Chiral P*-monodentate phosphite ligand for Pd-catalysed asymmetric allylation reactions

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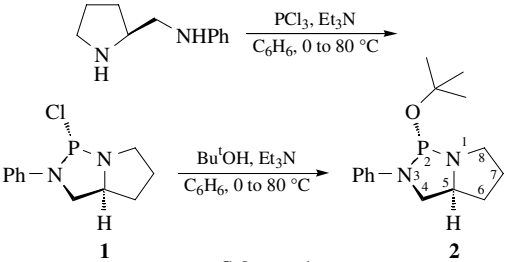
Monodentate diamidophosphite ligand **2** with stereogenic phosphorus and carbon atoms, which is easily available from (*S*)-2-phenylaminomethyl pyrrolidine, is an effective chiral inductor in Pd-catalysed asymmetric allylation reactions.

Transition metal catalysed asymmetric allylation reactions are one of the most powerful tools for the formation of carbon–carbon and carbon–heteroatom bonds. Palladium is usually a metal of choice in these processes with P,N- and P,P-bidentate ligands being the most common chiral inductors.[1] Very few examples of the application of P-monodentate ligands have been reported. Namely, several amidophosphinites[2] and phosphines[3–5] were tested in Pd-catalysed asymmetric allylation reactions resulting in the formation of C–C bonds, while amidophosphinites[6] were used for C–C and C–N bond formation. Note that all those ligands contained at least one P–C bond. Therefore, to the best of our knowledge, no examples of chiral monodentate phosphites applications to Pd-catalysed asymmetric allylation have been reported so far. It is quite strange because the presence of three P–N (or P–O) bonds in phosphite molecules provides excellent opportunities for the fine tuning of such important features as the π-acidity of ligands, their stability and steric demands. Remarkably, the latest impressive achievements in the enantioselective hydrogenation, conjugate addition and hydrosilylation/oxidation reactions are associated with monodentate phosphite ligands.[7] Moreover, the phosphite derivatives of BINOL have shown good results in the asymmetric allylation of cinnamyl acetate with dimethyl malonate, with $[Ir(COD)Cl]_2$ being used as a pre-catalyst.[8–10]

On the other hand, many P,N-bidentate phosphite ligands, including those prepared from (*S*)-2-phenylaminomethyl pyrrolidine,[11–14] have been successfully used in Pd-catalysed asymmetric allylation reactions.[1,7,15] In this report, we demonstrate that it is not necessary for the phosphite ligands to have any nitrogen-containing functionality, for example, quinoline[11] or oxazoline,[14] to achieve high enantioselectivity.

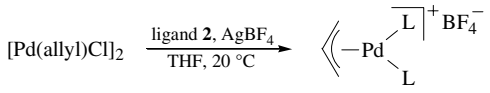
Ligand **2** was prepared from readily available (*S*)-2-phenylaminomethyl pyrrolidine[16] (Scheme 1).



1 **2**

Scheme 1

Intermediate (2*R*,5*S*)-2-chloro-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane **1**[14] was isolated in good yield (71%) and used for the synthesis of ligand **2** under mild conditions.† Both compound **1** and ligand **2** are stable in a dry atmosphere and, if needed, can be easily purified by distillation *in vacuo*. Ligand **2** has (*R*)-configuration of the P*-stereogenic centre, according to the characteristic $^2J_{C(8),P}$ value in its ^{13}C NMR spectra (35.5 Hz).[13,17] Starting from **2**, cationic Pd^{II} complex **3** was prepared (Scheme 2).‡



3

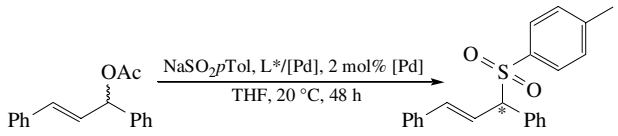
Scheme 2

Both ligand **2** and its complex **3** were tested in the Pd-catalysed asymmetric allylic sulfonylation reaction, as well as in the direct asymmetric synthesis of a carborane derivative.

