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

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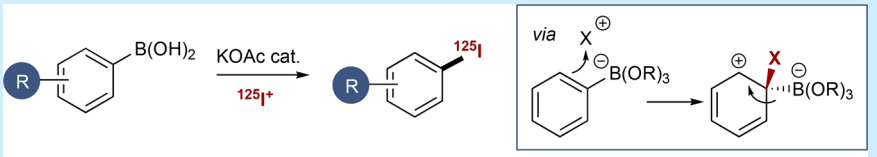
Supporting Information



- Base-catalyzed radiolabeling, 18 examples
- Experimental evidence for Cu-catalyzed processes operating without Cu
- Experimental evidence for general base-catalyzed *ipso*-substitution pathway

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 ^{125}I-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).[1,2] The use of molecular halogen (X_2) 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).[4] Iodo-, bromo-, and chlorodeboronation operate effectively with X^+ reagents (e.g., halosuccinimide reagents), and while fluorodeboronation using F^+ sources has been achieved,[3b,c,f] the majority of approaches for C−F installation employ alternative catalytic manifolds that utilize F^-.[2,5]

In terms of metal-free processes, in 1930, Challenger reported the halodeboronation of $PhB(OH)_2$ using aqueous X_2 as well as with CuX_2, with the latter also proceeding via a pathway involving X_2 produced *in situ* by the known redox of $CuX_2 \rightarrow CuX + X_2$.[3a] In the 1950s, Kuivila established kinetic parameters for specific aryl boronic acid halodeboronation using X_2 in both acidic and basic buffer, proposing an *ipso*-substitution proceeding via a boronate generated *in situ* as the most likely mechanism (Scheme 1d).[6,7] Boronate-based *ipso*-substitution has also been proposed in halodeboronation reactions of aryl potassium trifluoroborates ($ArBF_3K$).[3f,g,i,j]

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 organoboron to the resulting Cu(III) intermediate, and subsequent reductive elimination (generalized in Scheme 1d).[4a,b,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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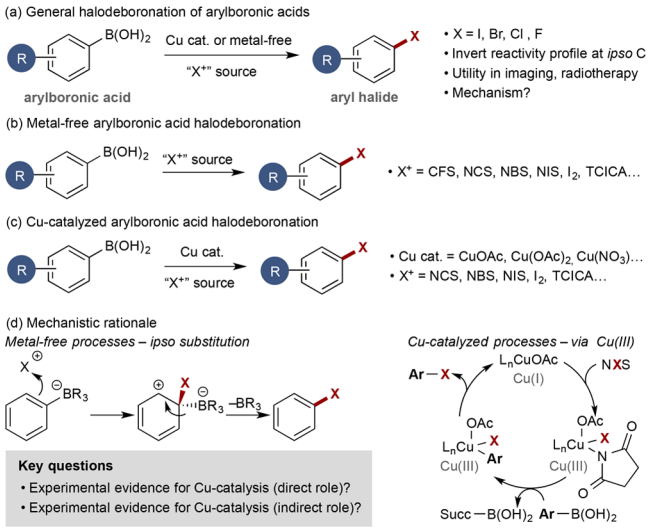
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Halodeboronation of Boronic Acids and Derivatives: (a) General Reaction; (b) Metal-Free Methods; (c) Cu-Catalyzed Approaches; (d) Proposed Mechanisms[a]



