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Palladium-Catalyzed 1,4-Addition of Diarylphosphines to α,*β*-Unsaturated Aldehydes

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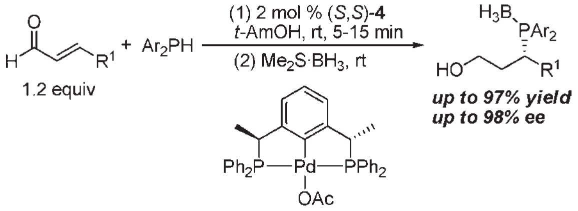
ABSTRACT



A highly stereoselective asymmetric 1,4-addition of diarylphosphines to α,*β*-unsaturated aldehydes catalyzed by a bis(phosphine) pincer−Pd complex has been developed for the synthesis of chiral phosphines with excellent stereoselectivity (up to 98% ee) under mild conditions. The application of the current method to the synthesis of enantiopure bisphosphine and its pincer−Pd complex has also been demonstrated.

Enantioselective conjugate addition is one of the most important processes in asymmetric catalysis.[1] It comprises the reactions of various electron-deficient alkenes with nucleophiles to furnish valuable optically active compounds. In this process, α,*β*-unsaturated aldehydes have been frequently used as electrophilic components to react with various carbon,[1b−d] nitrogen,[1g] sulfur,[1h] and oxygen[1i] nucleophiles, because of the versatility of their carbonyl group for further functionalization. On the other hand, the asymmetric addition of phosphorus nucleophiles to α,*β*-unsaturated aldehydes have been scarcely investigated,[2,3] although the obtained phosphorus adducts can be very useful precursors for the preparation of chiral phosphine ligands for asymmetric catalysis.[4] Recently, Melchiorre and Cordova independently reported the first asymmetric conjugate addition of diphenylphosphine to α,*β*-unsaturated aldehydes in the presence of proline-derived organocatalysts with excellent enantioselectivities and yields.[5] Aside from these two examples, no other catalytic methods were reported in the above reaction. Recently, we successfully

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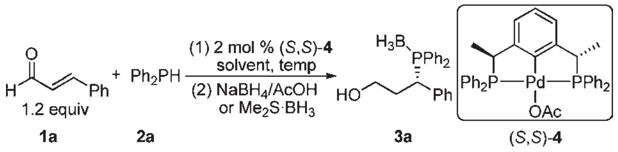
developed a highly stereoselective hydrophosphination of enones catalyzed by a Pd catalyst.[3a] To continue our research, in the current paper, we describe a bis(phosphine) (PCP) pincer Pd-catalyzed asymmetric addition of diarylphosphines to α,*β*-unsaturated aldehydes, producing chiral phosphorus compounds with excellent stereoselectivities and yields.

Table 1. Palladium-Catalyzed Asymmetric Addition of Diphenylphosphine to α,*β*-Unsaturated Aldehyde **1a**

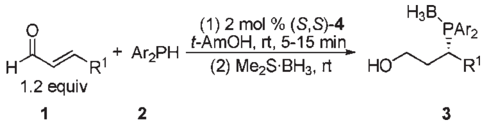


entry[a]	temp (°C)	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	0	THF	5	89	85
2	0	CH_2Cl_2	5	61	52
3	0	hexane	5	27	27
4	0	toluene	5	40	73
5	0	THF	5	54	92
6	−10	THF	5	58	97
7	−20	THF	5	40	94
8	0	CH_2Cl_2	3	69	66
9	0	$ClCH_2CH_2Cl$	3	43	93
10	0	toluene	3	55	82
11	0	Et_2O	3	33	78
12	0	CH_3CN	3	79	38
13	rt	dioxane	3	64	91
14	rt	*t*-BuOH	3	93	95
15	rt	*t*-AmOH	3	97	97

[a] The reactions in entries 1−4 were quenched with 3.5 equiv of $NaBH_4$/3.5 equiv of AcOH; the reactions in entries 5−15 were quenched with 3 equiv of $Me_2S \cdot BH_3$ (2 M in THF). [b] Isolated yields. [c] Determined by HPLC with hexane/2-propanol.

The current experiment started with the reaction of *trans*-cinnamaldehyde with diphenylphosphine in the presence of 2 mol % PCP pincer−PdOAc (*S*,*S*)-**4**[3a] catalyst as the model reaction (Table 1). Given the reversibility of this reaction,[6] the borohydride or borane as the reduced reagent was added to interrupt the existing equilibrium at the workup step through the reduction of carbonyl groups and the formation of more stable borane−phosphine complexes. The reaction proceeds well in THF at 0 °C with $NaBH_4$ as the reductant, to afford the 1,4-adduct **3a** with good yield and moderate ee (89% yield and 85% ee; entry 1). Other solvents exhibited inferior results (27−61% yield, 27−73% ee; entries 2−4). The reaction at −10 °C using $Me_2S \cdot BH_3$ as the reducing reagent instead of $NaBH_4$ significantly improved the enantioselectivity to 97%; however the yield was only 58% (entry 6). Lowering the temperature to −20 °C resulted in a decrease in the ee and yield of **3a** (entry 7). A solvent screen reveals that *t*-BuOH is a much better solvent than the others (entries 8−14). Furthermore, *tert*-amyl alcohol afforded the product with the best stereoselectivity and yield (97% ee and 97% yield; entry 15).

