

Ipsso-Borylation of Aryl Ethers via Ni-Catalyzed C–OMe Cleavage

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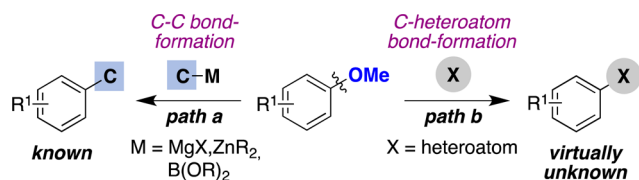
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S Supporting Information

ABSTRACT: A Ni-catalyzed *ipso*-borylation of aryl ethers via C(sp²)–OMe and C(sp³)–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 selecting the appropriate 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 activated aryl esters, carbamates, or sulfonates are used routinely, 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 carbon–

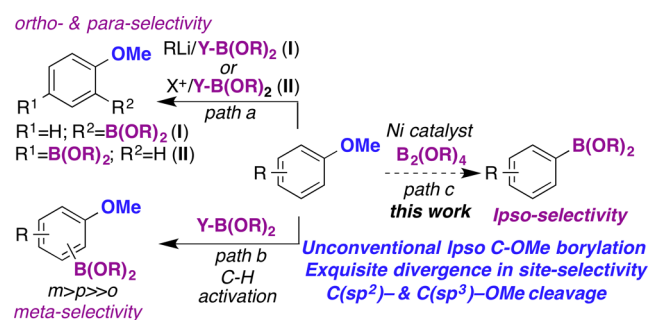
Scheme 1. Catalytic C(sp²)–OMe Bond Cleavage



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.

The pivotal role of organoboron reagents as synthetic intermediates has attracted the attention of both industrial and academic laboratories for decades.⁴ Not surprisingly, 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 the *ortho*, *meta*, or *para* position via *ortho*-metalation (Scheme 2, *path a*-I) or the intermediacy of aryl halides via electrophilic aromatic substitution (Scheme 2, *path a*-II)^{9,10} or C–H activation (Scheme 2, *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 organoboron reagents

Scheme 2. Borylation Events of Aryl Methyl Ethers

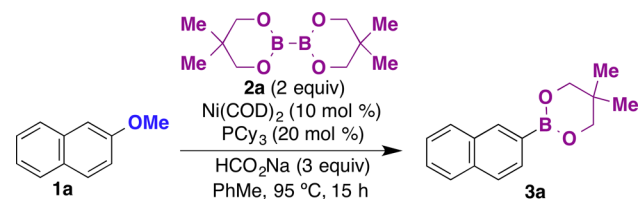


from simple precursors.¹¹ At the outset of our investigations, it was unclear whether such a scenario would be feasible, given the exceptional inertness of C–OMe bonds,² the natural proclivity of aryl ethers to promote functionalization at *ortho* or *para* positions,¹² and the virtual lack of precedents for carbon–heteroatom bond formation via C–OMe cleavage.³ If successful, this strategy not only would 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 endeavors.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(sp²)–O and even C(sp³)–O cleavage, thus exploiting a previously unrecognized opportunity in this field (Scheme 2, *path c*).^{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 judicious choice of the corresponding boron reagent.

We began our investigations by evaluating the reaction of **1a** with B₂(nep)₂ (**2a**). After extensive experimentation,¹⁶ we found that a cocktail containing Ni(COD)₂, PCy₃, and HCO₂Na promoted the targeted reaction at 95 °C, affording **3a** in 80% isolated yield (Table 1). Although HCO₂Na has commonly been employed as a 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 PCy₂Ph had a deleterious effect on reactivity, thus showing the subtleties of our protocol (entry 5). Similarly, *N*-heterocyclic carbenes

