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P,N-Bidentate aryl phosphite ligands based on chiral 2-imino-, 2-oxazolinyl and 2-oxazolidinyl phenols and their catalytic activity

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New P,N-hybrid aryl phosphites with distant imino, oxazolino and oxazolidino groups are effective chiral ligands in Pd-catalysed asymmetric allylic substitution reactions.

In asymmetric catalysis, chiral ligands induce stereoselectivity not only through steric factors but also by generating electronic asymmetry on the metal centre in the presence of different donor atoms.[1,2] A large number of chiral ligands with nitrogen and phosphorus functional moieties (P,N-ligands) has been prepared and their application to various transition metal-catalysed asymmetric reactions has been investigated.[1–7] The success of these mixed donor ligands arises from the fact that they are hemilabile ligands possessing a combination of hard and soft donor atoms. The π-acceptor character of phosphorus can stabilise a metal centre in a low oxidation state, while the nitrogen σ-donor ability makes the metal more susceptible to oxidative additions reactions. Therefore, different features associated with each donor atom provide a unique reactivity to the metal complexes.

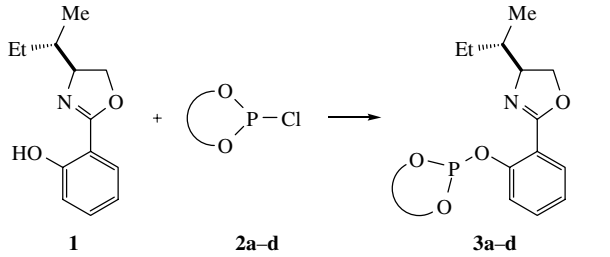
In comparison with traditional phosphines, optically active phosphites and amidophosphites seem to be more versatile ligands.[8–10] Therefore, P,N-bidentate ligands with three P–O and/or P–N bonds have become increasingly important during

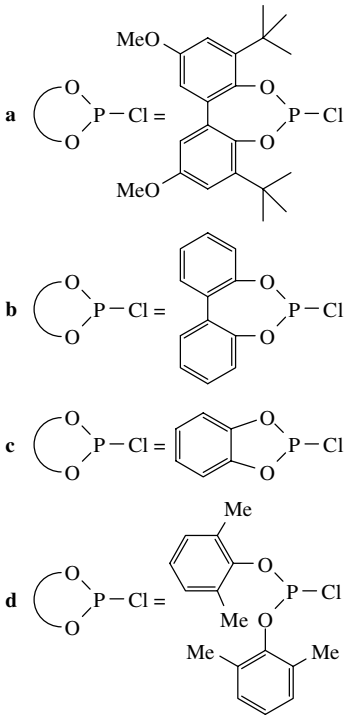
the last decade, and a wide range of such compounds have been synthesised.[1–3,6,7] At the same time, there are few examples of a direct comparison of catalytic activity of phosphites, which possess electronically almost identical P-centres, but differ substantially in steric demands of their P-containing fragment. There are also no examples of a direct comparison between P,N-bidentate ligands bearing the same phosphorus centre but different N-containing fragments (imine, oxazoline and oxazolidine) derived from one chiral synthone.

New P,N-bidentate aryl phosphites were synthesised by direct phosphorylation† of corresponding chiral 2-imino-, 2-oxazolinyl and 2-oxazolidinyl phenols.‡ Thus, **3a–d** were prepared starting from 2-[(*S*)-4-*sec*-butyl-4,5-dihydrooxazol-2-yl]phenol **1**[17] (ligand **3d** was described earlier[18]) (Scheme 1).

Being structural isomers, **5a**,**b** (Scheme 2) can be compared with **3d**: **5a** contains an 'opened oxazoline' fragment, and **5b** has a corresponding oxazolidine substituent. Note that **5b** is the only representative of a new group of P,N-ligands, oxazolidinophosphites.

All new ligands (**3a–d** and **5a**,**b**) were derived from the same chiral synthone, (*S*)-iso-leucinol [(2*S*,3*S*)-2-amino-3-methylpentan-1-ol], which is readily available by reduction of isoleucine.[19] Compounds **3a–d** and **5a**,**b**§ are readily soluble in common aprotic solvents and stable under dry conditions.