Table 2. Palladium-Catalyzed Asymmetric Addition of Diarylphosphines to α,*β*-Unsaturated Aldehydes

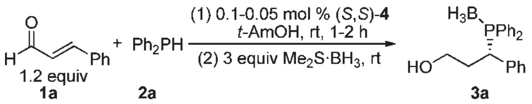


entry[a]	R^1	Ar	yield (%)[b]	ee (%)[c,d]
1	Ph	Ph	97	97
2	*p*-$MeOC_6H_4$	Ph	78	96
3	*m*-MeC_6H_4	Ph	92	98
4	*p*-$O_2NC_6H_4$	Ph	95	94
5	*p*-BrC_6H_4	Ph	92	94
6	*m*-ClC_6H_4	Ph	96	89
7	*m*-BrC_6H_4	Ph	93	94
8	*o*-ClC_6H_4	Ph	92	83
9	2-Naphthyl	Ph	96	96
10	cyclohexyl	Ph	96	81
11	Ph	3,5-diMeC_6H_3	86	91
12	Ph	*p*-$MeOC_6H_4$	85	87
13	Ph	*p*-ClC_6H_4	80	93

[a] The reaction was quenched with 3 equiv of $Me_2S \cdot BH_3$ (2 M in THF). [b] Isolated yields. [c] Determined by HPLC with hexane/2-propanol. [d] The absolute configurations of products were determined to be *S* by comparison of the specific optical rotation of the adduct (entry 1) with the value reported in the literature; see Supporting Information for details.

Under the optimum conditions with (*S*,*S*)-**4** as the catalyst, various α,*β*-unsaturated aldehydes having the electron-donating or -withdrawing groups on the aryl moiety both reacted with diphenylphosphine with excellent stereoselectivities and yields (78−97% yield, 83−98% ee; Table 2, entries 1−9). An alkyl substituted substrate under the current system afforded an adduct with a somewhat lower stereoselectivity (96% yield, 81% ee; entry 10). With respect to the nucleophilic component, phosphines bearing electron-donating or -withdrawing groups were effectively added to **1a**, forming products with high yields and enantioselectivities (80−86% yield, 87−93% ee; entries 11−13).

Considering that most of the reactions in Table 2 proceeded completely within 15 min and exhibited a high yield, the catalytic activity of the pincer−Pd catalyst **4** in the proposed reaction was investigated (eq 1). The reaction reached full conversion in 1 h using 0.1 mol % of catalyst **4**, and the adduct **3a** was isolated with 96% ee and 91% yield. Decreasing the catalyst loading further to 0.05 mol % also furnished the desired product with 95% ee and 85% yield. Hence, the pincer−Pd **4** complex (0.05 mol %) has a much



(1)

0.1 mol % (*S*,*S*)-**4**: 91% yield, 96% ee
0.05 mol % (*S*,*S*)-**4**: 85% yield, 95% ee

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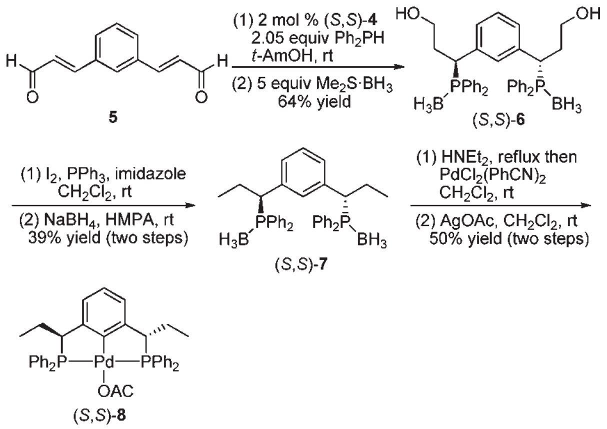
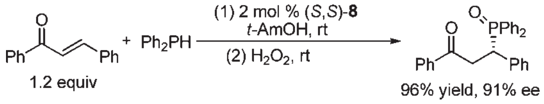
(6) (a) Moiseev, D. V.; Patrick, B. O.; James, B. R. *Inorg. Chem.* **2007**, *46*, 11467. (b) Moiseev, D. V.; Marcazzan, P.; James, B. R. *Can. J. Chem.* **2009**, *87*, 582.

higher catalytic activity[7] in the proposed reaction than the reported organocatalysts (10–20 mol %).[5]

Scheme 1. Application of the Current Method to the Synthesis of Chiral Bisphosphine and Its Pincer–Pd Complex



To demonstrate the utility of the current method, enantiopure bisphosphine and its PCP–Pd complex were prepared, and the products were subsequently used in asymmetric catalysis. The synthetic route is shown in Scheme 1. First, the meta-substituted bis α,*β*-unsaturated aldehyde **5** was reacted with diphenylphosphine in the presence of 2 mol % (*S*,*S*)-**4** catalyst. The bisphosphine adduct was isolated with 99% ee and 64% yield. Its hydroxyl group was then converted to H within two steps to provide an ethyl substituted bisphosphine–borane complex **7**, which is a very useful ligand precusor for the synthesis of various transition-metal PCP pincer complexes.[8] Next, the chiral bisphosphine **7** was transferred into its pincer–PdOAc complex (*S*,*S*)-**8**, which is an analogue of catalyst **4**. The use of (*S*,*S*)-**8** in the catalytic reactions shows that it can also catalyze the asymmetric addition of diphenylphosphine to enones with excellent enantioselectivity (96% yield and 91% ee; eq 2).[9]



(2)

In summary, we have developed the use of a pincer PdOAc catalyst for the highly stereoselective addition of diarylphosphines to α,*β*-unsaturated aldehydes. The phosphination products can be obtained with excellent yields and ee. The high catalytic activity of the pincer Pd catalyst and the applicability of the current method to the synthesis of chiral PCP pincer ligands for asymmetric reactions have also been demonstrated.

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Supporting Information Available. Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For the asymmetric addition of diphenylphosphine to *trans*-cinnamaldehyde with (*S*,*S*)-**8** catalyst, the product was isolated with 84% yield and 67% ee.