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Direct Synthesis of Chiral Tertiary Diphosphines *via* Pd(II)-Catalyzed Asymmetric Hydrophosphination of Dienones

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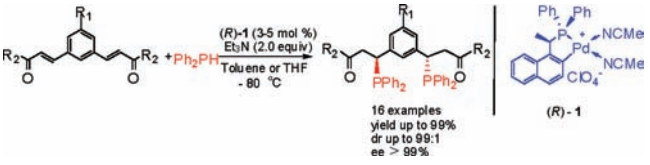
ABSTRACT



A highly diastereo- and enantioselective Pd(II)-catalyzed hydrophosphination of dienones with Ph_2PH involving formation of double C*−P bonds has been developed, providing a series of chiral tertiary diphosphines (chiral PCP pincer ligands) in high yields. A catalytic cycle for the reaction was proposed.

Chiral phosphines, both as ligands for transition metal catalysis and as organocatalysts, have made significant contributions to the development of enantioselective transformations.[1] Among chiral phosphines, diphosphines such as DIOP,[2] DIPAMP,[3] BINAP,[4] and DuPhos[5] have remarkable significance in asymmetric transformations.

Over the past decades, benzylic diphosphines ($1,3\text{-}C_6H_3\text{-}(CH_2P(R)_2)_2$, PCP) have also proven to be very important ligands providing rigid chelation with transition metals (Ni, Pd, Pt, Ru, Ir, *etc.*) to form pincer complexes which are widely used in organic and organometallic chemistry, and touching other fields as well.[6] However, the development of chiral PCP diphosphines has been comparatively slow.[7] Despite their importance, to date, chiral phosphines are predominantly prepared either by resolution or by the use of stoichiometric amounts of chiral auxiliaries or enantiopure substrates,[8] although some reports on catalytic synthesis of chiral monophosphines have appeared during the past decade.[9] Catalytic asymmetric synthesis of chiral diphosphines remains a challenge, presumably due to their

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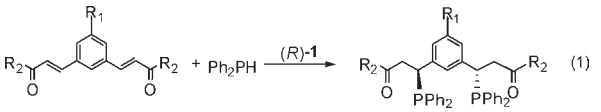
chelation with metal which could hinder the product eliminination process during the catalytic cycle. However, some efforts have been made toward catalytic synthesis of chiral diphosphines. Toste et al. reported a Ru-catalyzed enantioselective synthesis of P-stereogenic phosphine-boranes *via* alkylation which included one example of a PCP diphosphine with a chiral center at phosphorus.[10] Duan et al. reported a one-pot synthesis of a chiral PCP palladium pincer complex.[9e] Glueck et al. reported Pt-catalyzed asymmetric alkylation of bis(secondary phosphines) with aryl halides.[11] Considering the importance of chiral diphosphines and their scarcity of catalytic synthetic methods, it is of great significance to develop efficient catalysts and methodologies for direct and stereoselective preparation of chiral tertiary diphosphines.

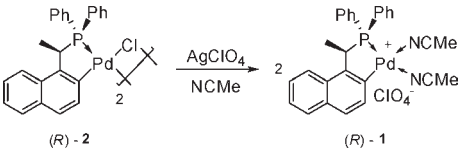
In preceding contributions, our group has reported the asymmetric synthesis of chiral diphosphines promoted by stoichiometric amounts of palladium complexes.[12] Herein, we report a highly efficient asymmetric hydrophosphination reaction between dienones and Ph_2PH catalyzed by (*R*)-**1** involving formation of two C*−P bonds (eq 1), for the direct preparation of chiral tertiary PCP diphosphines (avoiding any protection and deprotection process). Broad functional group tolerance is exhibited, and a wide range of substrates can be efficiently converted into the desired products in high yields with excellent diastereo- and enantioselectivities.



