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Diamidophosphites with isomeric carborane fragments: a comparison of catalytic activity in asymmetric Pd-catalyzed allylic substitution reactions

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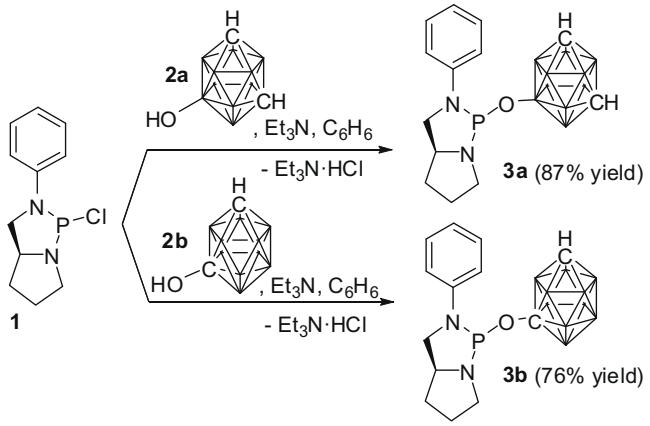
ABSTRACT

New chiral diamidophosphite ligands containing electron-donating 9-*meta*-carborane and electron-withdrawing 1-*meta*-carborane substituents have been synthesized. The ligand **3a** with an electron-donating group demonstrated high enantioselectivity in Pd-catalyzed allylic substitution reactions with C-, S- and N-nucleophiles (up to 98% ee). The isomeric diamidophosphite **3b** bearing an electron-withdrawing substituent showed in all cases, moderate-to-poor conversion and lower enantioselectivity.

Strategies for controlling the stereoselectivity and activity in catalytic reactions have usually relied on the design or manipulation of the steric environment of the catalytically active metal, but the electronic properties of the ligands can also exert a profound influence on the selectivity and rates of fundamental organometallic processes.[1–5] In asymmetric catalysis, variation of the electronic properties of the ligands has seldom been successfully exploited. Indeed, changing the donor/acceptor properties of similar ligands by the introduction of appropriate substituents leads to a simultaneous change in their steric properties, and this makes differentiation between the electronic and steric contributions of ligands to the enantioselectivity and activity of a catalyst difficult to estimate.[3,6–9] Recently, we designed the first examples of chiral mono- and bidentate phosphite-type ligands containing sterically congested carborane groups and reported their high efficiency in Rh-catalyzed asymmetric hydrogenation (up to 99.8% ee) and Pd-catalyzed allylic alkylation processes (up to 95% ee).[10–14] Also, we have taken advantage of these highly modular ligands to show that catalyst optimization can be performed easily by variation of the carbaboranyl substituents attached to the phosphorus atom.[12,13] No less important is the fact that even though all dicarba-*closo*-dodecaborane isomers (*ortho*, *meta* and *para*) have the same steric effect, each has very specific electronic properties depending on the position of the carborane cage substitution,[15] and thus, the influence of the electronic properties of the carborane substituent in related ligands on the enantioselectivity and conversion may be clearly studied.[12] In a programme aimed at the synthesis and application of carborane-containing ligands in asymmetric catalysis, we also sought to examine the effect of the electron-donating and electron-withdrawing properties of carborane substituents in asymmetric allylic substitution reactions.



Scheme 1. Synthesis of carborane-containing diamidophosphite ligands.

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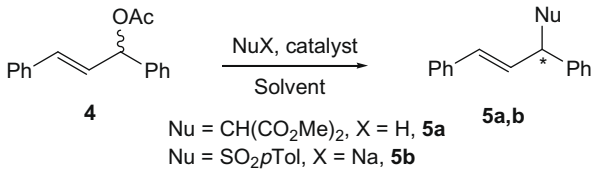
The new monodentate diamidophosphite ligands **3a,b** were synthesized by a convenient one-step phosphorylation of the corresponding 9-hydroxy-*meta*-carborane (**2a**) and 1-hydroxy-*meta*-carborane (**2b**) (Scheme 1). The ligands **3a,b** were characterized by ^{31}P, ^{13}C and ^{11}B NMR spectroscopy and by elemental analysis. The ligands are white solids and are air-stable under ambient conditions.

