New Types of *o*-Carborane-Based Chiral Phosphinooxazoline (Cab-PHOX) Ligand Systems: Synthesis and Characterization of Chiral Cab-PHOX Ligands and Their Application to Asymmetric Hydrogenation

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Abstract: *o*-Carborane-based chiral phosphinooxazoline (Cab-PHOX) ligands were synthesized for the first time and applied to the iridium- and rhodium-catalyzed hydrogenation of unfunctionalized and functionalized olefins with an enantioselectivity of up to 98% and 96%, respectively. The modularity of the Cab-PHOX ligands is highlighted by the facile preparation of a variety of sterically and electronically different ligands.

Key words: chiral phosphinooxazoline ligands, *o*-carborane-based bidentate ligands, asymmetric hydrogenation, unfunctionalized olefins, functionalized olefins

Phosphinooxazolines (PHOX, Figure 1)[1] are efficient, non C_2-symmetric, chiral P,N-chelating classes of ligand that were first described by Pfaltz,[2] Helmchen,[3] and Williams.[4] Their development was inspired by Crabtree's catalyst [(COD)Ir(PCy_3)(py)][PF_6],[5] which features a phosphine and pyridine ligand in its coordination sphere. Crabtree's catalyst is highly active in catalytic hydrogenation reactions, particularly in highly substituted olefins. The PHOX ligands were used successfully in transition-metal-catalyzed asymmetric reactions such as the hydrogenations of olefins,[6] allylic alkylations,[7] Heck reactions,[8] and other processes.[9] The efficiency of the PHOX ligands has been in part attributed to their ability to create distinguishable coordination sites *trans* to the phosphorus and nitrogen donors, thereby enhancing the selectivity.[10] Modification of the PHOX ligands is mainly undertaken at the α-carbon to the oxazoline nitrogen,[11] the two aryl groups on phosphorus,[11] and the arene backbone.[12]

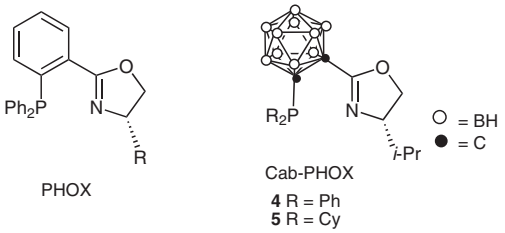

Figure 1 Chiral bidentate ligands PHOX and Cab-PHOX (**4**, **5**)

This paper reports a new class of *o*-carborane-based chiral PHOX ligands that are highly enantioselective for a wide range of substrates employing their iridium and rhodium complexes. Previously, we reported a systematic study of *o*-carborane-based chelating bidentate ligand systems as supporting ligands for metal complexes, such as C,N,[13] C,P,[14] S,P,[15] and Si,P.[16] Carboranes contain ten boron atoms in a small volume with a 3-dimensional peripheral size similar to that of a benzene molecule. Carborane ($C_2B_{10}H_{12}$) has three isomers, known as *ortho*- (1,2-$C_2B_{10}H_{10}$), *meta*- (1,7-$C_2B_{10}H_{10}$), and *para*-carborane (1,12-$C_2B_{10}H_{10}$), depending on the position of the two carbon atoms in the icosahedral cage framework; derivatives of these carboranes can be produced by replacing the acidic protons of one or both of the C–H units with other functional groups.[17] Therefore, it would be interesting to examine the possibility of transition-metal-catalyzed asymmetric reactions using *o*-carborane-based chiral bidentate PHOX ligand systems (Cab-PHOX, Figure 1). To the best of our knowledge, this is the first report of a P,N-chelating chiral Cab-PHOX ligand being a versatile ligand for metal-catalyzed asymmetric hydrogenation. Herein we report our results on the design and synthesis of a new class of *o*-carborane-based chiral PHOX ligands (**4** and **5**) starting from commercially accessible *o*-carborane, chlorodiphenyl- or chlorodicyclohexylphosphine, and L-valinol as a chiral amino alcohol, as well as their application to the iridium- and rhodium-catalyzed enantioselective hydrogenation of unfunctionalized and functionalized olefins.

