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Synthesis of Biaryl *P,N* Ligands by Novel Palladium-Catalyzed Phosphination Using Triarylphosphines: Catalytic Application of C−P Activation

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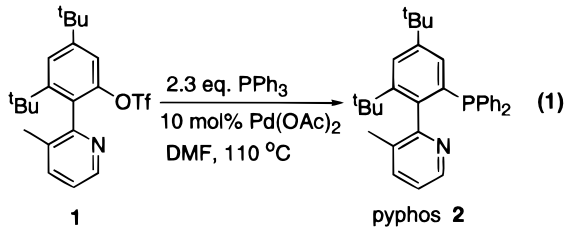
Summary: *The first application of palladium-catalyzed phosphination using tertiary phosphines as the diarylphosphinating agents for the synthesis of biaryl P,N ligands from their corresponding O,N triflates was reported.*

During the past few decades, tertiary phosphines have attracted considerable interest, especially as important ligands for transition metals and as versatile intermediates in organic synthesis.[1] Previous methods of transition-metal-catalyzed phosphination for introducing the diphenylphosphino group into aryl halides or triflates to yield the triarylphosphines have several drawbacks. The $Pd^0/Ph_2P(O)H$ route requires subsequent reduction by trichlorosilane.[2] The $Pd^0/Ph_2PH{\cdot}BH_3$ method is not applicable to amine- or pyridine-containing compounds and requires deprotection.[3] Air- and moisture-sensitive reagents are used in the Ni/Ph_2PH,[4] Ni/Ph_2PCl,[5] and Pd/Ph_2PSiMe_3 routes.[6] In the course of the synthesis of biaryl *P,N* ligands for asymmetric catalysis, we have discovered a novel one-step synthesis of atropisomeric *P,N* ligands from their corresponding *O,N* triflates under neutral conditions using triarylphosphine as the phosphinating agents.

$Pd(OAc)_2$ and Ph_3P were found to be a catalyst and a diphenylphosphinating agent, respectively, for aryl triflates. Pyridylphenyl triflate **1**, prepared by trifluoromethanesulfonation[7] of pyridylphenol,[8] was reacted with 2.3 equiv of triphenylphosphine catalyzed by 10 mol % of $Pd(OAc)_2$ in DMF at 110 °C for about 4 days to give pyphos **2** in 68% yield (eq 1). The rate of the



1 pyphos **2** (1)

formation and the yield of **2** increased when the catalyst loading was increased from 5 to 10 mol %. Further increase of the amount of catalyst caused a slight decrease of the product yield. Other palladium catalysts such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were also effective and gave comparable yields.[9] Other complexes, such as $Ni(OAc)_2$, $PdCl_2$, $Pd(MeCN)_2Cl_2$, $Pd(PPh_3)_2Cl_2$, $PtCl_2$, and $Pt(PPh_3)_4$ did not show any catalytic activity.

Polar aprotic solvents were found to be most suitable. *N,N*-Dimethylformamide (DMF) was the best solvent, while *N*-methyl-2-pyrrolidinone (NMP) and dimethyl sulfoxide (DMSO) gave lower phosphine yields. The reduction side product may be due to the competitive protonolysis of the Pd−aryl intermediate.[10] The much less polar solvent THF was found to be inferior, even with extended reaction time.

The amount of triphenylphosphine used was critical. When a stoichiometric amount of triphenylphosphine was added, only about 10% conversion of **1** to **2** was observed.[11] When the amount of triphenylphosphine[12] was increased up to 2.3 equiv, the rate of the reaction drastically increased and the yield was the highest. When more than 2.5 equiv of PPh_3 was used, the yield of the *P,N* product **2** rapidly dropped, and finally the reaction completely stopped when 4 equiv of triphenylphosphine was added. Presumably excess phosphine decreases the catalytic efficiency by lowering the

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(9) $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ gave 64% and 61% yields of pyphos **2**, respectively.

(10) Pedersen, J. R. *Acta Chem. Scand.* **1972**, *26*, 929−932.

(11) Percentage conversion was determined by ^1H NMR integration from the crude reaction mixture.

