Iron-Catalyzed Borylation of Alkyl Electrophiles

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S *Supporting Information*

ABSTRACT: The use of low-cost iron(III) acetoacetate (Fe(acac)$_3$) and tetramethylethylenediamine (TMEDA) enables the direct cross-coupling of alkyl halides with bis(pinacolato)diboron. This approach allows for the borylation of activated or unactivated primary, secondary, and tertiary bromides. Moreover, even the borylation of benzylic or allylic chlorides, tosylates, and mesylates are possible. The reactions proceed under mild conditions at room temperature and show broad functional-group compatibility and "robustness" as measured by a modified Glorius robustness screen.
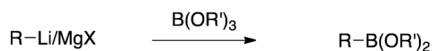
Alkylboronic esters represent an important class of reagents with broad utility in the field of organic synthesis.[1] The most common methods to access these functional groups include transmetalation from highly reactive organolithiums or Grignards (Scheme 1a)[2] and the hydroboration of olefins

Scheme 1. General Approaches to Access Alkyl Boronic Esters[a]

[a] R = alkyl; X = halide or *p*-toluenesulfonate.

(Scheme 1b).[3] Additionally, methods describing metal-catalyzed C−H activation (Scheme 1c)[4] and β-borylation of α,β-unsaturated carbonyls (Scheme 1d)[5] have been reported. To overcome drawbacks such as limited functional-group compatibility (Scheme 1a), regioselectivity (Scheme 1b and 1c), and narrow scope (Scheme 1d), recent efforts have focused on the direct Miyaura-type borylation of alkyl halides (Scheme

1e).[6] Currently, examples with Pd,[7] Ni,[8] Cu,[9] and Zn[10] have been reported. While these methods have vastly improved access to alkylboronic esters, expensive catalysts[7] and/or ligands[7,10,11] and a limited substrate scope[7−11] provide ample incentive to devise a more general strategy. Based on our recent findings that iron catalysts often perform better than their noble metal counterparts in coupling reactions,[12] we sought to explore the generality of an iron-catalyzed borylation reaction. Here we report a mild, room temperature borylation of alkyl halides using inexpensive and benign iron salts (Scheme 1e). The reaction shows a broad substrate scope and functional-group compatibility.
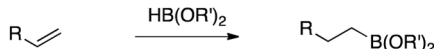
The project began with the observation that bis(pinacolato)-diboron (B$_2$pin$_2$) can couple with benzyl chloride in the presence of FeCl$_2$ and *n*-BuMgBr. Success with benzyl chloride offered the exciting possibility of creating a general method for the borylation of alkyl halides. Using 4-(4-methoxyphenyl)-2-bromobutane (**1w**) as a less reactive model substrate, a variety of iron sources, solvents, and ligands were evaluated (see Supporting Information (SI)). The presence of both iron and Grignard is required for the reaction. The ethylmagnesium bromide activates the B$_2$pin$_2$ and reduces the iron to its low-valent active state. Using ethylmagnesium bromide allowed for simple removal of the EtBpin side product under vacuum. While Fe(acac)$_3$ alone provided 23% yield of borylated product **2w**, the addition of TMEDA (10 mol %) increased the yield to 63%. While most iron precatalysts worked in the reaction, Fe(acac)$_3$ offered the optimal combination of reactivity and simple reaction setup. Solvents other than THF and ligands other than TMEDA proved inferior. While the reactions could be run with a slight excess of B$_2$pin$_2$, 15−20% higher yields were obtained with 3.5 equiv, likely due to overalkylation of B$_2$pin$_2$ by ethylmagnesium bromide.[13] Interestingly, either raising or lowering the temperature from ambient compromised yields and increased formation of the simple halide reduction product. Finally, the reaction appears to be catalyzed by iron since the use of 99.99% FeCl$_2$ resulted in a 74% yield and 99.9% Fe(acac)$_3$ resulted in a 91% yield (compared to 80% under standard conditions), while copper, nickel, palladium, chromium, and manganese salts all produced substantially diminished yields under our conditions (see SI).[14] Based on these observations, the reaction is performed by combining Fe(acac)$_3$ (10 mol %) with B$_2$pin$_2$ (3.5 equiv) in THF followed by the addition of TMEDA (10 mol %), ethylmagnesium bromide (4.5 equiv), and the electrophile (Scheme 2). The addition of the electrophile last was critical to avoid the

unproductive side reactions between the Grignard and electrophile (e.g., E2).