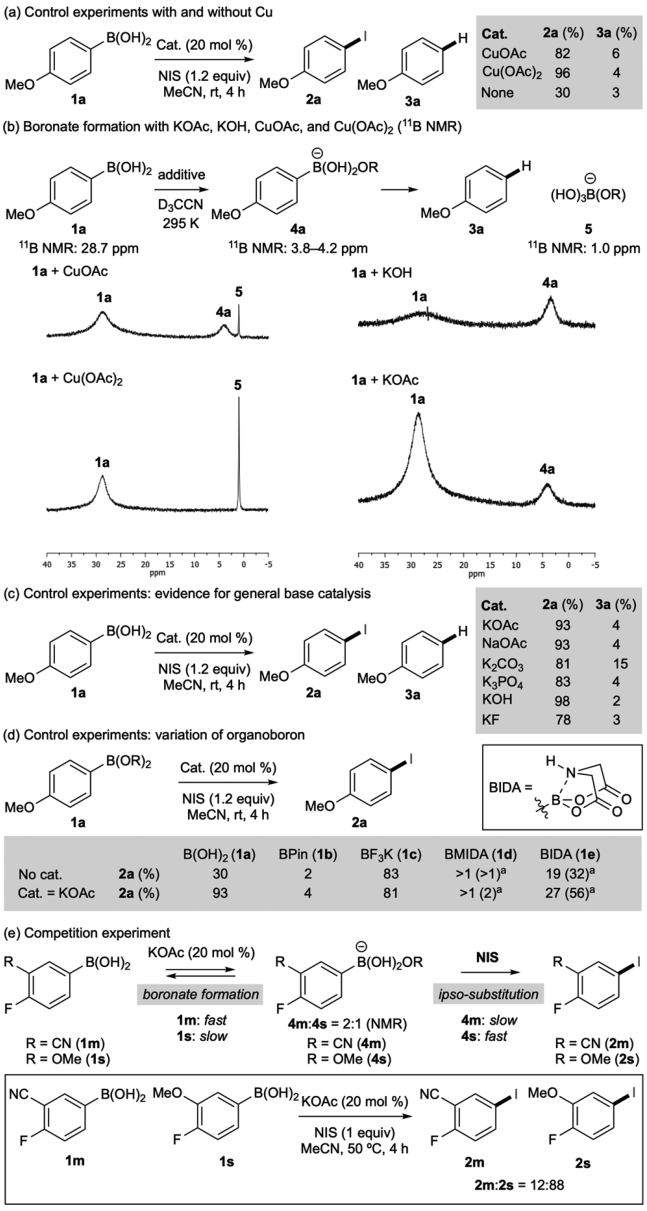
[a]NXS = *N*-halosuccinimide.

On the basis of our combined interests in Cu-catalyzed transformations of organoborons[8] and radiohalogenation of functionalized arenes,[9] 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:[4] boronic acid **1a** was identified as a workhorse substrate (previously investigated by Kuivila[7c]) and *N*-iodosuccinimide (NIS) was selected as a benchmark X^+ reagent (Scheme 2a). Consistent with literature precedent, using $Cu(OAc)_n$ (n = 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 (*vide infra*).[3d] 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[3a] and in agreement with additional studies.[10,11] Control experiments using KOAc and KOH resulted in the formation of the same signal for **4a**, as expected.[12] 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,[3] 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.

Scheme 2. Evidence To Support Halodeboronation via *ipso*-Substitution Pathway



Cat.	2a (%)	3a (%)
CuOAc	82	6
$Cu(OAc)_2$	96	4
None	30	3

Cat.	2a (%)	3a (%)
KOAc	93	4
NaOAc	93	4
K_2CO_3	81	15
K_3PO_4	83	4
KOH	98	2
KF	78	3

		$B(OH)_2$ (**1a**)	BPin (**1b**)	BF_3K (**1c**)	BMIDA (**1d**)	BIDA (**1e**)
No cat.	**2a** (%)	30	2	83	>1 (>1)[a]	19 (32)[a]
Cat. = KOAc	**2a** (%)	93	4	81	>1 (2)[a]	27 (56)[a]

[a]Reaction at 50 °C.

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.[11] 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_3K species **1c** operated equally effectively in the presence and absence of base as would be expected and consistent with several studies using BF_3K species.[3f,g,i,j] 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 ($^+BR_2$).[13]

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Org. Lett. XXXX, XXX, XXX−XXX

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 (BR_3) 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[7] 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.

