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Aryl Phosphoramides: Useful Electrophiles for Suzuki–Miyaura Coupling Catalyzed by a $NiCl_2$/dppp System (dppp = 1,3-Bis(diphenylphosphino)propane)

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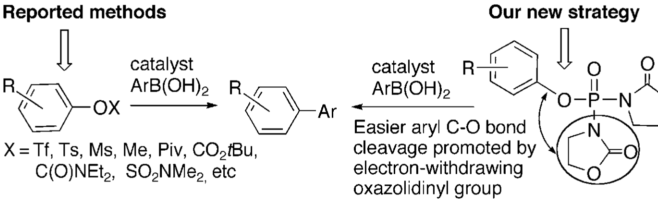
The transition-metal-catalyzed cross-coupling of phenol derivatives has emerged as an extremely attractive method in synthetic chemistry, because of the many advantages pertaining to the use of phenol derivatives.[1] So far, aryl triflates or nonaflates have frequently been investigated,[1–3] but their high cost and instability are deterrents to their extensive use.[4] As more affordable and manipulatable substitutes aryl sulfonates,[5–7] ethers,[8] and phosphates[9] are viable electrophiles. However, the successful coupling of these inert electrophiles often exhibits marked substrate specificity and necessitates rigorous catalysis, wherein air-sensitive, transition-metal complexes and bulky, electron-rich phosphine or N-heterocyclic-carbene ligands are usually required. More significantly, although the coupling reactions of phenol derivatives have been extensively studied, couplings under milder, more appealing Suzuki–Miyaura conditions are relatively rare.[5b–f,7,8c] Particularly, the Suzuki–Miyaura coupling of aryl phosphates has not been realized and has been shown to be extremely difficult, as exemplified by the Pd^0- and Ni^0-catalyzed coupling reactions of an *O,O*-diphenyl-*O*-vinylphosphate, which occur exclusively with vinyl functions under Suzuki–Miyaura conditions.[9e,f]

Recently, the Suzuki–Miyaura reactions of aryl esters,[10] carbamates,[11] carbonates,[11a] and sulfamates[11a] have been successfully achieved by using $[Ni(PCy_3)_2Cl_2]$ (Cy = cyclohexyl) as the catalyst or a catalyst system composed of $[Ni(PCy_3)_2Cl_2]$ and PCy_3 (or PCy_3HBF_4) ligands. The ready availability of aryl substrates and the facile handling of the catalysts render these processes highly attractive. Despite these significant advances, the coupling efficiency of most of these processes (except for aryl sulfamates) is moderate for non-fused, aromatic aryl substrates, even in the presence of a large excess of the boronic acid (4.0–5.0 equivalents) and the base (7.2–9.0 equiv). Therefore, the development of a system that allows efficient Suzuki–Miyaura coupling remains a challenge. Herein, we present the first Suzuki–Miyaura reactions of aryl phosphoramides as a highly efficient and broadly applicable methodology for the diverse synthesis of biaryls and heterobiaryls, which uses a cheaper, as well as much more stable, catalyst system consisting of $NiCl_2$ and 1,3-bis(diphenylphosphino)propane (dppp).



Scheme 1. New strategy for the activation of phenol derivatives; Tf = triflate, Ts = tosyl, Ms = methane sulfonyl, and Piv = pivaloyl.

During our search for a new methodology for phenol activation, we shifted our attention from the conventionally investigated aryl carbonyl- and sulfonyl-based derivatives to aryl phosphoramides (Scheme 1) and chose bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[12] as the reagent. We reasoned that the BOP moiety would be an effective leaving group after the abstraction of a phenolic oxygen atom, thanks to the electron-withdrawing nature of the two oxazolidinyl groups attached to the phosphorus atom, thereby facilitating the oxidative addition of a metal into the aryl C–O bond. Indeed, BOP-Cl exhibits an outstanding ability to activate the C–O bonds in carboxylic acids as seen its use

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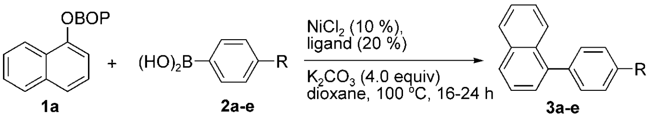
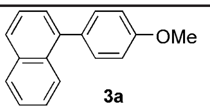
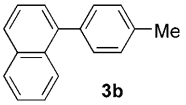
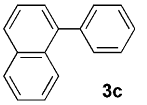
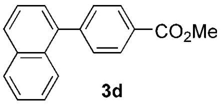
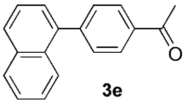
in the formation of amides, esters, and thioesters,[12] although its use in activating the phenolic C–O bond is virtually unknown.

