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Novel BIPHEN H2 based P,S-bidentate phosphoramidite ligand in palladium-catalyzed asymmetric allylation

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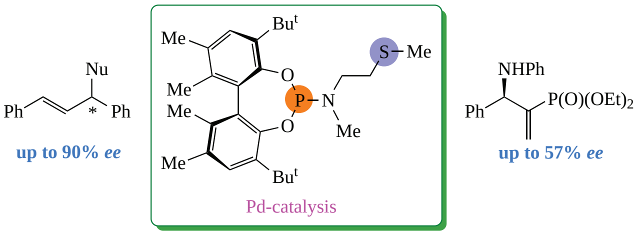
The reaction of *P,S*-phosphoramidite bearing (R_a)-BIPHEN H2 core and exocyclic amino sulfide as the new ligand with [Pd(π-allyl)Cl]$_2$ in the presence of AgBF$_4$ yielded a cationic metallochelate [Pd(π-allyl)(L)]BF$_4$. This new chiral inducer provided up to 90% *ee* in the Pd-mediated allylic substitution reaction of (*E*)-1,3-diphenylallyl acetate with various C- and N-nucleophiles. In the Pd-catalyzed amination of 2-diethoxyphosphoryl-1-phenylallyl acetate with aniline, *ee* values up to 57% were achieved.



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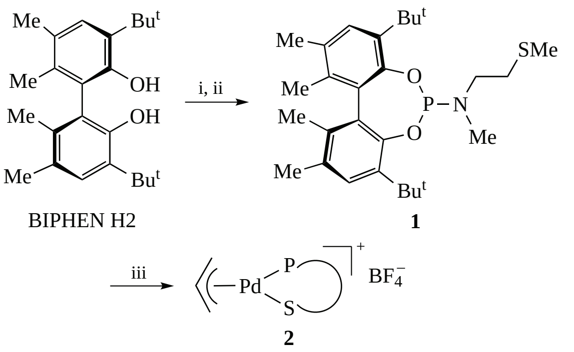
Phosphoramidites based on enantiomers of 3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol [(S_a)- and (R_a)-BIPHEN H2] constitute a very attractive but relatively small group of chiral phosphite-type ligands, which feature availability, robustness and modular structure. They have found successful applications in asymmetric transition-metal catalysis. Such stereoselectors are readily accessible from the enantiomers of BIPHEN H2 and various amines, so that their structural diversity can be easily achieved.[1] Nevertheless, no P,S-bidentate phosphoramidite derivatives of BIPHEN H2 have been described until now, while BINOL-based *P,S*-phosphoramidites are well-known.[2] Chiral P,S-bidentate ligands are very attractive due to their C_1 symmetry and differing electronic and steric demands of P and S donor centers, providing a pronounced asymmetry of the metal center surroundings. Additionally, sulfur atom becomes stereogenic upon coordination to the metal.[3] Herein, we report on the synthesis of the first BIPHEN H2 derived phosphoramidite ligand bearing a sulfur donor atom and its application in the Pd-mediated asymmetric allylic substitution processes. On the one hand, such catalytic processes, first of all classical model reactions, serve to benchmark the ligand capability to control chirality transfer in palladium catalysis.[4] On the other hand, allylic substitution is a versatile and highly efficient strategy in the asymmetric synthesis of valuable organic and natural compounds, such as esters and amides of enantioenriched unsaturated carboxylic acids,[5] allyl amines,[6] and β-amino-phosphonic acid.[7]

Condensation of (R_a)-BIPHEN H2 with PCl$_3$ followed by the reaction of the intermediate chlorophosphite with *N*-methyl-2-(methylthio)ethan-1-amine yielded ligand **1** (Scheme 1). Phosphoramidite **1** tolerates purification by flash chromatography, is well soluble in common organic solvents, is stable enough to be manipulated in air, and can be stored for a long time under dry atmosphere.