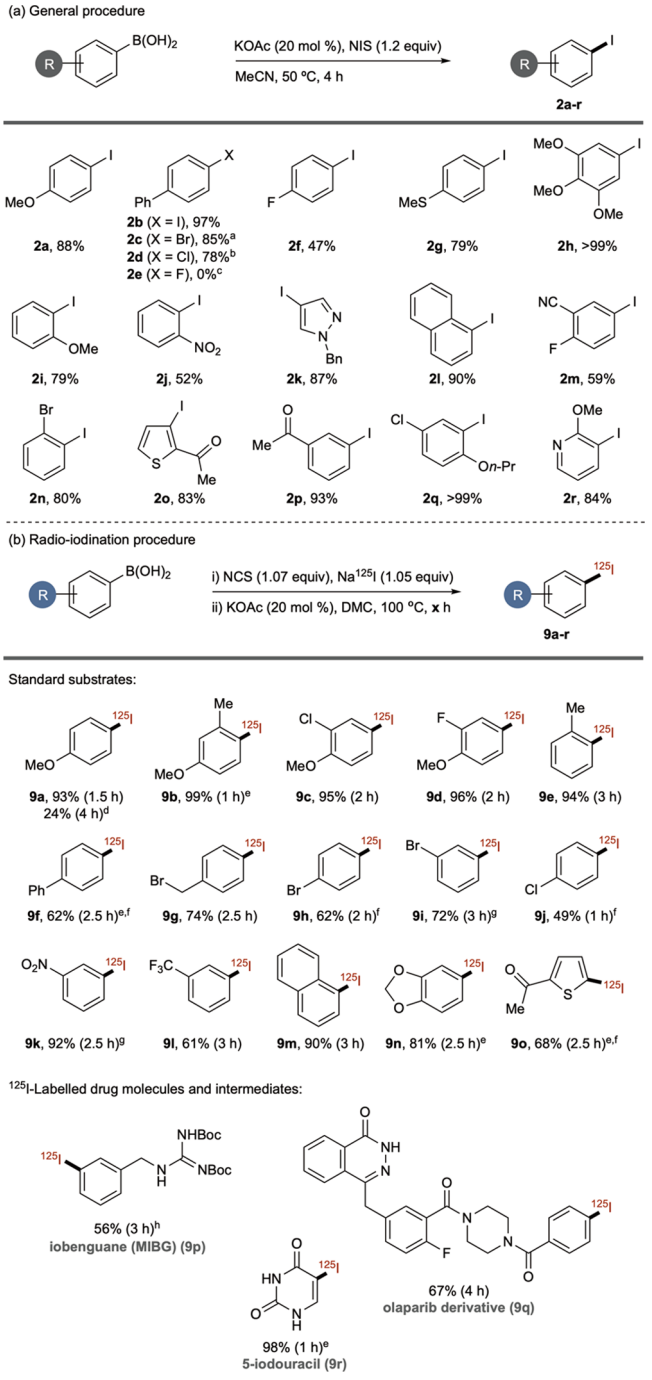
Regarding reactivity in the absence of base, this has been previously observed by Petasis and Olah.[3d] This is likely to proceed via the well-known boronic acid autoionization initially reported by Lorand and Edwards,[14] with yields increasing with temperature in agreement with this mechanism.

Kuivila proposed a boronate-driven *ipso*-substitution pathway for halodeboronation using X^+ reagents.[7] 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,[3b,c,f] 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 $^{125}I^-$ for imaging applications (Scheme 3b). An optimal transformation was developed using the known method for preparation of I^+ from I^-, stirring [^{125}I]NaI with NCS for 15 min in dimethyl carbonate (DMC).[9b,15] 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.

Scheme 3. Scope of the Base-Catalyzed Halodeboronation[g]



[g]Isolated yields. [a]Using NBS. [b]Using NCS. [c]Using NFSI. [d]No catalyst and 50 °C. [e]80 °C. [f]10 mol % KOAc. [g]Using MeCN as cosolvent. [h]50 mol % KOAc.

The utility of the method toward the production of valuable radiolabeled pharmaceuticals was also investigated (Scheme 3b). A di-Boc protected derivative of iobenguane (MIBG) (**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.[16] The method was also effective for the radioiodination of olaparib

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Org. Lett. XXXX, XXX, XXX–XXX

derivative (**9q**), a SPECT imaging agent of the cancer target, poly(ADP-ribose) polymerase-1.[17] Under the standard reaction conditions, this gave **9q** in 67% RCY. It should be noted that the KOAc-catalyzed ^{125}I-labeled synthesis of this compound was more efficient than a recently described gold(I)-mediated radio-iododeboronation.[9d] Finally, iodouracil (**9r**), a potent inhibitor of the anticancer target dihydropyrimidine dehydrogenase[18] and a precursor of uridine-derived SPECT imaging agents,[19] 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}I]iodouracil (**9r**). Uracil-5-boronic acid was radio-iodinated using [^{125}I]NaI (8−10 MBq) at 80 °C for 1 h. After HPLC purification, [^{125}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}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

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CFS, cesium fluoroxysulfate; DMC, dimethylcarbonate; IDA, iminodiacetoxy; MIDA, *N*-methyliminodiacetoxy; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NFSI, *N*-fluorobenzenesulfonimide; NIS, *N*-iodosuccinimide; RCY, radiochemical yield; SPECT, single photon emission computed tomography.

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