Communication

# Ipso-Borylation of Aryl Ethers via Ni-catalyzed C–OMe Cleavage

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# *Ipso*-Borylation of Aryl Ethers via Ni-catalyzed C–OMe Cleavage

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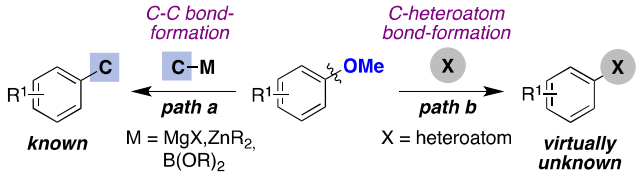
*Supporting Information Placeholder*

**ABSTRACT:** A Ni-catalyzed *ipso*-borylation of aryl ethers via C($sp^2$)– & C($sp^3$)–OMe cleavage is described. The transformation is characterized by its wide substrate scope under mild conditions and an exquisite divergence in site-selectivity that can be easily switched by an appropriate selection of the boron reagent.

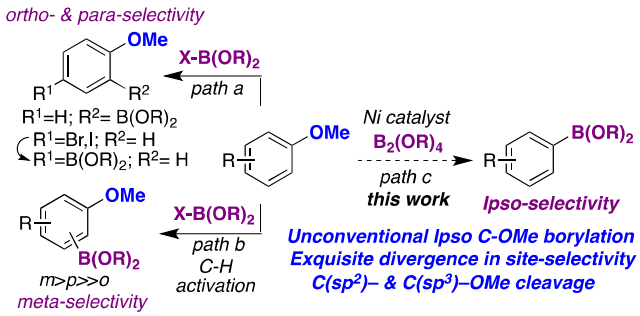
In recent years, C–O electrophiles have emerged as powerful alternatives to aryl halides as coupling partners in the cross-coupling arena.[1,2] While the utilization of activated aryl esters, carbamates or sulfonates has become routine, it comes as a surprise that aryl methyl ethers, the simplest derivatives in the phenol series, have received much less attention.[2] This is likely due to the high activation energy required for C–OMe scission and the low propensity of methoxy residues to act as leaving groups. Not surprisingly, these reactions remain essentially confined to C–C bond-formations using highly reactive, well-defined, stoichiometric and, in many cases, air-sensitive organometallic reagents (Scheme 1, *path a*).[2] Intriguingly, a C–heteroatom bond-formation has been virtually unexplored (*path b*),[3] thus constituting a unique opportunity to implement unconventional strategies not apparent at first sight in our chemical portfolio.

**Scheme 1. Catalytic C($sp^2$)-OMe Bond-Cleavage**.




The pivotal role of organoboron reagents as synthetic intermediates has attracted the attention of both industrial and academic laboratories for decades.[4] Not surprisingly, the recent years have witnessed the development of a myriad of catalytic methods for their synthesis.[5-8] At present, the inclusion of aryl methyl ethers has merely been employed as a control element for promoting C–B bond-forming reactions at either *ortho-*, *meta-* or *para*-position via *ortho*-metalation or the intermediacy of aryl halides via electrophilic aromatic substitution (Scheme 2, *path a*),[9,10] or C-H activation (*path b*).[6] From a synthetic standpoint, the ability to promote a complementary *ipso*-borylation of aryl methyl ethers would be highly rewarding, offering a counterintuitive, yet practical, new retrosynthetic approach to organoborane reagents from simple precursors.[11] At the outset of our investigations, it was unclear whether such scenario would be feasible given the exceptional inertness of C–OMe bonds,[2] the natural proclivity of aryl ethers to promote functionalization at *ortho-* or *para*-positions[12] and the virtual lack of precedents for C–heteroatom bond-formation via C–OMe cleavage.[3] If successful, such a strategy would not only open up new vistas in C–B bond-formation but also might represent a significant step-forward for implementing aryl methyl ethers as privileged counterparts in cross-coupling endeavours.[2] As part of our interest in C–O bond-functionalization,[13] we describe herein the first catalytic *ipso*-borylation of aryl methyl ethers via C($sp^2$)– and even C($sp^3$)–O cleavage, thus exploiting a previously unrecognized opportunity in this field.[14,15] This protocol is characterized by its wide scope under mild conditions and by an exquisite divergence in site-selectivity that can be modulated by a judicious choice of the corresponding boron reagent.