To examine the coupling efficiency of phenol substrates activated by BOP-Cl (known here as aryl BOPs), the cross-coupling of 1-naphthyl BOP (**1a**)[13] with 4-methoxyphenylboronic acid (**2a**) was performed under Suzuki–Miyaura conditions (Table 1). To our delight, a careful survey of various reaction parameters including the metal source, ligand, base, solvent, and temperature revealed that the coupling could proceed efficiently using a catalyst system composed of $NiCl_2$ and dppp, affording the desired product (**3a**)[14] in 96% yield under the optimized conditions of boronic acid (2.0 equiv), $NiCl_2$ (10 mol%), dppp (20 mol%), K_2CO_3 (4.0 equiv) in dioxane at 100 °C (Table 1, entry 1). In addition, 1,4-bis(diphenylphosphino)butane (dppb) and 1,2-bis(diphenylphosphino)ethane (dppe) were ideal ligands, providing **3a** in 84 and 76% yields, respectively (Table 1, entries 2 and 3). Under the optimized conditions, cross-couplings of 1-naphthyl BOP (**1a**) with several boronic acids (**2b**–**e**) were evaluated. The reaction was tolerant of various boronic acids the structures of which were modified by electron-rich (Table 1, entries 1–4), electron-neutral (Table 1, entry 5), or electron-deficient groups (Table 1, entries 6 and 7). Consequently, good to excellent yields were obtained for all boronic acids examined.

Table 1. Coupling of 1-naphthyl BOP (**1a**) with various arylboronic acids **2a**–**e**.[a]



a R = OMe; **b** R = Me; **c** R = H
d R = CO_2Me; **e** R = C(O)Me

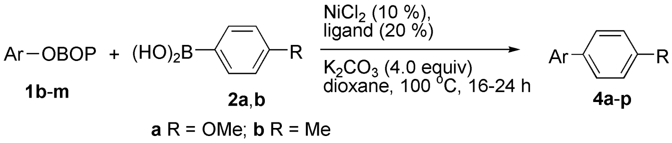
	Boronic acid (2)	Ligand	Product (3)	Yield [%][b]
1	**2a**	dppp	 3a	96
2	**2a**	dppb		84
3	**2a**	dppe		76
4	**2b**	dppp	 3b	79[c]
5	**2c**	dppp	 3c	90[c]
6	**2d**	dppp	 3d	92
7	**2e**	dppp	 3e	75

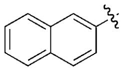
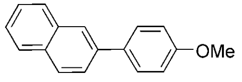
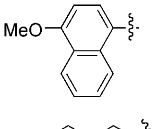
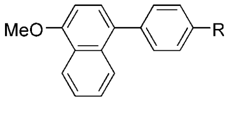
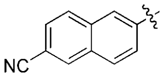
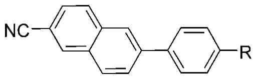
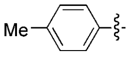
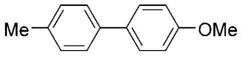
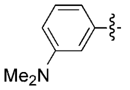
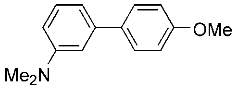
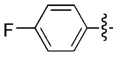
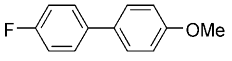
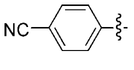
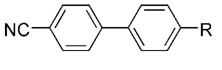
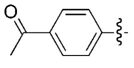
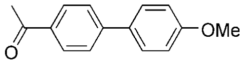
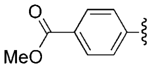
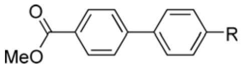
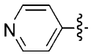
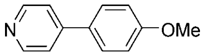
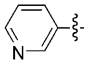
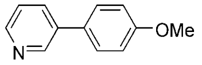
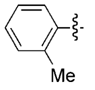
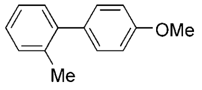
[a] Reaction conditions: 1-naphthyl BOP (**1a**) (0.5 mmol), boronic acid **2a**–**e** (1.0 mmol), $NiCl_2$ (10 mol%), ligand (20 mol%), K_2CO_3 (4.0 equiv), dioxane (6 mL), 100 °C, 16–24 h. [b] Isolated yield. [c] Yield was determined by quantitative ^1H NMR spectroscopy due to the contamination of a small amount of inseparable by-product derived from the homo-coupling of the boronic acids.