(12) Commercially available triphenylphosphine and recrystallized triphenylphosphine gave the same result: Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, U.K., 1988; p 302.

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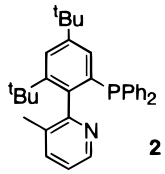
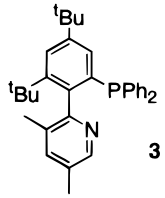
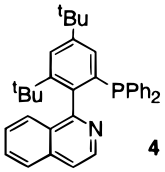
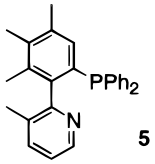
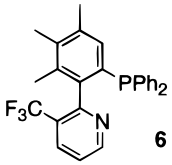
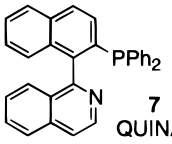
Table 1. Palladium-Catalyzed Phosphination of Various *O,N* Triflates with Triphenylphosphine

Entry	Products	Time / d	% yield[a]
1	 **2**	4.5	68
2	 **3**	4.5	60
3	 **4**	4.5	58
4	 **5**	4.0	53
5	 **6**	4.0	57
6	 **7** QUINAP	4.5	53

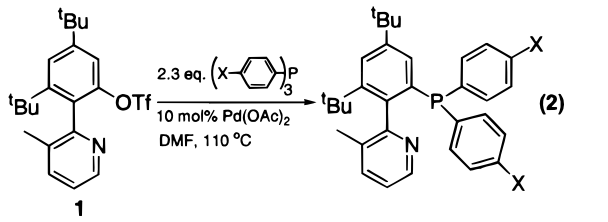
[a] The isolated yield is reported.

concentration of active and coordinatively unsaturated palladium species.[13]

The palladium-catalyzed phosphination method was applied to the synthesis of various new *P,N* ligands **2**−**6**[14] from their corresponding *O,N* triflates, and the results are summarized in Table 1. Both sterically and electronically different substrates had little influence on the rate of reaction and the yield of the product.

Substituted triarylphosphines were also effective diarylphosphinating agents for the synthesis of *P,N* ligands **8** and **9**, giving nearly the same yields (eq 2 and Table 2).[15] Preliminary rate studies showed that the electron-rich triarylphosphines exhibited faster rates of phosphination.[16]

Table 2. Palladium-Catalyzed Phosphination with Different *para*-Substituted Triarylphosphines

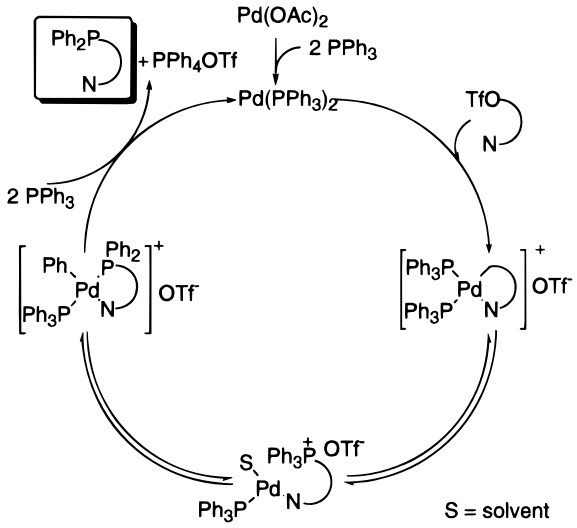


1

product	X	time/days	yield/%[a]
2	H	4.5	68
8	Me	4.5	60
9	OMe	3.5	60

[a] The isolated yield is reported.

Scheme 1



Scheme 1 illustrates a plausible mechanism for the reaction. Palladium(II) acetate is reduced *in situ* by triphenylphosphine to PdL_2 (L = triphenylphosphine).[17] The PdL_2 species undergoes oxidative addition with pyridylphenyl triflate **1** to give a Pd(II) species; subsequent reductive elimination with triphenylphosphine gives a phosphonium salt.[16] Then carbon−phosphorus bond activation of the phosphonium salt generates the coordinated *P,N* product.[13,18] Finally, ligand substitution by triphenylphosphine to give the Pd(II) complex regenerates the PdL_2 species and gives the free phosphine product and the tetraphenylphosphonium triflate.[19]

In summary, a novel, convenient, palladium-catalyzed phosphination of aryl triflates using economical triarylphosphines as the diarylphosphinating reagents has been newly developed. This synthetic methodology may soon have industrial application for the synthesis of various tertiary phosphines. Application of this phosphination method for the synthesis of other tertiary

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phosphines and their uses in asymmetric catalysis are in progress.

