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Copper-Catalyzed C–P Bond Construction via Direct Coupling of Phenylboronic Acids with H-Phosphonate Diesters

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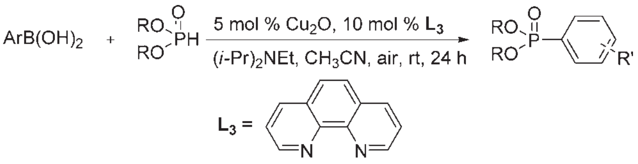
ABSTRACT



A mild and efficient method was developed for the copper-catalyzed additions of H-phosphonate diesters to boronic acids under the copper catalyst system Cu_2O/1,10-phenanthroline. To the best of our knowledge this finding is the first example of a copper-catalyzed synthesis of aryl phosphonates from arylboronic acids and H-phosphonate dialkyl esters.

The importance of phosphorus compounds in organic synthesis,[1] materials,[2] and medicinal chemistry[3] has been well documented for years. The creation of new organophosphorus compounds and, naturally, of new phosphination reactions could thus have a great impact on various fields of chemical science. The most efficient routes to these compounds involve palladium-catalyzed cross-coupling of aryl halides with diaryl and dialkyl phosphites.[4] In general, most efforts in the cross-coupling methods currently are geared toward a wide variety of phosphorus nucleophiles, i.e. phosophonates esters, hypophosphite, dialkyl- or diaryl-phosphine oxides, phosphines, and phosphine–borane complexes.[5] While palladium catalysts can be replaced by copper in many coupling processes,[6] this

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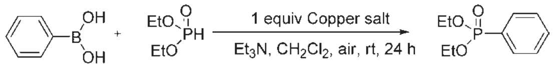
cheaper and more convenient alternative form of catalysis was not often used in aryl−P bonds formation.[7]

Recent reinvestigation of Chan and Lam[8] type chemistry showed that many of the carbon−heteroatom bond formations may be carried out using boronic acids and cupric acetate [$Cu(OAc)_2$] as the catalyst. Although the majority of efforts have been focused on the formation of carbon−nitrogen,[9] −oxygen,[10] and −sulfur bonds,[11] limited protocols for the direct coupling of arylboronic acid with secondary phosphonates have been published.[12] Here, we report a more convenient and inexpensive copper-catalyzed method for the synthesis of aryl phosphonates. The advantage of this method was that the coupling reaction could be performed under milder conditions compared to that of the classical Hirao arylation protocols.[4,5]

Table 1. Optimization of Copper Source[a]



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

entry	catalyst	yield (%)[b]
1	$Cu(OAc)_2$	5[c]
2	$Cu(OAc)_2$	35
3	CuO	trace
4	$CuCl_2$	28
5	$CuBr_2$	7
6	$Cu(OTf)_2$	56
7	CuCl	40
8	CuBr	14
9	CuI	43
10	Cu_2O	75[d]

[a] *Reaction conditions:* **1a** (1 mmol), **2a** (0.5 mmol), copper salt (0.05 mmol), triethylamine (1.5 mmol), 1,10-phenanthroline (0.05 mmol) in 2 mL of CH_2Cl_2 at room temperature in air, 24 h. [b] Isolated yield based on H-phosphonate diester **2a**. [c] Copper salt (0.5 mmol), without 1,10-phenanthroline. [d] Copper salt (0.25 mmol).

First, the reaction was performed under "classical" Chan−Lam conditions, using 1 equiv of $Cu(OAc)_2$, 2 equiv of phenylboronic acid **1a**, 1 equiv of H-phosphonate diester **2a**, and 3 equiv of triethylamine at room temperature in CH_2Cl_2. After 24 h, the desired P−C product was formed in a 5% yield and ^{31}P NMR spectroscopy showed the starting material disappeared (Table 1, entry 1). These results indicated that the cross-coupling was feasible, and hence a deeper study of the reaction was conducted. It has been demonstrated that certain additives could be employed to enhance the efficiency of copper-catalyzed reactions.[7,13] Therefore, we decided to test commercially available 1,10-phenanthroline as a ligand for the copper-catalyzed phosphonation of aryl boronic acid. Various copper salts were tested for the proposed reaction using 1,10-phenanthroline as a ligand in air at rt (Table 1, entries 2−10). Cu_2O, which is relatively inexpensive and easy to

