VIP Cross-Coupling Reactions

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Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters**

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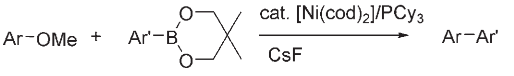
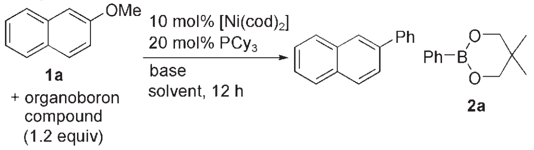
Palladium- and nickel-catalyzed cross-coupling reactions have been recognized as an indispensable tool for current organic synthesis.[1] Among these reactions, Suzuki–Miyaura coupling[2–7] is, arguably, of the greatest practical importance of these methods because of the attractive features of organoboronic acids: widespread availability, stability to air and moisture, and low toxicity. Recently, tremendous progress has been made in the development of more elaborate catalyst systems that allow the couplings to be conducted at room temperature,[3] to use unreactive chlorides,[4] and to use alkyl electrophiles.[5,6] Despite these significant advances, the electrophilic coupling partner for use in Suzuki–Miyaura coupling remains limited, for the most part, to organic halides and sulfonates; although the use of less available electrophiles, including diazonium salts,[7a] ammonium salts,[7b] aryltriazene/BF_3,[7c] azoles,[7d] and phosphonium salts[7e] has been reported. Aryl methyl ethers, which are as readily available as aryl halides, have never been used in the Suzuki–Miyaura coupling reaction, except for the ruthenium-catalyzed system,[8] which requires a ligating group at the *ortho* position for the reaction to proceed. Herein, we describe a method for the nickel-catalyzed cross-coupling of aryl methyl ethers with boronic esters [Eq. (1)].

The advantages of using aryl alkyl ethers in the metal-catalyzed cross-coupling reaction have been documented by Wenkert[9a,b] and Dankwardt[9c] in the nickel-catalyzed reaction with Grignard reagents (i.e., Kumada–Tamao–Corriu-type coupling). Although functional-group compatibility and availability of the starting Grignard reagents for these initial methods are rather limited, these pioneering studies offer a starting point for the development of cross-coupling reactions between aryl methyl ethers and organoboron reagents. Thus, we investigated the reaction of 2-methoxynaphthalene (**1a**) with organoboron compounds in the presence of a catalytic amount of [Ni(cod)$_2$] (cod = cycloocta-1,5-diene) and PCy_3 (Table 1). Whereas attempts with boronic acid (Table 1, entry 1) and borates (Table 1, entries 2 and 3) were unsuccessful, cross-coupling with boronic ester **2a** furnished the product in modest yield (Table 1, entry 4). Although the reaction did not proceed in the absence of base, the use of a mild base (CsF) proved reasonably effective (Table 1, entry 5). Ligand screening did not lead to a fruitful result (none: 0%, P*t*Bu_3: 0%, P*t*Bu_2Me: 22%, P(cylopentyl)$_3$: 13%, PMe_3: 0%, PPh_3: 0%, dmpe: 0%, binap: 0%, IPr·HCl: 0%; dmpe = 1,2-bis(dimethylphosphanyl)ethane, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl). However, product yield was improved when toluene was used as the solvent: 89% at 80°C (Table 1, entry 7) and 93% at 120°C (Table 1, entry 8).



(1)

Table 1: Optimization of reaction conditions.[a]



Entry	Organoboron compd.	Base	T [°C]	Solvent	Yield [%][b]
1[c]	$PhB(OH)_2$	NaOH	80	dioxane	0
2	$PhBF_3K$	NaOEt	80	dioxane	0
3	$NaBPh_4$	NaOEt	80	dioxane	8
4	**2a**	NaOEt	80	dioxane	64
5	**2a**	CsF	80	dioxane	54
6[d]	**2a**	CsF	80	dioxane	47
7[d]	**2a**	CsF	80	toluene	89
8[d]	**2a**	CsF	120	toluene	93

[a] Reaction conditions: **1a** (0.5 mmol), organoboron compound (0.6 mmol), [Ni(cod)$_2$] (0.05 mmol), PCy_3 (0.10 mmol), NaOEt (0.75 mmol) or CsF (2.25 mmol), toluene (1.5 mL) in a sealed tube. [b] Yields of 2-phenylnaphthalene measured by GC. [c] Toluene/H_2O = 3:1 was used as a solvent. [d] PCy_3 (0.20 mmol) and **2a** (0.75 mmol) were used.

