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# Sterically Controlled Iodination of Arenes via Iridium-Catalyzed C–H Borylation

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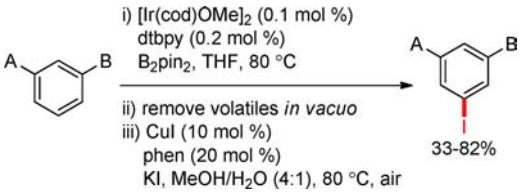
## ABSTRACT

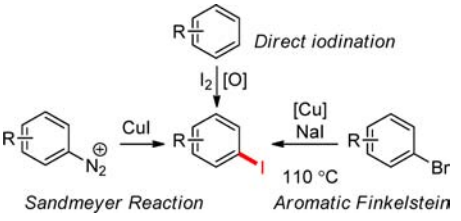



**A mild method to prepare aryl and heteroaryl iodides by sequential C–H borylation and iodination is reported. The regioselectivity of this process is controlled by steric effects on the C–H borylation step and is complementary to existing methods to form aryl iodides. The iodination of boronic esters has potential for the synthesis of radiolabeled aryl iodides, as demonstrated by the concise synthesis of a potential tracer for SPECT imaging.**

Aryl iodides are common intermediates in organic synthesis. The ease by which they undergo oxidative addition makes them valuable precursors to aryl organometallic reagents[1] and the aryl halide of choice for many transition metal-catalyzed processes.[2] Furthermore, the decay of the radioisotopes of iodine has allowed aryl iodides to be used as imaging agents for Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT).[3] Compounds containing $^{131}$I also have been used to treat tumors.[4]

Despite their utility, aryl iodides are more expensive, and fewer aryl iodides are commercially available than aryl bromides and aryl chlorides. Traditional methods to form aryl iodides include direct iodination,[5] which requires oxidizing conditions, and the Sandmeyer reaction, which requires the generation of a diazonium salt (Scheme 1).[6] Such methods are either intolerant of functional groups or involve multistep sequences to reach the aryl iodide. More recently, the aromatic Finkelstein reaction, developed by Buchwald and co-workers, has allowed the interconversion of aryl bromides to the corresponding iodide.[7]

**Scheme 1.** Traditional Methods to Synthesize Aryl Iodides




In all of these reactions, the position of the iodine in the product is determined by the electronic properties of the arene (from nitration in the case of the Sandmeyer reaction or bromination in the case of the aromatic Finkelstein reaction). In contrast to these reactions, directed C–H iodination catalyzed by palladium[8a,b] and rhodium complexes[8c]

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reported recently occur *ortho* to the directing group. Herein, we report a mild copper-catalyzed iodination of aryl pinacol boronic esters. By combining this process with the iridium-catalyzed C−H borylation of arenes[9] the iodination of arenes occurs with selectivity based on steric effects, rather than electronic or directing effects.

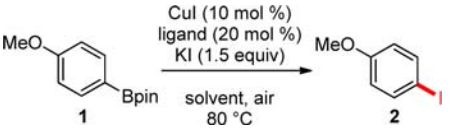
Previously, we reported the combination of borylation and bromination, and the combination of borylation and chlorination, by the conversion of arylboronic esters to aryl halides with stoichiometric amounts of $CuBr_2$ and $CuCl_2$ respectively.[10] However, the corresponding reaction with CuI did not lead to iodination. Although the iododeboronation of arylboronic acids,[11a−d] trifluoroborate salts[11e,f] and borates[11g] has been reported, the conversion of aryl pinacol boronic esters to aryl iodides has not;[12] the iodination of pinacolboronate esters is needed for the conversion of arenes to aryl iodides via C−H borylation.

Thus, we sought conditions for the conversion of pinacol-substituted arylboronates to aryl iodides. The effects of ligand, solvent, reaction time, and temperature on the conversion of the arylboronate ester and the yield of iodoarene are summarized in Table 1. The reaction of *p*-methoxyphenyl pinacol boronate ester (**1**) with CuI and a substoichiometric amount of phenanthroline in air led to 4-iodoanisole (**2**) in good yield (Table 1). By adding KI as the iodide source, the reaction occurred with a substoichiometric amount of CuI. In contrast, iodide **2** was not formed when elemental iodine was used in place of KI. CuBr and CuCl also catalyzed the reaction, but the product was contaminated in these cases with the corresponding aryl bromide and aryl chloride. The reactions conducted with other bidentate nitrogen ligands occurred to lower conversions, and increasing the reaction temperature above 100 °C led to catalyst decomposition and competing protodeboronation.

We hypothesized that transmetalation of the boronic ester was the rate-determining step in the catalytic cycle. To increase the rate of transmetalation, we investigated reactions in protic solvents.[13] Although the reactions in methanol occurred faster than those in DMF, the reactions in mixtures of methanol and water occurred much faster than those in one solvent, and complete conversion of the boronic ester occurred within 1 h.

