Palladium(II)-catalyzed asymmetric hydrophosphination of enones: efficient access to chiral tertiary phosphines†

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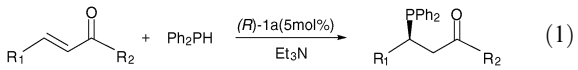
Chiral tertiary phosphines were synthesized by asymmetric hydrophosphination of aromatic enones catalyzed by an organopalladium complex with high yields and stereoselectivity. The procedure offers practical access to chiral tertiary phosphines.

Chiral phosphines, as highly valuable ligands in metal complexes and efficient organocatalysts, are widely used in enantioselective transformations in organic and organometallic chemistry,[1] as well as other actively developing fields including chemotherapy, pest control, and bioorganic chemistry.[2] However, they are generally prepared by resolution or by using stoichiometric amounts of chiral auxiliaries or enantiopure substrates.[2,3] Asymmetric hydrophosphination, the stereocontrolled addition of a P–H bond to unsaturated C–C bonds, provides direct, atom-efficient access to potentially useful chiral phosphines. Surprisingly, very few catalytic asymmetric syntheses of chiral phosphines by hydrophosphination have been reported[4] due to poor stereoselectivity and the lack of efficient methodologies and catalysts. Among the few asymmetric catalyses reported, Pt^0-(Me-Duphos) and Pt^0-(diphos) complexes catalyze hydrophosphination of vinyl esters and vinyl nitriles with low enantioselectivity;[5] Ni^{II} complex catalyzes hydrophosphination of methacrylonitrile;[6] organocatalysts catalyze hydrophosphination of nitroalkenes and α,β-unsaturated aldehydes.[7] However, phosphine-oxides, phosphine-sulfides or phosphine-boranes were usually obtained as products instead of tertiary phosphines due to the fact that these phosphines are quite air sensitive and difficult to handle and achieve. Reduction or removal of borane is therefore necessary in order to get the desired tertiary phosphines. Consequently, developing practical and efficient processes allowing the direct conversion of inexpensive substrates into the desired tertiary chiral phosphines is desirable.

Organopalladium complex (*R*)-{Pd[$Me_2NCH(Me)C_{10}H_6$]-(μ-Cl)}$_2$ (I) is widely used as a resolving agent or chiral template in organic and organometallic chemistry.[8] Our group has widely used it and its derivative (*R*)-**1a** (Table 1) in stoichiometric amounts as a promoter in Diels–Alder,[9] hydroamination,[10] hydrophosphination,[11] and hydroarsination[12] reactions. Based on preliminary studies, herein, we report a new method for synthesis of a series of chiral tertiary phosphines by asymmetric hydrophosphination of aromatic enones catalyzed by (*R*)-**1a** (eqn (1)). In some instances, the enantiomerically enriched or enantiomerically pure free tertiary chiral phosphines could be achieved directly after a simple recrystallization.

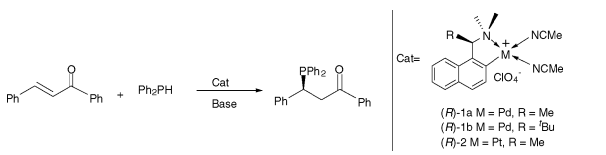


(1)

Initially, we attempted the complex (*R*)-**1a** catalyzed addition of Ph_2PH to *trans*-chalcone (5 mol% (*R*)-**1a** in the presence of Et_3N). The reaction can be conveniently monitored by $^{31}P\{^1H\}$ NMR spectroscopy. We were gratified to find that the reaction was very facile and the $^{31}P\{^1H\}$ NMR spectroscopy indicated the full conversion of Ph_2PH after approximately 23 h at −80 °C in THF. After completion of the reaction, the obtained product was treated with 0.5 equiv. of enantiopure chiral Pd complex (I) leading to formation of two diastereomers. The ee was determined from $^{31}P\{^1H\}$ NMR of the diastereomers.[6] The absolute configurations of the major and minor products were determined from X-ray crystal diffraction analysis of the corresponding diastereomers to be *S* and *R*, respectively.