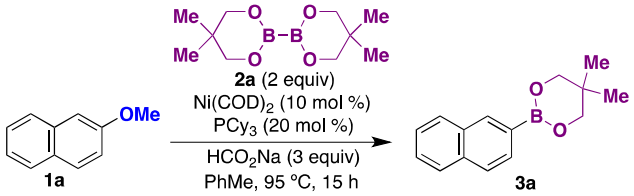
**Scheme 2. Borylation Events of Aryl Methyl Ethers.**




We began our investigations by evaluating the reaction of **1a** with $B_2(nep)_2$ (**2a**). After extensive experimentation,[16] we found that a cocktail containing $Ni(COD)_2$, $PCy_3$ and $HCO_2Na$ promoted the targeted reaction at 95 ºC, affording **3a** in 80% isolated yield. Although $HCO_2Na$ has commonly been employed as reducing agent in cross-coupling reactions,[17] marginal formation

of naphthalene was detected in the crude mixtures (<9%). Interestingly, the utilization of other bases provided inferior results (entries 11 and 12).[18] As anticipated, the nature of the ligand employed had a profound influence on the reaction outcome (entries 5-7). Strikingly, the inclusion of otherwise related $PCy_2Ph$ had a deleterious effect on reactivity, thus showing the subtleties of our protocol (entry 5). Similarly, *N*-heterocyclic carbenes provided **3a** in lower yields (entries 6 and 7).[19] Notably, a difference in reactivity was found when operating under a $NiCl_2(PCy_3)_2$, $Ni(PCy_3)_2(C_2H_4)$ or $[Ni(PCy_3)_2]_2N_2$ regime (entries 8-10). Although tentative, we believe that COD might be acting as a non-innocent ancillary ligand to stabilize the putative $Ni(PCy_3)_2$ species and prevent decomposition pathways.[20] The lack of reactivity of $B_2(pin)_2$ (**2b**; entry 13) is noteworthy, suggesting an intimate interplay between steric effects and productive C–B bond-formation. In line with this notion, ethoxy, isopropoxy or benzyloxy groups gave lower conversions to **3a**.[16] As anticipated, control experiments revealed that all reaction parameters were critical for success (entries 2-4).[16]

