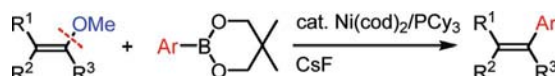


Nickel-Catalyzed Cross-Coupling
Reaction of Alkenyl Methyl Ethers with
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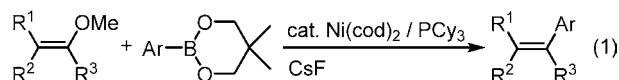
ABSTRACT



The Ni(0)-catalyzed cross-coupling of alkenyl methyl ethers with boronic esters is described. Several types of alkenyl methyl ethers can be coupled with a wide range of boronic esters to give the stilbene derivatives.

Transition metal-catalyzed cross-coupling reactions have become some of the most important transformations in organic synthesis.¹ Among them, the Suzuki–Miyaura cross-coupling reaction has been recognized as an excellent tool for carbon–carbon bond formation,² because boron reagents are highly functional group tolerant, readily available, stable to air and moisture, and nontoxic. Despite significant advances, the electrophilic partner used in the Suzuki–Miyaura reaction has primarily been limited to organohalides and sulfonic esters.³ Recently, we reported that aryl methyl ethers serve as electrophiles in Suzuki–Miyaura reactions^{4a} via the cleavage of unreactive C–OMe bonds under nickel catalysis.^{5,6} Subsequently, Shi^{7a} and Garg^{7b} independently reported Suzuki–Miyaura reactions of aryl carboxylates as an electrophile. In our reaction, we observed that the fused aromatic systems, such as methoxynaphthalenes, exhibited superior reactivity to nonfused aromatic systems. We surmised that the reactivity profile might be determined largely by the

aromaticity of the substrate. This hypothesis led us to apply nonaromatic substrates, alkenyl methyl ethers, to our Ni-catalyzed cross-coupling as the electrophilic coupling partner (eq 1). Herein, we report our results along this line.



We initially examined the cross-coupling reaction of (*Z*)-methyl styryl ether (**Z-1a**) with boronic ester **2a** under conditions similar to those reported for aryl methyl ethers.^{4a} As a result, the cross-coupling product **3a** was obtained in

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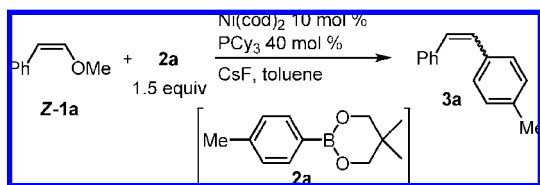
(1) For general reviews of metal-catalyzed cross-coupling reactions, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002.

(2) (a) Miyaura, N. *Top. Curr. Chem.* **2002**, 219, 11. (b) Suzuki, A.; Brown, H. C. *Organic Synthesis via Boranes*; Aldrich: Milwaukee, WI, 2003; Vol. 3. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457.

(3) Other minor electrophiles applicable to Suzuki–Miyaura reaction: Diazonium salts: (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, 106, 4622. Phosphonium salts: (b) Hwang, L. K.; Na, Y.; Lee, J.; Do, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, 44, 6166. Ammonium salts: (c) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, 125, 6046. Sulfonium salts: (d) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, 119, 12376. Azoles: (e) Liu, J.; Robins, M. J. *Org. Lett.* **2004**, 6, 3421. Aryltriazene/BF₃: (f) Saeki, T.; Son, E.-C.; Tamao, K. *Org. Lett.* **2004**, 6, 617. Nitriles: (g) Yu, D.-G.; Yu-M.; Guan, B.-T.; Li, B.-J.; Zheng, Y.; Wu, Z.-H.; Shi, Z.-J. *Org. Lett.* **2009**, 11, 3374. Carboxylic anhydrides: (h) Gooßen, L. J.; Paetzold, J. *Adv. Synth. Catal.* **2004**, 346, 1665. Sulfonyl chlorides: (i) Dubbaka, S. R.; Vogel, P. *Org. Lett.* **2004**, 6, 95. Zhang, S.; Zeng, X.; Wei, Z.; Zhao, D.; Kang, T.; Zhang, W.; Yan, M.; Luo, M. *Synlett* **2006**, 1891.

(4) (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, 47, 4866. See also: (b) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, 126, 2706.

