Organic Letters
Letter
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# Application of Cooperative Iron/Copper Catalysis to a Palladium-Free Borylation of Aryl Bromides with Pinacolborane

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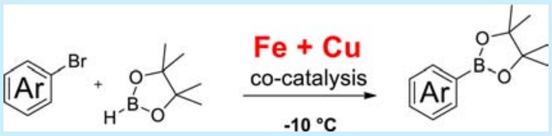
*Supporting Information*

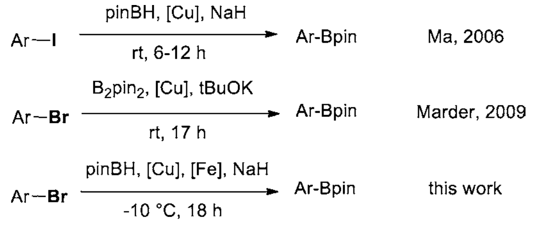
**ABSTRACT:** A new cooperative copper/iron catalysis for the borylation of various aryl bromides with pinacolborane, at −10 °C, is reported. Use of the toxic, precious metal Pd is avoided. The mechanism of the protodebromination side reaction is discussed.



Cyclic arylboronic esters are highly useful reagents in the organic chemist's toolbox, mainly as intermediates for the Suzuki–Miyaura transition-metal-catalyzed cross-coupling.[1,2] They avoid some drawbacks of arylboronic acids: difficult purification, poor stability on storage, and protodeboronation. They are mainly prepared via treatment of trialkoxyboranes by arylmagnesium or aryllithium reagents, and continued effort is devoted to increase the scope and robustness of these procedures.[2a,3] An alternate approach was initiated by the work of Miyaura and Murata on the Pd-catalyzed borylation of aryl halides with bis(pinacolato)diboron[4a] ($B_2pin_2$) or pinacolborane[4b] (4,4,5,5-tetramethyl-1,3,2-dioxaborolane, pinBH, **1**). The latter reagent is attractive in terms of atom economy and ease of preparation,[5] and many transition-metal catalyzed direct couplings of aryl halides with pinBH to produce boronic esters have been reported.[6,7]

Among these methods, Zhu and Ma[8] reported the copper-catalyzed borylation of aryl iodides with pinacolborane at room temperature (Scheme 1). This process is restricted to aryl iodides, bromides reacting only marginally. Cu-catalyzed borylation of aryl bromides is also possible if $B_2pin_2$ (or bis(neopentylglycolato)diboron) is used.[9]

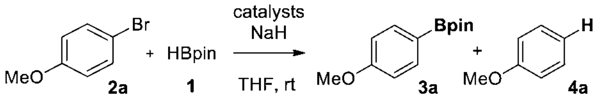
**Scheme 1. Copper-Catalyzed Borylation by pinBH**



Since Ma's results show that CuI readily effects the formation of C–B intermediates at room temperature, we wondered if the system could be extended to less reactive halides by means of a cocatalysis.[10] In our hypothesis Cu could accomplish the formation of the B–metal bond, while insertion in the carbon–halogen bond could be effected by Fe,[11] and transmetalation would follow. Fe–Cu cocatalyzed reactions have already attracted considerable attention: applications in C–N, C–O, and C–S bond formations, alkynylation, C–H functionalizations, and conjugate addition reactions have been proposed.[12,13]

We started our investigation by testing the procedure described by Ma[8] on 4-bromoanisole, a good substrate in Pd-catalyzed borylations with PinBH (Scheme 2). As described, the reaction was extremely sluggish. In the presence of a catalytic amount of $Fe(acac)_3$, we were delighted to observe a fast and complete conversion of 4-bromoanisole. Nevertheless, the boronic ester **3a** was obtained in low yield, the main product being anisole **4a** issued from protodebromination (PDB). $Fe(acac)_3$ alone did not produce any reaction.

**Scheme 2. Fe–Cu Cocatalysis in the Borylation of 2a**[a]



| | |
|---|---|
| CuI 10 mol % | 19% conversion in 48 h<br>15% yield of **3a** |
| CuI 10 mol % +<br>$Fe(acac)_3$ 10 mol % | 100% conversion in 0.5 h<br>25% yield of **3a** |
| $Fe(acac)_3$ 10 mol % | no conversion after 6 h |

[a]Conditions: 1 mmol **2a**, 1.5 equiv pinBH, 1.5 equiv NaH, 1 mL THF; conversion determined by GC; isolated yields

We next studied the effect of various parameters on the Fe–Cu borylation,[14] with particular attention to the selectivity (borylation/PDB ratio). 2-Bromonaphthalene **2b** was chosen as the model substrate since it is moderately prone to PDB in

