Mechanism of Cu-Catalyzed Aryl Boronic Acid Halodeboronation Using Electrophilic Halogen: Development of a Base-Catalyzed Iododeboronation for Radiolabeling Applications

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Supporting Information

ABSTRACT: An investigation into the mechanism of Cu-catalyzed aryl boronic acid halodeboronation using electrophilic halogen reagents is reported. Evidence is provided to show that this takes place via a boronate-driven ipso-substitution pathway and that Cu is not required for these processes to operate: general Lewis base catalysis is operational. This in turn allows the rational development of a general, simple, and effective base-catalyzed halodeboronation that is amenable to the preparation of 125I-labeled products for SPECT applications.

Halodeboronation of aryl boronic acids is a useful method for the synthesis of aryl halides and has found important applications in the generation of radiolabeled products for in vivo imaging and radiotherapy (Scheme 1a).3,12 The use of molecular halogen (X2) and electrophilic halogen (X+) sources is very common with several approaches developed, including metal-free (Scheme 1b)3 and metal-promoted methods: Cu-catalysis is particularly prominent in this latter area (Scheme 1c).3 Iodo-, bromo-, and chlorodeboronation operate effectively with X− reagents (e.g., halosuccinimide reagents), and while fluordeboronation using F− sources has been achieved,5,6,7 the majority of approaches for C−F installation employ alternative catalytic manifolds that utilize F−.5,6

In terms of metal-free processes, in 1930, Challenger reported the halodeboronation of PhB(OH)2 using aqueous X2 as well as with CuX2, with the latter also proceeding via a pathway involving X− produced in situ by the known redox of CuX2 → CuX + X2.5a In the 1950s, Kuivila established kinetic parameters for specific aryl boronic acid halodeboronation using X− in both acidic and basic buffer, proposing an ipso-substitution proceeding via a boronate generated in situ as the most likely mechanism (Scheme 1d).6b Boronate-based ipso-substitution has also been proposed in halodeboronation reactions of aryl potassium trifluoroborates (ArBF3K).36,6a,1

In contrast, despite a number of variants, the mechanism of Cu-catalyzed halodeboronation reactions using X+ reagents remains underdeveloped, mainly relying on plausible constructs with limited empirical support.4 Mechanistic proposals have suggested a process via oxidative addition of Cu(I) to a halosuccinimide or derivative, transmetalation of an organo-boron to the resulting Cu(III) intermediate, and subsequent reductive elimination (generalized in Scheme 1d).3a,b,c,e However, there is little evidence to support this proposed mechanism. Accordingly, based on the broad utility of halodeboronation methods, a functional understanding would be valuable to assist in the development and expansion of applications.

Here we provide a mechanistic investigation of arylboronic acid halodeboronation using X+ reagents, showing that these reactions proceed via a common base-catalyzed ipso-substitution mechanism, and that specific “Cu-catalyzed” reactions do not require Cu to proceed. This allows rational design of a simple KOAc-catalyzed halodeboronation, amenable to the transition metal-free preparation of SPECT radiotracers.

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On the basis of our combined interests in Cu-catalyzed transformations of organoborons and radiohalogenation of functionalized aranes, we sought to understand Cu-catalyzed halodeboronation to allow tailoring of specific applications. Accordingly, we initiated our study by evaluating Cu-catalyzed halodeboronation of boronic acids using N-halosuccinimides. A general benchmark reaction was constructed on the basis of previously published methods: boronic acid 1a was identified as a workhorse substrate (previously investigated by Kuivila) and N-iodosuccinimide (NIS) was selected as a benchmark X+ reagent (Scheme 2a). Consistent with literature precedent, using Cu(OAc)\(_x\) (\(x = 1, 2\)) as a catalyst, the desired iodoarene 2a was delivered in good yield, with ca. 5% protodeboronation. However, the iododeboronation was evident in the absence of any catalyst, albeit in low yield (30%), consistent with observations by Petasis and Olah. Accordingly, we sought to determine the origin of rate enhancement using Cu. 