The conditions for the asymmetric hydrophosphination of *trans*-chalcone were screened and the results are given in Table 1. The examination of solvents revealed that THF is

Table 1 Catalyst, solvent, base, and temperature effects on the reaction of Ph_2PH and *trans*-chalcone[a]



Entry	Cat	Solvent	*T*/°C	Base	ee (%)[b]
1	(*R*)-**1a**	DCM	−80	Et_3N	62
2	(*R*)-**1a**	Acetone	−80	Et_3N	68
3	(*R*)-**1a**	Toluene	−80	Et_3N	68
4	(*R*)-**1a**	THF	−80	Et_3N	77
5	(*R*)-**1a**	$CHCl_3$	−40	Et_3N	49
6	(*R*)-**1a**	NCMe	−40	Et_3N	31
7	(*R*)-**1a**	THF	−40	Et_3N	74
8	(*R*)-**1a**	THF	20	Et_3N	51
9	(*R*)-**1a**	THF	20	none	49[c]
10	(*R*)-**1a**	THF	−80 to 20	DBU	27
11	(*R*)-**1a**	THF	−80	^{t}BuOK	16
12	(*R*)-**1b**	THF	20	Et_3N	—
13	(*R*)-**2**	THF	20	Et_3N	−25

[a] Conditions: 0.35 mmol Ph_2PH, 5 mol% of Cat, 1.1 equiv. of *trans*-chalcone, 0.5 equiv. of base were reacted at the given temperature. The reaction was stopped till full conversion of Ph_2PH, unless otherwise noted. [b] ee was determined from $^{31}P\{^1H\}$ NMR integration of the signals. [c] Stopped at half conversion of Ph_2PH.

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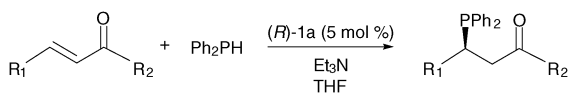
the best option with 77% ee. Similar selectivity was obtained in acetone and toluene with 68% ee followed by DCM with 62% ee. The ee value decreased to 49% and 31% in chloroform and acetonitrile respectively at −40 °C. We further surveyed the temperature effect. The ee decreased from 77% at −80 °C to 74% at −40 °C, and 51% at room temperature. Base also plays an important role in the reaction. In the absence of base, there is no reaction at all at −80 °C, and only half conversion was observed at room temperature after 8 days. The results of screening of bases showed that Et_3N is the appropriate choice. Higher temperature is necessary if DBU is added as a base with associated low ee (22%). If ^{t}BuOK is used as a base, the reaction is completed very fast, but the selectivity is quite low (16% ee). The amount of catalyst loading, as well as concentration of base, has little effect on selectivity, but impacts the rate of the reaction. We designed (*R*)-**1b** with a more steric *tert*-butyl group on the auxiliary in order to improve ee. However, it does not catalyze the reaction even at room temperature. When the platinum analogue (*R*)-**2** was employed for this reaction to study metal effects, the reaction could not move at −80 °C, but it can be completed at room temperature with 25% ee and the product stereoselectivity was reversed (entry 13).

With optimal conditions established, a range of aromatic enones was screened for the asymmetric hydrophosphination reaction catalyzed by (*R*)-**1a**. The results are presented in Table 2. The data in Table 2 shows that the substituents on the substrates influence the reactivity and selectivity. If R_2 is a more bulky moiety such as 2-Naph (entry 2), the reactivity and selectivity both decreased compared with Ph (entry 1). However, if R_1 is replaced by 2-Naph (entry 3), the selectivity improved to 86% ee while reactivity decreased. Therefore, we screened a range of substrates with electron withdrawing and donating groups at R_1 (entries 4 to 7). As expected, substrates

Table 2 (*R*)-**1a**-Catalyzed asymmetric hydrophosphination of various aromatic enones with Ph_2PH[a]



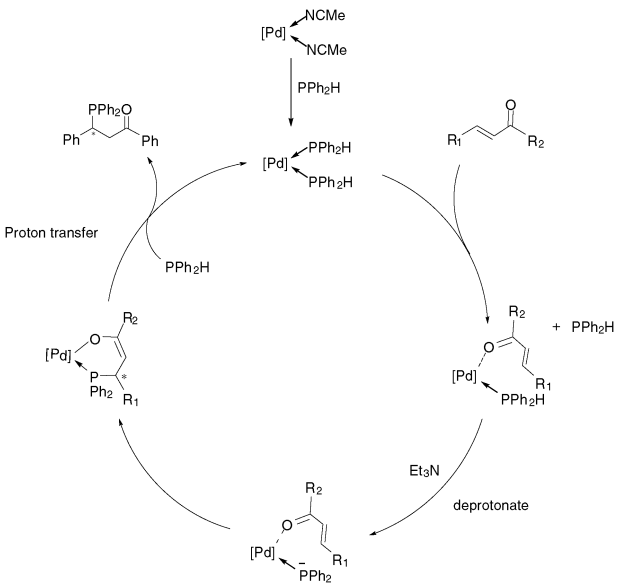
Entry	R_1, R_2	Temp./°C	Time	Yield[b] (%)	ee[c] (%)
1	Ph, Ph	−80	23 h	65 (99)	98 (77)
2	Ph, 2-Naph	−80	50 h	53 (99)	94 (74)
3	2-Naph, Ph	−80	60 h	(99)	(86)
4	2-Naph, 1-Naph	−80	6 d	48 (97)	96 (57)
5	4-ClPh, Ph	−80	40 h	70 (99)	98 (77)
6	Ph, 4-ClPh	−80[d]	6 d	(96)	(57)
7	4-BrPh, Ph	−80[d]	7 d	(92)	(51)
8	4-NO_2Ph, Ph	−80	6 d	67 (99)	88 (70)
9	3-NO_2Ph, Ph	−80	4 d	41 (99)	85 (55)
10	4-OHPh, Ph	−80	7 d	40 (98)	99 (73)
11	4-MeOPh, Ph	20	40 h	(97)	(33)