Anisole, formed by protodeboronation of **1**, was the only side product observed. This side product was formed in greater amounts at higher temperatures and higher concentrations of water. Thus, a compromise was struck between rate of reaction and extent of protodeboronation. Reaction of the arylboronate ester in a 4:1 mixture of methanol and water at 80 °C gave iodide **2** in a promising 63% yield within 1 h. The reaction of the arylboronate ester at 50 °C formed iodide **2** in comparable yield after 9 h.

**Table 1.** Effect of Reaction Conditions on the Yield of the Iodination of a Model Aryl Pinacol Boronate Ester




| | ligand | solvent | time (h) | conversion (%) | yield[a] (%) |
|---|---|---|---|---|---|
| 1[b] | phen | DMF | 39 | 100 | 58 |
| 2[c] | phen | DMF | 47 | 84 | 36 |
| 3 | phen | DMF | 23 | 88 | 51 |
| 4 | bpy | DMF | 23 | <5 | 0 |
| 5 | dtbpy | DMF | 23 | 25 | <5 |
| 6 | $Me_4$phen | DMF | 23 | 30 | 8 |
| 7[d] | phen | DMF | 39 | 100 | 50 |
| 8 | phen | MeOH/$H_2O$ (4:1) | 1 | 100 | 63 (62) |
| 9 | phen | MeOH/$H_2O$ (1:1) | 1 | 100 | 27 |
| 10[e] | phen | MeOH/$H_2O$ (4:1) | 9 | 100 | 57 |

[a] Corrected GC yield using 1,3,5-trimethoxybenzene as an internal standard (0.10 mmol scale); isolated yield in parentheses (1.25 mmol scale). [b] 1.5 equiv of CuI (without KI). [c] 0.1 equiv of phen. [d] 100 °C. [e] 50 °C. pin = pinacol; phen = 1,10-phenanthroline; bpy = 2,2′-bipyridine; dtbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; $Me_4$phen = 3,4,7,8-tetramethyl-1,10-phenanthroline.

The conditions in entry 8 of Table 1 were successfully combined with the iridium-catalyzed C−H borylation to form aryl iodides from arenes with steric control. After the borylation step, the volatile materials were evaporated *in vacuo* before addition of the reagents and solvent for the iodination reaction. No further purification of the intermediate boronate ester was required prior to iodination. The presence of the iridium catalyst and HBpin byproduct from the borylation reaction did not affect the yield of the iodination reaction.

A variety of aryl iodides were synthesized by the two-step, one-pot process in good to excellent yields (Scheme 2). The iodination reaction was found to tolerate a range of functional groups, including tertiary amines, esters, amides and nitriles. Substrates containing ketones underwent iodination; however, some oxidation of the ketone to the corresponding ester was also observed when 3-bromopropriophenone was used as the substrate.[14] Most striking, the reactions of arylboronates containing an aryl bromide, chloride and fluoride were all tolerated without any halide exchange. Electron-deficient substrates underwent iodination in higher yield than electron rich arenes, although this

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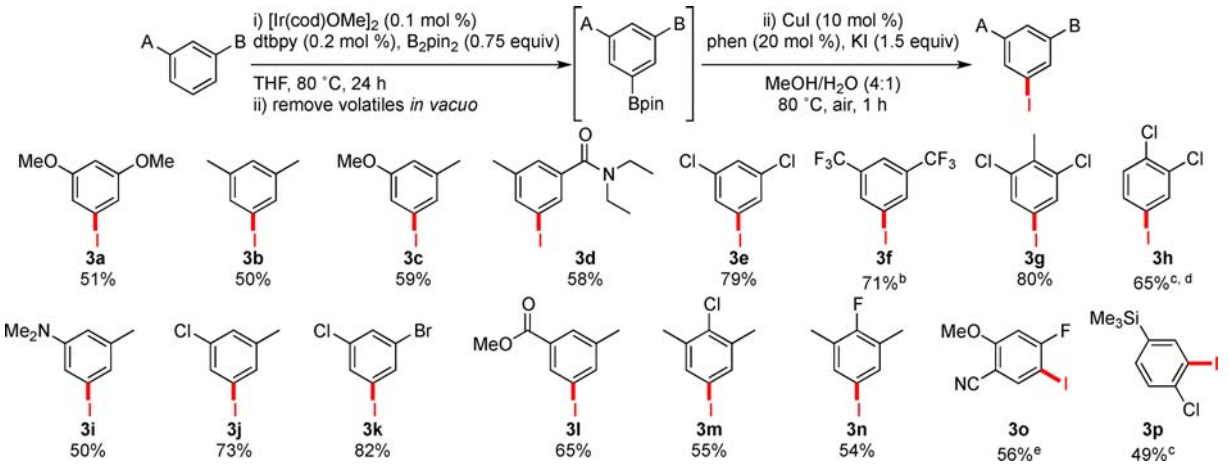
(12) The iodination of neopentyl glycol boronic esters has been reported: Kabalka, G. W.; Akula, M. R.; Zhang, J. *Nucl. Med. Biol.* **2002**, *29*, 841 However, these cannot be prepared by C-H borylation.

