Allylic Phosphination

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Palladium-Catalyzed Enantioselective Allylic Phosphination**

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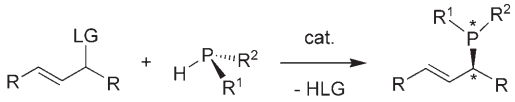
Chiral phosphines are pre-eminent ligands in asymmetric catalysis and are utilized in applications ranging from laboratory syntheses to industrial processes.[1] Despite their wide-spread use in enantioselective catalysis, there are surprisingly few syntheses of chiral phosphines by enantioselective methods. Thus, it is of interest to develop such reactions because catalytic asymmetric transformations in which the P–C bond and stereogenic centers are simultaneously formed might allow access to new chiral motifs, give more efficient syntheses of valuable chiral ligands, and stimulate the development of new enantioselective processes.

Recently, a few strategies for catalytic P–C bond formations have emerged that give enantiomerically enriched phosphines.[2] It is noteworthy that these systems frequently find close parallels in N–C bond formations. For example, organolanthanide compounds catalyze both intramolecular hydroaminations and hydrophosphinations, apparently through analogous mechanisms.[3] Also, our group has described a nickel(II) catalyst which is active for asymmetric hydroamination and hydrophosphination of vinyl nitriles.[4] Finally, of particular relevance are palladium-catalyzed aryl–X/E–H (E = N, P) coupling reactions, which have shown tremendous synthetic utility.[5] Thus, new catalytic asymmetric phosphine synthesis might be guided by examples from the corresponding amine chemistry. In this context, it is of interest to note that although asymmetric allylic amination is a prominent method for the preparation of chiral amines,[6] there are no reports of asymmetric allylic phosphination (Scheme 1). Additionally, a pendant allylic group would offer



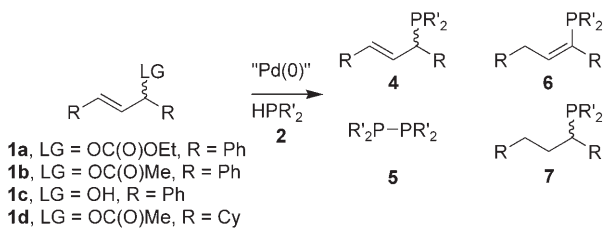
Scheme 1. General formulation of allylic phosphination. LG = leaving group.

the possibility of further functionalizations, and allylic alkylations and aminations have been shown to be useful in synthesis.[7]

There are, however, several examples of non-enantioselective catalytic syntheses of allylic phosphonates, which all involve Pd^0- or Ni^0-catalyzed coupling of phosphonates and allylic substrates.[8] Furthermore, Moreno Mañas and coworkers have synthesized allylic phosphonium salts by the reaction of allylic pyridinium salts and triphenylphosphine in the presence of $[Pd(PPh_3)_4]$.[9] Most notably, this complex was shown 25 years ago by Fiaud to catalyze the reaction of lithium diphenylphosphide with aliphatic allylic acetate derivatives to afford the corresponding substitution products.[10] However, to our knowledge these transition-metal-catalyzed reactions do not appear to have ever been attempted in the presence of chiral ligands. Finally, the advent of organocatalytic processes in recent years has led to the development of an enantioselective 1,4-addition of secondary phosphines to α,β-unsaturated aldehydes, giving products in up to 98% *ee*.[11]

Based on previous work in the area of asymmetric allylic substitutions[12] and on our hydroamination/hydrophosphination chemistry,[4] we began to pursue asymmetric allylic phosphination. We initially examined reactions of 1,3-diphenylallyl ethyl carbonate (**1a**; Scheme 2) and diphenylphosphine (**2**) in the presence of chelating chiral ferrocenyl P,N ligands and palladium precursors. The P,N ligands, especially 1-{1-[2-(diphenylphosphino)ferrocenyl]ethyl}-3-(*tert*butyl)-1-*H*-pyrazole (**3**; see Figure 1) have been shown to be effective ligands for Pd-catalyzed asymmetric allylic aminations of the same substrate.[13] The reaction was conveniently monitored by NMR spectroscopy ($^{31}P\{^1H\}$, ^{31}P, ^1H, ^{31}P–^1H HMQC), the results of which indicate that the reaction proceeds to full conversion of the secondary phosphine substrate after approximately 48 h at 40 °C. However, the reactions were not selective (Scheme 2), giving the allylic phosphine product **4**, the product formed by dehydrocoupling of the secondary phosphine, **5**,[14] and a small amount of the vinyl isomer **6** resulting from a 1,3-hydrogen shift.