(1)

Our group had previously reported the synthesis of the chiral dimeric phosphapalladacycle complex (*R*)-**2**.[13] Initially, we employed it as a catalyst for the hydrophosphination but found out that it could not efficiently catalyze the reaction. We then generated the phosphapalladacycle complex (*R*)-**1** by treatment of (*R*)-**2** with $AgClO_4$ in the presence of acetonitrile in high yields (Scheme 1). The structure was confirmed by single crystal X-ray diffraction analysis.[14]

Scheme 1. Formation of the Phosphapalladacycle Catalyst (*R*)-**1**



To our delight, (*R*)-**1** showed high reactivity and excellent stereoselectivity when it was employed as a catalyst instead of (*R*)-**2** for the same reaction at −80 °C. The reaction was conveniently monitored by $^{31}P\{^1H\}$NMR spectroscopy. The diastereomeric ratio (dr = *rac*/*meso*) was determined from the $^{31}P\{^1H\}$ NMR spectrum of the crude product, and the enantiomeric excess (ee) was determined from the $^{31}P\{^1H\}$ NMR spectrum of the derivatives which resulted from treatment of the phosphine product with an enantiopure palladacycle containing a chiral naphthylamine auxiliary (*R*)-**3**.[9h,i] X-ray crystal diffraction analysis of one such derivative (R_1 = H, R_2 = Ph) revealed that the absolute configurations of chiral carbon centers of the major product were *S* (Figure 1).[14]

Various reaction conditions were subsequently screened, and the results are given in Table 1. The results revealed that toluene is the best solvent for the reaction with 99:1 dr and >99% ee (entry 4). Good selectivity was also achieved in THF, acetone, and benzene. We further surveyed the temperature effect. It was found that the ee value decreased to 98% at −40 °C and 93% at 20 °C (entries 6 to 7). Yield also decreased when the temperature was raised due to formation of unidentified side products. Base also plays an important role in the reaction. In the absence of base, only trace conversion was observed under the same conditions. The results from the screening of various bases showed that Et_3N is the best one for the reaction due to its appropriate basicity level and its easy removal under vacuum which contributes to obtaining clean products. As expected, when the equally accessible (*S*)-**1** is employed as the catalyst for the reaction, the same enantioselectivity was achieved with reversal in configuration at the chiral center (entry 5). The amount of catalyst loading has little effect on the selectivity but affects the rate of the reaction. A longer reaction time is required to complete the reaction with decreasing catalyst loading.

With the optimal conditions established, a range of aromatic dienones were screened for the asymmetric hydrophosphination reaction catalyzed by (*R*)-**1**. The results are

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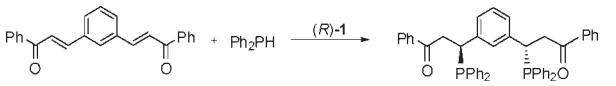
Table 1. Screening of Reaction Conditions[a]



entry	solvent	temp (°C)	base	yield[b] (%)	dr[c]	ee[d] (%)
1	CH_2Cl_2	−80	Et_3N	43	81:19	99
2	Acetone	−80	Et_3N	99	87:13	99
3	THF	−80	Et_3N	99	94:6	99
4	Toluene	−80	Et_3N	99	99:1	>99
5[e]	Toluene	−80	Et_3N	99	99:1	>−99
6	Toluene	−40	Et_3N	99	98:2	98
7	Toluene	20	Et_3N	90	96:4	93
8	Benzene	20	Et_3N	90	96:4	99
9	Toluene	−80	None	trace	–	–
10	Toluene	−80	DBU	14	–	–
11	Toluene	−80	^{t}BuOK[f]	trace	–	–

[a] Conditions: 0.30 mmol of Ph_2PH, 5 mol % of cat., 0.5 mmol of dienone, 2.0 equiv of base, and 5 mL of solvent were reacted at the given temperature for 24 h, unless otherwise noted. [b] Yield was calculated from $^{31}P\{^1H\}$ NMR of the crude product. [c] dr was calculated from $^{31}P\{^1H\}$ NMR. Errors may occur due to overlap. [d] ee was determined from $^{31}P\{^1H\}$ NMR integration of the signals. [e] (*S*)-**1** was employed as the cat. [f] Solid ^{t}BuOK was used.