The structure of compound **1** was confirmed by elemental analysis and NMR spectroscopy. Its ^{31}P{^{1}H} NMR spectrum exhibits two broadened singlets [δ_P 141.53 (49%), 142.48 (51%) in CDCl$_3$ and δ_P 143.02 (55%), 144.38 (45%) in d_8-toluene], their relative intensities perceptibly depending on the solvent nature. The nitrogen atom of the phosphoramidite molecule is known to adopt an almost perfect trigonal configuration.[4(c)] Normally, the rotation around the N–P bond is fast,[8] but it is reasonable to assume that in the presence of bulky *tert*-butyl



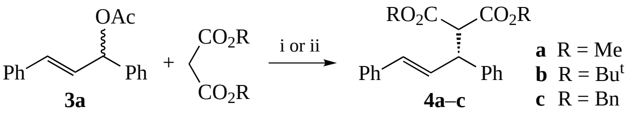
Scheme 1 *Reagents and conditions*: i, PCl$_3$ (23 equiv.), NMP (cat.), reflux; ii, MeNHCH$_2$CH$_2$SMe, Et$_3$N (2 equiv.), PhMe; iii, [Pd(π-allyl)Cl]$_2$ (0.5 equiv.), AgBF$_4$, THF.

substituents in 3,3′ positions of the BIPHEN H2 skeleton this rotation becomes slow on the NMR timescale.[1(*l*)] So, two signals can be attributed to two possible rotamers or π-diastereomers. In support of this interpretation, heating a solution of **1** in d_8-toluene up to 100 °C leads to the coalescence of the ^{31}P signals while subsequent cooling to 25 °C returns the initial state (Figure S1 of the Online Supplementary Materials). The ^1H and ^{13}C resonances for compound **1** are also broadened at room temperature, especially the signals of the exocyclic $MeNCH_2CH_2SMe$ substituent.

Complexation of phosphoramidite **1** with [Pd(π-allyl)Cl]$_2$ in the presence of $AgBF_4$ affords a cationic chelate **2** (see Scheme 1). This complex was characterized by mass spectrometry (MALDI-TOF MS) and multinuclear ($^{31}P\{^1H\}$, ^1H, ^{13}C, DEPT, ^{13}C-^1H HSQC, ^{13}C-^1H HMBC, ^1H-^1H COSY and ^1H-^1H NOESY) NMR spectroscopy in CD_2Cl_2 solution. In contrast to the parent ligand **1**, the NMR signals of chelate **2** are narrow, allowing detailed spectroscopic analysis. The ^{31}P, ^1H and ^3C spectra of **2** showed a 2 : 3 mixture of two isomers in equilibrium, which can be attributed to two Pd-η^3-*exo* and *endo* diastereomers.[9] For both diastereomers, the carbon atoms of the SMe groups resonate as doublets ($^3J_{C,P}$ 2.2 and 2.4 Hz), which is diagnostic for the coordination of the S atom with the metal center. Besides, the ^{13}C NMR chemical shifts and $^2J_{C,P}$ of two allylic terminal carbons differ significantly, indicating that in both cases more electrophilic allyl terminus is located *trans* to phosphorus (for details, see Figures S2 and S3 of the Online Supplementary Materials).

First, we tested phosphoramidite **1** and complex **2** in the Tsuji–Trost reaction between (*E*)-1,3-diphenylallyl acetate **3a** as the electrophile and three dialkyl malonates as the C-nucleophiles (Scheme 2). The allylic alkylation was performed according to the standard procedure using [Pd(π-allyl)Cl]$_2$ as the palladium source with a combined base of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc. The desired products **4a**–**c** were obtained with *ee* values up to 86, 80 and 90%, respectively (Table 1, entries 3, 9 and 14). The major enantiomer had (*R*)-configuration in all cases. The asymmetric induction in THF was higher than that in CH_2Cl_2. The effect of the **1**/Pd molar ratio on the enantioselectivity was not unidirectional and depended on the nature of the C-nucleophile, while the conversion of substrate **3a** was higher when the **1**/Pd molar ratio was 1 : 1. The enantioselectivity increased and the conversion decreased with lowering the reaction temperature from room to –20 °C (entries 1 and 3, 12 and 14). In general, the individual cationic palladium complex **2** and the corresponding catalytic system formed *in situ* from **1** and [Pd(π-allyl)Cl]$_2$ demonstrated comparable efficiency.

Next, we extended our studies to Pd-catalyzed allylic amination reactions (Scheme 3). In both transformations, the (*S*)-enantiomers of products **5a**,**b** were predominant. In the case of pyrrolidine as the N-nucleophile, the conversion of substrate **3a** and the enantioselectivity were higher in CH_2Cl_2 as the reaction medium (Table 2, entries 1–4). When the reaction was carried out at –20 °C, 78% *ee* was achieved (entry 5). The use of (*E*)-1,3-diphenylallyl ethyl carbonate **3b** as the electrophile slightly improved the reaction rate and, with the **1**/Pd molar ratio of 2 : 1, the asymmetric induction (entries 3, 4 *vs.* 7, 8). The allylic amination of substrates **3a**,**b** with phthalimide proceeded with a moderate conversion to give the desired product **5b** with 75 and 71% *ee*, respectively (entries 10 and 12).