These preliminary results are in sharp contrast to the reported examples in which electron-deficient ligands such as dppp and dppe proved to be inefficient for the $[Ni(cod)_2]$- (cod = cyclooctadiene) and $[Ni(PCy_3)_2Cl_2]$-catalyzed Suzuki–Miyaura couplings of phenol derivatives such as aryl tosylates[5d] and esters.[10a] However, in comparison with the frequently used $[Ni(cod)_2]$ and $[Ni(PCy_3)_2Cl_2]$ catalysts and PCy_3 and PCy_3HBF_4 ligands, the $NiCl_2$ catalyst and the dppp, dppb, or dppe ligands employed herein are more affordable[15] and, most importantly, exhibit a much higher resistance to air and water disruption.[16] In addition, the use of nonhygroscopic K_2CO_3 as the base instead of the frequently used hygroscopic K_3PO_4[8,10,11] represents an added merit, since it has been shown that the hygroscopicity of K_3PO_4 is detrimental to this reaction.[11b] Thus, the improved air and water stability of our catalyst system and base are of crucial importance for the Ni^0-catalyzed Suzuki–Miyaura reactions of phenol derivatives when large-scale operations are considered. Also, the aryl BOP substrates can be easily prepared from the reaction of phenols with BOP-Cl[13] and display high stability, as shown by the fact that the reactivity remains unchanged after storage for least a couple of months under atmospheric conditions. Finally, it is particularly noteworthy that aryl phosphates, which are homologues of aryl BOPs, were shown to be unreactive under Suzuki–Miyaura conditions catalyzed by either by Pd^0 or by Ni^0.[9e,f] These results further reflect the high reactivity of aryl BOPs. Consequently, due to these indisputable advantages, we believe that the methodology presented in this work will provide an important advance in transition-metal-catalyzed Suzuki–Miyaura coupling of phenol derivatives, although the cost of the preparation of aryl BOPs is higher than that for the preparation of other substrates.

To further probe the applicability of this methodology, coupling reactions of a range of aryl BOPs (**1b**–**m**) with 4-methoxy- or 4-methylphenylboronic acid (**2a** and **b**) were carried out under the optimized conditions (Table 2). 2-Naphthyl BOP (**1b**) underwent smooth coupling to give **4a** in 84% yield (Table 2, entry 1). In addition, naphthyl analogues with a strongly electron-donating OMe group (**1c**, Table 2, entries 2 and 3) or a strongly electron-withdrawing CN group (**1d**, Table 2, entries 4 and 5) can also be converted into the corresponding biaryl products **4b**–**e** in high yields. Moreover, the non-fused aromatic (i.e., less electron-deficient) substrates also serve as superb electrophiles (**1e**–**j**, Table 2, entries 6–13), producing the desired products **4f**–**m** in excellent yield for a variety of derivatives including those with electron-rich, -neutral, and -deficient substituents on the phenyl periphery. Such an effective Ni-catalyzed coupling of non-fused aryl substrates was previously observed only with aryl sulfamates by using $[Ni(PCy_3)_2Cl_2]$ as the catalyst.[11a] Notably, the transformation was tolerant of a broad range of functional groups. Both naphthyl and phenyl BOPs

Table 2. Cross-coupling of various aryl BOPs (**1b–m**) with 4-methoxyl- and 4-methylphenylboronic acids (**2a** and **b**).[a]



	Ar-OBOP (**1**)		Product (**4**)		Yield [%][b]
1		**1b**		**4a**	84
2		**1c**		**4b**; R = OMe	76
3		**1c**		**4c**; R = Me	75
4		**1d**		**4d**; R = OMe	92
5		**1d**		**4e**; R = Me	92
6		**1e**		**4f**	75
7		**1f**		**4g**	76
8		**1g**		**4h**	92
9		**1h**		**4i**; R = OMe	89
10		**1h**		**4j**; R = Me	80
11		**1i**		**4k**	82
12		**1j**		**4l**; R = OMe	74[c]
13		**1j**		**4m**; R = Me	71
14		**1k**		**4n**	80[c]
15		**1l**		**4o**	85
16		**1m**		**4p**	46