The sulfonylation of 1,3-diphenylpropen-2-yl acetate with sodium *p*-toluenelsulfinate (Scheme 3) was carried out following the method described earlier.[14]

The obtained results are summarized in Table 1. Complex **3** was found to be the most effective catalyst providing 97% *ee* (entry 3). Remarkably, this is the highest enantioselectivity achieved in the reaction up to date (*v.* 93% *ee* obtained in the case of P,N-bidentate phosphinooxazoline ligands[18]).

The allylation reaction of methyl phenyl(2-phenyl-*ortho*-carboran-1-yl)acetate **4** with methyl prop-2-enyl carbonate (Scheme 4) is of interest as the first example of direct asymmetric synthesis in the carborane series.[19]



Scheme 3

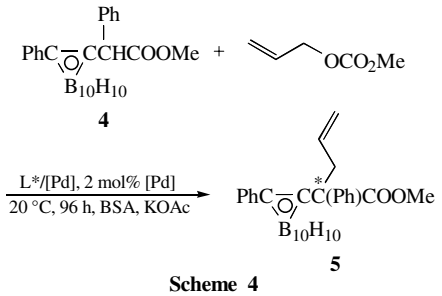
† *Preparation of compound* **2**. A solution of Bu^tOH (0.51 ml, 5.40 mmol) in benzene (3 ml) was added dropwise to a vigorously stirred solution of compound **1** (1.297 g, 5.40 mmol) and Et_3N (0.73 ml, 5.40 mmol) in benzene (8 ml) at 0 °C. The resulting mixture was warmed to 80 °C for a short time, then cooled down to 20 °C. The $Et_3N{\cdot}HCl$ solid was filtered off, and the filtrate was evaporated *in vacuo*. The residue was distilled *in vacuo* to obtain **2** as a colourless liquid (1.319 g, 88% yield). Bp 70–72 °C/1 Torr. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 145.77–115.45 (C_{Ar}), 74.29 (d, COP, $^2J_{C,P}$ 7.2 Hz), 62.46 [d, C(5), $^2J_{C,P}$ 8.0 Hz], 52.45 [d, C(4), $^2J_{C,P}$ 6.5 Hz], 47.83 [d, C(8), $^2J_{C,P}$ 35.5 Hz], 31.58 [s, C(6)], 30.73 (d, Me, $^3J_{C,P}$ 8.4 Hz), 25.95 [d, C(7), $^3J_{C,P}$ 4.6 Hz]. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 128.43. MS (EI, 70 eV), *m/z* (I, %): 278 $[M]^+$ (2), 221 $[M - Bu^t]^+$ (25), 205 $[M–Bu^tO]^+$ (6). Found (%): C, 64.52; H, 8.42; N, 10.28. Calc. for $C_{15}H_{23}N_2OP$ (%): C, 64.73; H, 8.33; N, 10.06.

‡ *Preparation of compound* **3**. A solution of ligand **2** (0.222 g, 0.8 mmol) in $CHCl_3$ (15 ml) was added dropwise to a stirred solution of $[Pd(Allyl)Cl]_2$ (0.073 g, 0.2 mmol) in the above solvent (15 ml) at 20 °C. The reaction mixture was stirred at 20 °C for 1 h and then a solution of $AgBF_4$ (0.078 g, 0.4 mmol) in THF (15 ml) was added. The solution was stirred for another 1 h at 20 °C, filtered, concentrated to ~0.5 ml, and precipitated with diethyl ether. The obtained precipitate was separated by centrifugation, washed with diethyl ether (2×10 ml) and dried in air and *in vacuo* (1 Torr). Yellow solid (0.316 g, 93% yield). Mp 172–174 °C. ^{31}P NMR (162 MHz, $CDCl_3$) δ_P: 106.16. ^{19}F NMR (188 MHz, $CDCl_3$) δ_F: –75.41. MS (FAB), *m/z* (I, %): 703 $[M - BF_4]^+$ (100), 662 $[M - BF_4 - allyl]^+$ (13). Found (%): C, 49.92; H, 6.38; N, 6.85. Calc. for $C_{33}H_{51}BF_4N_4O_2P_2Pd$ (%): C, 50.11; H, 6.50; N, 7.08.