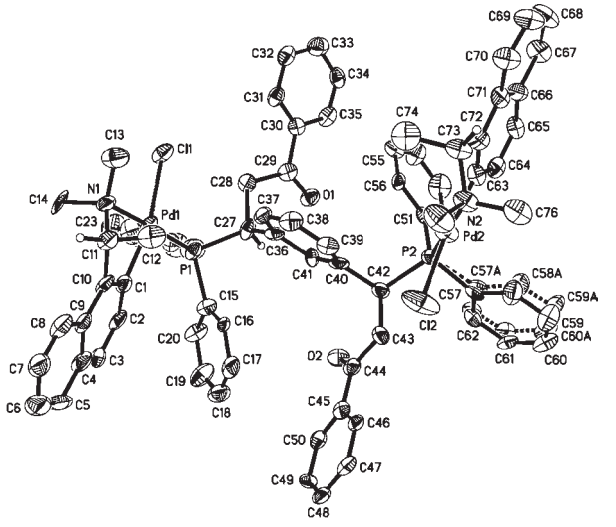
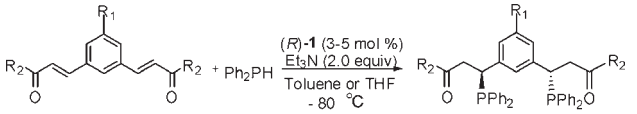


Figure 1. Molecular structure and absolute stereochemistry of the derivative (R_1 = H, R_2 = Ph) with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral centers and solvent are omitted for clarity.

presented in Table 2 and showed that the reaction proceeded to almost full conversion of Ph_2PH under the given conditions, allowing the transformation of a wide range of aromatic dienone substrates to the chiral diphosphine products. Since the solubility of some dienone substrates was poor in toluene, THF was used as the solvent for such cases. The process tolerates a broad range of functional groups such as halogens (F, Cl, Br), trifluoromethyl, alkyl, heterocyclic ring (pyridinyl, thienyl, furyl), naphthyl, *etc*. Both electron-withdrawing and -donating group substituted aromatic dienones are suitable substrates for hydrophosphination with excellent enantioselectivities. However, those bearing electron-withdrawing groups are more reactive than those bearing electron-donating groups. The substituent on the backbone (R_1) also provides the possibility to fine-tune electronic and steric properties for the design of novel chiral PCP pincer complexes.

Table 2. Substrate Scope of the (*R*)-**1**-Catalyzed Asymmetric Hydrophosphination of Dienones[a]



