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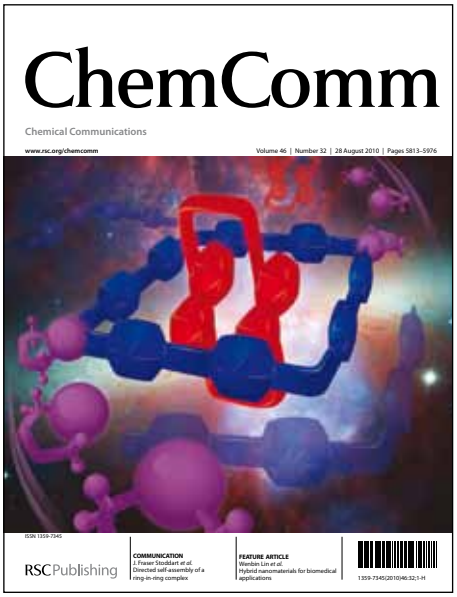

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Palladium-catalyzed asymmetric addition of diarylphosphines to *N*-tosylimines†

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A bis(phosphine) pincer Pd complex-catalyzed asymmetric addition of diarylphosphines to *N*-tosylimines was developed for the synthesis of chiral phosphine sulfides with high stereoselectivities (up to 96% ee) in mild conditions.

The catalytic asymmetric addition of nucleophiles to imines is one of most important synthesis routes for chiral amines. Various carbon and heteroatom nucleophiles have been extensively employed in this process during the past decades.[1] Among phosphorus nucleophiles, phosphites are the most frequently used substrates in reactions with imines, which produce optically active α-amino phosphonic acid derivatives (eqn (1)).[2,3] The obtained α-amino phosphonates and their derivatives have received a considerable amount of attention because of their potential biological activity as antibiotics,[4] anti-viral agents,[5] and enzyme inhibitors.[6] The use of secondary phosphine oxides as nucleophiles in enantioselective addition reactions with imines (eqn (2)) have only been recently investigated. Particular examples include that highly enantioselective chiral guanidinium-catalyzed addition of phosphine oxides and H-phosphinates to *N*-tosylimines that was reported by Tan et al.,[7a] the Zn-catalyzed addition of dialkyl phosphine oxides to chiral (*S*)-*N*-*tert*-butanesulfinyl imines that was reported by Wang et al.,[7b] and the asymmetric addition of diarylphosphine oxides to *N*-benhydryl imines, which is catalyzed by chiral magnesium BINOL phosphate, that was reported by Antilla et al..[7c] However, investigations on the catalytic asymmetric addition of trivalent secondary phosphines to imines have not been reported to date (eqn (3)).[8-9] This process can generate optically active α-amino trivalent phosphine, which can serve as chiral P,N-ligands to transition metals.[10] The phosphorus atom in these compounds can also be functionalized with reducing reagents or oxidants to produce chiral borane-phosphine complexes or phosphine sulfides that have α-amino groups. Notably, the potential biological properties of chiral α-amino borane-phosphines or phosphine sulfides have not been explored because of the absence of direct synthetic methods.

In our previous study, a highly stereoselective hydrophosphination of electron-deficient alkenes catalyzed by a Pd catalyst was successfully conducted.[8d,8j,8l] As a continuation of our research, a bis(phosphine) (PCP) pincer Pd-catalyzed addition of diarylphosphines to *N*-tosylimines to produce chiral phosphine sulfides with high enantioselectivities and yields is described in this study.

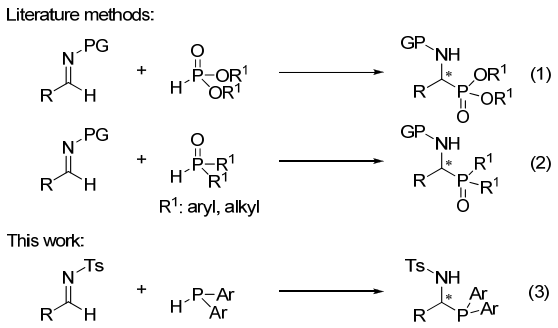
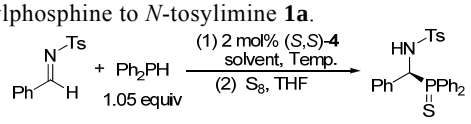


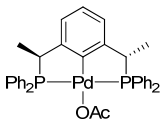
Table 1. Palladium-catalyzed addition of diphenylphosphine to *N*-tosylimine **1a**.



1a **2a** **3a**

Entry	Solvent	T (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	CH_2Cl_2	rt	2	81	31
2	THF	rt	2	55	22
3	$ClCH_2CH_2Cl$	rt	2	77	26
4	dioxane	rt	2	89	40
5	toluene	rt	2	88	38
6	DME	rt	2	99	61
7	Et_2O	rt	2	91	77
8	MTBE	rt	3.5	85	87
9	MTBE	−30	4	90	93
10	MTBE	−60	6.5	53	80

[a] Isolated yields. [b] Determined by chiral HPLC with hexane/2-propanol.



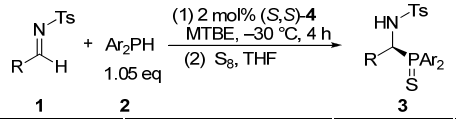
(*S*,*S*)-**4**

The addition reaction of diphenylphosphine to *N*-tosylimine **1a**, with 2 mol% PCP pincer–PdOAc (*S*,*S*)-**4**[11,12] as the catalyst, was investigated (Table 1). Given the air sensitivity of the trivalent phosphorus atom, the formed product was oxidized to the phosphine sulfide using S_8 prior to analysis.

