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Nickel-Catalyzed C–P Cross-Coupling of Arylboronic Acids with P(O)H Compounds

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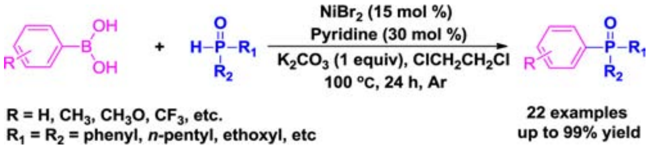
ABSTRACT



A novel and efficient Ni-catalyzed coupling of a wide range of arylboronic acids with H-phosphites, H-phosphinate esters, and H-phosphine oxides has been developed, providing a general and powerful tool for the synthesis of various aryl-phosphorus compounds, especially for valuable triarylphosphine oxides, in good to excellent yield. This protocol is the first Ni-catalyzed C–P bond-forming reaction between arylboronic acids and P(O)H compounds.

Transition-metal-catalyzed C–P bond construction for the synthesis of aromatic organophosphorus compounds has aroused great interest among synthetic chemists in the past 20 years due to their wide applicability in a variety of fields. Particularly, triarylphosphine oxides are an extremely important class of chemicals, which have made a great contribution to organic synthesis,[1] polymers,[2] pharmaceuticals[3] and photoelectric materials,[4] and coordination chemistry as ligands after their reduction.[5] The preparation of triarylphosphine oxides has attracted much attention for their important roles. A number of efficient approaches for the metal-catalyzed synthesis of triarylphosphine oxides have been developed over the years, including the Ni-,[6] Cu-,[7] Mn-,[8] and Pd-catalyzed[9] coupling of secondary phosphine oxides with various aryl partners.

Nevertheless, despite the fact that arylboronic acids are the most extensively used substrates in transition-metal-catalyzed C_{sp^2}–X bond cross-couplings in the effective

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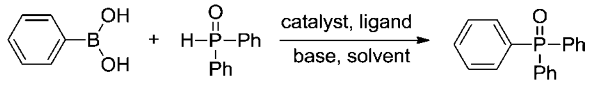
formation of C$-$C[10] and C$-$N[11] bonds owing to their commercial availability and structural diversity, the C$-$P bond-forming reactions using arylboronic acids substrates are far more challenging, and there are only two reported examples.[9b,12] Recently, the first Pd-catalyzed cross-coupling of arylboronic acids with H-phosphonates have been reported,[9b] which exemplified that arylboronic acids are potential coupling partners for C$-$P bond formation. However, their general use poses severe limitations owing to the limited substrate scope, as well as the requirement of microwave irradiation, environmentally unbenign *p*-benzoquinone as the oxidant, and DMF with a high boiling point as the solvent, which are neither economically attractive nor environmentally benign. Very recently, our group[12] reported C$-$P bond construction via a Chan$-$Lam type reaction using arylboronic acids under mild conditions, but the method also heavily suffered from a poor substrate scope, only affording a trace of triarylphosphine oxides using secondary phosphine oxides as substrates owing to their oxidation by the catalytic system. Therefore, it is a highly exigent and preferred endeavor to find a readily available, inexpensive, and efficient transition-metal catalyst for the synthesis of valuable triarylphosphine oxides via the cross-coupling of arylboronic acids with secondary phosphine oxides. As part of our endeavors to develop environmentally friendly new methods for the construction of P$-$C bonds,[6f,7f,12,13] we decided to tackle this problem and herein disclose the first versatile Ni-catalyzed cross-coupling of readily available arylboronic acids with P(O)H compounds in general and secondary phosphine oxides in particular under mild conditions. To the best of our knowledge, this method is the first example of a Ni-catalyzed cross-coupling of arylboronic acids with P(O)H compounds leading to aryl phosphonate, aryl phosphinate and particularly, arylphosphine oxides.