New *o*-carborane-based chiral PHOX (Cab-PHOX, **4** and **5**) ligands were synthesized according to the mechanism shown in Scheme 1. The starting materials, phosphino-*o*-carboranes Cab^{PR2} (**1** R = Ph; **2** R = Cy)[18] and 2-bromo-4-isopropyl-oxazoline **3**,[19] can be prepared easily using the procedure reported in the literature. Cab^{PPh2} (**1**) or Cab^{PCy2} (**2**) was treated with 1.1 equiv of Bu^{n}Li followed by the addition of 1.1 equiv of 2-bromo-4-isopropyl-oxazoline (**3**) in THF at –78 °C (Scheme 1). The target Cab-PHOX ligands (**4** and **5**) were obtained in high yields (88–93%), which were subsequently transformed into their corresponding transition-metal complexes according to a mod-

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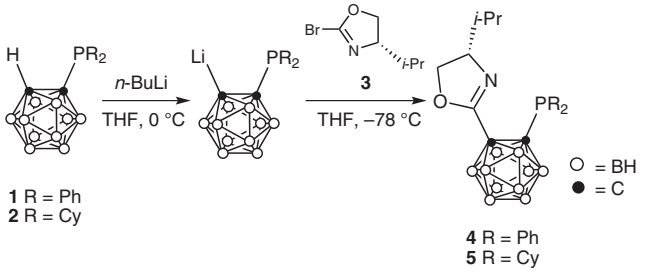


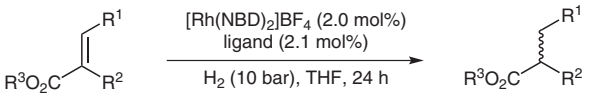
Scheme 1 Synthesis of new chiral Cab-PHOX ligands **4** and **5**

ification of the standard procedure (see Supporting Information).

Hydrogenation of α,β-unsaturated carboxylic acids and α-dehydroamino acid derivatives has been a typical reaction to test the efficiency of new chiral ligands. Indeed, a number of chiral phosphine ligands with great structural diversity are found to be effective for Rh-catalyzed hydrogenation of these acid derivatives.[20] Thus, in the first set of experiments, we performed the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives to benchmark the potential of **4** and **5** for asymmetric catalysis. Here, it is worth noting that there is virtually no precedence for the PHOX-type ligand to be employed in asymmetric hydrogenation of functionalized olefins such as those mentioned above. Hydrogenation was conducted under a H_2 pressure of 10 bar in the presence of 2 mol% of the catalysts prepared in situ from $[Rh(NBD)_2]BF_4$ and 2.1 mol% of chiral ligands (**4** and **5**), and the results are summarized in Table 1. The results are remarkable in that extremely high enantioselectivity (up to 96% ee) and catalytic activity are achieved. It should be pointed out that few systems have been reported on Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acids such as (*E*)-2-methylcinnamic acid (or ester), although some successful results have been obtained with Ru-based catalysts.[21] Enantioselectivity is a function of both substrates and ligands. Namely, of two substrates, (*E*)-2-methylcinnamate and (*Z*)-2-acetamidoacrylate, the latter gives the lower ee (%) and the lower chemical yield (entry 1 and 2). When the comparison is made between phosphine moieties (PPh_2 and PCy_2) the former gives higher ee (%) in the hydrogenation of (*E*)-2-methylcinnamate (entries 3–6).

Encouraged by the results shown in Table 1, we further pursued the Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins, **12**–**15**, which belong to a class of substrates that resist high enantioselectivity by conventional Ru- and Rh-phosphine-type catalysts.[22] Recently, however, a breakthrough has been made independently by Pfaltz[23] and Kim[24] who have demonstrated that Ir-complexes of PHOX or (iminophosphoranyl)ferrocenes can catalyze a variety of unfunctionalized olefins with very high enantioselectivities (up to 99% ee). The reaction was carried out in CH_2Cl_2 at room temperature for 24 hours under a H_2 pressure of 10 bar in the presence of 2 mol% of catalysts prepared in situ from $[Ir(cod)_2]BAr_F$

Table 1 Rh-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Functionalized Olefins[a]