In the hope that a less-basic leaving group would inhibit the formation of the side products and increase selectivity for the chiral allylic phosphine, the allylic acetate **1b** (Scheme 2) was investigated as the substrate. In the presence of **3** (6 mol%) and $[Pd(dba)_2]$ (5 mol%; dba = dibenzylideneace-



1a, LG = OC(O)OEt, R = Ph
1b, LG = OC(O)Me, R = Ph
1c, LG = OH, R = Ph
1d, LG = OC(O)Me, R = Cy

Scheme 2. Products observed in asymmetric allylic phosphination. R′ = Ph (**4**).

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tone) in dichloromethane at 40 °C, diphenylphosphine and **1b** react in 24 h to afford the desired allylic phosphine **4**, accompanied by side products accounting for 44 % yield. These have been identified as the diphosphine **5** (26 %), the vinyl isomer **6** (10 %) and the reduced derivative **7** (8 %). Unfortunately, under these conditions the reaction affords product **4** with a enantiomeric excess of only 17 %.

A stoichiometric reaction, in which the palladium products could be detected, reveals the likely reason for the low selectivities obtained upon catalytic phosphination. The ^{1}H and $^{31}P\{^{1}H\}$ NMR spectrum of a mixture of the catalyst precursor $[Pd\{\eta^3\text{-}(1,3\text{-}Ph_2C_3H_3)\}(\mathbf{3})]SbF_6$ and 1 equivalent of diphenylphosphine shows resonance signals corresponding to the non-coordinated ligand **3** after 10 min at room temperature in $[D_8]$THF. This result indicates that the secondary phosphine Ph_2PH and $[Pd(\eta^3\text{-}(1,3\text{-}Ph_2C_3H_3)(\mathbf{3})]SbF_6$ rapidly react by ligand substitution rather than the expected nucleophilic attack, thus forming achiral, but catalytically active species, such as the $[Pd(\eta^3\text{-allyl})(R_2PH)_2]^+$ ion.

Therefore, we sought catalysts containing ligands that are less labile than ligand **3** in the presence of excess secondary phosphines. In contrast to P,N ligands, chiral bis(phosphines) are expected to form more stable complexes with palladium and thus ligand exchange in the presence of a large excess of secondary phosphine might be less favorable. Therefore, (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine ((*R*)-(*S*)-Josiphos, **8**; Figure 1) was investigated as chiral ligand in the title reaction of racemic 1,3-diphenylallyl acetate (**1b**). Note that allylic amination and alkylations were among the first asymmetric reactions for which Josiphos has been found to be a highly effective ligand.[12b,15]

The catalyst may be generated in situ either from the ligand and $[Pd(dba)_2]$ or from the isolable complex $[Pd(\eta^3\text{-}(1,3\text{-}Ph_2C_3H_3)(\mathbf{8})]SbF_6$ (**9**). We initially focused our interest on the optimization of the reaction with diphenylphosphine as the nucleophile with equimolar amounts of **1b** in different solvents, leading to **4** (Table 1). Qualitatively, the reaction appears to produce less side products and to be more selective (up to 96 % *ee*) in solvents such as benzene and toluene. It is interesting to note that the reaction with 1,3-diphenyl-2-propen-1-ol (**1c**) as allylic substrate, leads to a highly enantioselective product formation (96 % *ee*), however with incomplete conversion. Replacing the phenyl substituents by cyclohexyl groups in the substrate (**1d**) gives a disappointing result, in terms of yield (20 %), product distribution, and enantioselectivity (40 % *ee*).

We also investigated an additional set of Josiphos-related ligands (Figure 1) in the reaction leading to **4**. Ligand **10** is a Josiphos bearing 3,5-bis(trifluoromethyl)phenyl substituents instead of phenyl. This ligand has an increased difference in the donor ability of the two phosphorus atoms and leads to a faster catalytic reaction with a selectivity comparable to that obtained with Josiphos (Table 2, compare with Table 1). For comparison, we also examined *R*-binap ([1,1′-binaphthalene]-2,2′diylbis(diphenylphosphine)) as a classical representative of C_2 symmetric diphosphines. The reaction is somewhat sluggish with this ligand and the main product is formed as only 56 % of a product mixture that is obtained in relatively low yield. Moreover, the enantioselectivity does not go beyond approximately 39 % *ee*, with the sense of chiral induction corresponding to that of (*R*)-(*S*)-Josiphos. We encountered a very similar situation when the enantiomerically enriched product **4** (ca. 95 % *ee*) was used as chiral

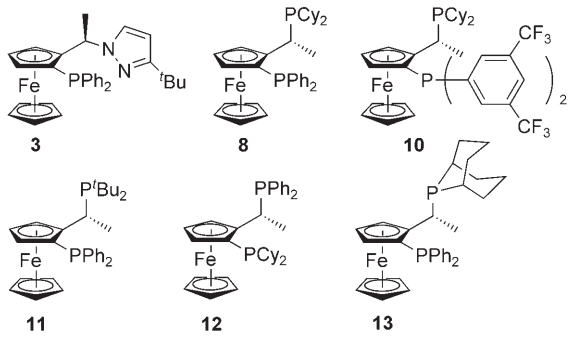


Figure 1. Josiphos-type ligands of (*R*)–(*S*) configuration used in this study.

