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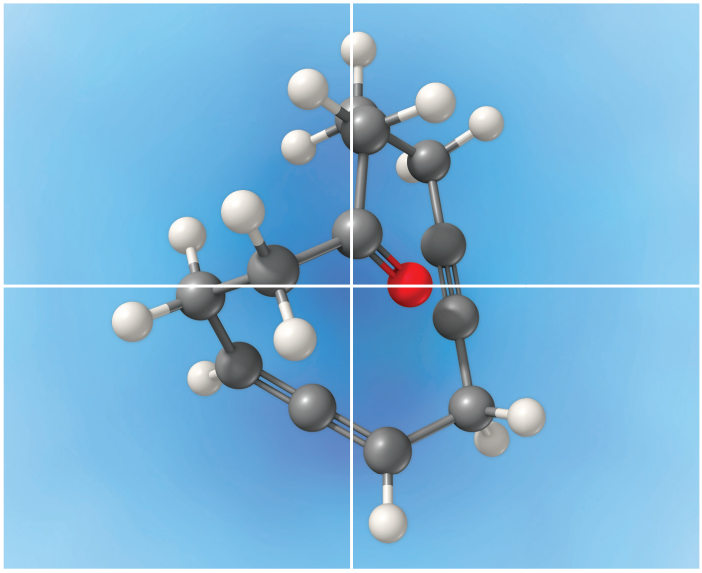

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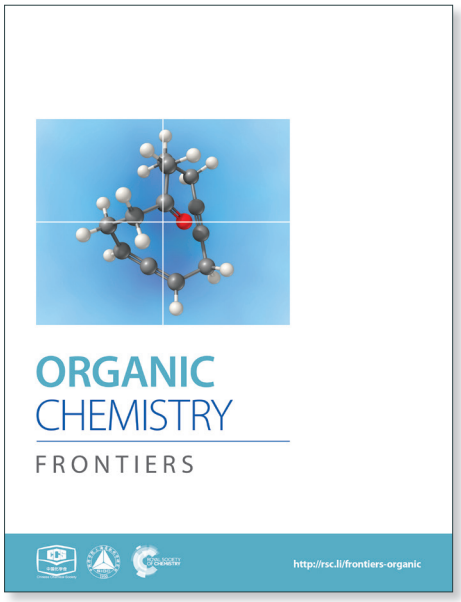

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RESEARCH ARTICLE

Palladium-catalyzed 1,4-addition of secondary alkylphenylphosphines to α,β-unsaturated carbonyl compounds for the synthesis of phosphorus- and carbon-stereogenic compounds†

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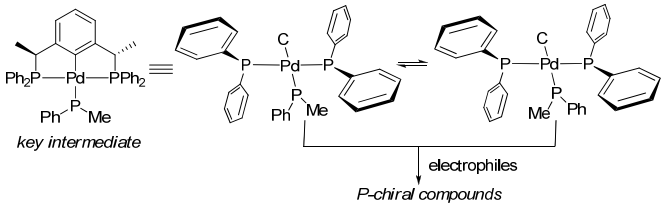
Highly stereoselective 1,4-addition of alkylphenylphosphines to α,β-unsaturated carbonyl compounds catalyzed by PCP or NCN pincer–Pd complexes is described to synthesize chiral phosphorus compounds bearing both P- and C-stereogenic centers with good to excellent enantioselectivity (up to 99.6% ee).

Chiral phosphines are ligands widely used in catalytic reactions to control reactivity and enantioselectivity.[1] Among these phosphines, axially chiral, carbon-stereogenic, or planar-chiral phosphine ligands, such as binap, diop, and josiphos, are frequently used to construct optically active compounds from prochiral starting materials. By contrast, phosphorus (P)-chiral phosphines are relatively less employed in catalysis.[2] The first reported chiral phosphine ligand contains only one P-stereogenic center,[3] likely because the preparation of P-chiral compounds is synthetically more challenging compared with other compounds.[4] Reported methods always involve the optical resolution of racemates or desymmetrization of prochiral compounds with stoichiometric amounts of chiral reagents. These methods also require multiple-step transformations. Direct construction of a P–C bond, along with P-chiral center formation via asymmetric catalysis, appears to be a promising approach to solving this synthetic problem.[5,6] Several methods, including transition metal-catalyzed arylation and alkylation of secondary phosphines with good to excellent enantioselectivities, have been reported by Glueck et al. and Toste/Bergman et al., respectively.[7] Asymmetric Michael addition of methylphenylphosphine to enones was recently reported to generate P- and C-chiral phosphorus compounds with up to 82% ee by Leung et al.[8] However, certain limitations still in terms of the extent of stereoselectivity and generality of the substrates must be addressed. In the present study, we describe a palladium-catalyzed asymmetric addition of disubstituted phosphines to α,β-unsaturated carbonyl compounds for the synthesis of P- and C-stereogenic phosphorus compounds with good to excellent enantioselectivities.