**Received:** March 6, 2014
**Published:** April 16, 2014

dx.doi.org/10.1021/ol500675q | *Org. Lett.* 2014, 16, 2366–2369

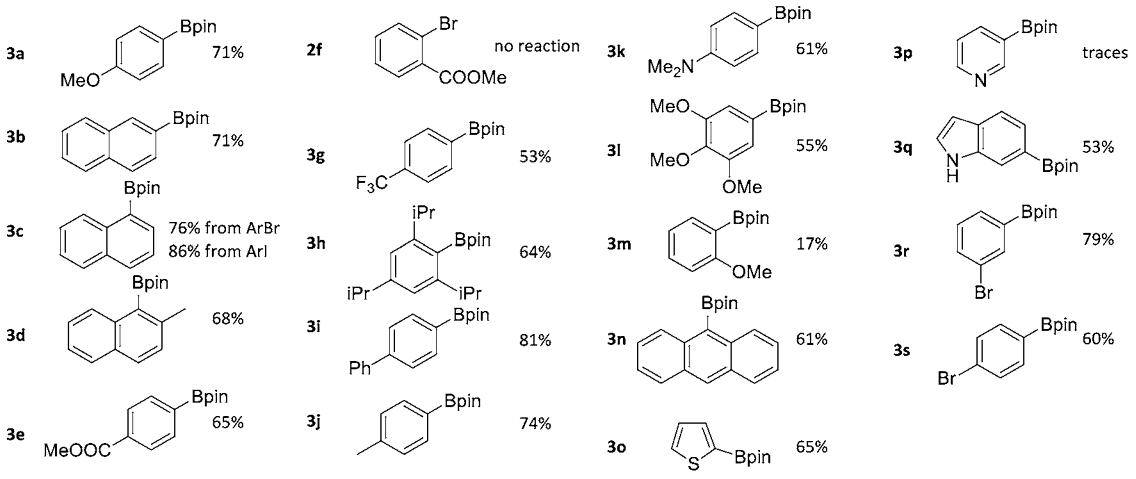


**Figure 1.** Substrate scope. Isolated yields; conversions were complete; the byproduct was **4** from PDB. Conditions: CuI 10 mol %, Fe(acac)$_3$ 10 mol %, TMEDA 1.5 equiv, NaH 1.5 equiv, pinBH 2.5 equiv, −10 °C, 18 h.

related Pd-catalyzed reactions.[6c] The effect of ligands was first considered: we found that in THF at 20 °C, TMEDA favorably improved the selectivity, up to 50% with 0.2 equiv ligand. Increasing the amount of TMEDA was beneficial to the reproducibility of this selectivity (consistently 45−50% with 1.5 equiv of TMEDA). Other nitrogen ligands (TEA, hexamethylenetetramine, tetramethylmethylenediamine, pentamethyldiethylenetriamine, DABCO, phenanthroline, terpyridine), as well as DMA, gave poorer conversions or selectivities. Noticeably, phosphine ligands led only to PDB product **4b** (DPEPhos,[15] P(*t*-Bu)$_3$) or to no reaction (*S*-Phos,[15] BINAP).

In the presence of TMEDA (1.5 mol equiv), at rt, we varied the copper and iron salts:[14] CuI provided the best results in terms of conversion and selectivity. CuBr or CuCN led to a better selectivity, but the reaction stalled (incomplete conversion). Various iron sources were also tested,[14] with Fe(acac)$_3$/CuI remaining the most efficient catalytic system. THF was the best solvent, albeit some desired product was obtained in diethyl ether, dioxane, NMP, and TMEDA.[14]

In contrast with what is observed in palladium-catalyzed borylations with pinBH, weak bases (triethylamine, LiH, lithium pivalate) failed to promote the reaction. NaH or KH produced the highest borylation level, while KHMDS or LiHMDS were less efficient. The behavior of alkoxides was erratic.[14]

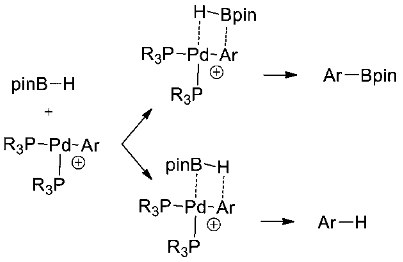
An interesting effect was observed when the temperature was lowered: the catalytic reaction worked to completion overnight at temperatures as low as −10 °C with improved selectivity (up to 71%). This is to our knowledge the lowest proposed temperature for transition-metal catalyzed borylation. At −15 °C, precipitation of salts blocked the catalysis.