To examine the catalytic efficiency of these ligands, we first tested them in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**4**) with dimethyl malonate (Scheme 2). The results summarized in Table 1 show that the conversion and enantioselectivities proved to be dramatically influenced by the donor/acceptor character of the carboranyl substituent in the ligand structure. The Pd catalyst with ligand **3a** based on the donor 9-*meta*-carborane ($\delta_i = -0.12$)[15] exhibited high enantioselectivity (up to 98% ee) and high conversions (Table 1, entries 1 and 2). The electron-withdrawing 1-*meta*-carboranyl substituent ($\delta_i = +0.21$)[15] in ligand **3b** leads to a significant decrease in the conversion (Table 1, entries 3 and 4), and the enantiomeric excesses were also lower. It should be noted that in all cases, the best combination of activity and enantioselectivity was achieved with an L/Pd molar ratio of 2/1.

In the allylic sulfonylation of 1,3-diphenyl-2-propenyl acetate (**4**) with *p*-TolSO$_2$Na as the S-nucleophile, diamidophosphite **3a** again showed excellent activity and very good enantioselectivity (Scheme 2, Table 2, entries 1 and 2). The ligand **3b** bearing a strong electron-accepting 1-*meta*-carboranyl group led to a large decrease in the enantioselectivity and activity of the catalyst (Table 2, entries 3 and 4), compared to ligand **3a** containing the electron-donating 9-*meta*-carborane substituent.

To expand the utility of these diamidophosphites and to investigate further the influence of the carborane component, we also examined the Pd-catalyzed enantioselective allylic amination of 1,3-diphenyl-2-propenyl acetate (**4**) with di-*n*-propylamine and pyrrolidine (Scheme 3). The results in Table 3 show again that the enantioselectivity of the reaction is sensitive to the electronic effect of the carborane moiety, which further confirms the favourable influence of the electron-donating carboranyl group. The use of the 9-*meta*-carborane-derived ligand **3a** in the amination of **4** with di-*n*-propylamine gave the product **5c** in very good enantioselectivity, and excellent conversion was observed (Table 3, entries 1 and 2). In contrast, ligand **3b** bearing the electron-withdrawing 1-*meta*-carboranyl group showed very low activity, the enantioselectivities being moderate: 44 and 55% ee, depending on the L/Pd molar ratio.

We also screened ligands **3a** and **3b** in the closely related reaction of **4** with pyrrolidine (Scheme 3, Table 3). In this case, diamidophosphite **3a** provided high activity, but the enantioselectivity was lower compared to the amination with di-*n*-propylamine. It is interesting that in the amination with pyrrolidine, ligand **3b** bearing the electron-withdrawing substituent gave product **5d** with enantioselectivity close to that obtained with diamidophosphite **3a** having the electron-donating carborane group, when a molar ratio L/Pd = 1/1 was used. Nevertheless, the strong electron-withdrawing 1-*meta*-carboranyl group in ligand **3b** resulted in low activity, as was observed in all other cases.



Scheme 2. Pd-catalyzed allylic sulfonylation and alkylation of 1,3-diphenyl-2-propenyl acetate (**4**).