Steric bulk of the substituents at the ether oxygen atom had a significant effect on the efficiency of the cross-coupling

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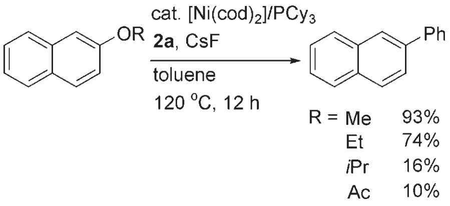
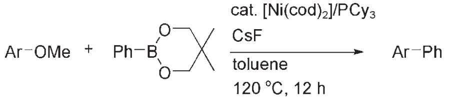
reaction [Eq. (2)]. Primary alkyl ethers, such as methoxy and ethoxy groups, furnished the coupling products in good yields, whereas reactions of secondary alkyl ethers proved to be much less efficient. Similarly, the acetoxy group, which is, in general, a better leaving group, was not an efficient coupling partner in this reaction.

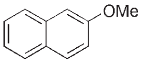
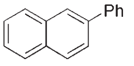
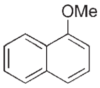
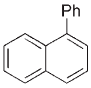
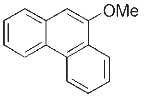
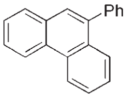
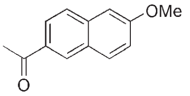
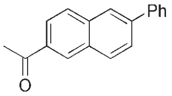
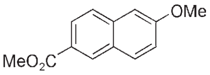
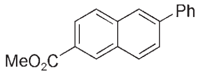
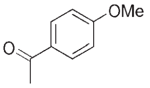
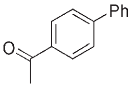
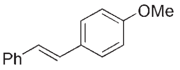
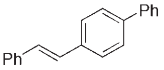


(2)

The scope of the nickel-catalyzed cross-coupling of aryl methyl ethers was subsequently investigated (Table 2).[10] A methoxy group connected to a fused aromatic system, such as naphthalene (Table 2, entries 1 and 2) and phenanthrene (Table 2, entry 3), was efficiently replaced with a phenyl group. The advantage of utilizing boronic esters as the nucleophilic coupling partner is demonstrated by the tolerance of functional groups, such as ketones and esters (Table 2, entries 4 and 5). In these cases, addition to the carbonyl moiety did not occur. In sharp contrast to Ni-catalyzed coupling with Grignard reagents,[9] the simple anisole was completely inactive under the catalytic conditions employed in this study. Examination of a series of anisole derivatives revealed that those bearing an electron-withdrawing group had greater reactivity in this cross-coupling reaction than those without an electron-withdrawing group. For example, the reaction of 4-acetylanisole with boronic ester **2a** furnished the biphenyl derivative in 55% yield (Table 2, entry 6). Anisole derivatives containing a styryl group also afforded the corresponding coupling products, although the yield was less than that observed for the naphthalene derivatives (Table 2, entry 7).

Table 2: Nickel-catalyzed cross-coupling of aryl methyl ethers with **2a**.[a]

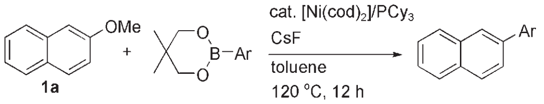


Entry	Aryl methyl ether	Product	Yield [%][b]
1			93
2			74
3			92
4			57
5			62
6			55
7			14

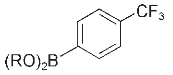
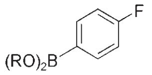
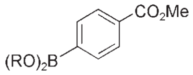
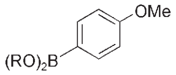
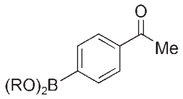
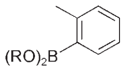
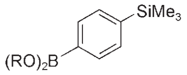
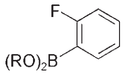
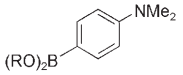
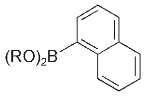
[a] Reaction conditions: aryl methyl ether (0.5 mmol), **2a** (0.75 mmol), [Ni(cod)$_2$] (0.05 mmol), PCy$_3$ (0.20 mmol), CsF (2.25 mmol), toluene (1.5 mL) in a sealed tube. [b] Yields of isolated products.