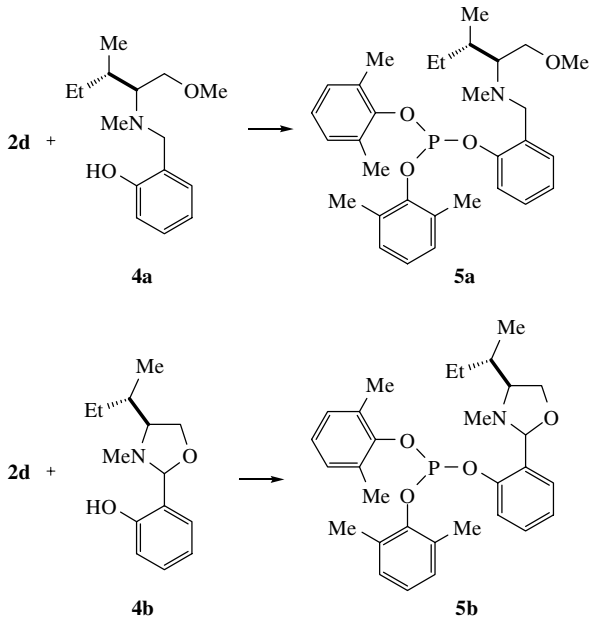




Scheme 1

† *General procedure*. A solution of an appropriate chlorophosphite (**2a**, **2b**,[11] **2c**[12] or **2d**;[13] 4.2×10^{-3} mol) in benzene (15 ml) was added dropwise to a stirred solution of a corresponding 2-functionalised phenol (**1**, **4a** or **4b**; 4.2×10^{-3} mol) and Et_3N (0.6 ml, 4.2×10^{-3} mol) in the same solvent (15 ml) at 0 °C. The reaction mixture was then heated to boiling, allowed to cool down, stirred for 0.5 h at 50 °C, allowed to cool to room temperature and filtered. The solvent was removed in a vacuum (40 Torr), and the residue was dried in a vacuum (1 Torr, 2 h).

‡ Syntheses of 2-{(*E*)-[(2*S*,3*S*)-1-methoxy-3-methylpentan-2-ylimino]-methyl}phenol **4a** and 2-[(4*S*)-4-*sec*-butyl-3-methyloxazolidin-2-yl]-phenol **4b** are analogous to the previously described procedures.[14–16]



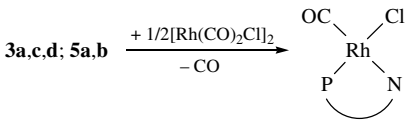
Scheme 2

Chelate chlorocarbonyl Rh^{I} complexes were obtained¶ with **3a**,**c**,**d** and **5a**,**b** (Scheme 3).

Important spectroscopic data of the complexes are summarised in Table 1. The ν(CO) and ^1J(P,Rh) parameters in the IR and ^{31}P NMR spectra act as sensitive indicators, which characterise the mode of complexation of the P,N-ligands and allow us to make a conclusion on the electronic properties of donor centres.[1,15,20] The values of ν(CO) and ^1J(P,Rh) for compounds **6a**,**c**,**d** and **7a**,**b** clearly indicate the strong π-acceptor ability of phosphorus centres in ligands **3a**,**c**,**d** and **5a**,**b** and also show that all these ligands have similar electronic characteristics.[15,21,22] Two doublet signals in the ^{31}P NMR spectrum of **6a** indicate the presence of two atropisomers of **6a**, like in the case of oxazolinophosphite **3a**. In the ^{31}P NMR spectra of **7a**,**b**, besides major peaks (Table 1), some additional signals are visible: δ 114.6, ^1J(P,Rh) 298.4 Hz (10%) and δ 113.4, ^1J(P,Rh) 302.9 Hz (15%) for **7a**; δ 122.9, ^1J(P,Rh) 283.6 Hz (25%) and δ 110.6 Hz, ^1J(P,Rh) 300.1 Hz (37%) for **7b**. This can be explained by the occurrence of three or more conformers of compounds **7a**,**b** (see refs. 15 and 23).