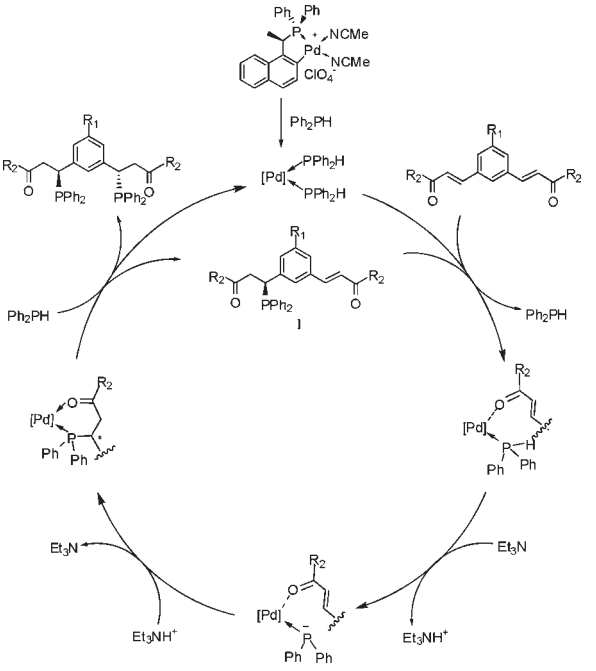
entry	R_1	R_2	time (h)	**6**	yield[b] (%)	dr[c]	ee[d] (%)
1[e]	H	Ph	8	**6a**	99	99:1	>99
2[e]	H	4-FC_6H_4	45	**6b**	99	99:1	>99
3[e]	H	3-FC_6H_4	45	**6c**	99	94:6	>99
4	H	4-ClC_6H_4	6	**6d**	99	98:2	>99
5	H	3-ClC_6H_4	6	**6e**	99	98:2	>99
6	H	4-BrC_6H_4	6	**6f**	94	95:5	>99
7	H	3-BrC_6H_4	6	**6g**	98	98:2	>99
8[e]	H	4-MeC_6H_4	72	**6h**	99	99:1	>99
9[e]	H	3-MeC_6H_4	72	**6i**	99	98:2	>99
10	H	4-$CF_3C_6H_4$	6	**6j**	94	92:8	99
11	H	2-Naph	44	**6k**	99	97:3	>99
12	H	2-Pyridinyl	10	**6l**	95	93:7	>99
13	H	2-Thienyl	48	**6m**	98	99:1	>99
14	H	2-Furyl	36	**6n**	98	97:3	>99
15	Me	Ph	48	**6o**	88	97:3	>99
16	Br	Ph	7	**6p**	98	95:5	>99

[a] Conditions: 0.40 mmol of Ph_2PH, 5 mol % of cat., 8 mL of THF, 0.5 equiv of dienone, and 2.0 equiv of Et_3N were reacted at −80 °C, unless otherwise noted. [b] Yield was calculated from $^{31}P\{^1H\}$ NMR of the crude product. [c] dr was calculated from $^{31}P\{^1H\}$ NMR. Errors may occur due to overlap. [d] ee was determined from $^{31}P\{^1H\}$ NMR integration of the signals. [e] Toluene was used as the solvent. 3 mol % of cat. was loaded.

Bifunctional symmetrical substrates with two equivalent reactive sites present special opportunities or problems in asymmetric catalysis.[11] After the first addition of the P−H bond to dienone, the selectivity of the second addition of the P−H bond may be the same (*rac* product) or different (*meso* product) depending on the nature of the catalyst and substrates involved. In this reaction, high *rac* selectivity was achieved. In the catalyst system, the palladium serves as a Lewis acid for both Ph_2PH and dienones and makes the 1,4-addition proceed smoothly in an intramolecular manner. The stability of the *ortho*-palladated C,P chiral auxiliary toward displacement by free phosphines in conjunction with the fact that the phosphine species involved

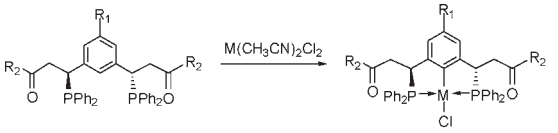
are inherently labile on the Pd(II) center is a crucial factor which aids the catalytic cycle (Scheme 2).

Scheme 2. Proposed Catalytic Cycle



It should be noted that the chiral PCP diphosphines are versatile ligands forming pincer complexes with a broad range of metals. As an illustration, we used the directly

Scheme 3. Synthesis of Chiral PCP Pincer Complexes



synthesized chiral PCP ligand and selected metals (Pd and Pt) for synthesis of chiral PCP pincer complexes in high yields (Scheme 3). Such kinds of pincer complexes have been reported as efficient catalysts for asymmetric transformations.[7,9e]

In summary, we have developed a novel method for the straightforward preparation of chiral tertiary diphosphines by hydrophosphination of dienones catalyzed by a phosphopalladacyle in high yields with excellent diastero- and enantioselectivities. We are currently studying the extension of this method for the synthesis of other chiral tertiary phosphine ligands.

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Supporting Information Available. Experiment procedure; characterization data; single crystal X-ray data; ^{1}H, ^{13}C, $^{31}P\{^{1}H\}$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.