Solvent screening at room temperature indicated that methyl *tert*-butyl ether (MTBE) is the optimal solvent, affording the product **3a** with 87% ee and 85% yield (Table 1, entry 8). The phosphine sulfide with the highest stereoselectivity (90% yield, 93% ee; entry 9) was obtained when the reaction temperature was decreased to −30 °C.

With optimized conditions obtained, various substrates **1** that bear electron-donating or -withdrawing groups on the aromatic ring reacted with diphenylphosphine to produce the chiral phosphine sulfides in high yields with good stereoselectivities (84–99% yield, 78–96% ee; Table 2, entries 1–7).[13] It's worth pointing out that 2-thiofuryl and 3-thiofuryl substituted *N*-tosylimines, which show strong ability to coordinate with late transition metals via the sulfur atom, also can be used as the substrate to afford the corresponding products with good ee and yields (90–95% yield, 86–91% ee; entries 8 and 9). With respect to the nucleophilic component, phosphines that have electron-donating or -withdrawing groups can be coupled with imines to form products with good yields and enantioselectivities as well (89–97% yield, 84–86% ee; entries 10 and 11). In addition, secondary phosphines bearing two different groups, such as phenyl and methyl moieties, were also employed to react with *N*-tosylimines. The corresponding products having both P-stereocenter and C-stereocenter were obtained in good yields, but with low diastereoselectivities and enantioselectivities (entries 12 and 13).[14] The absolute configuration of the product was determinated to be *S* through X-ray crystal diffraction analysis of the phosphine sulfide (Table 2, entry 4; Figure 1).[15]

Table 2. Palladium-catalyzed asymmetric addition of secondary phosphines to *N*-tosylimines.



1 **2** **3**

Entry	R	Ar_2PH	Yield[a] (%)	ee[b] (%)
1	Ph	Ph_2PH	90	93
2	*p*-$MeOC_6H_4$	Ph_2PH	98	96
3	*m*-$MeOC_6H_4$	Ph_2PH	84	95
4	*p*-MeC_6H_4	Ph_2PH	93	94
5	*p*-ClC_6H_4	Ph_2PH	99	86
6	*m*-BrC_6H_4	Ph_2PH	89	78
7	2-naphthyl	Ph_2PH	86	84
8	2-thiofuryl	Ph_2PH	90	91
9	3-thiofuryl	Ph_2PH	95	86
10	Ph	$(p\text{-}ClC_6H_4)_2PH$	97	86
11	*p*-$MeOC_6H_4$	$(p\text{-}MeOC_6H_4)_2PH$	89	84
12[c]	*m*-$MeOC_6H_4$	Ph(Me)PH	96 (1:0.9)[d]	(0;0)[e]
13[c]	2-thiofuryl	Ph(Me)PH	87 (1.5:1)[d]	(0;16)[e]

[a] Isolated yields. [b] Determined by chiral HPLC with hexane/2-propanol. [c] Ph(Me)PH was used instead of Ph_2PH as the nucleophile. [d] the ratios of two diastereomers in parentheses were determined by ^1H NMR analysis of the crude products. [e] the ee of the major and minor diastereomers in parentheses.

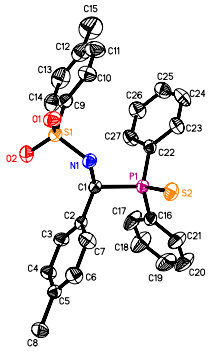
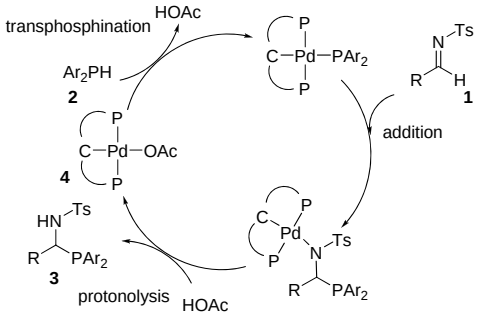


Figure 1. X-ray structure of the phosphine sulfide (Table 2, entry 4) with the thermal ellipsoids drawn at the 50% probability level.

The proposed catalytic cycle for this process is shown in Scheme 1. First, the transphosphination between the diarylphosphine and the pincer–PdOAc produces a Pd-PAr_2 intermediate[8d], the similar metal-PAr_2 intermediates have been reported in phosphorus-addition reactions of electronic-deficient alkenes[3g,3i], and asymmetric phosphination reactions of alkyl and aryl halides.[9] This Pd-PAr_2 species then reacts with *N*-tosylimine to generate a Pd-amido intermediate. Finally, protonolysis of the amido-Pd bond by AcOH in the system then regenerates the active catalyst and releases the addition product **3**.



Scheme 1. Proposed catalytic cycle for the Pd-catalyzed addition of diarylphosphines to *N*-tosylimines.

In summary, a PCP pincer palladium-catalyzed asymmetric addition of diarylphosphines to *N*-tosylimines was developed for the synthesis of chiral phosphine sulfides in mild conditions. Exploration of the obtained phosphorus compounds as the ligand in asymmetric reactions is undergoing.

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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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15 CCDC 894186 contains 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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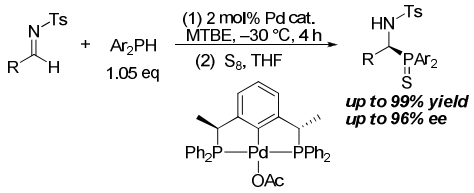

An asymmetric addition of diarylphosphines to *N*-tosylimines catalyzed by a bis(phosphine) pincer–Pd complex has been developed for the synthesis of chiral phosphine sulfides with high stereoselectivities.