\(^{11}\)B NMR was informative (Scheme 2b). Boronate signals attributed to 4a were clearly observed in the presence of CuOAc, along with some protodeboronation (production of B(OH)\(_4^-\) (5)). 4a was not observed in the presence of Cu(OAc)\(_2\), with significant protodeboronation to deliver 5 as the main outcome. Protodeboronation in the presence of Cu(II) is consistent with initial observations by Challenger and in agreement with additional studies. Control experiments using KOAc and KOH resulted in the formation of the same signal for 4a, as expected. On the basis of the observed formation of boronate in the presence of CuOAc, the implication of boronate-driven protodeboronation in the presence of Cu(OAc)\(_2\) and that metal-free ipso-halodeboronation is well-known, we queried whether Cu was required in these processes.

Exposure of 1a to KOAc delivered 2a in excellent yield and with a profile commensurate to Cu(OAc)\(_2\) (Scheme 2c). A brief analysis of other bases revealed the process was generally effective in the presence of all Lewis bases capable of forming a boronate. Collectively, these data supported the hypothesis that “Cu-catalyzed” ipso-halodeboronation was actually a general base-catalyzed phenomenon and that Cu had no direct role in the catalysis.

An ipso-halodeboronation pathway was further supported by straightforward control reactions using specific organoboron reagents with established reactivity profiles (Scheme 2d). If proceeding via boronate, BPin species 1b would be expected to be less reactive than the equivalent boronic acid 1a based on the lower propensity to form boronates. Exposure of 1b to NIS gave trace amounts of product 2a in the presence and absence of catalytic KOAc. As a preformed stoichiometric boronate, the BF\(_3\)K species 1c operated equally effectively in the presence and absence of base as would be expected and consistent with several studies using BF\(_3\)K species. BMIDA 1d should not be capable of halodeboronation as this species is not capable of forming a boronate and, while formally zwitterionic, would require the significantly unfavorable loss of a divalent cationic boron leaving group (\('BR_2\)).
Indeed, 1d did not react with NIS either at rt or 50 °C. However, the related BIDA compound 1e, lacks the N-Me unit of BMIDA and is therefore capable of proton loss from the ligating N—H and liberation of a neutral (BR3) leaving group (not possible for BMIDA). On evaluation, 1e did deliver the expected product in up to moderate yield and was again accelerated by KOAc. Collectively, these data were consistent with a boronate ipso-substitution pathway.

Additional support for ipso-substitution came from a straightforward competition experiment (Scheme 2e). Exposing a mixture of boronic acids 1m and 1s to 20 mol % KOAc delivered a mixture of boronates 4m and 4s, favoring the more Lewis acidic boronate 4m (ca. 2:1 4m:4s). However, since the ipso-substitution is rate limiting and boronate formation/equilibration precedes this event, the 1:1 competition experiment should yield 2s as the main product. Indeed, a ratio of ca. 9:1 2s:2m was observed in this experiment.

Regarding reactivity in the absence of base, this has been previously observed by Petasis and Olah. This is likely to proceed via the well-known boronic acid autoionization initially reported by Lorand and Edwards, with yields increasing with temperature in agreement with this mechanism.

Kuivila proposed a boronate-driven ipso-substitution pathway for halodeboronation using X⁺ reagents. However, the absence of NMR spectroscopy and access to modern organoboron reagents at the time of study precluded spectroscopic evidence of boronate formation. The body of data presented here strongly supports Kuivila’s proposal of boronate-driven ipso-substitution.

On the basis of these observations, we proposed that a general and very straightforward base-catalyzed halodeboronation, in line with our SPECT labeling interests, might be realized. Assessing a range of standard variables quickly led to a simple and high yielding cold iododeboronation, which was evaluated on a series of simple substrates (Scheme 3a; see Supporting Information for full details of solvent, temperature, catalyst loading, time, etc.). Using 20 mol % KOAc as catalyst in MeCN at 50 °C allowed smooth halodeboronation in short reaction times, favorable for downstream applications (vide infra). Iodo-, bromo-, and chlorodeboronation were all effective; however, in contrast to preceding studies, fluorodeboronation using F⁺ sources was completely ineffective. Consistent with the mechanistic proposal and the above analyses (Scheme 2e), electron-deficient substrates were more sluggish substrates. Some limitations were found with amine substrates; for example, anilines were found to generate several products presumably due to reaction with NIS at the aniline nitrogen.