**Table 1. Optimization of the Reaction Conditions.**[a]

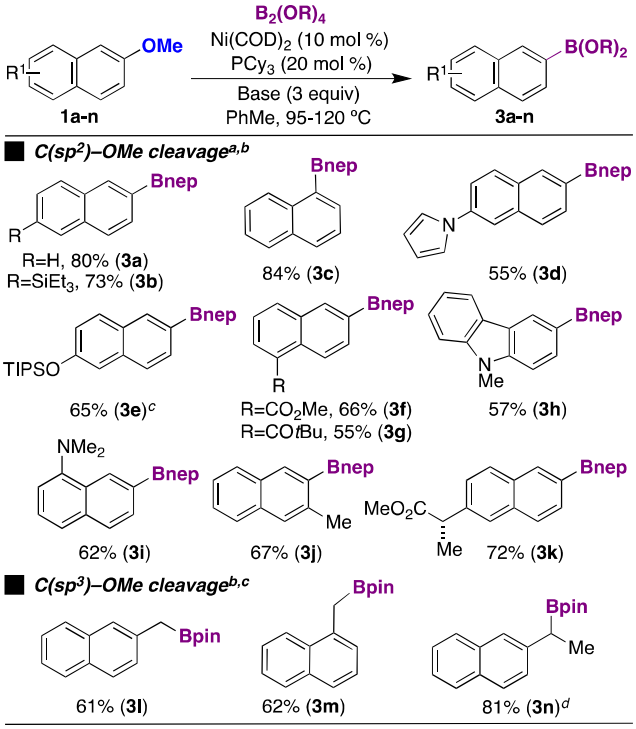



| Entry | Deviation from standard conditions | **3a** (%)[b] |
|---|---|---|
| 1 | none | 88 (80)[c] |
| 2 | without $Ni(COD)_2$ | 0 |
| 3 | without $PCy_3$ | 0 |
| 4 | without $HCO_2Na$ | 42 |
| 5 | $PCy_2Ph$ instead of $PCy_3$ | 0 |
| 6 | IPr·HCl instead of $PCy_3$[d] | 0 |
| 7 | ICy·$HBF_4$ instead of $PCy_3$[d] | 48 |
| 8 | $NiCl_2(PCy_3)_2$ instead of $Ni(COD)_2/PCy_3$ | 0 |
| 9 | $Ni(PCy_3)_2(C_2H_4)$ instead of $Ni(COD)_2/PCy_3$ | 61 |
| 10 | $[Ni(PCy_3)_2]_2(N_2)$ instead of $Ni(COD)_2/PCy_3$ | 64 |
| 11 | $PhCO_2Na$ instead of $HCO_2Na$ | 73 |
| 12 | CsF instead of $HCO_2Na$ | 65 |
| 13 | $B_2(pin)_2$ (**2b**) instead of $B_2(nep)_2$ (**2a**) | 2 |

[a] Conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $Ni(COD)_2$ (10 mol%), $PCy_3$ (20 mol %), $HCO_2Na$ (1.50 mmol) in PhMe (2.0 mL) at 95 ºC, 15 h. [b] GC yields using decane as internal standard. [c] Isolated yield. [d] +NaO*t*Bu (25 mol%).

With a reliable procedure in hand, we next turned our attention to explore the preparative scope of our catalytic *ipso*-borylation technique via $C(sp^2)$–OMe bond-cleavage (Table 2). As shown, a wide variety of naphthyl ethers possessing a diverse set of substitution patterns could perfectly be tolerated, obtaining in all cases good yields of **3a-3k**. The chemoselectivity profile of our method was nicely illustrated by the fact that silyl groups (**3b**), silyl ethers (**3e**), esters (**3f** and **3k**), ketones (**3g**) and amines (**3i**) could all be equally accommodated. Importantly, the presence of nitrogen-containing heterocycles did not interfere with productive C–B bond-formation (**3d** and **3h**). As shown for **3j**, the reaction was not hampered by the presence of *ortho*-substituents. It is worth noting that no racemization of the chiral center in **3k** was observed when exposing enantioenriched **1k** (96% *ee*) under our optimized reaction conditions. Intriguingly, the inclusion of CsF and $B_2pin_2$ (**2b**) cleanly afforded **3l** and **3m** via $C(sp^3)$–OMe cleavage.[21-23] Likewise, benzyl methyl ethers posessing β-hydrogens posed no problems, obtaining **3n** in 81% yield.[24,25]