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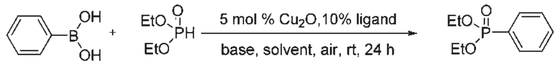
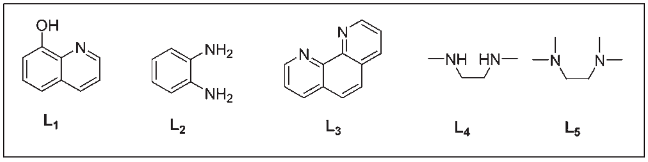
handle, showed relatively higher catalytic efficiency compared with other copper salts and thus was chosen as the catalyst for further optimization.

Table 2. Ligand and Base Effects on Reactivity[a]



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

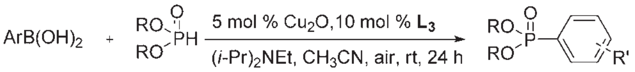


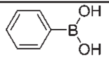
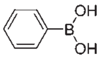
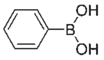
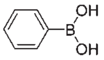
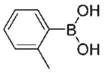
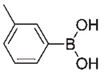
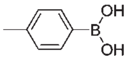
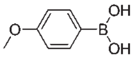
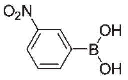
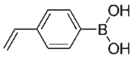
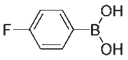
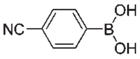
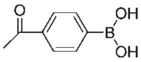
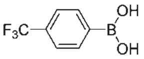
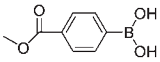
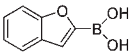
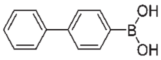
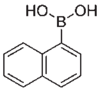
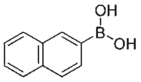
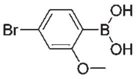
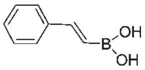
entry	solvent	base	ligand	yield (%)[b]
1	CH_2Cl_2	Et_3N	$\mathbf{L_1}$	trace
2	CH_2Cl_2	Et_3N	$\mathbf{L_2}$	21
3	CH_2Cl_2	Et_3N	$\mathbf{L_3}$	75
4	CH_2Cl_2	Et_3N	$\mathbf{L_4}$	66
5	CH_2Cl_2	Et_3N	$\mathbf{L_5}$	19
6	CH_3CN	Et_3N	$\mathbf{L_3}$	91
7	toluene	Et_3N	$\mathbf{L_3}$	54
8	THF	Et_3N	$\mathbf{L_3}$	81
9	DME	Et_3N	$\mathbf{L_3}$	82
10	DMSO	Et_3N	$\mathbf{L_3}$	23
11	CH_3CN	pyridine	$\mathbf{L_3}$	54
12	CH_3CN	$(i\text{-Pr})_2NEt$	$\mathbf{L_3}$	96
13	CH_3CN	K_2CO_3	$\mathbf{L_3}$	35[c]
14	CH_3CN	Cs_2CO_3	$\mathbf{L_3}$	17[c]
15	CH_3CN	$(i\text{-Pr})_2NEt$	$\mathbf{L_3}$	37[d]
16	CH_3CN	$(i\text{-Pr})_2NEt$	$\mathbf{L_3}$	9[e]
17	CH_3CN	$(i\text{-Pr})_2NEt$	$\mathbf{L_3}$	56[f]

[a] *Reaction conditions:* H-phosphonate diester (0.5 mmol), $PhB(OH)_2$ (1 mmol), Cu_2O (0.025 mmol), base (1.5 mmol), ligand (0.05 mmol) in 2 mL of solvent at room temperature in air, 24 h. [b] Isolated yield based on H-phosphonate diester **2a**. [c] 0.75 mmol of base was used. [d] 0.5 mmol of $PhB(OH)_2$ was used. [e] In ambient nitrogen. [f] In ambient oxygen.

