

Nickel(II)-Catalyzed Borylation of Alkenyl Methyl Ethers via C–O Bond Cleavage

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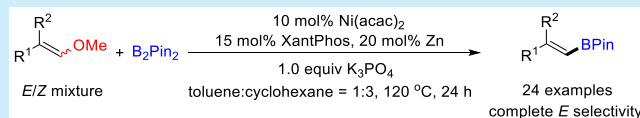


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Supporting Information

ABSTRACT: A new protocol has been developed for the borylation of conjugated alkenyl methyl ethers using B_2Pin_2 via C–O bond cleavage catalyzed by Ni(II). In this cross-coupling reaction, both *E/Z* isomers of alkenyl ethers are converted into (*E*)-alkenyl boronic esters with good reactivity. This transformation exhibits high chemoselectivity in the presence of competitive C–O bonds such as aryl ether, ester, amide, and thioether groups, thus providing a new method for the construction of various alkenyl boronates.



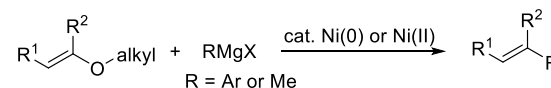
Transition-metal-catalyzed activation of unreactive bonds constitutes an indispensable part in the formation of new chemical bonds and new scaffolds. In particular, C–O bond activation has attracted considerable interest and has provided a novel solution in precision synthesis and woody-biomass energy utilization.¹ Various transition-metal catalysts have been employed for this transformation, and among them, nickel catalyzed cross-coupling via oxidative insertion into C–O bonds has been extensively studied. Cross-coupling reactions of aryl or alkyl esters² and aryl or benzyl ethers³ with Grignard reagents or boronates are well-developed using nickel catalysts. In the 1970s and 1980s, several groups including the Wenkert, Kumada and Kocienski groups reported nickel-catalyzed C–O bond phenylation or alkylation of alkenyl ethers using Grignard reagents as the coupling partner.⁴ However, only several endocyclic alkenyl or alkenyl ethers with simple substitutions worked well under these conditions. More recently, C–O bond cleavage in alkenyl ethers was extended to more complex substrates using cheaper nickel catalysts or milder reaction conditions⁵ (Scheme 1a).

Compared with Grignard reagents, boron reagents are stable to air and moisture, highly functional group tolerant and readily available, and are excellent candidates in cross-coupling reactions such as C–O bond functionalization. In 2009, aryl boronic esters were successfully employed by Chatani and co-workers in the Ni(0)-catalyzed cross-coupling reaction with alkenyl methyl ethers.⁶ Recently, air-stable Ni(II) catalysts were also applied into this C–O arylation process to form alkenyl–aryl bonds⁷ (Scheme 1b). However, instead of the sufficient study of C–C bond formation, the C–O bond borylation of alkenyl ethers are rarely explored. Here, we aim to expand these conditions to the synthesis of alkenyl boronates through nickel catalyzed C–O activation of alkenyl ethers.

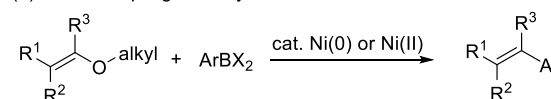
As important synthetic intermediates in the olefin modifications, alkenyl boronates are often obtained from electrophilic addition of hydroboron to corresponding

Scheme 1. Nickel Catalyzed Cross-Coupling of Alkenyl Ethers with Grignard Reagents or Boron Reagents

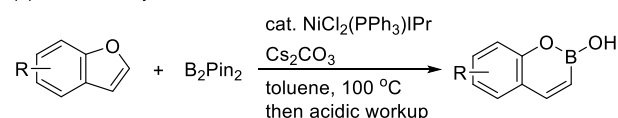
(a) Cross-coupling with Grignard reagents