**Table 2. *Ipso*-Borylation of Naphthyl Methyl Ethers**

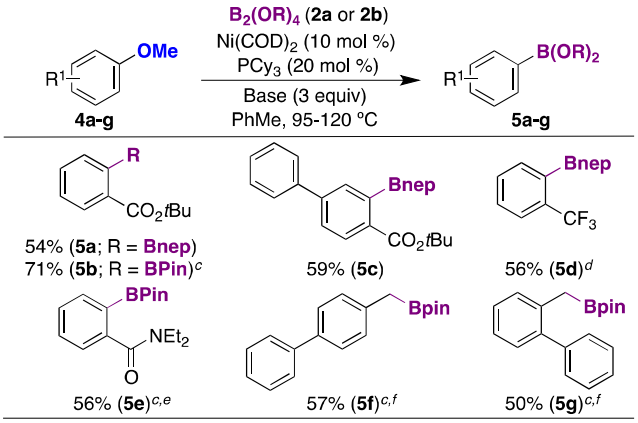



[a] As for Table 1 (entry 1) using **2a**. [b] Isolated yields, average of at least two independent runs. [c] 120 ºC. [d] As for Table 1 (entry 1), but employing **2b** (1.00 mmol) and CsF (1.50 mmol) at 120 ºC. [d] Determined by GC (decane as internal standard). Bnep: 5,5-dimethyl-1,3,2-dioxaborolane; Bpin: 4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

A close inspection into the literature data indicates that regular arenes are several orders of magnitude less reactive than non π-extended systems in C–O bond-cleavage protocols.[26,27] At present, such lack of reactivity has been overcome primarily by employing stoichiometric and highly reactive organometallic species,[1,2] thus representing a drawback from a practical and synthetic point of view. In light of these precedents, we wondered whether our Ni-catalyzed *ipso*-borylation event could be applied to more challenging aryl methyl ethers. Although such scenario proved to be difficult, we speculated that the presence of suitable *ortho*-substituents might facilitate the elusive C–OMe bond-cleavage in anisole

derivatives. As shown in Table 3, this was indeed the case for a variety of aryl methyl ethers possessing *ortho*-esters (**5a-5c**), trifluoromethyl groups (**5d**) or amides (**5e**).[28,29] Importantly, the presence of such groups in *para* or *meta* position gave negligible conversion to products, thus providing compelling evidence that electronic effects are not the only factor coming into play.[30] In contrast to the results of Table 1 (entry 13), we found that $B_2(pin)_2$ (**2b**) could be utilized for effecting the C($sp^2$)–OMe bond-cleavage (**5b**, **5e**).[31] As for Table 2, we found that a C($sp^3$)–OMe bond-cleavage was within reach (**5f** and **5g**).

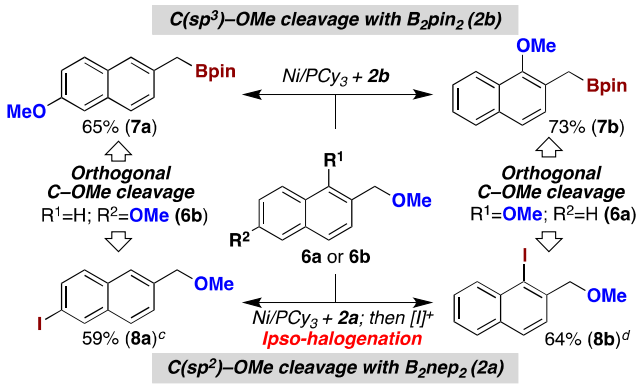
**Table 3. *Ipso*-Borylation of Aryl Methyl Ethers.**[a,b]




[a] As for Table 1 (entry 1). [b] Isolated yields, average of at least two independent runs. [c] Using **2b** (1.0 mmol). [d] $HCO_2Na$ (0.50 mmol) [e] GC yield using decane as internal standard. [f] CsF (1.00 mmol) at 120 ºC.