With the availability of mild reaction conditions for the borylation of secondary bromides, a variety of substrates were evaluated (Scheme 2). Unlike the reported Pd,[7] Cu,[9] and Zn[10] methods, the reaction provided access to primary, secondary, tertiary, benzylic, and allylic boronic esters in modest-to-excellent yields. As can be seen in Scheme 2a, unactivated primary bromides work well in the reaction (**1a**−**1c**), while unactivated primary alkyl chlorides and tosylates furnished only trace yields (**1d** and **1e**). Primary benzylic chlorides generally provided high yields (**1f**−**1n**), but benzyl tosylate (**1r**) and cinnamyl chloride (**1t**) only proceeded in 31% and 28% yield, respectively. Although the yields for the chlorides and tosylates are currently low, these examples represent the first borylative couplings of alkyl chlorides and tosylates without in situ conversion to the iodides using tetrabutylammonium iodide (TBAI).[9b] Unfortunately, the reaction does not tolerate the use of unactivated secondary chlorides (**1v** and **1cc**, Scheme 2b). Interestingly, the secondary benzylic chloride **1ii** proceeded in higher yield than the analogous bromide (**1jj**) due to rapid dimerization of **1jj** (Scheme 2b). The success of secondary allylic bromide **1ll**, however, demonstrates that not all activated bromides homocouple under the reaction conditions. To date, few examples exist for borylation of tertiary halides, with the nickel-based method by Fu and co-workers[8] offering the only examples beyond 1-bromoadamantane.[9b,c] Our examination of tertiary halides revealed that unactivated and activated bromides (**1mm**, **1oo**, **1pp**, and **1rr**) work in the reaction, while tertiary chlorides proceed in low yield (**1nn** and **1qq**, Scheme 2c). The reaction also performs well on gram scale. For example, 1.0 g of **1w** provides an 87% yield of borylated product **2w** under the optimized reaction conditions (Scheme 3).

Next, we sought to evaluate the functional-group tolerance of the reaction. To that end, a modified-Glorius robustness screen proved highly informative without the need for lengthy substrate preparation.[15] The standard borylation reaction was performed in the presence of a variety of additives containing common functional groups or heterocycles (see SI). A variety of versatile and synthetically useful functional groups such as esters, ketones, aldehydes, amides, internal alkenes, and alkyl amines were found to have little-to-no effect on the borylation reaction. By contrast, terminal alkenes, terminal alkynes, and carboxylic acids significantly inhibited the formation of product. Interestingly, functional groups such as aldehydes, ketones, terminal alkenes, and terminal alkynes are consumed in the reaction while nitriles, amides, and esters are not. The reaction proceeded well in the presence of quinoline, pyrrole, methylimidazole, benzofuran, and indole, while 3-methylbenzo-thiophene moderately inhibited the reaction—consistent with the lower yield of the reaction for substrate **1q**. Importantly, none of the functional groups or structural motifs tested completely shut down the borylation.

Based on the interesting reactivity profile observed in Scheme 2, we conducted simple competition experiments (Scheme 4). Not surprisingly, the competition between a primary bromide and a primary chloride using 1-bromo-6-chlorohexane (**3**) produced borylation predominantly at the primary bromide to form monoborylated product **4** with some additional coupling at the primary chloride to form **5** (Scheme 4a). Interestingly, the competition between a primary bromide and secondary bromide in 1,4-dibromopentane (**6**) revealed