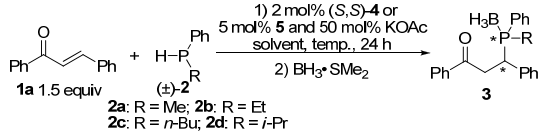
Scheme 1 Proposed protocol for P-chiral compound synthesis.

We previously reported the bisphosphine (PCP) pincer Pd-catalyzed asymmetric addition of diarylphosphines to electron-deficient alkenes for the synthesis of diverse chiral phosphine compounds.[9] A Pd-diphenylphosphido intermediate was generated from the reaction of diphenylphosphine with Pd catalyst and proposed as the active nucleophile toward electrophiles in the catalytic cycle.[9a] We hypothesized that the use of secondary phosphine nucleophiles bearing two different groups (e.g., methylphenylphosphine) could generate two Pd-phosphido diastereomers within a chiral environment induced by two methyl groups at the benzylic position of the catalyst. Subsequent functionalization of these intermediates could lead to the formation of P-stereogenic phosphorus compounds (Scheme 1)

We initiated the reaction of alkylphenyl phosphines with chalcone in the presence of pincer-Pd catalysts. The reaction of methylphenylphosphine **2a** with enone **1a** in the presence of catalyst (*S*,*S*)-**4**[10,11] only afforded products in low ee and dr (Table 1, entry 1).[12] Solvent screening and temperature reduction to −30 °C did not lead to satisfactory results (entries 2–5). Changing the methyl group to ethyl and n-butyl groups in the P nucleophiles increased the ee and diastereomeric ratios of products (entries 6–7). Interestingly, introduction of an isopropyl group to substrate **2d** significantly improved the ee of the product to 99% as well as its diastereoselectivity (entry 8; dr>10/1). To increase stereoselectivity in the reaction of methylphenyl phosphine with chalcone, bisimidazoline (NCN) pincer catalysts **5a**–**5i** were synthesized and examined.[13] Catalyst (*S*,*S*)-**5a** derived from (*S*)-phenylglycinol bearing a 4-methoxyphenyl group on the nitrogen atom afforded two diastereomers with good ee (entry

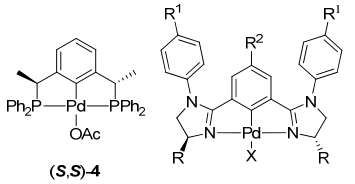
9: 74 and 83% ee; 1.3/1 dr) at −30 °C.[14] By changing the substituted groups on the imidazoline ring to benzyl, isopropyl, and isobutyl groups, catalysts **5b–5d** produced products with decreased enantioselectivity (entries 10–12). Investigations on temperature effects showed that reaction at room temperature yields products with 81% and 91% ee (entry 14). By changing the substituted group to 4-tolyl on the nitrogen atom or installation of a methoxy group at the phenyl ring of the catalyst, catalysts (*S*,*S*)-**5e** and **5f** did not exhibit beneficial effects on the ee and dr (entries 15–16). Use of catalysts **5g** and 5**h** featuring chloride or iodide anions caused a decrease in ee (entries 17–18). Changing KOAc to K_2CO_3 or removing KOAc in the reaction led to decreased ee (entries 19–20). Catalyst **5i** bearing acetate anions also afforded products with lower ee than **5a** (entry 21) via a slightly peculiar manner, the reason for which remains unclear at this point. Afterward, extensive examination of the solvents revealed that dichloromethane is optimal compared with other solvents (entries 22–25) at room temperature; toluene and tert-amyl alcohol afforded products with slightly low ee. Unexpectedly, using toluene as the solvent at −5 °C, products with the highest ee were isolated (entry 27: 87% and 96% ee). Further temperature reduction to −10 °C decreased the ee of both diastereomers (entry 28: 86% and 79% ee). For P nucleophiles **2b–2c**, catalyst **5a** only produced the corresponding products with moderate ee compared with catalyst **4** (entries 29–31).

Table 1 Palladium-catalyzed addition of alkylphenylphosphines **2** to chalcone **1a**.