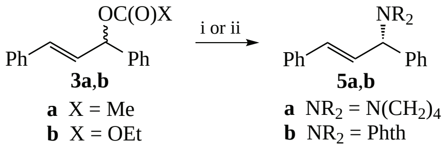


Scheme 2 *Reagents and conditions*: i, [Pd(π-allyl)Cl]$_2$, **1**, BSA, KOAc, solvent, room temperature, 24 h; ii, the same, with individual complex **2** as the catalyst.

Table 1 Allylic alkylation of substrate **3a** with malonates catalyzed by **1**/Pd system or complex **2** (see Scheme 1).

Entry	Molar ratio **1**/Pd	Solvent	Conversion (%)	Product	*ee* (%)[a]
1	1 : 1	THF	100	**4a**	77 (*R*)
2	2 : 1	THF	10	**4a**	50 (*R*)
3[b]	1 : 1	THF	49	**4a**	86 (*R*)
4[c]	1 : 1	THF	100	**4a**	81 (*R*)
5	1 : 1	CH_2Cl_2	100	**4a**	63 (*R*)
6	2 : 1	CH_2Cl_2	61	**4a**	49 (*R*)
7	1 : 1	THF	80	**4b**	77 (*R*)
8	2 : 1	THF	19	**4b**	79 (*R*)
9[c]	1 : 1	THF	45	**4b**	80 (*R*)
10	1 : 1	CH_2Cl_2	100	**4b**	70 (*R*)
11	2 : 1	CH_2Cl_2	71	**4b**	75 (*R*)
12	1 : 1	THF	100	**4c**	82 (*R*)
13	2 : 1	THF	40	**4c**	80 (*R*)
14[b]	1 : 1	THF	23	**4c**	90 (*R*)
15[c]	1 : 1	THF	100	**4c**	82 (*R*)
16	1 : 1	CH_2Cl_2	100	**4c**	71 (*R*)
17	2 : 1	CH_2Cl_2	70	**4c**	71 (*R*)

[a] The conversion of substrate **3a** and enantiomeric excess of **4a** were determined by HPLC (Kromasil 5-CelluCoat, $C_6H_{14}/Pr^iOH = 99:1$, 0.6 ml min^{-1}, 254 nm, *t*(*R*) = 20.4 min, *t*(*S*) = 22.4 min); **4b** – (Daicel Chiralcel AD-H, $C_6H_{14}/Pr^iOH = 95:5$, 1.0 ml min^{-1}, 254 nm, *t*(*R*) = 8.3 min, *t*(*S*) = 12.0 min); **4c** – (Daicel Chiralcel AD-H, $C_6H_{14}/Pr^iOH = 4:1$, 1.0 ml min^{-1}, 254 nm, *t*(*R*) = 15.6 min, *t*(*S*) = 19.0 min). The absolute configurations were assigned by comparison of the reported HPLC retention times (*cf.* ref. 10). [b] At –20 °C. [c] With complex **2** as the catalyst.

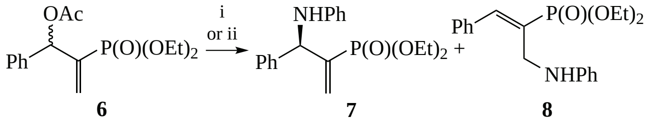


Scheme 3 *Reagents and conditions*: i, [Pd(π-allyl)Cl]$_2$, **1**, pyrrolidine or phthalimide, K_2CO_3, solvent, room temperature, 24 h; ii, the same, with individual complex **2** as the catalyst.

Table 2 Allylic amination of substrates **3a**,**b** with pyrrolidine or phthalimide catalyzed by **1**/Pd system or complex **2** (see Scheme 3).