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Table 1. Optimization of the Reaction Conditions^a

entry	deviation from standard conditions	yield 3a (%) ^b
1	none	88 (80) ^c
2	without Ni(COD) ₂	0
3	without PCy ₃	0
4	without HCO ₂ Na	42
5	PCy ₂ Ph instead of PCy ₃	0
6	IPrHCl 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 ₂ H 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 ₂ Na instead of HCO ₂ Na	73
12	CsF instead of HCO ₂ Na	65
13	B ₂ (pin) ₂ (2b) instead of B ₂ (nep) ₂ (2a)	2

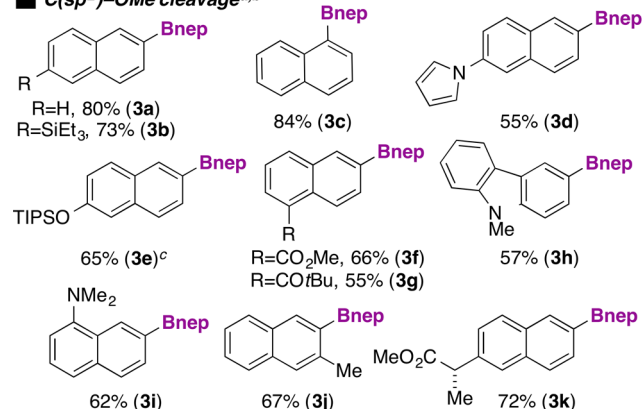
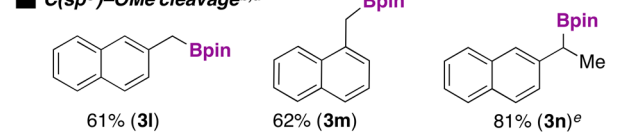
^aConditions: **1a** (0.50 mmol), **2a** (1.00 mmol), Ni(COD)₂ (10 mol %), PCy₃ (20 mol %), and HCO₂Na (1.50 mmol) in PhMe (2.0 mL) at 95 °C, 15 h. ^bGC yields using decane as internal standard. ^cIsolated yield. ^d+NaOtBu (25 mol%).

provided **3a** in lower yields (entries 6 and 7).¹⁹ Notably, a difference in reactivity was found when operating under a NiCl₂(PCy₃)₂, Ni(PCy₃)₂(C₂H₄), or [Ni(PCy₃)₂]₂N₂ regime (entries 8–10). Although tentative, we believe that COD might be acting as a non-innocent ancillary ligand to stabilize the putative Ni(PCy₃)₂ species and prevent decomposition pathways.²⁰ The lack of reactivity of B₂(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

With a reliable procedure in hand, we next turned our attention to explore the preparative scope of our catalytic ipso-borylation technique via C(sp²)-OMe bond cleavage (Table 2). As shown, a wide variety of naphthyl ethers possessing a diverse set of substitution patterns could be perfectly tolerated, giving 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**, **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**, **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** (96% ee) was observed when exposing enantioenriched **1k** under our optimized reaction conditions. Intriguingly, the inclusion of CsF and B₂pin₂ (**2b**) cleanly afforded **3l** and **3m** via C(sp³)-OMe cleavage.^{21–23} Likewise, benzyl methyl ethers having β-hydrogens posed no problems, giving **3n** in 81% yield.^{24,25}

A close inspection into the literature data indicates that regular arenes are several orders of magnitude less reactive than π-extended systems in C–O bond cleavage protocols.^{26,27} At

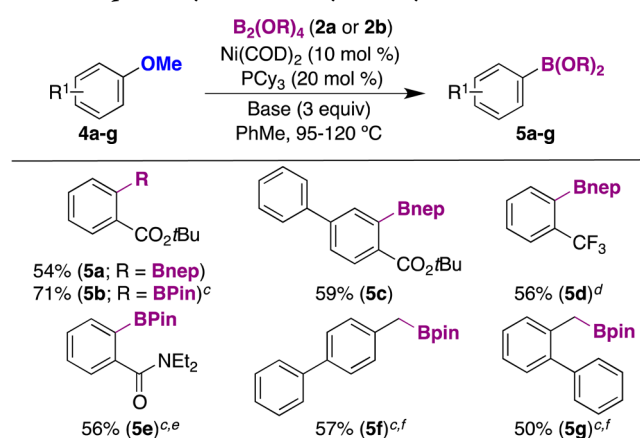
Table 2. Ipso-Borylation of Naphthyl Methyl Ethers