[a] Reaction conditions: aryl BOP **1a–m** (0.5 mmol), boronic acid **2** (1.0 mmol), $NiCl_2$ (10 mol %), dppp (20 mol %), K_2CO_3 (4.0 equiv), dioxane (6 mL), 100 °C, 16–24 h. [b] Isolated yield. [c] Yield was determined by quantitative ^1H NMR spectroscopy due to the contamination of a small amount of inseparable by-product derived from the homo-coupling of the boronic acid.

with a cyano substituent can be converted to cyano substituted products in excellent yields (Table 2, entries 4, 5, 9, and 10). In contrast, we note, from the literature, that efforts to realize a similar product by the Ni^0-catalyzed Suzuki–Miyaura coupling of 4-cyanophenyl carbamate gave only a 28 % isolated yield owing to a competing reaction between the cyano and carbamate groups.[11b] Finally, heteroaromatic derivatives are also good substrates (**1k** and **l**, Table 2, entries 14 and 15), delivering products **4n** and **o** in high yields. However, the reaction of sterically hindered substrates (**1m**, Table 2, entry 16) proved to be somewhat challenging, providing the biaryl **4p** in only 46 % yield (Table 2, entry 16).

In summary, we have presented a new strategy for phenol activation by using BOP-Cl and have demonstrated for the first time that Suzuki–Miyaura couplings of the derived aryl BOPs can be an efficient and broadly applicable method for the synthesis of biaryls and heterobiaryls. As an important advantage, this method exhibits high reaction efficiency, particularly towards non-fused aromatic substrates, although, the cost of the synthesis of aryl BOPs is somewhat more expensive than alternative reagents. In addition, the use of a cheaper and, more significantly, markedly more stable $NiCl_2$ and dppp catalyst system, and the nonhygroscopic K_2CO_3 as the base further reinforces the value of this transformation. Finally, the reactivity of aryl BOPs, as exemplified by their Suzuki–Miyaura reaction, implies that aryl BOPs may also be suitable partners for other cross-couplings, such as Stille and Heck reactions, which are also appealing transformations catalyzed by transition metals. These reactions remain largely unexplored for the use of phenol derivatives as the electrophiles. Investigations into these reactions and the orthogonal reactivity of aryl BOP and other substrates, such as aryl sulfonates, esters, carbamates, carbonates, sulfamates, and halides, are currently underway.

Experimental Section

General procedure for the preparation of biaryls: the coupling of 1-naphthyl BOP (1a) and 4-methoxyphenylboronic acid (2a) as a representative example: $NiCl_2$ (0.05 mmol, 6.39 mg) and dppp (0.1 mmol, 41.2 mg) were added to a 25 mL Schlenk tube equipped with a magnetic stirring bar, and the tube was evacuated under high vacuum and backfilled with N_2 (3×10 min). Dried dioxane (2 mL) was then injected by using a syringe and the reaction mixture was stirred for 3 h at 100 °C to give a dark red heterogeneous solution. After cooling, the reaction vessel was charged in situ with 1-naphthyl BOP (**1a**; 0.5 mmol, 181 mg), 4-methoxyphenylboronic acid (**2a**; 1.0 mmol, 152 mg), anhydrous K_2CO_3 (2.0 mmol, 276 mg), and dry dioxane (4 mL). The reaction mixture was further stirred at 100 °C for 24 h. After completion of the reaction (as monitored by TLC), the reaction mixture was poured into water (30 mL) and then extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 10:1, v/v) to give the desired 1-(4-methoxyphenyl)naphthalene (**3a**) as a white powder (112 mg, 96 %).

Acknowledgements

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Keywords: biaryls · nickel · phenols · phosphane ligands · Suzuki–Miyaura coupling

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[15] The ligand costs of PCy$_3$ and PCy$_3$HBF$_4$ are at least four times higher than dppp, dppe, and dppb by Kanto Kagaku Co., Inc. The approximate catalyst costs by Strem Chemicals are: NiCl$_2$ (98 %) = 985 CNY mol^{-1}, [Ni(cod)$_2$] = 95 722 CNY mol^{-1}, and [NiCl$_2$(PCy$_3$)$_2$] = 205 018 CNY mol^{-1} (CNY = Chinese Yuan).

[16] As a caution, in the reagent catalogues PCy$_3$ is air and moisture sensitive, [Ni(cod)$_2$] is sensitive to many media including air, moisture, light, and heat and [Ni(PCy$_3$)$_2$Cl$_2$] is relatively more stable than [Ni(cod)$_2$], but is also sensitive to air and moisture. However, no such caution is noted for NiCl$_2$, dppp, dppb, or dppe.

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