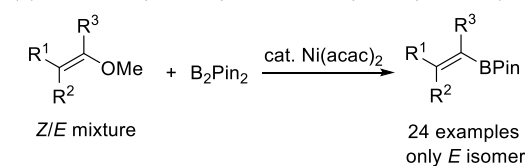
(b) Cross-coupling with aryl boronates



(c) Nickel-catalyzed boron insertion of benzofurans



(d) Nickel-catalyzed borylation of alkenyl methyl ethers (**This work**)



alkynes.⁸ Besides, alkenyl ethers are readily available from simple aldehydes or ketones, therefore increasing accessibility of alkenyl boronates with different substitutions (e.g., trisubstituted alkenyl groups). As a special example of borylation of alkenyl ethers, Yorimitsu et al. reported the

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nickel-catalyzed boron insertion into the benzofuran C–O bond (Scheme 1c).⁹ On this hand, we reported a new approach of air-stable Ni(acac)₂-catalyzed borylation of alkenyl methyl ethers with B₂Pin₂ reagent (Scheme 1d).

At the outset of the study, we decided to employ Ni(II) catalyst, which can in situ generate Ni(0) species under a catalytic amount of reductant, thus avoiding the use of oxygen- and moisture-sensitive Ni(0) catalyst. Styryl methyl ether (**1a**) was selected as the model substrate to test this borylation process with B₂Pin₂. After an extensive study, the optimized standard conditions (10 mol % Ni(acac)₂, 15 mol % XantPhos, 20 mol % zinc powder, and 1.0 equiv of K₃PO₄ in mixed solvent (toluene/cyclohexane = 1:3) under a N₂ atmosphere at 120 °C (Table 1, entry 1)) was obtained with the formation of

Table 1. Optimization of the Nickel-Catalyzed C–O Bond Borylation of **1a^a**

entry	deviation from “standard conditions”	yield ^b (%)
1	none	81
2	no Ni(acac) ₂	0
3	no XantPhos	0
4	no Zn	20
5	Ni(cod) ₂ instead of Ni(acac) ₂	53 ^c
6	5 mol % of Ni(acac) ₂ was used	58
7	Ni(PPh ₃) ₂ Cl ₂ instead of Ni(acac) ₂	25
8	PCy ₃ instead of XantPhos	38
9	IPr-HCl instead of XantPhos	0
10	Mn instead of Zn	67
11	DIBAL instead of Zn	41
12	no K ₃ PO ₄	68
13	toluene as solvent	72
14 ^d	styryl ethyl ether (3) instead of 1a	75
15 ^d	styryl benzyl ether (4) instead of 1a	78

^aReaction conditions: all reactions were carried out using **1a** (0.5 mmol) and B₂Pin₂ (1.0 mmol) in 1.25 mL of toluene and 3.75 mL of cyclohexane at 120 °C for 24 h under nitrogen atmosphere. ^bIsolated yields after purification by column chromatography. ^cReaction was carried out without Zn. ^dE/Z mixtures of **3** and **4** were used.

styryl boronic ester **2a** in 81% yield. Complete E-isomer of **2a** was acquired regardless of the E/Z mixture of alkenyl methyl ethers used. Without nickel catalyst or phosphine ligand, no products could be generated (Table 1, entries 2 and 3). The absence of Zn provided a dramatic decline of the product yield (Table 1, entry 4), and 53% yield of **2a** was obtained using Ni(cod)₂ as the catalyst (Table 1, entry 5), which indicated that the reaction was possibly initiated with Ni(0) compound and went through an oxidative addition procedure to form the Ni(II) complex. Cutting the catalyst amount to 5 mol % would affect the conversion of **1a** (Table 1, entry 6). Ni(PPh₃)₂Cl₂ instead of Ni(acac)₂ would give a diminished yield of **2a** (Table 1, entry 7). Monodentate ligand PCy₃ also showed decreased result with 38% yield, and N-heterocyclic carbene was invalid for this borylation (Table 1, entries 8 and 9). Using Mn powder as auxiliary reductant instead of Zn gave a lower yield of **2a** (Table 1, entry 10). Another reductant like DIBAL