We also investigated the functional-group tolerance with respect to the boronic ester component (Table 3). Both electron-deficient (Table 3, entries 1–3) and -rich (Table 3, entry 5) boronic esters afforded the coupling products in good yields. The trimethylsilyl functional group also survived, even in the presence of a fluoride base (Table 3, entry 4). 4-Methoxyphenylboronic acid also serves as a good coupling partner; the methoxy group on the benzene ring remained intact (Table 3, entry 7). Sterically demanding boronic esters were also used successfully (Table 3, entries 8 and 10). It should be noted that the reaction proceeds cleanly in all cases, and remaining mass balance is unconverted starting material **1a**.

Table 3: Nickel-catalyzed cross-coupling of **1a** with various boronic esters.[a]

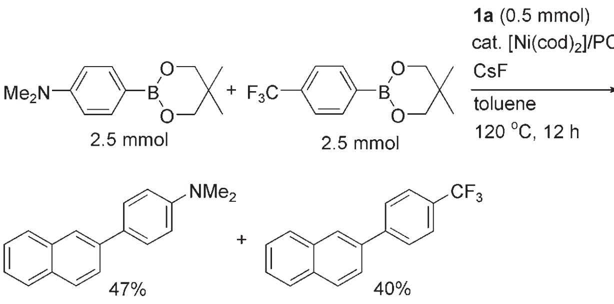


1a

Entry	Boronic ester	Yield [%][b]	Entry	Boronic ester	Yield [%][b]
1		94	6		36
2		83	7		68
3		78[c]	8		74
4		92	9		65
5		79	10		89

[a] Reaction conditions: **1a** (0.5 mmol), boronic ester (0.75 mmol), [Ni(cod)$_2$] (0.05 mmol), PCy$_3$ (0.20 mmol), CsF (2.25 mmol), toluene (1.5 mL) in a sealed tube. [b] Yields of isolated products. [c] [Ni(cod)$_2$] (0.10 mmol) and PCy$_3$ (0.40 mmol) were used.

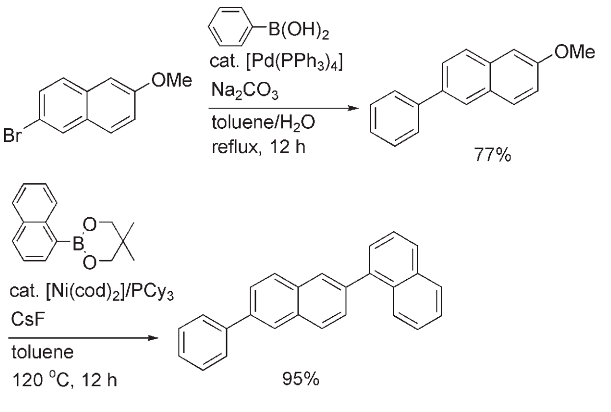
It is plausible that the reaction proceeds through a typical cross-coupling mechanism, as follows: 1) oxidative addition of a C–OMe bond to Ni^0;[8b] 2) transmetalation of the aryl group on the fluoride-activated boronic ester to Ar–Ni^{II}–OMe; and, 3) C–C bond formation by reductive elimination. The results of a competitive experiment revealed that the electronic nature of the boronic ester does not significantly affect the yield of product [Eq. (3)], suggesting that oxidative addition of a C–OMe bond is rate-limiting in this catalysis.