Table 1
Allylic alkylation with dimethyl malonate (CH_2Cl_2, BSA [*N,O*-bis(trimethylsilyl)acetamide], KOAc)[a]

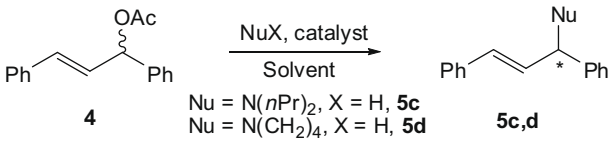
Entry	Ligand	L/Pd	Conversion[b] (%)	ee[b] (%)
1	**3a**	1/1	98	94 (*S*)
2	**3a**	2/1	97	**98 (*S*)**
3	**3b**	1/1	38	70 (*S*)
4	**3b**	2/1	49	92 (*S*)

[a] All the reactions were carried out with 2 mol % of $[Pd(allyl)Cl]_2$ at room temperature for 48 h.
[b] The conversion of substrate **4** and enantiomeric excess of **5a** were determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/*i*-PrOH = 99:1, 0.6 ml/min, 254 nm).

Table 2
Allylic sulfonylation with sodium *para*-toluenesulfonate (THF)[a]

Entry	Ligand	L/Pd	Yield (%)	ee[b] (%)
1	**3a**	1/1	97	87 (*S*)
2	**3a**	2/1	98	92 (*S*)
3	**3b**	1/1	30	30 (*S*)
4	**3b**	2/1	26	46 (*S*)

[a] All the reactions were carried out with 2 mol % of $[Pd(allyl)Cl]_2$ at room temperature for 48 h.
[b] Enantiomeric excess of **5b** was determined by HPLC (Daicel Chiralcel OJ, C_6H_{14}/*i*-PrOH = 4:1, 0.5 ml/min, 254 nm).



Scheme 3. Pd-catalyzed allylic amination of 1,3-diphenyl-2-propenyl acetate (**4**).

Table 3
Pd-catalyzed allylic amination of 1,3-diphenyl-2-propenyl acetate (**4**) with di-*n*-propylamine and pyrrolidine[a]

Entry	Ligand	L/Pd	Conversion (%)	ee (%)
Allylic amination with di-n-propylamine (THF)[b]				
1	**3a**	1/1	95	90 (+)
2	**3a**	2/1	100	83 (+)
3	**3b**	1/1	5	44 (+)
4	**3b**	2/1	8	55 (+)
Allylic amination with pyrrolidine (THF)[c]				
5	**3a**	1/1	100	75 (*R*)
6	**3a**	2/1	100	77 (*R*)
7	**3b**	1/1	21	74 (*R*)
8	**3b**	2/1	15	60 (*R*)

[a] All the reactions were carried out with 2 mol % of $[Pd(allyl)Cl]_2$ at room temperature for 48 h.
[b] The conversion of substrate **4** was determined by ^1H NMR spectroscopy. Enantiomeric excess of **5c** was determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/*i*-PrOH/$HNEt_2$ = 1000:1:1, 0.4 ml/min, 254 nm, $t(+) = 8.2$ min, $t(-) = 9.1$ min).
[c] The conversion of substrate **4** and enantiomeric excess of **5d** were determined by HPLC (Daicel Chiralcel OD-H, OD-H, C_6H_{14}/*i*-PrOH/$HNEt_2$ = 200:1:0.1, 0.9 ml/min, 254 nm).

In summary, new chiral diamidophosphite ligands containing isomeric carboranyl substituents have been synthesized. The ligand **3a** with the electron-donating 9-*meta*-carboranyl group demonstrated high enantioselectivity in the Pd-catalyzed allylic substitution reactions with C-, S- and N-nucleophiles (up to 98% ee), and complete-to-very high conversion of 1,3-diphenyl-2-propenyl acetate (**4**) was observed. The isomeric diamidophosphite **3b** bearing an electron-withdrawing substituent showed, in all cases, moderate-to-poor conversion and lower enantioselectivity.