which was demonstrated effectively in Suzuki–Miyaura cross-coupling of alkenyl ethers^{7b} only presented 41% yield (Table 1, entry 11). Addition of base could promote the conversion of **1a**, and a slightly lower yield (68%) could be found without K₃PO₄ (Table 1, entry 12). Reaction in a single solvent, toluene, would result in some decomposition of the boronic ester **2a** (Table 1, entry 13), and this could be limited by change to mixed solvent of toluene and cyclohexane. The reaction of styryl ethyl ether (**3**) and styryl benzyl ether (**4**) was also checked under standard conditions; to our delight, we found that ethyl and benzyl ethers could undergo the C–O bond cleavage process smoothly to generate **2a** in, respectively, 75% and 78% yield (Table 1, entries 14 and 15), which indicated the applicability of this borylation method in alkenyl alkyl ethers.

We then applied the standard reaction conditions to various alkenyl methyl ethers with different substitutions in the conversion to alkenyl boronic esters (Figure 1). Introduction of electron-donating groups such as methyl (**2b,c**) and tertiary butyl (**2e**) to the benzene ring had little effect, and styryl boronic ester derivatives were obtained with good yields. Even sterically hindered *o*-methyl-substituted ether **1d** could proceed with 58% yield. The 4-methoxy substrate, which was converted to aryl boronic ester through nickel-catalyzed aryl C–O bond cleavage by Martin and co-workers,^{3h} gave 82% yield of **2f** with the methoxy group preserved. Arylamines were also compatible under these conditions. Although nickel-catalyzed borylation of tertiary anilines via C–N bond activation was reported by Shi’s group, **2g** with a dimethylamino group was obtained in 88% yield.¹⁰ Other electron-donating substrates such as **1h** could convert to biphenyl alkenyl boronic ester **2h** in 76% yield under this conditions. Since C–S bond hydrogenation and borylation were well developed within aryl thioethers,¹¹ 4-methylthio-styryl methyl ether **1i** was selected to test the chemoselectivity of this borylation procedure. Excitingly, product **2i** was obtained in 85% yield without any C–S bond cleavage observed. Some electron-withdrawing substituted styryl ethers were also tested, and products containing fluorine and trifluoromethyl groups were all generated with good yields (**2j–l**). Aryl carboxylic esters and amides are common structures for decarbonylative borylation via nickel- or palladium-catalyzed C–O or C–N bond cleavage,¹² while under our conditions the C–O bond cleavage of alkenyl ethers was more dominant, and **2m** and **2n** were afforded in 68% and 76% yields, respectively. We next examined several sterically hindered substrates, and 3,5-dimethylstyryl boronic ester **2o**, 3,5-dimethoxystyryl boronic ester **2p**, and boronic ester with dihydrobenzofuran skeleton **2q** were all obtained in reasonable yields. Naphthyl was also tolerated to provide **2r** in 79% yield. Importantly, trisubstituted alkenyl methyl ether **1s** could undergo this borylative process and gave the complete E isomer of **2s**, although in moderate yield. Substrate-containing heterocyclic moieties such as carbazole proceeded in excellent yield (81%) to provide product **2t**. When we used benzofuran as the starting material, similar results to Yorimitsu’s report⁹ were achieved to afford benzoxaborin **2u** in 61% yield. In addition to the ethers with a styryl skeleton, conjugated enyl methyl ethers could also react to generate the corresponding boronic esters. Cyclohexenyl vinyl boronic ester **2v** was obtained in 56% yield. (–)-Perillaldehyde- and (–)-myrtenal-based methyl ethers provided **2w** and **2x** in 51% and 42% yields, respectively.

