3H, $CH(CH_3)_2$], 1.51 – 1.68 [m, 2H, CH_2(COD) + $CH(CH_3)_2$], 1.73 – 1.83 [m, 1H, CH_2(COD)], 1.88 – 2.08 [m, 2H, CH_2(COD)], 2.36 – 2.59 [m, 4H, CH_2(COD)], 2.71 – 2.78 [m, 1H, C*H*(COD)], 3.18 – 3.24 [m, 1H, C*H*(COD)], 4.01 – 4.07 [m, 1H, $H_2C(5)$], 4.32 [dd, *J* = 9.1, 9.6 Hz, 1H, *H*C(4)], 4.44 [dd, *J* = 3.0, 9.6 Hz, 1H, $H_2C(5)$], 5.09 – 5.18 [m, 1H, C*H*(COD)], 5.28 – 5.36 [m, 1H, C*H*(COD)], 6.45 (t, *J* = 3.3 Hz, 1H, H_{Ar}), 6.92 – 6.95 (m, 1H, H_{Ar}), 7.27 – 7.33 (m, 3H, H_{Ar}), 7.51 (s, 4H, TFPB), 7.57 – 7.66 (m, 4H, H_{Ar}), 7.71 (s, 8H, TFPB); ^{31}P NMR (121 MHz, $CDCl_3$): δ = 61.7 (s); IR (KBr): ν = 2698w, 2359w, 2042w, 1608 m, 1516w, 1484w, 1439 m, 1423w, 1355s, 1278s, 1217w, 1126s, 1063w, 1000w, 961w, 887 m, 839 m, 744 m, 713 m, 682 m, 670 m cm^{-1}; MS (FAB): 663 (M^+); anal. calcd. for $C_{62}H_{47}BF_{24}IrNOP$: C 48.80, H 3.10, N 1.84; found: C 48.67, H 3.20, N 1.64.

General Hydrogenation Procedure

To a 60-mL autoclave with a glass inset and a magnetic stirrer was added substrate (0.20 mmol), catalyst (1 mol %), and 0.5 mL of dichloromethane (inert atmosphere is not necessary). The autoclave was sealed and pressurized to 50 bar with hydrogen. The reaction mixture was stirred for 2 h at rt, the pressure was released, and after evaporation of the solvent heptane (3 mL) was added. The resulting mixture was filtered through a syringe filter and the filtrate was directly analyzed by GC and chiral HPLC to determine the conversion and ee (for analytical procedures and data, see refs.[14,15]).

Acknowledgements

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[8] *N*-Phosphinoindolyloxazolines were also prepared, using a different route starting from indole-2-carboxylic acid (P. G. Cozzi, unpublished results).

[9] Analogous phosphines derived from **4** were found to be unstable and could not be isolated in pure form.

[10] Ligand **8** was obtained as an oil.

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