Further screening of the catalytic reaction conditions involved examination of various ligands to promote the formation of the aryl phosphonates (Table 2, entries 1–5). The most efficient one was ligand $\mathbf{L_3}$, 1,10-phenanthroline, which gave **3a** in 75% yield. The effect of the solvent was also investigated (Table 2, entries 6–10). Moderate yields of the desired P–C product **3a** were obtained using acetonitrile as a solvent (91%) (Table 2, entry 6). Other solvents resulted in lower yields of **3a**: i.e. toluene (54%), DME (82%), and THF (81%) (Table 2, entries 6–10). The effect of base confirmed that $(i\text{-Pr})_2NEt$ was the best choice for this transformation (Table 2, entries 11–14). In general, 2 equiv of boronic acid are necessary to achieve optimal yields (Table 2, entry 15). This is due to the competing side reaction of the formation of PhOH and PhOPh.[12c] To evaluate the importance of air, the arylation of H-phosphonate diester was performed in pure nitrogen, which only gave a yield of 9% (Table 2, entry 16). This indicates that the oxygen is essential, probably because oxygen could oxidize the copper complex to Cu(III), facilitating the reductive elimination of aryl phosphonates.[14] However, when the reaction was performed under pure oxygen instead of air, the yield also dropped from 96% to 56% (Table 2, entry 17). This could be due to the accelerating

Table 3. Copper-Catalyzed Cross-Coupling of Arylboronic Acids with H-Phosphonate Diesters[a]



entry	$ArB(OH)_2$	R	product	yield (%)[b]
1		Et	**3a**	96
2		Me	**3b**	72
3		*i*-Pr	**3c**	95
4		Bn	**3d**	54
5		Et	**3e**	75
6		Et	**3f**	86
7		Et	**3g**	84
8		Et	**3h**	83
9		Et	**3i**	78
10		Et	**3j**	94
11		Et	**3k**	79
12		Et	**3l**	64
13		Et	**3m**	90
14		Et	**3n**	71
15		Et	**3o**	85
16		Et	**3p**	47
17		Et	**3q**	76
18		Et	**3r**	68
19		Et	**3s**	78
20		Et	**3t**	71
21		Et	**3u**	78

[a] *Reaction conditions:* H-phosphonate diester (0.5 mmol), $PhB(OH)_2$ (1 mmol), Cu_2O (0.025 mmol), $(i\text{-Pr})_2NEt$ (1.5 mmol), $\mathbf{L_3}$ (0.05 mmol) in 2 mL of CH_3CN at room temperature in air, 24 h. [b] Isolated yield based on H-phosphonate diester.

effect of pure oxygen on the competing side reaction of the formation of tetraethyl hypodiphosphate, which was detected by ^{31}P NMR.[15]

With these optimized reaction conditions, a variety of substrates were surveyed to explore the scope and limitations of the reaction (Table 3). H-phosphonate diesters bearing different alkyl groups (Table 3, entries 1−3) and boronic acids bearing different aryl groups with electron-donating or electron-withdrawing substituents (Table 3, entries 6−9) coupled efficiently under these reaction conditions. The dibenzyl phosphonate resulted in a less satisfying yield of 54% of product **3d** due to partial dealkylation and oxidation, which was detected by ^{31}P NMR spectroscopy (Table 3, entry 4). Employing the sterically demanding *o*-tolylboronic acid (Table 3, entry 5) resulted in a reduced yield (75%) compared with the *p*-substituted counterpart (84%) (Table 3, entry 7). The reaction is tolerant of a wide range of functional groups, including cyano, ketones, and ester groups (Table 3, entries 12−15). The only studied heteroaromatic boronic acid resulted in a less satisfying yield of 47% of product **3p** (Table 3, entry 16). Interestingly, aryl halides are also tolerated, without cross-coupling being observed (Table 3, entry 20). Finally, a vinylboronic acid was coupled to **2a**, proceeding stereoselectively and with retention of the original stereochemistry to give the desired product **3u** in 78% yield (Table 3, entry 21).

In conclusion, we have developed a novel copper-catalyzed carbon−phosphorus bond formation protocol from aromatic boronic acids under mild conditions. This reaction further extends the scope of copper-catalyzed aryl and alkenylboron cross-coupling chemistry, and we anticipate its use in both complex molecule synthesis and P-chiral organophosphorus compounds synthesis applications. Further investigations are in progress.

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Supporting Information Available. General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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