Table 1. Nickel-Catalyzed Cross-Coupling Reaction of (Z)-Methyl Styryl Ether **Z-1a** with Tolly Boronic Ester **2a**^a



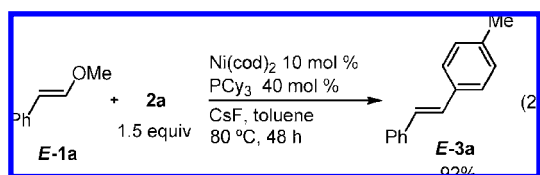
entry	temp (°C)	time (h)	yield (%) ^b	<i>E/Z</i> ^c
1	80	2	90	34/66
2	80 then 120	2 then 24	87	95/5
3	60	12	92	36/64
4	50	12	64	20/80
5	50	5	30	12/88

^a Reaction conditions: **Z-1a** (0.5 mmol), **2a** (0.75 mmol), Ni(cod)₂ (0.05 mmol), PCy₃ (0.2 mmol), CsF (0.6 mmol), and toluene (1.5 mL) at 120 °C in a sealed tube. ^b Isolated yield. ^c The ratio was determined by ¹H NMR.

86% yield (entry 1, Table 1). As expected, alkenyl ether **Z-1a** exhibited higher reactivity than aryl methyl ether: the reaction was completed within 2 h at 80 °C. Although the product was formed as a mixture of *E/Z* isomers at 80 °C, the *E*-isomer can be obtained selectively by further heating the mixture at 120 °C for 24 h (entry 2). On the other hand, selectivity for **Z-3a** was improved by conducting the reaction at a lower temperature (entries 3–5).

It should be noted that isomerization of **Z-1a** did not isomerize to **E-1a** when exposed to catalytic conditions [Ni(cod)₂/PCy₃ at 80 °C]. In contrast, **Z-3a** was partially isomerized under catalytic conditions (*E/Z* = 76/24). These results indicate that **Z-1a** initially provides **Z-3a**, part of which isomerizes to **E-3a** under the reaction conditions.

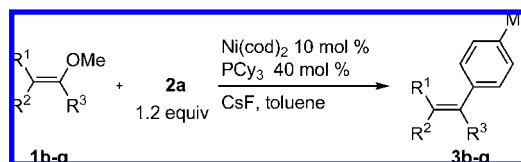
On the other hand, the reaction of the corresponding *E*-isomer **E-1a** afforded **E-3a** stereoselectively, although it required 48 h for completion (eq 2). On the basis of the observations obtained thus far, the stereochemistry of the vinyl ether moiety was originally retained in this reaction. This indicates that the reaction proceeds through the oxidative addition of a C–OMe bond, as we had initially envisioned.⁸



The scope of the nickel-catalyzed cross-coupling of alkenyl methyl ethers⁹ was subsequently investigated (Table 2). Both

(5) Cross-coupling reactions of aryl methyl ethers with Grignard reagents: (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. (b) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894. (c) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428. (d) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437. (e) Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268.

Table 2. Nickel-Catalyzed Cross-Coupling Reactions of Various Alkenyl Ethers with **2a**^a



entry	alkenyl methyl ether	time	temp (°C)	yield (%) ^b
1	1b (<i>E/Z</i> = 1 / 1)	18	80	95 (7 / 3)
2	1c (<i>E/Z</i> = 1 / 1)	12	120	64 (3 / 1)
3	1d (<i>E/Z</i> = 1 / 1)	12	120	76 (<i>E</i> only)
4	1e	12	120	86
5	1f	12	120	85
6	1g (<i>E/Z</i> = 1 / 1)	12	120	75 (<i>E</i> only)

^a Reaction conditions: alkenyl methyl ether (0.5 mmol), **2a** (0.6 mmol), Ni(cod)₂ (0.05 mmol), PCy₃ (0.2 mmol), CsF (0.6 mmol), and toluene (1.5 mL) at 80 or 120 °C in a sealed tube. ^b Isolated yield. Values in parentheses refer to the *E/Z* ratio of the coupling product.

electron-rich (entry 1) and electron-deficient (entry 2) substrates efficiently underwent the cross-coupling. A vinyl ether bearing an aliphatic substituent also serves as a good coupling component (entry 3). The vinyl ether having two substituents at the β-position, as in **1e**, afforded the corresponding product **3e** in good yield (entry 4). Moreover, introduction of a substituent at the α-position did not deteriorate the efficiency of the reaction, demonstrating the insensitivity of the present catalysis toward steric demand (entry 5). The cross-coupling reaction of alkenyl methyl ether having an indole ring was also applicable (entry 6).