Lowering the amount of Fe from 10% to 1% at −10 °C changed neither conversion nor selectivity. Without Fe, the reaction was again sluggish.[8] In contrast, decreasing the amount of copper from 10% to 1% was detrimental for both conversion (respectively 100% and 77% overnight) and selectivity (respectively 71% and 52%). Since it was sometimes found that copper and iron reagents contained traces of Pd and Ni that were the actual active catalytic species,[16] we checked that the sources of CuI and Fe(acac)$_3$ could be changed without variation of the outcome.[14]

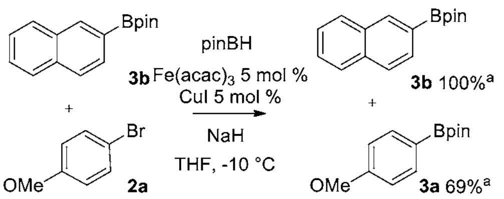
In these optimized conditions (1.5 equiv of TMEDA, NaH, THF, −10 °C, 18 h), the borylation proceeded in moderate to good yields with a variety of aryl bromides (Figure 1). 4-Chloro-toluene or 2-naphthyl tosylate did not react. With all tested bromides, the PDB product **4** was the only side product. In particular, reductive homocoupling was never detected. The selectivity did not depend much on the nature of the substituents, except for the curious case of the *o*-methoxy substitution (compare **3m** with **3a** or **3l**). The borylation was effective with sterically hindered aryl bromides (**3d**, **3h**, **3n**) as well as with some heteroaromatic halides (**3o**, **3q**). As expected,[8] an aryl iodide produced a good isolated yield (**3c**). An interesting substituent effect was observed in the reaction of *meta*- and *para*-dibromobenzene (**3r**, **3s**) where exclusive monoborylation yielded the corresponding bromo-boronic esters.[17]

Although efficient, the present cocatalytic system remains practically hampered by a side reaction leading to the PDB product **4**. The same side product occurred to variable extents in many reported transition-metal catalyzed borylations with pinBH,[18] but the exact mechanism of its formation remains poorly documented. In the case of Pd catalysis, a generally accepted hypothesis received support from DFT calculations by Marder and Lin.[19] It involves, at the rate-limiting step, two isomeric transition states issued from the same intermediate (Scheme 3) and leading, one to the arylboronic ester, the other to the arene, to competing reactions. To check if the arene **4** was issued from degradation of Ar-Bpin **3** in our conditions, the borylation of **2a** was run in the presence of boronic ester **3b** (Scheme 4): the spectator boronic ester remained unaffected, ruling out the protodeborylation of **3** in the reaction medium.

**Scheme 3. Competing Protodebromination with Pd Catalysts[19]**



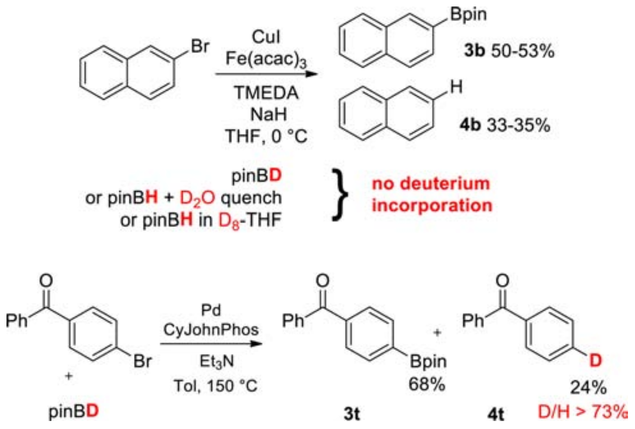
**Scheme 4. Reaction in the Presence of a Preformed Boronic Ester**



[a] GC yields (internal standard).

Quenching a reaction mixture with $D_2O$ also failed to result in any deuterium incorporation in **4** (Scheme 5).

**Scheme 5. Deuterium Experiments**



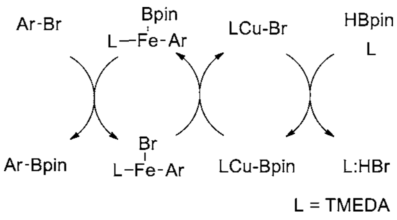
We prepared deuterated pinacolborane (DBpin) from $NaBD_4$[20] and used it in our standard Fe/Cu catalyzed reaction with **2b**. We found no deuterium incorporation in the naphthalene byproduct **4b** (Scheme 5). As a crosscheck we also used DBpin in a palladium-catalyzed borylation of *p*-bromobenzophenone **2s** (known[6c] to be prone to PDB in these conditions). The boronic ester **3t** and benzophenone **4t** were isolated in respectively 68% and 24% yield. More than 73% of the benzophenone was deuterated ($^1H$ NMR, MS).