Table 1. Optimization of Reaction Conditions[a]



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

entry	catalyst	solvent	base	ligand	yield (%)[b]
1	Ni(OAc)$_2$	DCE	K$_2$CO$_3$	pyridine	71
2	Ni(PPh$_3$)$_2$Cl$_2$	DCE	K$_2$CO$_3$	pyridine	62
3	Ni(acac)$_2$	DCE	K$_2$CO$_3$	pyridine	61
4	NiCl$_2$	DCE	K$_2$CO$_3$	pyridine	80
5	**NiBr$_2$**	**DCE**	**K$_2$CO$_3$**	**pyridine**	**91**
6	NiBr$_2$	dioxane	K$_2$CO$_3$	pyridine	72
7	NiBr$_2$	toluene	K$_2$CO$_3$	pyridine	78
8	NiBr$_2$	DMF	K$_2$CO$_3$	pyridine	trace
9	NiBr$_2$	DCE	Et$_3$N	pyridine	25
10	NiBr$_2$	DCE	pyridine	pyridine	12
11	NiBr$_2$	DCE	Cs$_2$CO$_3$	pyridine	40
12	NiBr$_2$	DCE	K$_2$CO$_3$	2,2′-bpy	90
13	NiBr$_2$	DCE	K$_2$CO$_3$	dppp	trace
14	NiBr$_2$	DCE	K$_2$CO$_3$	TMEDA	68
15	NiBr$_2$	DCE	K$_2$CO$_3$	1,10-Phen	28
16	NiBr$_2$	DCE	K$_2$CO$_3$	pyridine	90[c]
17	NiBr$_2$	DCE	K$_2$CO$_3$	pyridine	74[d]
18	NiBr$_2$	DCE	K$_2$CO$_3$	pyridine	72[e]

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), catalyst (15 mol %), ligand (15 mol %) for bidentate, 30 mol % for monodentate), base (0.5 mmol), solvent (1.5 mL), 100 °C, 24 h, under argon. [b] Isolated yield based on **2a**. [c] Under air. [d] At 80 °C. [e] Using 10 mol % of NiBr$_2$.

Initially, we attempted to explore an effective catalytic system for the coupling of phenylboronic acid with diphenylphosphine oxide in the presence of Ni(OAc)$_2$ (15 mol %), pyridine (30 mol %), K$_2$CO$_3$ (1 equiv), and ClCH$_2$CH$_2$Cl (DCE, 1.5 mL) under an argon atmosphere at 100 °C (Table 1, entry 1). A screening of the catalysts illustrated that NiBr$_2$ was the best catalyst for this reaction (entries 1$-$5), affording the desired product **3a** in 91% yield (entry 5). The transformation could hardly proceed without NiBr$_2$ participation, revealing that the NiBr$_2$ catalyst was essential to achieve a high yield of product **3a**. To advance the process further, the effect of solvents was also detected, such as 1,4-dioxane, toluene, DMF, and 1,2-dichloroethane, which categorically demonstrated 1,2-dichloroethane as the most suitable choice (entries 5$-$8). Encouraged by the above promising results, different bases were also investigated. It was found that pyridine only afforded the desired product in a poor yield of 12% (entry 10), and the other bases, such as Et$_3$N and Cs$_2$CO$_3$, gave rise to 20% and 40% yields, respectively (entries 9 and 11). Gratifyingly, the use of K$_2$CO$_3$ in 1,2-dichloroethane enhanced the product yield significantly (91%, entry 5), demonstrating that bases play a crucial role in this catalytic system. A subsequent survey on the role of ligands for the aforementioned coupling disclosed