On the basis of the results of Tables 1-3, we concluded that the nature of the boron reagent might not be entirely innocent in the reaction outcome. Challenged by such perception, we speculated that an *orthogonal site-selective C–B bond-formation* via C–OMe bond-cleavage could be achieved. To such end, we examined the reactivity of **6a** and **6b** under a **2a** or **2b** regime (Figure 1). Interestingly, while the utilization of **2b** lead exclusively to **7a** and **7b** via C($sp^3$)–OMe cleavage, a C($sp^2$)–B bond-formation was invariably observed with **2a**.[32] At present, we have no explanation for such intriguing dichotomy. Encouraged by these results, we wondered whether our Ni-catalyzed *ipso*-borylation could be employed as a manifold to promote an unprecedented *ipso*-halogenation of aryl methyl ethers,[33] thus complementing classical *ortho*- or *para*-electrophilic aromatic halogenation techniques.[34] As shown in Figure 1 (*bottom*), this turned out to be the case and a one-pot borylation/iodination sequence allowed for rapidly obtaining **8a** and **8b** in good overall yield.[35] Taken together, the results of Tables 2-3 and Figure 1 tacitly suggest that our novel *ipso* Ni-catalyzed C–OMe borylation will foster new explorations in carbon-heteroatom bond-forming reactions via unconventional C–O bond-cleavage.

**Figure 1. Orthogonal Borylation via C–OMe Cleavage.**[a,b]




[a] C($sp^3$)–OMe cleavage: **6a** or **6b** (0.50 mmol), **2b** (1.00 mmol), $Ni(COD)_2$ (10 mol%), $PCy_3$ (20 mol%), CsF (1.50 mmol) in PhMe (2.0 mL) at 120 ºC. [b] C($sp^2$)–OMe cleavage: as for Table 1 (entry 1), followed by NaI (1.50 mmol) and chloramine T·$3H_2O$ (1.50 mmol) in 4mL THF/$H_2O$ (1:1) at rt. [c] Borylation conducted at 120 ºC. [d] Borylation conducted with $HCO_2Na$ (0.15 mmol)

In summary, we have developed the first *ipso*-borylation of aryl methyl ethers via Ni-catalyzed C–OMe bond-cleavage, complementing classical *ortho-, meta-* and *para*-borylation techniques. This protocol is distinguished by its broad substrate scope and by an intriguing selectivity switch depending on the boron reagent employed. Further investigations into related projects will be reported in due course.

## ASSOCIATED CONTENT

**Supporting Information**. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

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No competing financial interests have been declared.

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(22) No reaction took place in the absence of $Ni(COD)_2$/$PCy_3$.

(23) Although $B_2(nep)_2$ could be utilized as coupling partner, we found that the resulting benzyl neopentylboronates were rather unstable, thus preventing their isolation in pure form.

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(28) No C–B bond-formation was found when utilizing electron-donating dimethylamino groups in *ortho*-position. For the utilization of other anisole derivatives, see ref. 16.

(29) In sharp contrast with the utilization of *ortho tert*-butyl esters, we found that *ortho* methyl esters provided lower yields (~25% GC yields), thus revealing an intimate interplay between steric effects and C–B bond-formation.
(30) No biaryl formation via Suzuki-Miyaura coupling of *in situ* generated aryl boronates with aryl ethers was observed.
(31) Intriguingly, while **5e** was cleanly obtained with $B_2pin_2$, an otherwise related reaction with $B_2(nep)_2$ did not result in productive C–B bond-formation.
(32) Unreacted starting material and marginal reduction of C–OMe bond account for the mass balance.
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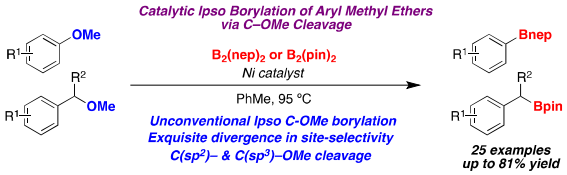
(35) The isolation of the corresponding aryl neopentyl boronates was particularly cumbersome due to the instability of the boronic esters during purification by column chromatography.


Catalytic Ipso Borylation of Aryl Methyl Ethers
via C–OMe Cleavage
OMe
R1
R2
OMe
R1
B2(nep)2 or B2(pin)2
Ni catalyst
PhMe, 95 °C
Unconventional Ipso C-OMe borylation
Exquisite divergence in site-selectivity
C(sp2)– & C(sp3)–OMe cleavage
Bnep
R1
R2
Bpin
R1
25 examples
up to 81% yield