(13) Use of KO*t*Bu to enhance transmetalation led to competing formation of the homodimer of the boronic ester.

(14) Also, during the iodination of 6-fluorotetralone, competing aromatization to the corresponding naphthol was observed.

**Scheme 2.** Scope of the Combination of C−H Borylation and Iodination of the Arylboronate Ester[a]



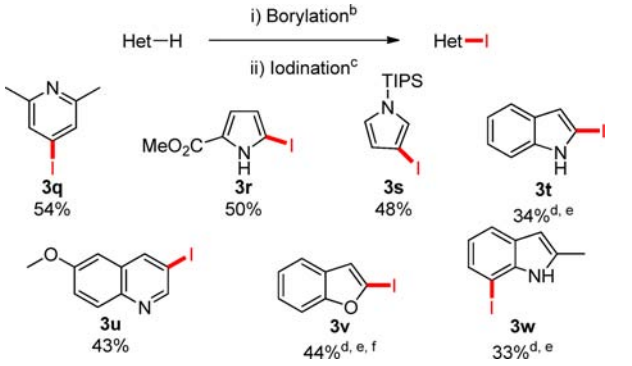

[a] Isolated yield (1.25 mmol scale). [b] Iodination for 3 h at 80 °C. [c] $B_2pin_2$ as limiting reagent (2 equiv of arene); yield based on 2 atoms of boron incorporated. [d] Contains ~3% diiodide by $^1H$ NMR. [e] 1 mol % $[Ir(cod)(OMe)]_2$, 2 mol % dtbpy. cod = 1,5-cyclooctadiene.

higher yield resulted, in part, from the higher yield of the C−H borylation step. The only observed side product was the starting arene, resulting from protodeboronation of the intermediate boronic ester.

In all examples, the product was obtained as a single constitutional isomer with selectivity arising from the sterically controlled C−H borylation reaction. The iodide was formed at the least sterically hindered position, regardless of the electronic properties of the arene. Most important, this selectivity is complementary to that of existing methods for generating aryl iodides. Reactions with 1,4-substituted arenes preferentially formed the product containing an iodide *ortho* to the less bulky group. A single isomer was obtained when the smaller group of the 1,4-arene was either fluoride or chloride.

The combined reaction was also suitable for the iodination of a range of heteroarenes (Scheme 3), although in slightly lower yield than the iodination of arenes. The lower yields, as compared to the yields for the iodination of arenes, can be attributed to a more facile protodeboronation of the intermediate boronic esters. Indoles underwent the protodeborylation particularly rapidly. Bicyclic heteroarenes were iodinated exclusively on the ring containing the heteroatom, with the borylation step occurring at the 2-position of benzofuran and indole and the 3-position of the quinoline.[15] However, substitution at the 2-position of indole allowed selective iodination at the 7-position with the nitrogen directing the borylation.[16] In addition, pyrroles were selectively iodinated at the 2-position in the absence of a group on nitrogen or at the 3-position when the pyrrole contained a sterically demanding TIPS group at nitrogen.[15]

**Scheme 3.** Scope of C−H Borylation−Iodination of Heteroarenes[a]




[a] Isolated yield (1.25 mmol scale). [b] $[Ir(cod)OMe]_2$ (0.1 mol %), dtbpy (0.2 mol %), $B_2pin_2$ (0.75 equiv), THF, 80 °C, 24 h. [c] CuI (10 mol %), phen (20 mol %), KI (1 equiv), MeOH/$H_2O$, 80 °C, 1 h. [d] $B_2pin_2$ as limiting reagent using 4 equiv of heteroarene. [e] Yield based on 2 atoms of boron incorporated from $B_2pin_2$. [f] 2 mol % $[Ir(cod)(OMe)]_2$, 4 mol % dtbpy. TIPS = triisopropylsilyl.

The combination of high functional-group tolerance and short reaction time makes this method suitable for late-stage incorporation of radiolabeled iodide for the synthesis of imaging agents and anticancer agents.[17] In addition, the ability to carry pinacol boronate esters intact though many synthetic sequences makes it an excellent handle for late stage functionalization.[18]

With iodide as the limiting reagent, and only a small excess of boronic ester, a range of boronic esters were successfully iodinated in good to excellent yield (Scheme 4).