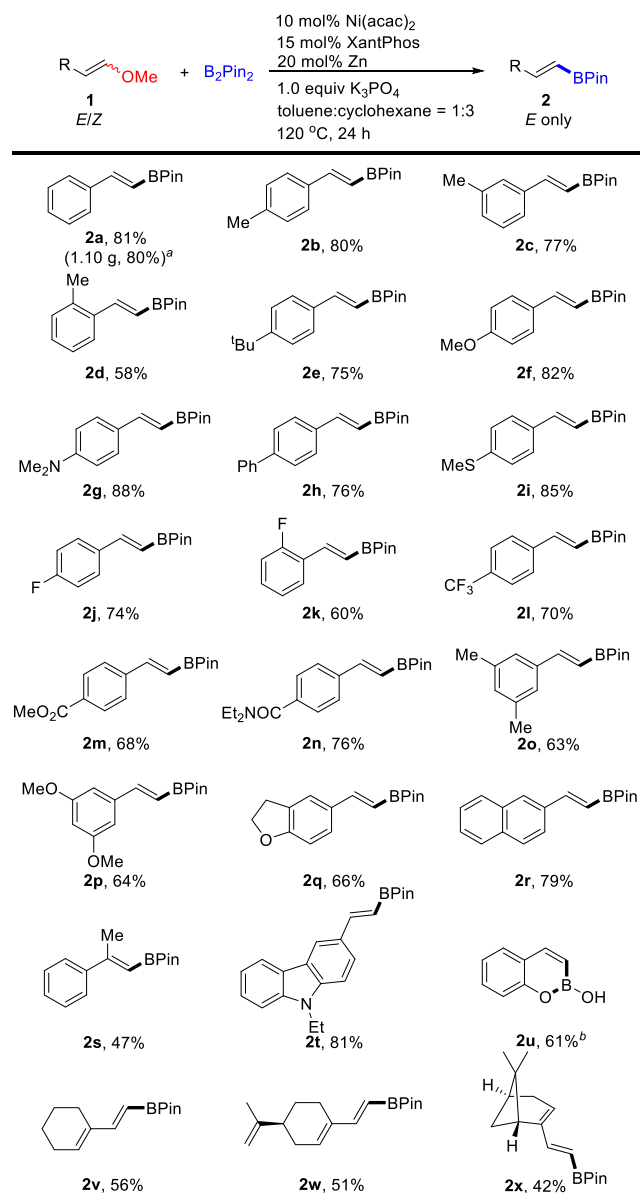
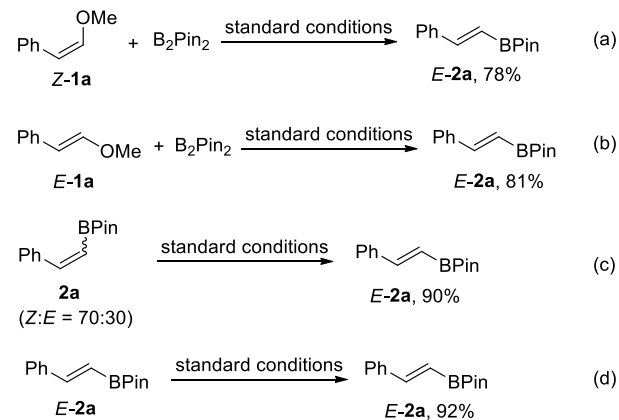


Figure 1. Cross-coupling of alkenyl methyl ether **1** with B_2Pin_2 . Reaction conditions: all reactions were carried out using **1** (0.5 mmol) and B_2Pin_2 (1.0 mmol) in 1.25 mL of toluene and 3.75 mL of cyclohexane at 120 °C for 24 h under nitrogen atmosphere. Yields were obtained after purification by column chromatography on silica gel. ^aIsolated yield of the gram-scale reaction. ^bBenzofuran (**1u**) was used as cross-coupling partner.

This cross-coupling reaction proceeds with high chemoselectivity and broad substrate scope and more importantly affords only the *E*-isomers. In order to better understand this *E*-selectivity in the transformations, a series of control experiments were carried out. Two isomers of *Z*-**1a** and *E*-**1a** were tested under the standard reaction conditions, and *E*-**2a** was obtained in both reactions in almost identical yields (Scheme 2a,b). Previously, Marek and co-workers reported C–O bond arylation of alkenyl ethers that primarily generated *E/Z* mixtures of aryl olefins, which would convert to *E*-isomer under the reaction conditions.^{7b} We therefore tested a mixture of **2a** (*Z/E* = 70:30), which was synthesized according to Lee and Yun's procedure,¹³ for possible isomerization under our conditions. We found that only *E*-**2a** was obtained in 90% yield

Scheme 2. Control Experiments for Mechanistic Studies



from the *Z/E* mixture, whereas no isomerization was observed with pure *E*-**2a** (Scheme 2c,d). Therefore, we conclude that it is most likely that an *E/Z* mixture was initially produced in the C–O borylation process, followed by *Z*-isomer converting to the thermodynamically more stable *E*-isomer under the reaction conditions.