■ C(sp²)-OMe cleavage^{a,b}■ C(sp³)-OMe cleavage^{b,d}

^aAs for Table 1 (entry 1) using **2a**. ^bIsolated yields, average of at least two independent runs. ^c120 °C. ^dAs for Table 1 (entry 1), but employing **2b** (1.00 mmol) and CsF (1.50 mmol) at 120 °C. ^eDetermined by GC (decane as internal standard). Bnep = 5,5-dimethyl-1,3,2-dioxaborolane; Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

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 a 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 at the *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 B₂(pin)₂ (**2b**) could be utilized to effect the C(sp²)-OMe bond cleavage in regular arenes (**5b**, **5e**).³¹ As for Table 2, we found that a C(sp³)-OMe bond cleavage was within reach (**5f**, **5g**).

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 this perception, we speculated that *orthogonal site-selective C–B bond formation* via C–OMe bond cleavage could be achieved. To this end, we examined the reactivity of **6a** and **6b** under a **2a** or **2b** regime (Figure 1). Interestingly, while the utilization of **2b** led exclusively to **7a** and **7b** via C(sp³)-OMe cleavage, a C(sp²)-B bond formation was invariably observed with **2a**.³² At present, we have no explanation for such an intriguing

Table 3. *Ips*o-Borylation of Aryl Methyl Ethers^{a,b}

^aAs for Table 1 (entry 1). ^bIsolated yields, average of at least two independent runs. ^cUsing 2b (1.0 mmol). ^dHCO₂Na (0.50 mmol) ^eGC yield using decane as internal standard. ^fCsF (1.00 mmol) at 120 °C.

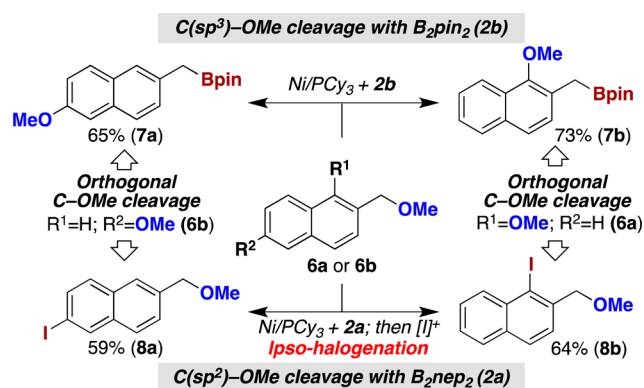


Figure 1. Orthogonal borylation via C–OMe cleavage. Conditions for C(sp³)–OMe cleavage: 6a or 6b (0.50 mmol), 2b (1.00 mmol), Ni(COD)₂ (10 mol %), PCy₃ (20 mol %), and CsF (1.50 mmol) in PhMe (2.0 mL) at 120 °C. Conditions for C(sp²)–OMe cleavage: as for Table 1 (entry 1), followed by NaI (1.50 mmol) and chloramine T·3H₂O (1.50 mmol) in 4 mL of THF/H₂O (1:1) at rt (1h). For 8a, borylation was conducted at 120 °C. For 8b, borylation was conducted with HCO₂Na (0.15 mmol).

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 and 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.

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 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. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03955.

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Notes

The authors declare no competing financial interest.

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(28) No C–B bond formation was found when electron-donating dimethylamino groups of simple anisoles were used in the *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 (see ref 26f).

(31) Intriguingly, while **5e** was cleanly obtained with B₂pin₂, an otherwise related reaction with B₂(nep)₂ did not result in productive C–B bond formation.

(32) Unreacted starting material and marginal reduction of the C–OMe bond account for the mass balance.

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