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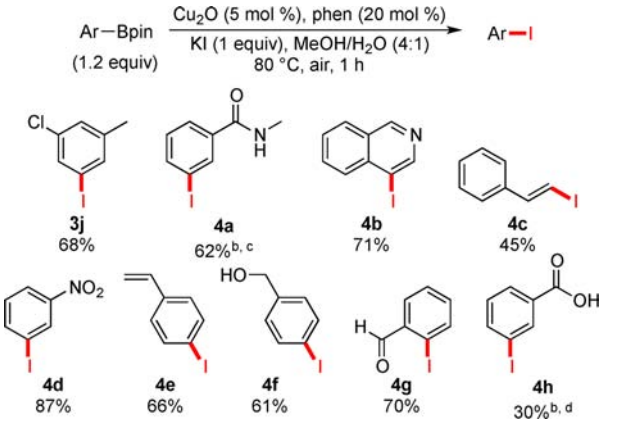
**Scheme 4.** Iodination of Arenes with Limiting Iodide[a]




[a] Isolated yield (1.25 mmol scale). [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c] 0.1 mmol scale. [d] 48 h at 80 °C, 18% boronic ester remaining.

Additional functional groups that were found to be tolerated by the iodination reaction (with limiting iodide) included alcohol, alkene and nitro groups, as well as an aldehyde in the *ortho* position. A benzoic acid substrate was tolerated, but the rate of the reaction was much slower; only 80% conversion of the boronic ester occurred after 48 h. This slow rate is presumably due to displacement of phenanthroline by the carboxylic acid on copper, forming a less active catalyst. Alkenylboronic esters were also successfully iodinated, but in lower yield. The reaction also occurred with $Cu_2O$, instead of CuI, as the source of the copper catalyst, in comparable yield. This change in catalyst would allow >99% radiochemical purity to be obtained with Na*I used in place of KI. Although we did not explore reactions with NaI extensively, initial studies on the reactions of Table 1 with NaI in place of KI gave the iodoarene in comparable yield.

The iodination method was applied to the concise synthesis of SPECT Imaging Agent **11** (Scheme 5). This compound, when enriched with $^{125}I$, has been reported to have potential to act as a SPECT tracer for the identification of amyloid beta plaques.[19] The boronic ester moiety was introduced through amide coupling of amine **8** and carboxylic acid **9**. The key iodination step proceeded to give iodide **11** in 66% yield, with iodide as the limiting reagent. By using limiting $Na^{125}I$ in the final step of this reaction, we anticipate that enriched **11** could be prepared in high radiochemical purity without the need to carry a radioactive isotope through more than one step of a synthesis.

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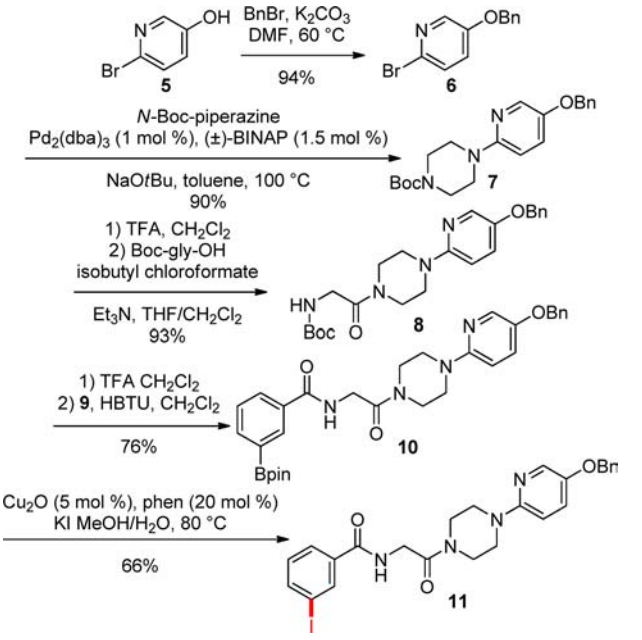
**Scheme 5.** Synthesis of Potential SPECT Imaging Agent **11**[a]




[a] dba = dibenzylideneacetone, TFA = trifluoroacetic acid, HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, **9** = 3-carboxyphenylboronic acid pinacol ester.

In conclusion, we report a mild method to prepare aryl and heteroaryl iodides through a telescoped combination of C−H borylation and iodination of the arylboronate ester. The sterically controlled regioselectivity, due to the C−H borylation step, is complementary to the regioselectivity of existing methods for arene iodination. The iodination of boronic esters has potential for the synthesis of radiolabeled aryl iodides, as demonstrated by the concise synthesis of compound **11**.

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**Supporting Information Available.** Experimental procedures and full spectroscopic data for all new compounds. The Material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.