Analogously to complexation with Rh^{I}, the new P,N-hybrid aryl phosphites form metal chelates with Pd^{II} (Scheme 4).††

Duplication of peaks in the ^{31}P NMR spectra‡‡ of compounds **8d** and **9b** (Table 1) indicates the presence of their *exo*- and

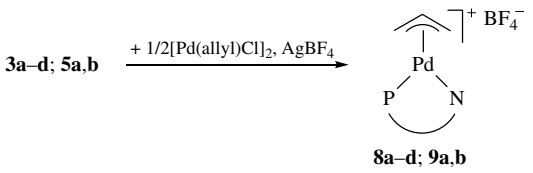


Scheme 3

§ All compounds gave spectroscopic and analytical data consistent with the proposed structures, for example: (4″*S*)-2-[2′-(4″-*sec*-butyl-2″-oxazolin-2″-yl)phenoxy]di(*o*-*tert*-butyl-*p*-methoxybenzo)[*d*,*f*][1,3,2]-dioxaphosphepine **3a**: yellow oil (2.3 g, 91% yield). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 164.0, 161.2 (C=N), 156.0–112.7 (C_{Ar}), 71.2, 70.0 (CHN), 69.3, 69.2 (CH_2O), 55.5, 55.4, 55.3, 55.2 (MeO), 39.2, 39.1 (*C*HMe), 35.3, 35.2, 35.1, 35.0 (*C*Me$_3$), 30.9, 30.4 (C*Me*$_3$), 25.9, 25.7 (*C*H_2Me), 14.9, 14.8 (CH*Me*), 11.3, 11.1 (CH_2*Me*). ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 139.1 (54%), 135.4 (46%). MS (EI, 70 eV), *m*/*z* (I, %): 605 [M]$^+$ (10), 521 (100), 162 (95). Found (%): C, 69.58; H, 7.45; N, 2.12. Calc. for $C_{35}H_{44}NO_6P$ (%): C, 69.40; H, 7.32; N, 2.31.

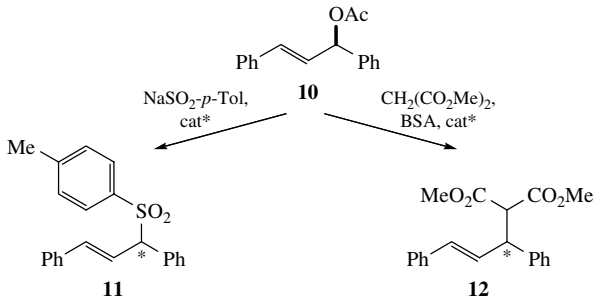
¶ Rhodium complexes **6a**,**c**,**d** and **7a**,**b** were synthesised for ^{31}P NMR and IR experiments in chloroform analogously to published procedures.[15]

†† Syntheses of cationic palladium complexes **8a–d** and **9a**,**b** were performed as reported earlier.[23]



Scheme 4

endo-isomers.[18,23] These isomers were not isolated as individual compounds. This was not observed for complexes **8a–c** and **9a** because of either the fast interconversion of the isomers or the absence of one of the isomers. Like in the case of **3a** and **6a**, duplication of ^{31}P NMR peaks of **8a** is caused by the presence of two atropisomers. Analogously to rhodium complexes **7a**,**b**, palladium chelates **9a**,**b** are also represented by several conformers and, therefore, have additional signals in their ^{31}P NMR spectra: δ 128.1, 126.0, 124.1 (45%) for **9a**; δ 129.9 (16%) for **9b**. These signals can be rationalised by non-selective chelation resulting in small amounts of [Pd(allyl)(η^2-P^N)(η^1-P^N)]BF_4 complexes with various Pd/L molar ratios.[23] Noteworthy, **8c** is rather unstable since its ^{31}P NMR spectrum contains peaks of destruction products in the range δ 16.7–11.6, which become visible after a few hours after dissolution and increase in intensity with time.



Scheme 5

Tables 2 and 3 display the results of enantioselective Pd-catalysed allylic substitution[§§] (Scheme 5) using P,N-bidentate aryl phosphites **3a–d**; **5a**,**b** and cationic palladium complexes **8a–d** and **9b**. Complex **9a** was not used because of a large number of its conformers (see above).