6–8 **9–11**

Entry	Substrate	R^1	R^2	R^3	Ligand	Yield (%)[b]	ee (%)[c]
1	**6**	H	NHAc	Me	**4**	22	65 (*S*)
2					**5**	50	84 (*S*)
3	**7**	Ph	NHAc	Me	**4**	90	96 (*S*)
4					**5**	85	83 (*S*)
5	**8**	Ph	H	H	**4**	24	94 (*S*)
6					**5**	20	87 (*S*)

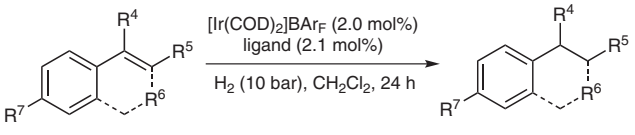
[a] Absolute configurations of the products are given in parentheses after the ee values. Conditions: H_2 pressure = 10 bar in all entries; all reactions performed at r.t. for 24 h; catalyst loading 2.0 mol% in all entries. All reactions were performed in freshly distilled THF.
[b] GC yield.
[c] Determined by chiral capillary GC on a Chiralsil-Val column (25 m) and the product configuration by a comparison with the literature values.

[BAr_F = tetrakis-3,5-bis(trifluoromethyl)phenylborate] and 2.1 mol% of **4** and **5**. The results are summarized in Table 2. Indeed, our systems demonstrate excellent enantioselectivity (up to 98% ee) and catalytic activity (up to 97%) regardless of the types of ligand or substrate. These results may well be compared with those obtained with Pfaltz's or Kim's Ir-systems for the hydrogenation of related trisubstituted nonfunctionalized olefins (see entry 9, Table 2 for comparison).[23,24] The steric bulkiness of substrate seems to play a minor role on chemical yields and ee (%) as deduced from Table 2. For instance, a dramatic decrease in both yield and ee (%) is observed with the substrate **12** that carries a bulky phenyl group. In addition, the size of the phosphine substituents, occupying the semi-hindered quadrant, is important for substrates, such as compounds **12** and **15** (entries 1, 2, 7, and 8, Table 2), where a change from phenyl to cyclohexyl leads to a slightly increase in enantioselectivity in both cases. Allylic alcohol **14** (entries 5 and 6, Table 2) worked exceptionally well for all Ir complexes.

In conclusion, we have developed a new class of readily available, *o*-carborane-based chiral PHOX ligands **4**[25] and **5**[26] for use as ligand for cationic Rh- and Ir-complexes in catalytic asymmetric hydrogenation. They provide a new entry into powerful catalysts for asymmetric hydrogenation a series of α,β-unsaturated carboxylic acids (or esters) and unfunctionalized olefins. In some cases they may even serve as practical catalysts.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 2 Ir-Catalyzed Hydrogenation of Unfunctionalized Olefins[a]



12–15 **16–19**

Entry	Substrate	R^4	R^5	R^6	R^7	Ligand	Yield (%)[b]	ee (%)[c]
1	**12**	Me	Ph	H	H	**4**	40	73 (*S*)
2						**5**	30	82 (*S*)
3	**13**	Me	CO_2Et	H	H	**4**	96	93 (*S*)
4						**5**	89	98 (*S*)
5	**14**	H	CH_2OH	CH_3	H	**4**	90	95 (*S*)
6						**5**	97	96 (*S*)
7	**15**	Me	H	$(CH_2)_2$	OMe	**4**	85	88 (*S*)
8						**5**	95	90 (*S*)
9	**12**	Me	Ph	H	H	**PHOX**	>99	99 (*S*)[d]

[a] Absolute configurations of the products are given in parentheses after the ee values. Conditions: H_2 pressure = 10 bar in all entries; all reactions performed at r.t. for 24 h; catalyst loading 2.0 mol% in all entries. All reaction performed in freshly distilled (CaH_2, ethanol free) CH_2Cl_2.
[b] GC yield.
[c] Determined by chiral capillary GC on a Chiralsil-Val column (25 m).
[d] The highest ee (%) obtainable with PHOX.[23f]