Thus, it appears that the mechanism of the formation of **4** is different in the two catalytic systems.

It was also reported[9] that running a Cu-catalyzed borylation with $B_2pin_2$ in $d_8$-THF resulted in deuterium incorporation in the protodebrominated byproduct; it was not the case when the Fe/Cu-cocatalyzed borylation was conducted in $d_8$-THF (Scheme 5). Obviously the only possible source of H is NaH. Probably, a concurrent reduction of the aryl bromide is mediated by one of the transition metals present.[21]

Our working hypothesis is summarized in Scheme 6. In close analogy with the Cu-assisted Sonogashira coupling, two catalytic cycles would cooperate via a transmetalation. Low-valent Fe (likely produced by reduction with pinBH[22]) could easily insert into the aryl-bromine bond.[11] $Cu^{I}$ and a base would deprotonate the B−H bond in dialkoxyborane. The obtained boryl-copper intermediate[9,23] would transfer its boryl group to Fe in a transmetalation step, followed by reductive elimination. In such a mechanism, as opposed to the Pd-catalyzed borylation (Scheme 3), the H-atom of the dialkoxyborane would not at any point of the cycle be in the same coordination sphere as the aryl group. This would explain the absence of deuterated byproduct in the above experiments with pinBD.

**Scheme 6. Hypothetic Mechanism**



Intriguingly, this would involve the removal of the hydridic H of pinBH by a base. We performed DFT calculations[14] to address this point (Figure 2). Starting from a cationic Cu/diamine complex,[24] an exothermic (−9.6 kcal) coordination to the B−H bond of pinBH is found. The calculated B−H−Cu angle in this complex is 101.5°, and the Cu−B distance is only 2.23 Å,[14] consistent with a Cu *σ*-H−B interaction.[25] We could not find a pathway for the deprotonation of this intermediate with NaH,[26] but the interaction of the cationic Cu−BH complex with an external molecule of diamine leads to the expected deprotonation with a +13.4 kcal energy barrier, to produce the postulated CuBpin species and an ammonium salt. The latter could be deprotonated by solid NaH. We are currently investigating alternate radical pathways[27] or involvement of nanoparticular metals.[22]

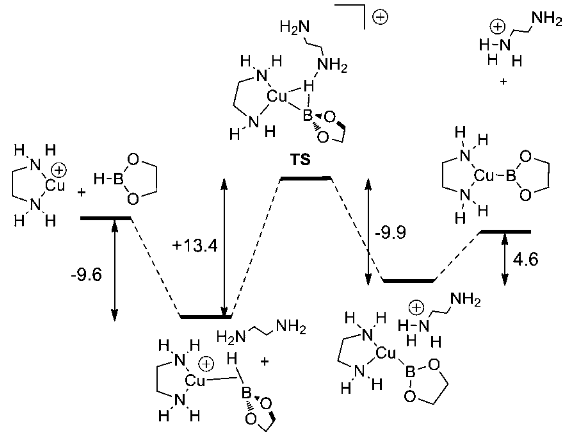


**Figure 2.** A possible mechanism for the formation of borylcopper species. Gibbs free energies in THF, in kcal/mol at the B3LYP/6-31+G(d,p) level, SDD for Cu-atom.

To conclude, we disclosed a new catalytic borylation of aryl bromides with readily available pinacolborane, cooperatively catalyzed by inexpensive, environment-friendly Fe and Cu salts. The catalytic system is operative below 0 °C, which confers some interesting selectivity: *m*- and *p*-dibromobenzene could be cleanly monoborylated. Although the method is inferior in yields to Cu-catalyzed borylations described by Ma[8] or Marder[5,9] this work demonstrates the dramatic increase in reactivity that we could obtain with the introduction of a cocatalyst. Thus, the present study illustrates the large potential of the concept of cooperative action[10] of two transition metals, where each metal is competent for different steps in the catalytic cycle, these steps being connected by transmetalation.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Typical experimental procedure, tables of selected results, characterization data of all products, DFT calculation details and geometries, copies of $^{1}$H and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was supported by the French Agence Nationale de la Recherche, program EMMA 043-01, 2011-14 (BOROCAT).

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(5) Note that $B_2pin_2$ is now available in bulk for <$1/g.

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