Table 1: The effect of various solvents on product distribution and enantioselectivity in the formation of **4** catalyzed by the Pd(Josiphos) system.[a]

Substrate	Solvent	Prod. Distrib. (% **4**:**5**:**6**:**7**)[b]	Yield of **4** [%][c]	(*ee* of **4** [%])
1b	C_6H_6	89:11:0:0	79	94[d] (96[e])
1b	toluene	78:11:4:7	74	79[d] (81[e])
1b	CH_2Cl_2	73:6:7:14	68	87[d] (91[e])
1b	THF	84:6:6:4	81	51[d] (49[e])
1b	MeOH	70:1:1:19	68	78[d] (83[e])
1b	dioxane	77:15:6:2	75	65[d] (68[e])
1c	C_6H_6	96:4:0:0	54	97[d] (96[e])
1d	C_6H_6	42:40:0:18	20	n.d.[d] (40[e])

[a] Reaction conditions: 5 mol % $[Pd(dba)_2]$, 5.2 mol % **8**, 40 °C. [b] Products distribution is given as ratio between: **4**, **5**, **6**, **7**; see Scheme 2. [c] Yield of isolated product, based on Ph_2PH. [d] Determined by HPLC, see Supporting Information for details; n.d. = not determined. [e] Determined by $^{31}P\{^{1}H\}$-NMR, see Supporting Information for details.

Table 2: The effect of the chiral ligands on product distribution and enantioselectivity in the Pd-catalyzed formation of (*E*)-1-diphenylphosphino-1,3-diphenylpropene.[a]

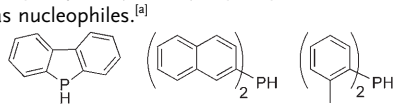
Ligand	*t* [h]	Prod. Distrib. (% **4**:**5**:**6**:**7**)[b]	Yield of **4** [%][c]	(*ee* of **4** [%])
10	4	97:1:1:1	92	82[d] (85[e])
11	52	79:6:6:9	78	69[d] (68[e])
12	188	71:3:9:17	40	80[d] (82[e])
13	50	72:20:3:5	65	82[d] (89[e])
R-binap	52	56:11:13:20	48	38[d] (39[e])
4[f]	52	49:12:11:28	42	11[d] (11[e])
4[g,h]	52	51:9:12:26	50	18[d] (20[e])

[a] Reaction Conditions: 5 mol % $[Pd(dba)_2]$, 5.2 mol % ligand, 40 °C, CH_2Cl_2. [b] Products distribution is given as ratio between: **4**:**5**:**6**:**7**, see Scheme 2. [c] Yield of isolated product, based on Ph_2PH. [d] Determined by HPLC, see Supporting Information for details. [e] Determined by $^{31}P\{^{1}H\}$-NMR, see Supporting Information for details. [f] ca. 95 % enantiomeric purity. [g] 10.4 mol % ligand.

ligand. This is a strong indication that the reaction does not display any significant autocatalytic effect.

Four additional secondary phosphines were used as nucleophiles in the Pd(Josiphos)-catalyzed reaction of **1b**. Whereas dicyclohexylphosphine (**14**) gave a relatively slow reaction and afforded the new allylic phosphine in low enantioselectivity (45% *ee*, 5*H*-benzo[*b*]phosphindole (**15**) afforded the desired product in 84% isolated yield and 80% *ee* (Table 3). Note that with this cyclic phosphine full conversion was reached after approximately 20 min, indicating a rate increase by approximately two orders of magnitude as compared with both diphenyl- and dicyclohexylphosphine. However, also in this case the same type of byproducts was observed, with the dehydrocoupling product of the nucleophile accounting for 14%. Not surprisingly, bis(2-naphthyl)-phosphine (**16**) gave the product in fairly high enantioselectivity (83% *ee*) and good yield. On the other hand, with the bulkier bis(2-tolyl)phosphine (**17**) the product could only be obtained with 42% *ee*, despite both satisfactory yield and product distribution.