With the cold method established, we evaluated the compatibility of the method for iododeboronation using ¹²⁵I⁻ for imaging applications (Scheme 3b). An optimal transformation was developed using the known method for preparation of ¹²⁵I⁻ from ¹²⁵I, stirring ¹²⁵I⁻[NaI with NCS for 15 min in dimethyl carbonate (DMC). In accordance with the control studies (Scheme 2a), radio-iododeboronation of 1a without base gave a radiochemical yield (RCY) of 24% (Scheme 3b). A combination of KOAc (20 mol %) and a reaction temperature of 100 °C, resulted in efficient radioiodination (93%) and in a fast reaction time (1.5 h). This optimized method was applied to a series of boronic acids and found to be tolerant of various functional groups and substitution patterns. In agreement with the cold studies, elevated temperatures were important for complete conversion of electron-deficient substrates.

The utility of the method toward the production of valuable radiolabeled pharmaceuticals was also investigated (Scheme 3b). A di-Boc protected derivative of iobenguane (MBG) (9p), a commercially available radiopharmaceutical used for the SPECT imaging of human norepinephrine transporter-expressing cancers was prepared in 56% RCY, although 50 mol % of KOAc was required for this transformation. The method was also effective for the radiodionation of olaparib
derivative (9q), a SPECT imaging agent of the cancer target, poly(ADP-ribose) polymerase-1. Under the standard reaction conditions, this gave 9q in 67% RCY. It should be noted that the KOAc-catalyzed \(^{125}\text{I}\)-labeled synthesis of this compound was more efficient than a recently described gold(I)-mediated radio-iododeboronation. Finally, iodouracil (9r), a potent inhibitor of the anticancer target dihydro- pyrimidine dehydrogenase and a precursor of uridine-derived SPECT imaging agents, was radioiodinated in 98% RCY after 1 h. In comparison to other approaches, the use of this base-catalyzed method, which avoids transition-metal catalysts, allows a more rapid and operationally simpler approach for the preparation and purification of radioiodinated compounds for imaging applications. These advantages were exemplified with validation of the method for the synthesis and purification of \(^{125}\text{I}\)-iodouracil (9r). Uracil-5-boronic acid was radio-iodinated using \(^{125}\text{I}\)-NaI (8–10 MBq) at 80 °C for 1 h. After HPLC purification, \(^{125}\text{I}\)-iodouracil (9r) was isolated in 58 ± 1.3% radioactivity yield. The radiochemical purity of 9r was measured as >99% (n = 3), with a molar activity of 0.53 ± 0.047 GBq μmol\(^{-1}\) (n = 3).

In summary, we have provided a mechanistic rationale for halodeboronation of aryl boronic acids, demonstrating that the process proceeds via a boronate-driven ipso-substitution pathway, providing evidence that specific Cu-catalyzed processes do not require Cu. These observations have allowed the development of a simple base-catalyzed halodeboronation that is amenable to the preparation of \(^{125}\text{I}\)-labeled products for imaging applications.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at: DOI: 10.1021/acs.orglett.9b00942. Experimental procedures, characterization data, copies of spectra (PDF)

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**Notes**

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**ABBREVIATIONS**

CFs, cesium fluoroxysulfate; DMC, dimethylcarbonate; IDA, inominodiacetoxy; MIDA, N-methylaminodiacetoxy; NBS, N-bromosuccinimide; LCS, N-chlorosuccinimide; NFSI, N-fluorobenzensulfonimide; NIS, N-iodosuccinimide; RCY, radiochemical yield; SPECT, single photon emission computed tomography.

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