An array of boronic esters proved to be applicable to this catalysis (Table 3). Both electron-deficient (entry 1) and electron-rich (entry 2) boronic esters afforded the desired

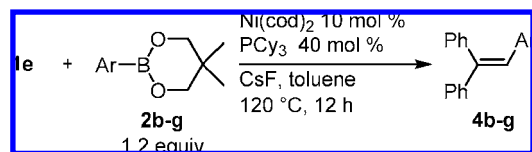
(6) Catalytic amination of aryl methyl ethers: Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, 38, 710.

(7) (a) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468. (b) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. See also: (c) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 10124.

(8) If the reaction proceeds through the addition of arylnickelate complex followed by β-OMe elimination, inversion of the stereochemistry would be expected.

(9) The alkenyl methyl ether can be readily prepared either by Wittig reaction of the corresponding carbonyl compounds or by the acid-mediated elimination of MeOH of the corresponding dimethyl acetals. See the Supporting Information for details.

Table 3. Nickel-Catalyzed Cross-Coupling Reactions of **1e** with Various Boronic Esters^a



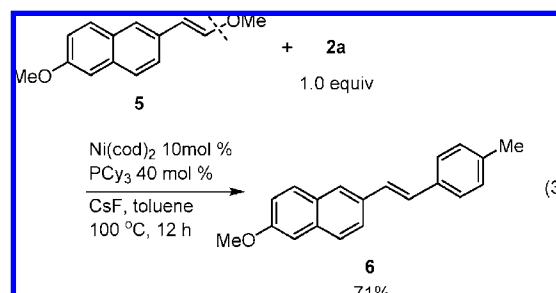
entry	boronic ester	product	yield (%) ^b
1			79
2			89
3			83
4			83
5			74
6 ^c			52

^a Reaction conditions: **1e** (0.5 mmol), **2b–g** (0.6 mmol), Ni(cod)₂ (0.05 mmol), PCy₃ (0.2 mmol), CsF (0.6 mmol), and toluene (1.5 mL) at 120 °C in a sealed tube. ^b Isolated yield. ^c Ni(cod)₂ (0.1 mmol), PCy₃ (0.4 mmol), CsF (0.6 mmol), and toluene (2.5 mL) at 120 °C in a sealed tube.

cross-coupling products in good yields. The coupling reaction with trimethylsilyl boronic ester proceeded without injuring the silyl moiety (entry 2). Sterically demanding boronic esters were also used successfully, providing the corresponding arylated compounds in good yields (entries 4 and 5). The extended conjugated system **4g**, which is reported to be applicable to the organic emitting layer of OLEDs,¹⁰ could be synthesized by using a biphenyl boronic ester (entry 6).

(10) For recent examples, see: (a) Kim, S.-K.; Park, Y.-I.; Kang, I.-N.; Park, J.-W. *J. Mater. Chem.* **2007**, *17*, 4670. (b) Ogata, A.; Anno, S.; Kurata, T.; Xu, S.; Tsubouchi, A.; Takeda, T. *Synlett* **2007**, *11*, 1715.

We next investigated the relative reactivity of the methoxy groups located at vinylic and aromatic positions using **5** (eq 3). As a result, the methoxy group at the vinylic position was arylated exclusively to furnish the stilbene derivative **6** in 71% yield. Since the methoxy group in **6** is amenable to further synthetic elaboration based on the methods established by us,^{4a,6} and by others,⁵ the present method can be used for the orthogonal functionalization of conjugated molecules.¹¹



In summary, we have established the Ni-catalyzed cross-coupling reaction of alkenyl methyl ethers with aryl boronic esters, which proceeds through the cleavage of vinylic C–OMe bonds.¹² Additional research with respect to the synthesis of π -conjugated molecules using this method and the development of new catalytic reactions via C–OMe bond cleavage is ongoing in our laboratory.

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Supporting Information Available: Detailed experimental procedures and characterization of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) Quite recently, Rh-catalyzed coupling reaction of vinyl acetates with boronic esters was reported: Yu, J.-Y.; Kuwano, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 7217.