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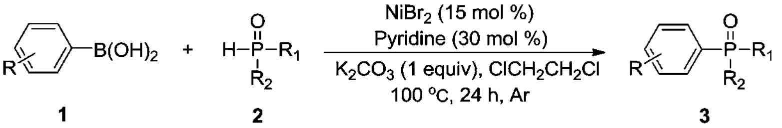
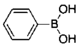
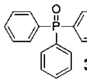
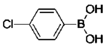
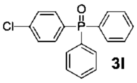
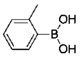
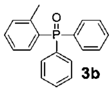
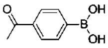
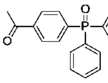
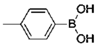
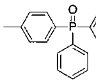
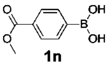
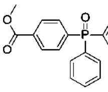
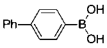
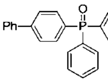
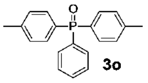
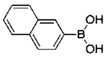
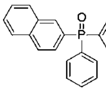
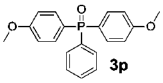
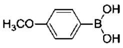
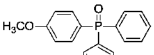
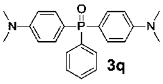
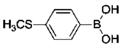
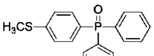
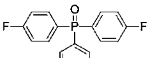
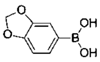
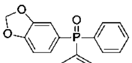
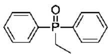
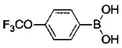
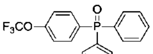
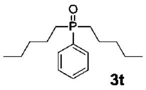
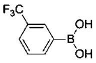
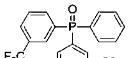
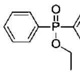
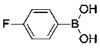
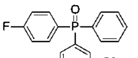
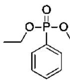
Table 2. Substrate Scope of Ni-Catalyzed Coupling of Arylboronic Acids with *P*-Nucleophiles[a]



2a: $R_1 = R_2$ = phenyl **2b**: $R_1 = R_2$ = *p*-tolyl **2c**: $R_1 = R_2$ = *p*-methoxylphenyl **2d**: $R_1 = R_2$ = *p-N, N*-dimethylphenyl
2e: $R_1 = R_2$ = *p*-fluorophenyl **2f**: R_1 = phenyl, R_2 = ethyl **2g**: $R_1 = R_2$ = pentyl **2h**: R_1 = phenyl, R_2 = ethoxyl
2i: $R_1 = R_2$ = ethoxyl

entry	1	2	product	yield (%)[b]	entry	1	2	product	yield (%)[b]
1	 **1a**	**2a**	 **3a**	91	12	 **1l**	**2a**	 **3l**	50
2	 **1b**	**2a**	 **3b**	92	13	 **1m**	**2a**	 **3m**	80[c]
3	 **1c**	**2a**	 **3c**	95	14	 **1n**	**2a**	 **3n**	83[c]
4	 **1d**	**2a**	 **3d**	75	15	**1a**	**2b**	 **3o**	99
5	 **1e**	**2a**	 **3e**	94	16	**1a**	**2c**	 **3p**	95
6	 **1f**	**2a**	 **3f**	97	17	**1a**	**2d**	 **3q**	92
7	 **1g**	**2a**	 **3g**	56	18	**1a**	**2e**	 **3r**	90
8	 **1h**	**2a**	 **3h**	91	19	**1a**	**2f**	 **3s**	98
9	 **1i**	**2a**	 **3i**	80	20	**1a**	**2g**	 **3t**	83[c]
10	 **1j**	**2a**	 **3j**	70	21	**1a**	**2h**	 **3u**	73
11	 **1k**	**2a**	 **3k**	81	22	**1a**	**2i**	 **3v**	90[c]

[a] Reaction conditions: arylboronic acid (0.75 mmol), *P*-nucleophile (0.5 mmol), NiBr$_2$ (15 mol %), pyridine (30 mol %), K$_2$CO$_3$ (0.5 mmol), ClCH$_2$CH$_2$Cl (1.5 mL), 100 °C, 24 h, under argon. [b] Isolated yield. [c] Using 2,2′-bipyridyl (15 mol %) instead of pyridine (30 mol %), under air.

pyridine as the most favored one to push the reaction forward (entries 5, 12–15). Without the ligand, a considerably lower yield was observed under similar reaction conditions. The reaction could also successfully proceed under dry air and gave a 90% yield (entry 16), indicating that the coupling was insensitive to the oxygen. Decreasing the reaction temperature to 80 °C led to a lower yield of 74% and raising the temperature did not increase the yield (entry 17). The loading of NiBr$_2$ was also evaluated, and the use of 10 mol % of NiBr$_2$ resulted in a significant decrease in reaction yield (72%, entry 18).