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(25) **Synthesis of Cab-PHOX 4**
To a stirred solution of Cab^{PPh2} **1** (0.99 g, 3.0 mmol) in 30 mL of THF, which was cooled to –10 °C, was added 2.5 M *n*-BuLi (1.2 mL, 3.0 mmol) via a syringe. The resulting solution was stirred at –10 °C for 1 h and then added 2-bromooxazoline **3** (0.63 g, 3.3 mmol) through a cannula. The reaction temperature was maintained at –10 °C for 1 h. Subsequently the reaction mixture was warmed slowly to r.t. After stirring for an additional 12 h, the solvent was removed

under vacuum, and the resulting residue was taken up by fresh column chromatography (R_F = 0.6; hexane–benzene, 1:1). Chiral Cab-PHOX **4** was isolated from the reaction solution in 93% yield (1.23 g, 2.8 mmol).
HRMS: *m/z* calcd for $[^{11}B_{10}{}^{12}C_{20}{}^{14}N^{1}H_{30}{}^{16}O^{31}P]^+$: 439.5421; found: 439.5432. Anal. Calcd: C, 54.65; H, 6.88; N, 3.19. Found: C, 54.85; H, 7.02; N, 3.12. IR spectrum (KBr pellet): ν = 2604 (B–H), 1700 (C=N), 2982 (C–H), 2990, 3014 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 [d, 3 H, $CH(CH_3)_2$, $^3J_{CH–CH3}$ = 6.6 Hz], 0.99 [d, 3 H, $CH(CH_3)_2$, $^3J_{CH–CH3}$ = 6.9 Hz], 1.92 [m, 1 H, $CH(CH_3)_2$], 4.16 (m, 1 H, CHN), 4.19 (t, 1 H, CH_2O, $^2J_{C–H}$ = 8.4 Hz), 4.45 (t, 1 H, CH_2O, $^2J_{C–H}$ = 8.1 Hz), 7.43–7.82 (m, 10 H, PPh_2). ^{11}B NMR (96.3 MHz, $CDCl_3$): δ = –3.12 (1 H), –5.74 (1 H), –8.93 (2 H), –12.49 (2 H), –14.02 (4 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.2, 18.6, 30.5, 67.3, 70.5, 73.8, 81.7, 126.3, 126.5, 127.1, 127.7, 128.3, 128.6, 129.2, 129.7, 130.7, 131.2, 131.6, 132.8, 168.5. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 12.7 (PPh_2).

(26) **Synthesis of Compound 5**
A procedure analogous to the preparation of compound **4** was used but instead starting from Cab^{PCy2} **2** (1.02 g, 3.0 mmol). Compound **5** was obtained as pale yellow oil (R_F = 0.5; hexane–benzene, 1:1; 1.19 g, 2.64 mmol, 88%).
HRMS: *m/z* calcd for $[^{11}B_{10}{}^{12}C_{20}{}^{14}N^{1}H_{42}{}^{16}O^{31}P]^+$: 451.6373; found: 451.6387. Anal. Calcd: C, 53.19; H, 9.37; N, 3.10. Found: C, 53.33; H, 9.34; N, 3.11. IR spectrum (KBr pellet): ν = 2600 (B–H), 1698 (C=N), 2985 (C–H), 2996 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 [d, 3 H, $CH(CH_3)_2$, $^3J_{CH–CH3}$ = 6.3 Hz], 0.97 [d, 3 H, $CH(CH_3)_2$, $^3J_{CH–CH3}$ = 6.9 Hz], 1.25 (m, 1 H, P-*cyclo*-CH), 1.35 (m, 2 H, P-*cyclo*-CH_2), 1.79 (m, 2 H, P-*cyclo*-CH_2), 1.86 (m, 1 H, CHN), 1.99 (m, 2 H, P-*cyclo*-CH_2), 3.97 (m, 1 H, CHN), 4.08 (t, 1 H, CH_2O, $^3J_{CH–CH2}$ = 8.7 Hz), 4.34 (t, 1 H, CH_2O, $^3J_{CH–CH2}$ = 9.3 Hz). ^{11}B NMR (96.3 MHz, $CDCl_3$): δ = –4.24 (1 B), –6.19 (1 B), –9.48 (2 B), –10.51 (2 B), –14.90 (4 B). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.7, 16.9, 23.1, 23.4, 25.4, 25.8, 27.4, 27.7, 29.9, 30.3, 30.8, 64.2, 70.4, 73.5, 84.3, 168.2. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 32.3 (PCy_2).