The best results in allylic sulfonylation were achieved with **3d** (up to 92% ee, Table 2, entries 10–12).[18] The rest of the ligands gave only moderate optical (up to 63% ee for **8a**, entry 3) and chemical yields of product **11**. Low yields of compound **11** are caused by low conversion, no by-products being observed. Enantioselectivity significantly depends on steric hindrances of ligands: for less bulky **3b** and **3c** it was much lower than for sterically hindered **3a** (electronic properties of all the ligands are very similar). Notably, acyclic iminophosphite **5a** provides no conversion, while its isomer, oxazolidinophosphite **5b**, is a good chiral inductor (up to 54% ee, entry 15), though still not so enantioselective as oxazolinophosphite **3d**. A dramatic decrease in optical yield while increasing the molar ratio L*/[Pd] from 1/1 to 2/1(entries 15 and 16) can be explained by breaking the chelate metal cycle.

In allylic alkylation (Scheme 5), almost all aryl phosphites gave high enantioselectivity (77–98% ee, Table 3). In contrast to allylic sulfonylation, optical yield in this reaction is much less dependent on the steric demands of ligands. Again, acyclic iminophosphite **5a** is inefficient (ee up to 18%, entry 16), probably due to a large number of conformers for its metal derivatives (see above). Complexes **8a**,**b**,**d** provide excellent conversion and > 90% ee (entries 4,8,13). Good results of cationic complex **9b** with oxazolidinophosphite **5b** (77% ee) are also notable, despite they are still lower than those of oxazoline analogue **8d**.

It is well known that optical and chemical yields in catalytic reactions often strongly depend on the nature of a counter ion in

Table 1 Selected spectroscopic data for compounds **6a**,**c**,**d**, **7a**,**b** and **8a–d**, **9a**,**b** (in $CHCl_3$).

Compound	^{31}P NMR		IR, ν(CO)/cm^{-1}
	δ_P	^1J(P,Rh)/Hz	
6a	137.3 (53%)	286.0	2025
	135.6 (47%)		
6c	135.9	301.4	2034
6d[a]	136.2	287.0	2024
7a	134.4	290.4	2032
7b	119.3	297.6	2030
8a	138.9 (57%)		
	128.0 (43%)		
8b	146.2		
8c	130.4		
8d[a]	141.7, 140.5		
9a	133.9		
9b	127.5, 127.2		

[a]According to ref. 18.

[‡‡] All palladium complexes gave spectroscopic and analytical data consistent with the proposed structures, for example: [Pd(**3a**–P^N)(allyl)]$^+BF_4^-$ **8a**: light yellow powder, (0.31 g, 92% yield). MS (FAB), *m*/*z* (I, %): 752 [M – BF_4]$^+$ (100), 711 [M – BF_4 – allyl]$^+$ (18), 493 (23). Found (%): C, 54.51; H, 6.02; N, 1.51. Calc. for $C_{38}H_{49}BF_4NO_6PPd$ (%): C, 54.33; H, 5.88; N, 1.67.

[§§] The catalytic experiments were carried out according to published procedures.[24]

Table 2 Enantioselective allylic sulfonylation of **10** with $NaSO_2$-*p*-Tol (in THF).

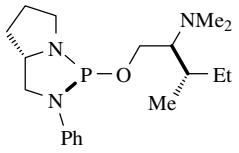
Entry	Catalyst	L*/[Pd]	Isolated yield (%)	ee (%)[a]
1	[Pd(allyl)Cl]$_2$/**3a**	1/1	18	46 (*S*)
2	[Pd(allyl)Cl]$_2$/**3a**	2/1	—	—
3	**8a**	1/1	15	63 (*S*)
4	[Pd(allyl)Cl]$_2$/**3b**	1/1	18	7 (*R*)
5	[Pd(allyl)Cl]$_2$/**3b**	2/1	10	3 (*R*)
6	**8b**	1/1	23	24 (*S*)
7	[Pd(allyl)Cl]$_2$/**3c**	1/1	15	11 (*S*)
8	[Pd(allyl)Cl]$_2$/**3c**	2/1	16	2 (*S*)
9	**8c**	1/1	10	8 (*S*)
10	[Pd(allyl)Cl]$_2$/**3d**[b]	1/1	45	84 (*S*)
11	[Pd(allyl)Cl]$_2$/**3d**[b]	2/1	48	88 (*S*)
12	**8d**[b]	1/1	50	92 (*S*)
13	[Pd(allyl)Cl]$_2$/**5a**	1/1	—	—
14	[Pd(allyl)Cl]$_2$/**5a**	2/1	—	—
15	[Pd(allyl)Cl]$_2$/**5b**	1/1	15	54 (*S*)
16	[Pd(allyl)Cl]$_2$/**5b**	2/1	48	3 (*S*)
17	**9b**	1/1	23	35 (*R*)

[a]ee and absolute configuration of products were established by HPLC [(*R*,*R*)-Whelk-01, hexane/Pr^{i}OH, 4:1, 1 ml min^{-1}, 254 nm]. [b]According to ref. 18.