With the optimized conditions shown in footnote *a*, Table 2, the scope of this method was extended to the reaction of a wide range of arylboronic acids with different P(O)H substrates. As demonstrated in Table 2, the substrates bearing different functional groups were all efficiently coupled under these reaction conditions to provide the corresponding P-arylated derivatives with good to excellent isolated yields, showing that this protocol is a general and practical method for the preparation of various valuable triarylphosphine oxides. Thus, a variety of functional groups, such as methyl, phenyl, alkoxyl, carboxyl, carbonyl, fluoro, chloro, trifluoromethyl, methylthio and dimethylamino groups, were all tolerated. The *p*-tolylboronic acid and sterically demanding ortho-substituted counterpart afforded similar yields of 95%

and 92%, respectively, illustrating that steric hindrance is not evident in this coupling reaction (Table 2, entries 2–3). 4-Phenyl phenylboronic acid and 2-naphthylboronic acid also coupled efficiently in high yield (**3d**, **3e**, 75%, 94%, respectively, entries 4–5). Substituted phenylboronic acids with electron-donating methoxy and 3,4-methylenedioxy groups reacted smoothly with **2a** to provide products **3f** and **3h** in excellent yield (entries 6 and 8). However, phenylboronic acid type substrates with electron-withdrawing groups, such as trifluoromethoxy, trifluoromethyl, fluoro, and chloro, resulted in yield reduction (entries 9–12). The results indicated that the yields depended primarily upon the electronic properties of phenylboronic acid compounds. Notably, electron-rich 4-(methylthio)phenylboronic acid produced a lower yield of 56%, which can be attributed to the sulfur species dramatically deactivating the catalyst (entry 7).[14] It is noticeable that no coupling products were detected by ^{31}P NMR using **1m** and **1n** as substrates and pyridine as the ligand under argon. However, to our delight, when 2,2′-bipyridyl was employed as the ligand under air, the coupling proceeded smoothly to obtain **3m** and **3n** in 80% and 83% yield, respectively (entries 13 and 14).

The versatility of the reaction was further demonstrated for the coupling of different P(O)H substrates with phenylboronic acid to afford the corresponding products in good to excellent isolated yields. In regard to substituted diphenylphosphine oxides, either the electron-donating groups such as methyl, methoxy and *N,N*-dimethyl or an electron-deficient group such as fluoro all underwent efficient coupling, generating the corresponding triarylphosphine oxides in more than 90% yield (entries 15–18). In addition, ethyl(phenyl)phosphine oxide **2f** and ethyl phenylphosphinate **2h** were also used as the coupling partners using pyridine as the ligand under argon and gave the desired products in 98% and 73% yield, respectively (entries 19 and 21). Notably, using 2,2′-bipyridyl as the ligand under air, dipentylphosphine oxide **2g** and diethyl phosphonate **2i** were also found to be suitable substrates, and the corresponding coupling products **3t** and **3v** were obtained in high yields (entries 20 and 22). These results indicated that the choice of reaction conditions probably relied on the electronic properties of P(O)H compounds. Obviously, this approach with broad substrate applicability afforded a strong tool for the preparation of various valuable P-arylated motifs.

In conclusion, we have successfully developed a simple and highly efficient Ni-catalyzed cross-coupling of a wide range of P(O)H compounds with readily available arylboronic acids under relatively mild reaction conditions, and this method is the first example of Ni-catalyzed phosphorylation or phosphinylation of arylboronic acids to synthesize various aryl-phosphorus compounds, especially for valuable triarylphosphine oxides. As one of its notable features, the protocol exhibits good compatibility with various types of phosphorus substrates and allows them to be coupled efficiently, such as H-phosphites, H-phosphinate esters and particularly, easily oxidized H-phosphine oxides, which did not smoothly react with arylboronic acids according to the known literature due to their oxidation. Most attractively, the method allows the cross-coupling to be performed without the need of the oxidant in most cases, thus facilitating operation on the benchtop. Moreover, a variety of useful functional groups are also tolerated, which is attributed to the mild conditions. Finally, the use of a commercially available, cheap and highly stable $NiBr_2$ catalyst represents an added advantage of the method. Owing to these advantages, we believe the method would open a new avenue for the C–P bond-forming reactions and should find broad application in modern synthetic chemistry. A plausible mechanism is proposed (see Supporting Information), and the detailed mechanistic investigation for this reaction is currently underway.

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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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[14] (a) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (b) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880.

The authors declare no competing financial interest.