A possible mechanism of this borylation is proposed in Figure 2. The reaction was initiated by the Ni(0) complex,

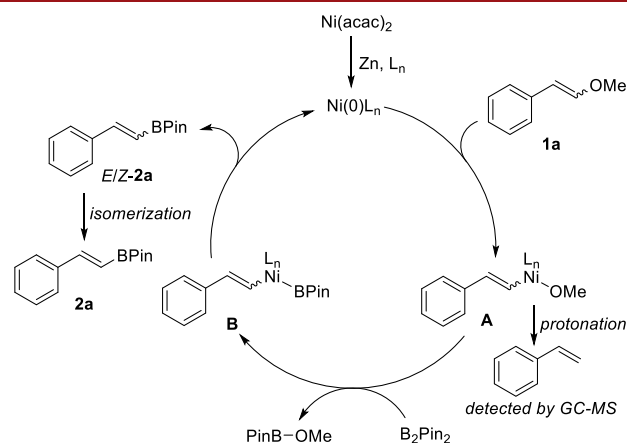


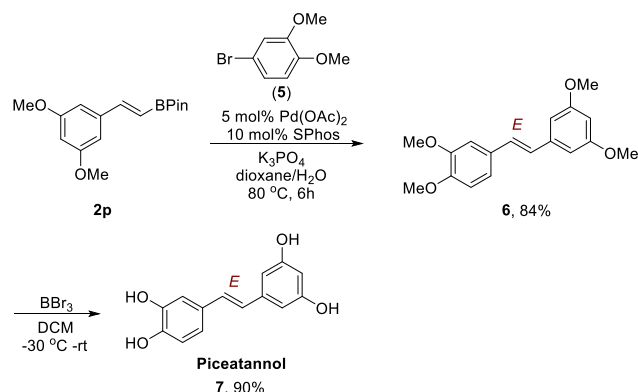
Figure 2. Probable catalytic cycle of borylation process with alkenyl methyl ether.

generated in situ from Ni(acac)_2 , inserting into the C–O bond of **1a**. The Ni(II) intermediate **A** is then obtained through oxidative addition, which could undergo protonation to form the styrene byproduct. The following transmetalation of **A** with B_2Pin_2 would provide the intermediate **B** as an *E/Z* mixture. Reductive elimination would give the two isomers of boronic esters *E/Z*-**2a** with the regeneration of Ni(0) complex. Final isomerization provides **2a** as a single *E*-isomer.

Alkenyl boronic esters are well-known to be crucial precursors in natural products and pharmaceutical synthesis. We thus tested the borylation reaction in the synthesis of bioactive compounds bearing *trans*-double bonds. Piceatannol and its derivatives are known to have antihyperglycemic, anticancer, and anti-inflammatory activities.¹⁴ The stilbene structure in such molecules can be constructed through Suzuki–Miyaura cross-coupling using alkenyl boronic esters. Therefore, **2p** was reacted with 4-bromoveratrole **5** to form compound **6** as only the *E*-isomer in excellent yield.

Deprotection of the methoxy groups gave *trans*-piceatannol **7** in high yield (Scheme 3).

Scheme 3. Concise Synthesis of Piceatannol (7)



In summary, we have developed the first nickel(II)-catalyzed C–O bond borylation of conjugated alkenyl ethers to form alkenyl boronic esters. This highly chemo- and stereoselective method provides diversely substituted olefins while tolerating multiple functional groups. Further C–O bond activation of alkenyl ethers and application of the alkenyl boronic intermediates for simplified drug synthesis are in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c02236>.

Experimental procedures, characterization data for all new compounds, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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