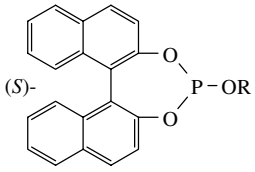
Table 3 Enantioselective allylic alkylation of **10** with dimethyl malonate.

Entry	Catalyst	L*/[Pd]	Solvent	Conv. (%)[a]	ee (%)[b]
1	[Pd(allyl)Cl]$_2$/**3a**	1/1	THF	82	96 (*S*)
2	[Pd(allyl)Cl]$_2$/**3a**	2/1	THF	56	93 (*S*)
3	**8a**	1/1	THF	32	95 (*S*)
4	**8b**	1/1	CH_2Cl_2	94	98 (*S*)
5	[Pd(allyl)Cl]$_2$/**3b**	1/1	THF	11	76 (*S*)
6	[Pd(allyl)Cl]$_2$/**3b**	2/1	THF	5	82 (*S*)
7	**8b**	1/1	THF	37	77 (*S*)
8	**8b**	1/1	CH_2Cl_2	96	91 (*S*)
9	[Pd(allyl)Cl]$_2$/**3c**	1/1	THF	2	57 (*S*)
10	[Pd(allyl)Cl]$_2$/**3c**	2/1	THF	10	72 (*S*)
11	**8c**	1/1	THF	97	66 (*R*)
12	**8c**	1/1	CH_2Cl_2	2	78 (*R*)
13	**8d**	1/1	THF	99	96 (*S*)
14	**8d**	1/1	CH_2Cl_2	97	88 (*S*)
15	[Pd(allyl)Cl]$_2$/**5a**	1/1	THF	2	7 (*R*)
16	[Pd(allyl)Cl]$_2$/**5a**	2/1	THF	3	18 (*R*)
17	[Pd(allyl)Cl]$_2$/**5b**	1/1	THF	2	21 (*R*)
18	[Pd(allyl)Cl]$_2$/**5b**	2/1	THF	4	34 (*R*)
19	**9b**	1/1	THF	51	76 (*R*)
20	**9b**	1/1	CH_2Cl_2	82	77 (*R*)

[a]Measured by HPLC. [b]Determined by HPLC (Daicel Chiralcel OD-H, hexane/Pr^{i}OH, 99:1; 0.5 ml min^{-1}, 254 nm).



13 98% ee[24]



14 97% ee[28]

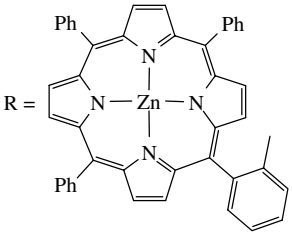


Figure 1

a cationic catalyst.[25,26] However, for the catalytic systems based on ligands **3a** and **3b**, no considerable influence of anion was found. A counter ion effect is more pronounced in the case of **3c** (compare entries 9 and 11). An extraordinary increase of both conversion and enantioselectivity (from 21 to 76% ee, entries 17 and 19) was observed when Cl^- was changed with BF_4^- in complex with oxazolidinophosphite **5b**. In our opinion, this effect might be caused not only by the nature of a counter ion but also by different structures of the catalytic complexes [Pd(**5b**–P^N)(η^1-allyl)Cl] and [Pd(**5b**–P^N)(η^3-allyl)]$^+BF_4^-$.[27] The solvent is not decisive, but in general CH_2Cl_2 is preferable (Table 3). Note that the optical purity of product **12** (96–98% ee, entries 4 and 13), achieved using complexes of aryl phosphites **3a**,**d**, is comparable to the results of leading modern ligands – phosphites **13** and **14** (Figure 1).

At the same time, **3a**,**d** are easily accessible, since they have no P-stereocentres or Zn^{II}-porphyrine fragments.

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