Entry	Substrate	Molar ratio **1**/Pd	Solvent	Conversion (%)	Product	*ee* (%)[a]
1	**3a**	1 : 1	THF	37	**5a**	67 (*S*)
2	**3a**	2 : 1	THF	25	**5a**	66 (*S*)
3	**3a**	1 : 1	CH_2Cl_2	70	**5a**	71 (*S*)
4	**3a**	2 : 1	CH_2Cl_2	96	**5a**	70 (*S*)
5[b]	**3a**	1 : 1	CH_2Cl_2	19	**5a**	78 (*S*)
6[c]	**3a**	1 : 1	CH_2Cl_2	100	**5a**	61 (*S*)
7	**3b**	1 : 1	CH_2Cl_2	100	**5a**	52 (*S*)
8	**3b**	2 : 1	CH_2Cl_2	100	**5a**	74 (*S*)
9	**3a**	1 : 1	CH_2Cl_2	67	**5b**	72 (*S*)
10	**3a**	2 : 1	CH_2Cl_2	40	**5b**	75 (*S*)
11[c]	**3a**	1 : 1	CH_2Cl_2	53	**5b**	73 (*S*)
12	**3b**	1 : 1	CH_2Cl_2	65	**5b**	71 (*S*)
13	**3b**	2 : 1	CH_2Cl_2	77	**5b**	68 (*S*)

[a] The conversion of substrates **3a**,**b** and enantiomeric excess of **5a** were determined by HPLC (Daicel Chiralcel OD-H, $C_6H_{14}/Pr^iOH = 95:5$, 0.4 ml min^{-1}, 254 nm, *t*(*R*) = 9.1 min, *t*(*S*) = 9.7 min); **5b** – (Daicel Chiralcel OD-H, $C_6H_{14}/Pr^iOH = 9:1$, 1.0 ml min^{-1}, 254 nm, *t*(*S*) = 7.5 min, *t*(*R*) = 9.0 min). The absolute configurations were assigned by comparison of the reported HPLC retention times [*cf.* refs. 9(*a*),(*b*),11]. [b] At –20 °C. [c] With complex **2** as a catalyst.



Scheme 4 *Reagents and conditions*: i, $[Pd(\pi\text{-allyl})Cl]_2$, **1**, $PhNH_2$, K_2CO_3, CH_2Cl_2, room temperature, 24 h; ii, the same, with individual complex **2** as the catalyst.

Table 3 Allylic amination of substrate **6** with aniline catalyzed by **1**/Pd system or complex **2** (see Scheme 4).

Entry	Molar ratio **1**/Pd	**7**/**8**[a]	*ee* (%)[b]
1	1 : 1	81 : 19	46 (*R*)
2	2 : 1	80 : 20	48 (*R*)
3[c]	1 : 1	79 : 21	57 (*R*)

[a] The conversion of substrate **6** and **7**/**8** ratio were determined by ^{31}P NMR. [b] The enantiomeric excess of **7** was determined by HPLC (Daicel Chiralcel OD-H, $C_6H_{14}/Pr^iOH = 9:1$, 1.0 ml min^{-1}, 254 nm, $t(S) = 5.9$ min, $t(R) = 6.9$ min). The absolute configurations were assigned by comparison of the reported HPLC retention times (*cf.* ref. 7). [c] With complex **2** as a catalyst.

In terms of activity and/or enantioselectivity in the benchmark allylic substitution reactions above, ligand **1** with the simple backbone compares favorably with the known BIPHEN H2 based *P*,*N*-phosphoramidites, which even possess an additional stereogenic center at the backbone chain.[1(*l*)]

We also examined the rare Pd-catalyzed asymmetric allylic amination of 2-diethoxyphosphoryl-1-phenylallyl acetate **6** with aniline in CH_2Cl_2 (Scheme 4, Table 3). Quantitative conversion of substrate **6**, good regioselectivities and *ee*'s of up to 57% (*R*) were obtained using the ligand **1** and its complex **2**. In this challenging asymmetric transformation, the ligand **1** is certainly inferior to the spiroketal-based bis-phosphines, but superior to some privileged chiral inducers, *e.g*., BINAP, SDP and the Trost ligand, in terms of conversion, regio- and enantioselectivities.[7]

In summary, *P*,*S*-phosphoramidite **1** is discovered to be a promising stereoselector being rather sensitive to the nature of nucleophile and conditions of the enantioselective Pd-catalyzed allylation. This ligand exhibits notable results in the non-trivial allylic amination of 2-diethoxyphosphoryl-1-phenylallyl acetate. Additional studies highlighting its potential in other asymmetric reactions are now in progress in our laboratories.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.019.

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