**Scheme 2. Substrate Scope of the Borylation Reaction**[a]
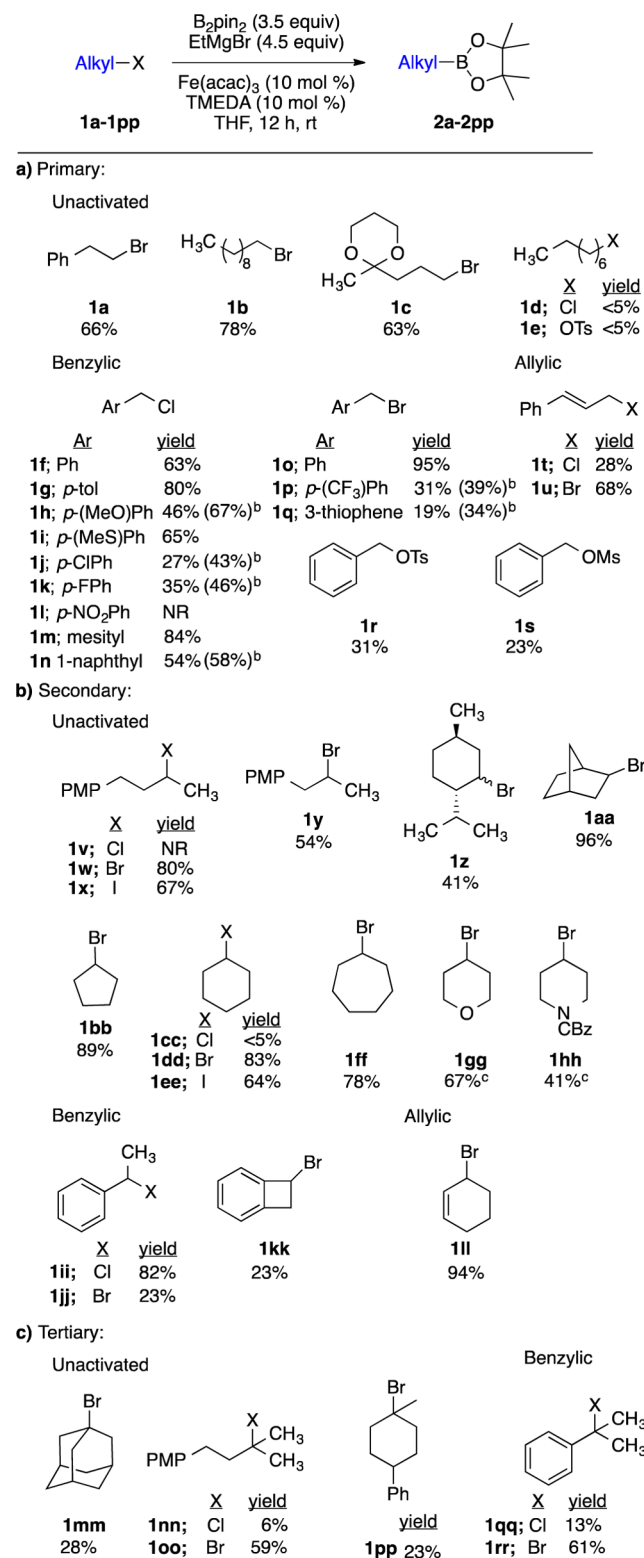
[a]All yields after isolation from silica column chromatography (except <5%, which was detected by GC or ^{1}H NMR). NR = no reaction. PMP = p-methoxyphenyl. [b] Change to reaction conditions: Fe(acac)₃ (5 mol %), TMEDA (5 mol %), 1 h. [c] Change to reaction conditions: Fe(acac)₃ (20 mol %), TMEDA (20 mol %).

almost no preference, indicating very similar reaction rates for primary and secondary bromides (Scheme 4b).

Scheme 3. Gram-Scale Borylation Reaction
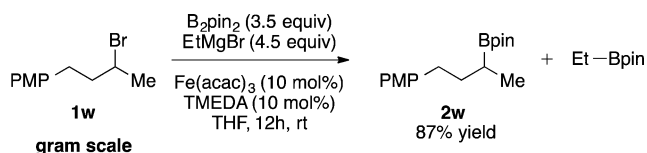
Scheme 4. Competition Experiments
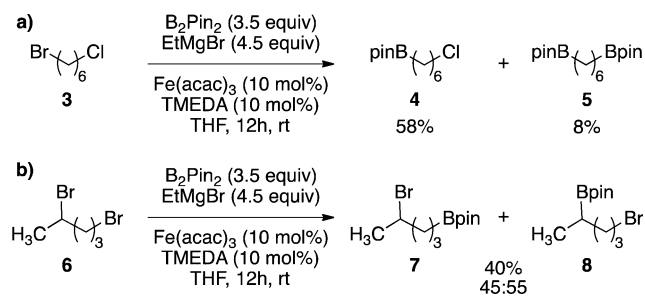
At this point in the investigation, little can be surmised about the mechanistic course of these reactions. Since EtBpin is formed in the reaction, it stands to reason that the alkyl halide acts as the electrophile while the B_2pin_2-ate complex functions as the nucleophile for coupling. Whether the reaction proceeds through an oxidative addition-first or transmetalation-first mode of coupling remains unknown. The only byproducts of the reaction are EtBpin and simple reduction of the starting electrophile. Whether the reaction proceeds through a radical-based mechanism remains an open question. For example, secondary benzylic bromide **1jj** produced only a 23% yield with 70% of the material forming the homodimer, a result consistent with benzylic radical formation. Yet, the success of benzyl tosylate **1r** and benzyl mesylate **1s** (Scheme 2a) provides evidence against benzylic radical formation for those substrates. Moreover, when substrate **1w** was subjected to standard reaction conditions in the presence of TEMPO (1 equiv) or BHT (1 equiv), the reaction proceeded as usual in 82% and 83% yields, respectively (compared to an 80% yield under standard conditions). Clearly detailed mechanistic studies are needed to clarify the mechanism(s) at work in these reactions.

In summary, we have developed a robust iron-catalyzed borylation of alkyl electrophiles. The reaction generally proceeds in high yields with an exceptional substrate scope. The reactivity and selectivity provide a reaction profile unique among the reported borylation methods, thereby offering greater generality. The extremely low cost and low toxicity of the reagents should simplify large-scale implementation of these reactions. Further efforts will be directed toward understanding the reaction mechanism of this interesting transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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