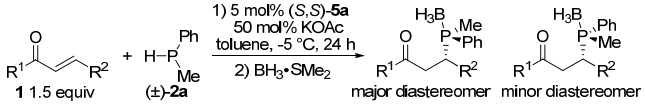
Entry	Phosphine	Catalyst	Solvent	Temp (°C)	Yield (%)[a]	Dr[b]	ee (%)[c]
1	**2a**	(*S*,*S*)-**4**	Toluene	rt	83	1.7/1	22/47
2	**2a**	(*S*,*S*)-**4**	Toluene	−5	55	1.9/1	32/43
3	**2a**	(*S*,*S*)-**4**	Toluene	−30	96	3.0/1	28/32
4	**2a**	(*S*,*S*)-**4**	CH_2Cl_2	−30	83	3.9/1	56/28
5	**2a**	(*S*,*S*)-**4**	THF	−30	88	2.5/1	40/47
6	**2b**	(*S*,*S*)-**4**	Toluene	−5	96	11/1	86/65
7	**2c**	(*S*,*S*)-**4**	Toluene	−5	85	4.7/1	58/86
8	**2d**	(*S*,*S*)-**4**	Toluene	−5	80	>10/1	99.5
9	**2a**	(*S*,*S*)-**5a**	CH_2Cl_2	−30	74	1.3/1	74/83
10	**2a**	(*S*,*S*)-**5b**	CH_2Cl_2	−30	93	1.7/1	53/75
11	**2a**	(*S*,*S*)-**5c**	CH_2Cl_2	−30	93	1.8/1	44/67
12	**2a**	(*S*,*S*)-**5d**	CH_2Cl_2	−30	75	2.0/1	24/51
13	**2a**	(*S*,*S*)-**5a**	CH_2Cl_2	0	83	1.3/1	81/90
14	**2a**	(*S*,*S*)-**5a**	CH_2Cl_2	rt	87	1.4/1	81/91
15	**2a**	(*S*,*S*)-**5e**	CH_2Cl_2	rt	81	1.3/1	60/85
16	**2a**	(*S*,*S*)-**5f**	CH_2Cl_2	rt	83	1.4/1	78/83
17	**2a**	(*S*,*S*)-**5g**	CH_2Cl_2	rt	87	1.4/1	80/88
18	**2a**	(*S*,*S*)-**5h**	CH_2Cl_2	rt	94	1.5/1	61/75
19[d]	**2a**	(*S*,*S*)-**5a**	CH_2Cl_2	rt	97	1.2/1	71/74
20[e]	**2a**	(*S*,*S*)-**5a**	CH_2Cl_2	rt	94	1.4/1	61/80
21[e]	**2a**	(*S*,*S*)-**5i**	CH_2Cl_2	rt	97	1.4/1	75/84
22	**2a**	(*S*,*S*)-**5a**	Toluene	rt	70	1.3/1	82/89
23	**2a**	(*S*,*S*)-**5a**	*t*-AmOH	rt	74	1.2/1	80/89
24	**2a**	(*S*,*S*)-**5a**	MeOH	rt	33	2.5/1	15/25
25	**2a**	(*S*,*S*)-**5a**	DMF	rt	77	1.5/1	58/71
26	**2a**	(*S*,*S*)-**5a**	Toluene	0	80	1.3/1	83/95
27	**2a**	(*S*,*S*)-**5a**	Toluene	−5	98	1.1/1	87/96
28	**2a**	(*S*,*S*)-**5a**	Toluene	−10	95	0.9/1	86/79
29	**2b**	(*S*,*S*)-**5a**	Toluene	−5	88	2.7/1	36/34
30	**2c**	(*S*,*S*)-**5a**	Toluene	−5	98	2.2/1	66/7
31	**2d**	(*S*,*S*)-**5a**	Toluene	−5	81	1.6/1	12/73

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC with hexane/2-propanol. [d] 50 mol% K_2CO_3 used.. [e] Without addition of KOAc.



The scope of substrates was examined under optimum conditions, and the results are shown in Table 2. Methylphenylphosphine reacted with enones bearing diverse substituted groups (i.e., alkyl, methoxy, halide, and nitro) smoothly, thereby yielding a series of phosphorus compounds with good to excellent enantiomeric excess (Table 2: entries 1–9). For substrates bearing an isopropyl moiety at the β-position, the ee of products is lower than that in the case of aryl groups (entry 10). α,β-Unsaturated N-acyl pyrroles have been reported to be good acceptors in asymmetric addition reactions.[15] The pyrrole group can be easily converted into various moieties.[16] Experimental results indicate that various α,β-unsaturated N-acyl pyrroles show properties comparable with those of enones in terms of ee and dr (entries 11–17), which further extends the applicability of the current catalytic system. Table 3 summarizes the reactions of isopropylphenylphosphines with α,β-unsaturated enones and N-acyl pyrroles. All of the products were isolated with almost perfect enantioselectivities and moderate to good diastereomeric ratios (Table 3: entries 1–8; 98 to 99.6% ee). To illustrate the utility of the current method, a bisenone was reacted with a secondary phosphine **2d** to yield a chiral bisphosphine bearing four stereogenic centers in 99% ee (Scheme 2); this biphosphine is a useful ligand for the preparation of P-chiral pincer metal catalysts.[6q,17]

Table 2 Palladium-catalyzed asymmetric addition of methylphenylphosphines to *α,β*-unsaturated carbonyl compounds.