(3)

Thus, the reactivity of aryl methyl ethers in Ni-catalyzed cross-coupling should reflect their relative reactivity toward oxidative addition of the C–OMe bond to Ni^0.[11] Notably, the range of aryl methyl ethers that can be used in Ni-catalyzed cross-coupling with boronic esters is relatively limited compared with that using Grignard reagents, even though both reactions apparently proceed by oxidative addition of C–OMe bonds. This difference might be explained by the assumption that a nickel ate complex, which is more nucleophilic than Ni^0, operates as an active catalytic species when Grignard reagents are used in the reaction.[12,13]

The new cross-coupling reaction was successfully applied to the synthesis of oligoarenes [Eq. (4)]. The cross-coupling of 2-bromo-6-methoxynaphthalene with phenylboronic acid under standard Suzuki–Miyaura conditions, followed by Ni-catalyzed cross-coupling of a methyl ether moiety, furnished naphthalene containing two different aryl groups.



(4)

In summary, we developed a Ni-catalyzed cross-coupling reaction of aryl methyl ethers with boronic esters. Although it has been reported that several inactive bonds, including C–F,[14] C–CN,[15] C–S,[16] and C–O,[9,17] can be cleaved and used for the cross-coupling reaction in the presence of Ni catalysts, these reactions require strong nucleophilic coupling partners, such as Grignard reagents. The method described herein represents the first general catalytic protocol that utilizes boronic acid derivatives in cross-couplings involving the cleavage of unreactive bonds.[18] Although improvement of the scope of the aryl methyl ethers requires additional studies, the advantage of utilizing boronic esters, as in the typical Suzuki–Miyaura reaction, is retained. Ongoing work seeks to explore additional active catalytic systems for this and related cross-coupling reactions.

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[10] Notes: a) The amount of PCy_3 was not optimized for each substrate. In the reaction of *p*-acetylanisole (see Table 2, entry 6), the use of 20 mol% of PCy_3 gave a inferior result (30% yield). Thus, we routinely conducted the reaction with 40 mol% of PCy_3; b) When the corresponding pinacolate was used for the reaction in Table 2, entry 1, the yield of the product was decreased (20% yield).

[11] Oxidative addition of aryl methyl ethers in this catalysis may involve an intermediate in which the aromaticity of the aryl methyl ether is lost, such as η^2-arene or Meisenheimer-type complexes. Polyaromatic compounds are expected to form such complexes more facilely, since part of the aromaticity is retained after complex formation.

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[13] Another possible explanation for the wider substrate scope in the cross-couplings with Grignard reagents is activation of C–O bonds by Lewis acidic magnesium salts. However, the addition of $MgBr_2$, LiCl, and BPh_3 in our system did not improve the reactivity of aryl methyl ethers. See: a) N. Yoshikai, H. Mashima, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 17978; b) Y. Nakao, A. Yada, S. Ebata, T. Hiyama, *J. Am. Chem. Soc.* **2007**, *129*, 2428.

[14] For leading examples, see: a) Y. Kiso, K. Tamao, M. Kumada, *J. Organomet. Chem.* **1973**, *50*, C12; b) V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp, W. A. Herrmann, *Angew. Chem.* **2001**, *113*, 3500; *Angew. Chem. Int. Ed.* **2001**, *40*, 3387; c) J. W. Dankwardt, *J. Organomet. Chem.* **2005**, *690*, 932; d) T. Saeki, Y. Takashima, K. Tamao, *Synlett* **2005**, 1771; e) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem.* **2005**, *117*, 7382; *Angew. Chem. Int. Ed.* **2005**, *44*, 7216. See also references [12b] and [13a].

[15] For a review, see: M. Tobisu, N. Chatani, *Chem. Soc. Rev.* **2008**, *37*, 300.

[16] For a review, see: T.-Y. Luh, Z.-J. Ni, *Synthesis* **1990**, 89.

[17] During preparation of this manuscript, another report on Kumada-type coupling of aryl methyl ethers with methylmagnesium halides was published: B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, *Chem. Commun.* **2008**, 1437. See also: B.-T. Guan, S.-K. Xiang, B.-Q. Wang, Z.-P. Sun, Y. Wang, K.-Q. Zhao, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 3268.

[18] A cross-coupling reaction between activated aryl fluorides and boronic acids has been reported: T. Schaub, M. Backes, U. Radius, *J. Am. Chem. Soc.* **2006**, *128*, 15964.