Table 3: Pd(Josiphos)-catalyzed allylic phosphination with five different phosphines as nucleophiles.[a]



15 **16** **17**

R_2PH	*t* [h]	Prod. Distrib. (% **4**:**5**:**6**:**7**)[b]	Yield of **4** [%][c]	(*ee* of **4** [%])[d]
2	48	89:11:0:0	79	96
14	74	65:28:6:1	44	45
15	0.3	84:14:0:2	84	80
16	48	91:6:1:2	85	83
17	48	88:8:2:2	82	42

[a] Reaction Conditions: 5 mol% [Pd(dba)$_2$], 5.2 mol% **8**, 40°C, C_6D_6. [b] Products distribution is given as ratio between: **4**:**5**:**6**:**7**, see Scheme 2. [c] Yield of isolated product, based on R_2PH. [d] Determined by $^{31}P\{^1H\}$-NMR, see Supporting Information for details.

Since no reliable conditions could be found for the direct chromatographic separation of the enantiomers of the product, two different methods relying on derivatization were used to determine the enantiomeric excess. The first one consists in measuring the diastereomeric ratio of the products **19** formed by treating the enantiomerically enriched **4** with bis-(chloro[2-[1-(dimethylamino)ethyl]ferrocenyl-C,N]-palladium(II)) (**18**), derived from (*S*)-[1-(dimethylamino)ethyl]-ferrocene. The major diastereomer of **19** was characterized by X-ray crystallography. Thus, the absolute configuration of the major enantiomer of **4** could be determined to be *R* by internal comparison (see Figure 2).

The second method consisted in analyzing by chiral HPLC the phosphine sulphide **20** obtained by the reaction of **4** with elemental sulfur. Crystals of the *R* enantiomer of this compound were obtained by slow diffusion of hexane into a concentrated CH_2Cl_2 solution of a sample at 96% *ee* (Figure 3).

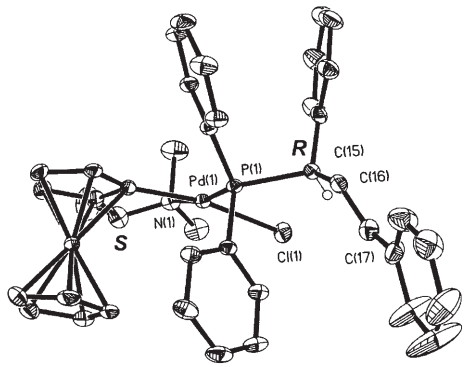


Figure 2. ORTEP diagram of compound **19** used for the determination of the absolute configuration of **4**. Only the hydrogen atom at the newly generated stereogenic center is shown at its calculated position; thermal ellipsoids set at 30% probability.

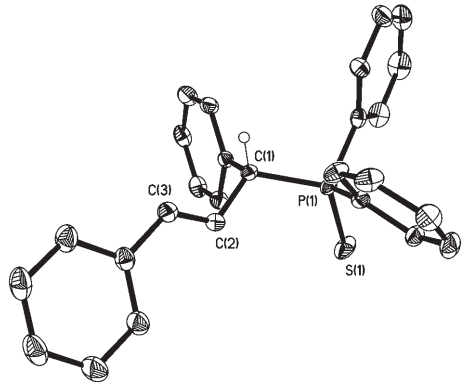


Figure 3. ORTEP diagram of the phosphine sulfide *R*-**20**. Hydrogen atoms are omitted for clarity, except for that at C(1); thermal ellipsoids are set at 30% probability.

In conclusion, we have shown that secondary phosphines may be used as nucleophiles in Pd-catalyzed enantioselective allylic substitution reactions. When using Josiphos as chiral ligand and 1,3-diphenylallyl acetate as substrate the new chiral allylic phosphine is obtained in good yield and up to 96% *ee*. Despite the current relatively narrow scope of the reaction, it may become a new method for the preparation of chiral, highly enantiomerically enriched phosphines that are otherwise difficult to synthesize.

Experimental Section

Representative Procedure for Pd-Catalyzed Allylic Phosphination: 1,3-diphenylallyl acetate (29 mg, 0.115 mmol, 1.00 equiv) was added to a mixture of Josiphos (4.8 mg, 8.046 μmol, 0.07 equiv) and [Pd(dba)$_2$] (3.3 mg, 5.747 μmol, 0.05 equiv) in 1 mL of the chosen solvent and the orange solution was stirred for 30 min. The secondary phosphine HPR_2 (0.115 mmol, 1.00 equiv) was then added and the mixture was heated to 40°C in an oil bath. To remove the catalyst and byproduct **5** the reaction solution was worked-up in a glove box by filtration through a short plug of silica gel (0.5 g) using toluene as an eluent. After removing the solvent in vacuo the product was isolated as a colorless solid.

The Supporting Information contains experimental procedures for the synthesis of selected new compounds. CCDC-668371 (**19**) and

CCDC-654095 (**20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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