All the reactions were carried out under a dry argon atmosphere in freshly dried and distilled solvents. Phosphorylating reagent **1** was prepared as described by us earlier.[6] 9-Hydroxy-*meta*-caborane (**2a**)[16] and 1-hydroxy-*meta*-caborane (**2b**)[17] were prepared as described. The Pd-catalyzed allylic substitution: sulfonylation of substrate **4** with sodium *para*-toluenesulfonate, alkylation with dimethyl malonate, amination with di-*n*-propylamine and pyrrolidine were performed according to the reported procedures.[6,7,18]

General procedure for the preparation of ligands **3a**,**b**: A solution of Et_3N (0.27 ml, 1.9 mmol) and the appropriate alcohol (0.291 g, 1.8 mmol) in benzene (8 ml) were added dropwise to a vigorously stirred solution of phosphorylating reagent **1** (0.433 g, 1.8 mmol) in benzene (8 ml). The mixture was heated to the boiling point and then cooled to 20 °C. Solid $Et_3N{\cdot}HCl$ was removed by filtration. The resulting solution was filtered through a short plug of silica gel, the solvent evaporated under reduced pressure (40 Torr) and the product dried in vacuo (1 Torr) for 1 h.

(2R,5S)-2-(meta-Carboran-9-yloxy)-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane **(3a)**: White powder; yield 0.57 g (87%); mp 124–126 °C. $^{31}P\{H\}$ NMR (162.0 MHz, $CDCl_3$, 25 °C): $\delta_P = 128.5$. $^{13}C\{H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta_C = 26.2$ [d, $^3J = 4.0$ Hz, C(7)], 31.5 [s, C(6)], 47.6 [d, $^2J = 35.7$ Hz, C(8)], 49.6 (s, $2CH_{carb}$), 53.2 [d, $^2J = 6.9$ Hz, C(4)], 62.5 [d, $^2J = 8.4$ Hz, C(5)], 115.1 (d, $^3J = 12.8$ Hz, CH_{Ar}), 118.4 (s, CH_{Ar}), 128.8 (s, CH_{Ar}), 145.6 (d, $^2J = 15.3$ Hz, C_{Ar}). $^{11}B\{H\}$ NMR (128.4 MHz, $CDCl_3$, 25 °C): $\delta_B = 6.7$ (s, 1B), −7.9 (s, 2B), −11.8 (s, 1B), −14.8 (s, 2B), −16.6 (s, 2B), −20.3 (s, 1B), −25.9 (s, 1B). MS (EI, 70 eV): *m/z* (%) = 364 (17) $[M]^+$, 259 (100). $C_{13}H_{25}B_{10}N_2OP$: calcd: C, 42.84, H, 6.91, N, 7.69; found: C, 43.03, H, 7.00, N, 7.64.

(2R,5S)-2-(meta-Carboran-1-yloxy)-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane **(3b)**: White powder; yield 0.50 g (76%); mp 111–114 °C. $^{31}P\{H\}$ NMR (162.0 MHz, $CDCl_3$, 25 °C): $\delta_P = 133.5$. $^{13}C\{H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta_C = 26.5$ [d, $^3J = 4.0$ Hz, C(7)], 31.2 [s, C(6)], 46.8 [d, $^2J = 40.8$ Hz, C(8)], 50.8 (s, $2CH_{carb}$), 53.1 [d, $^2J = 6.0$ Hz, C(4)], 62.3 [d, $^2J = 9.4$ Hz, C(5)], 115.1 (d, $^3J = 17.4$ Hz, CH_{Ar}), 119.6 (s, CH_{Ar}), 129.0 (s, CH_{Ar}), 144.5 (d, $^2J = 19.6$ Hz, C_{Ar}). $^{11}B\{H\}$ NMR (128.4 MHz, $CDCl_3$, 25 °C): $\delta_B = -4.7$ (s, 1B), −11.4 (s, 2B), −13.2 (s, 2B), −15.5 (s, 3B), −16.2 (s, 2B). MS (EI, 70 eV): *m/z* (%) = 364 (23) $[M]^+$, 259 (100). $C_{13}H_{25}B_{10}N_2OP$: calcd: C, 42.84, H, 6.91, N, 7.69; found: C, 42.96, H, 7.08, N, 7.60.

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