Experimental Section. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. *N*,*N*-Dimethylforamide (DMF) and *N*-methylpyrrolidinone (NMP) were distilled from magnesium sulfate under nitrogen. Silica gel was used for column chromatography. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$, and the chemical shifts were referenced internally with tetramethylsilane (δ 0.00 ppm) as the internal standard. ^{13}C NMR spectra were obtained at 75 MHz in $CDCl_3$ and referenced to the residual $CHCl_3$ (δ 77.0 ppm) in $CDCl_3$. ^{31}P NMR spectra were obtained at 162 MHz, and chemical shifts were referenced to 85% H_3PO_4 (δ 0.00 ppm) externally. Mass spectra were recorded in either the electron ionization (EI) or the fast atom bombardment (FAB) mode using *m*-nitrobenzyl alcohol (NBA) as the matrix.

General Procedure for Palladium-Catalyzed Phosphination. 2-(2′-(Diphenylphosphino)-4′,6′-di-*tert*-butyl-1′-phenyl)-3-methylpyridine (2, pyphos). 3,5-Di-*tert*-butyl-2-(3′-methyl-2′-pyridyl)phenyl trifluoromethanesulfonate **1** (1.07 g, 2.5 mmol), palladium acetate (56 mg, 0.25 mmol), and triphenylphosphine (1.51 g, 5.8 mmol) were dissolved in dry DMF (10 mL) under nitrogen. The solution was heated to 110−115 °C for 4.5 days, and the color of the solution changed from yellow to red. The reaction mixture was cooled, and DMF was removed under reduced pressure. The residue was purified by column chromatography on silica gel using a solvent mixture of hexane and ethyl acetate (6:1) as the eluent to obtain the crude product (R_f = 0.6). This crude product was further purified by column chromatography on silica gel using a solvent mixture of toluene and ethyl acetate (20:1) as the eluent to afford the pure 2-(2′-diphenylphosphino-4′,6′-di-*tert*-butyl-1′-phenyl)-3-methylpyridine (**2**, pyphos; 790 mg, 68%) as a white solid. R_f = 0.6 (toluene/ethyl acetate = 15:1). ^{1}H NMR: δ 1.13 (s, 9 H), 1.17 (s, 9 H), 1.94 (s, 3 H), 7.04−7.30 (m, 13 H), 7.60 (d, 1 H, J = 2.0 Hz), 8.34 (d, 1 H, J = 4.3 Hz). ^{13}C NMR: δ 19.9, 31.1, 32.4, 34.8, 37.2, 125.8, 127.9, 128 (d, J_{CP} = 8.0 Hz), 128.2 (d, J_{CP} = 4.6 Hz), 130.1, 131.2 (d, J_{CP} = 7.6 Hz), 131.1 (d, J_{CP} = 7.5 Hz), 133.4 (d, J_{CP} = 19.3 Hz), 134.0 (d, J_{CP} = 20.0 Hz), 137.1 (d, J_{CP} = 8.7 Hz), 138.0 (d, J_{CP} = 9.3 Hz), 138.2, 145.1, 147.1 (d, J_{CP} = 5.6 Hz), 149.7; ^{31}P NMR: δ −11.60. MS (EI): *m*/*z* (relative intensity) 465 (M^+, 80), 450 (88), 408 (100), 388 (82), 374 (22), 358 (35), 342 (23). HRMS (ESIMS): calcd for $C_{32}H_{36}NPH^+$ 466.2658, found 466.2622.

Acknowledgment. We thank the Research Grants Council of Hong Kong Central Allocation (ERB003) for financial support.

Supporting Information Available: Text giving details of the synthesis and spectral data for products **3**−**6**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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