Table 1 Enantioselective Pd-catalysed allylic sulfonylation of 1,3-diphenylpropen-2-yl acetate.

Entry	Catalyst precursor	L*/[Pd]	Isolated yield (%)	*ee*[a] (%)
1	$[Pd(allyl)Cl]_2$	1/1	32	94(*S*)
2	$[Pd_2(dba)_3{\cdot}CHCl_3]$	1/1	16	80(*S*)
3	**3**	2/1	44	97(*S*)

[a] *ee* measured by HPLC [(*R*,*R*)-Whelk-01].



Scheme 4

In addition, this is a relatively rare type of Pd-catalysed asymmetric allylation that produces a chiral centre not at the allyl moiety, but at the attacking nucleophile. The stereoselectivity of this allylation is difficult to control since the nucleophile approaches the allyl ligand of the intermediate η^3-allylpalladium complex from the side opposite to the transition metal atom and hence the chiral ligand.[19] The asymmetric reaction shown in Scheme 4 had been effected earlier using P,N-bidentate ligands,[13,19] the highest *ee* obtained up to date being 48%.[13] Our results obtained with ligand **2** and complex **3** are listed in Table 2. Note that in the case of complex **3** the enantioselectivity (about 70% *ee*) does not depend on whether THF or CH_2Cl_2 were used as the solvent. Furthermore, the same result was obtained when the catalyst was prepared from ligand **2** and $[Pd(allyl)Cl]_2$ *in situ*. The achieved enantioselectivity is rather high for the allylation reactions giving rise to the chiral centre at the attacking nucleophile.[19] Unfortunately, the reaction is very slow (the conversion of starting compound **4** was about 10% after 96 h in all cases),[§] but it is typical of such processes.[19]

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Table 2 Enantioselective Pd-catalysed allylation of carborane derivative **4**.

Entry	Catalyst precursor	L*/[Pd]	Solvent	*ee*[a] (%)
1	$[Pd(allyl)Cl]_2$	2/1	CH_2Cl_2	70
2	**3**	2/1	CH_2Cl_2	73
3	**3**	2/1	THF	68

[a] *ee* measured by HPLC [(*R*,*R*)-Whelk-01].

[§] *General procedure for the Pd-catalysed allylation of carborane derivative* **4**: To a solution of **3** (0.02 mmol) in 4 ml THF or CH_2Cl_2 {or to solution of $[Pd(allyl)Cl]_2$ (3.7 mg, 0.01 mmol) and ligand **2** (0.04 mmol) in 4 ml CH_2Cl_2 stirred for 20 min} ester **4** (185 mg, 0.5 mmol), methyl prop-2-enyl carbonate (0.12 ml, 1 mmol), BSA [*N*,*O*-bis(trimethylsilyl)acetamide, 0.15 ml, 0.6 mmol), and anhydrous KOAc (3 mg, 0.03 mmol) were added. The resulting homogeneous solution was kept at 20 °C for 96 h. The solvent was then removed *in vacuo*; the residue was dissolved in 30 ml of ether and washed with 5% HCl (2×20 ml), a saturated solution of $NaHCO_3$ (20 ml), and water. The organic layer was dried over Na_2SO_4, and the solvent was removed at a reduced pressure. The products were separated by column chromatography on silica gel [200×25 mm, eluent: petroleum ether–EtOAc (7:1)]. After removing the solvent, the obtained mixture of **5** and starting ester **4** was analysed by ^{1}H NMR spectroscopy.

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