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Solvent-free palladium-catalyzed phosphination of aryl bromides and triflates with triphenylphosphine

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Abstract—Palladium-catalyzed phosphination of substituted aryl bromides and triflates using triphenylphosphine as the phosphinating agent was developed using solvent-free conditions. This operationally simple method tolerates ketone, aldehyde, ester, nitrile and ether functional groups. © 2002 Elsevier Science Ltd. All rights reserved.

Solvent-free chemical synthesis has received much attention recently.[1,2] Solvent-free processes are not only environmentally benign but also economical.[3] Since solvent is not required, toxic wastes can be minimized or eliminated and so the cost of solvent and waste treatment is reduced. Furthermore, operational simplicity is an attractive feature. Recent advances in this area include, for example, aldol[4] and related reactions,[5] asymmetric-catalyzed addition[6] and catalyzed cross-coupling reactions.[7]

Aryl phosphines are an important class of ligands in transition metal-catalyzed reactions. We have recently reported that aryl bromides[8] and triflates[9] are converted into the corresponding aryl phosphines/arsines by palladium-catalyzed phosphination or arsination[9] with triaryl phosphines or triphenylarsine without the need of air-sensitive reagents or catalysts. We now report the results of an improved, operationally simple catalyzed phosphination in solvent-free conditions.

The results of this solvent-free phosphination are shown in Table 1. The prototype substrates of 4-bromoacetophenone and 4-acetylphenyl triflate were reacted with 2.3 equiv. of triphenylphosphine in the presence of 10 mol% palladium acetate catalyst at 115°C for 1.5 days and 1 day to yield 4-(diphenylphosphino)acetophenone in 44 and 40% yields, respectively (Table 1, entries 1 and 2). Consistent with earlier reports,[8,9] aryl triflates are more reactive than bromides. The triflates reacted faster by 50–80% presumably due to having a better leaving group.[10]

Nonaflates(ONf)[11] reacted at a similar rate and gave similar yields to the triflates (Table 1, entry 5). Other functional groups, such as aldehydes, esters, nitriles and methyl ethers, are tolerant to this phosphination reaction without the need of protecting groups[12] (Table 1). Even sterically more hindered *ortho*-substituted triflates reacted (Table 1, entries 15 and 17). The (2-cyanophenyl)diphenylphosphine product (Table 1, entry 17) is an important starting material for the synthesis of the optically active phosphinooxazoline *P*,*N* ligands of the Pfaltz type.[13] Nearly the same rate was observed for electronically different non-coordinating aryl bromides or triflates (Table 1, entries 1, 2, 8 and 9). The reactions of coordinating substrates which contained ester, aldehyde and nitrile groups (Table 1, entries 3 and 6), required longer reaction times for aryl bromides. Presumably the strongly coordinating substrates rendered the complex coordinatively saturated and hence with reduced catalytic efficiency.

The rate of the reaction was nearly the same for the bromides but much slower for the triflates in a manner consistent with the reactions carried out in DMF.[8,9] The yields of the products were, however, slightly higher.[8,9] Since anhydrous DMF and air-sensitive starting materials are not required, the reaction is operationally simple and user-friendly.

A plausible mechanism for this solvent-free phosphination is similar to our earlier suggested one.[8,9] $Pd(OAc)_2$ is reduced in situ by triphenylphosphine to Pd(0).[14]

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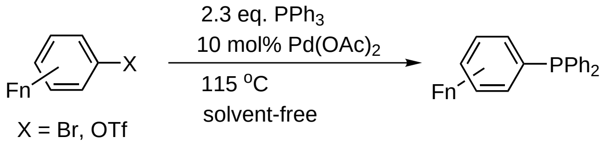
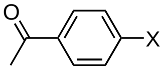
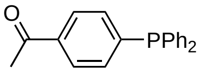
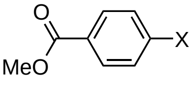
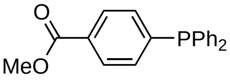
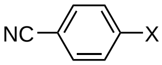
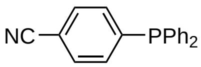
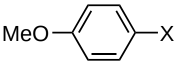
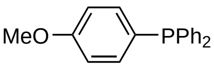
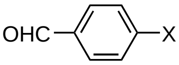
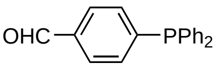
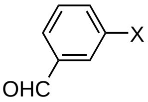
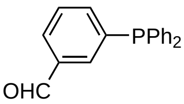
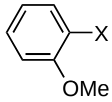
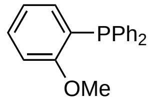
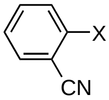
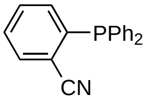
Table 1. Catalytic, solventless phosphination of aryl bromides, triflates and nonaflate



Entry	Substrate	X	Product	Time/d	%Yield
1		X = Br		1.5	44
2		X = OTf		1.0	40
3		X = Br		2.5	40
4		X = OTf		1.5	42
5		X = ONf		1.5	43
6		X = Br		2.5	38
7		X = OTf		1.0	38
8		X = Br		1.0	33
9		X = OTf		0.8	26
10		X = Br		2.5	40
11		X = OTf		2.5	42
12		X = Br		2.5	34
13		X = OTf		1.5	38
14		X = Br		After 7 days, no reaction	
15		X = OTf		3.5	27
16		X = Br		After 7 days, no reaction	
17		X = OTf		2.5	37

Subsequent oxidative addition with an aryl bromide or triflate yields an aryl Pd(II) species. Reductive elimination with triphenylphosphine then gives an aryltriphenylphosphonium salt[15] which undergoes oxidative addition of a C–P bond[16] with the palladium species to generate the coordinated phosphine product. Finally ligand substitution by triphenylphosphine regenerates the Pd(0) species and substituted phosphine product.

The exact physical state of the reaction is not clear at this stage. The reaction occurs either in the molten or solid state. While the reaction took place at 110°C, Ph_3P with a melting point of 80°C, is a liquid while tetraphenylphosphonium salts melt above 160°C.[15] However, the intermediate aryltriphenylphosphonium salt and aryldiphenylphosphine may be in the solid or liquid state depending on substituents. The reaction mixture did appear to be in the solid state by visual inspection. The reaction might occur in the interfacial molten state.[17] However, further experiments are needed to determine the physical state of the reaction to gain further understanding of the solvent-free phosphination.

In conclusion, an operationally simple and environmentally benign solvent-free catalyzed phosphination of aryl bromides and triflates with triphenylphosphines has been developed.

Experimental procedure: 4-Bromoacetophenone (100 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol) and PPh_3 (301 mg, 1.15 mmol) were placed in a Teflon stopcock flask. The flask was then evacuated and refilled with nitrogen three times. The mixture was heated to 115°C and the reaction was monitored by GC MS or TLC. After completion, the reaction mixture was cooled down and the crude product was purified by column chromatography on silica gel using a solvent mixture of hexane/ethyl acetate (20/1) as the eluent to give 4-(diphenylphosphino)acetophenone in 44% yield as white solids.

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