[a] Conditions: 0.35 mmol Ph_2PH, 5 mol% of (*R*)-**1a**, 5 mL THF, 1.1 equiv. of enone, 0.5 equiv. of Et_3N were reacted at the given temperature, unless otherwise noted. [b] Yields of isolated products after a recrystallization. In parentheses are the yields of isolated products before recrystallization. [c] ee after a recrystallization determined from $^{31}P\{^1H\}$ NMR integration of the signals. In parentheses are the ee's before recrystallization. [d] Temperature raised gradually to 0 °C for another day after indicated time.

with electron withdrawing groups are more active than those with electron donating groups. However, compared with *trans*-chalcone (entry 1), those with substituted groups are less active and need longer time to complete the reaction. This may be caused by the steric hindrance. Other non-aromatic substrates we tried such as 4-phenyl-3-buten-2-one and methyl cinnamate did not work under the same conditions. The obtained free phosphine products are quite air sensitive. It is worth highlighting that some of the free phosphine products could be purified to nearly optically pure phosphines by a simple recrystallization from DCM/acetone.[13] This can be accomplished using a Schlenk line under nitrogen protection which makes it a practical and efficient method to obtain optically pure chiral tertiary phosphines.

Based on the experimental results and studies, a possible catalytic cycle of the asymmetric hydrophosphination reaction of enones is proposed (Scheme 1).

The bisacetonitrile complex (*R*)-**1a** has two active sites. Ph_2PH could easily replace NCMe on the two sites to form the bisdiphenylphosphine complex. However, due to the strong *trans* effect, the Ph_2PH *trans* to carbon is labilized and could dissociate easily. Once the Ph_2PH dissociates, the enone substrate could coordinate to palladium. Regarding the addition of nucleophiles to enones catalyzed by palladium, the mechanism involving C=C bond coordination with palladium leading to formation of *C*-bound palladium enolate in equilibrium with *O*-enolate or oxa-π-allyl species has been proposed.[14] However, in our case, ^{13}C NMR analysis of the analogous [Pd](enone)(PPh_3) shows that the carbonyl oxygen is more likely to coordinate to palladium rather than the C=C moeity. Meanwhile, the coordinated phosphine is acidified by the palladium and thus is susceptible to be deprotonated by Et_3N easily to form the phosphido species. The phosphido intermediate undergoes a 1,4-addition with enone to form an *O*-enolate intermediate followed by proton transfer to generate the product. In order to better understand the mechanism, we treated stoichiometric (*R*)-**1a** with Ph_2PH to form [Pd](NCMe)(Ph_2PH) ($^{31}P\{^1H\}$ NMR: δ 12.7). A phosphido



Scheme 1 Proposed catalytic cycle.

complex [Pd](NCMe)(Ph_2P^-) ($^{31}P\{^1H\}$ NMR: δ −69.7) could be generated immediately when equivalent Et_3N was added with characteristic color change. However, the phosphido complex did not react with the enone at −80 °C to form the expected product. Therefore the free phosphines play an important role in driving the catalytic cycle and the palladium serves as a Lewis acid both for Ph_2PH and enone in this reaction.

During the preparation of this manuscript, Duan and co-workers[15] reported a similar hydrophosphination reaction catalyzed by a pincer palladium complex with phosphine-oxides as the product.

In conclusion, we have developed a novel palladium(II) catalyzed asymmetric hydrophosphination of aromatic enones to prepare chiral tertiary phosphines with high yields and stereoselectivity. The procedure provides practical direct access to potentially useful optically pure chiral phosphines. Further work to design a better catalyst and improve selectivity as well as extension to other substrates is in progress.

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