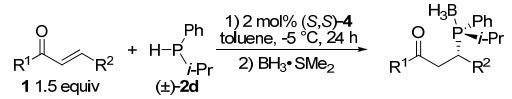


Entry	R^1	R^2	Yield(%)/(dr)[a,b]	Ee of major- and minor-product

				(%)[c,d]
1	Ph	Ph	98 (1.1/1)	87/96
2	Ph	4-MeC_6H_4	97 (1.1/1)	88/95
3	Ph	4-$MeOC_6H_4$	92 (1.2/1)	89/95
4	Ph	3-BrC_6H_4	94 (1.1/1)	87/96
5	Ph	4-BrC_6H_4	98 (1.1/1)	83/96
6	Ph	4-$O_2NC_6H_4$	94 (1.2/1)	87/97
7	Ph	4-$CF_3C_6H_4$	86 (1.3/1)	81/95
8	4-BrC_6H_4	Ph	88(1.2/1)	89/94
9	Me	4-BrC_6H_4	98(1.7/1)	89/94
10	Ph	*i*-Pr	91(2.6/1)	72/85
11	1-pyrrolyl	Ph	84(1.2/1)	86/93
12	1-pyrrolyl	4-MeC_6H_4	97(1.2/1)	84/93
13	1-pyrrolyl	2-naphthyl	91(1.2/1)	85/93
14	1-pyrrolyl	4-$MeOC_6H_4$	95(1.1/1)	83/92
15	1-pyrrolyl	4-$NO_2C_6H_4$	97(1.1/1)	85/93
16	1-pyrrolyl	3-BrC_6H_4	98(1.2/1)	84/95
17	1-pyrrolyl	4-BrC_6H_4	96(1.2/1)	86/96

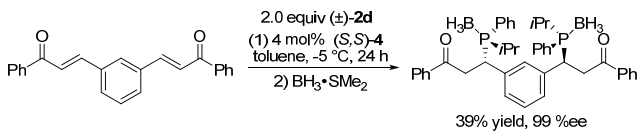
[a] Isolated yields. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC with hexane/2-propanol. [d] The absolute configurations of products were determined to be S,S_p for major diastereomers and S,R_p for minor diastereomers by X-ray crystal diffraction of 1,4-adducts in entries 9 and 17 (see Supporting Information for details).[18]

Table 3 Palladium-catalyzed asymmetric addition of isopropylphenylphosphine to *α,β*-unsaturated carbonyl compounds.



Entry	R^1	R^2	Yield(%)/(dr) [a,b]	ee (%)[b,c]
1	Ph	Ph	80(>10/1)	99.5
2	Ph	4-$MeOC_6H_4$	84(>10/1)	98
3	Ph	4-$NO_2C_6H_4$	85(>10/1)	99
4	3-BrC_6H_4	Ph	88(>10/1)	99.4
5	1-pyrrolyl	Ph	83(7/1)	98
6	1-pyrrolyl	4-BrC_6H_4	80(5/1)	99.6
7	1-pyrrolyl	3-BrC_6H_4	81(6/1)	99
8	1-pyrrolyl	2-Naphthyl	78(5/1)	>99.5

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC with hexane/2-propanol. [d] The absolute configurations of products were determined to be S,R_p by X-ray crystal diffraction of 1,4-adduct in entry 1 (see Supporting Information for details).[18]



Scheme 2 Synthesis of an optically pure P-stereogenic bisphosphine.

In summary, we have described the enantioselective addition of alkylphenylphosphines to *α,β*-unsaturated carbonyl compounds catalyzed by PCP and NCN pincer Pd catalysts to yield chiral phosphorus compounds bearing both P- and C-stereogenic centers with good to excellent enantioselectivity under mild conditions. Further studies will elucidate the stereochemistry-determining factors and applications of P-chiral compounds as ligands to transition metals in catalysis.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, and analytical data for all new compounds. See DOI: 10.1039/b000000x/.

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