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Rapid Cu-Catalyzed [^{211}At]Astatination and [^{125}I]Iodination of Boronic Esters at Room Temperature

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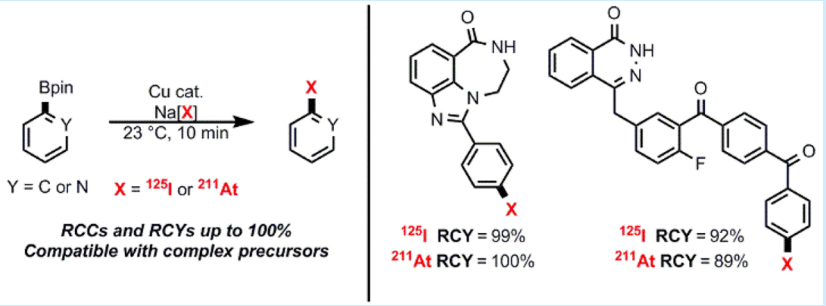
Supporting Information



ABSTRACT: Access to ^{211}At- and ^{125}I-radiolabeled compounds in excellent RCCs and RCYs was achieved in just 10 min at room temperature using a Cu catalyst. The reaction conditions are applicable to a broad class of aryl and heteroaryl boronic reagents with varying steric and electronic properties as well as late-stage astatination and iodination of anticancer PARP inhibitors. This protocol eliminates the traditional need for toxic organotin reagents, elevated temperatures, and extended reaction times, providing a more practical and environmentally friendly approach to developing α-emitting radiotherapeutics.

Radiohalides are powerful imaging, diagnostic, and therapeutic tools with vast applications in nuclear medicine.[1] Of such, the α-emitting radionuclide ^{211}At provides an attractive approach to developing cancer therapeutics by delivering high linear energy transfer (LET) radiation that, on the atomic level, is more efficient at causing DNA damage than β^- emitters.[2] While this radiation dose is highly cytotoxic to the targeted cancer cell, the surrounding healthy tissue is spared because of the 50−70 μm path length of the α particle.[3] Compared to other α-emitting nuclides such as ^{212}Bi ($t_{1/2}$ = 1 h), ^{213}Bi ($t_{1/2}$ = 46 min), and ^{226}Th ($t_{1/2}$ = 30 min), ^{211}At ($t_{1/2}$ = 7.2 h) displays a half-life that is economically viable for radiochemistry, quality control, and transportation, which allows the radionuclide to target less accessible tumor cells in living systems.[4] The 7.2 h half-life of ^{211}At is better suited to fast targeting vectors that are retained in tumors such as small molecules. Although many groups have explored astatinated peptides and antibodies, a recent study demonstrated that oxidative lysosomal degradation of these targeting agents results in dehalogenation in vivo.[5] While ^{225}Ac ($t_{1/2}$ = 10 days), ^{223}Ra ($t_{1/2}$ = 11.4 days), and ^{227}Th ($t_{1/2}$ = 18.7 days) have more favorable half-lives for antibodies, these α-emitters require ligand chelation in order to form stable chemical complexes that often escape the respective radiobioconjugates. These radionuclides also emit unwanted decay products and are ineffective after a single α decay, resulting in toxic daughter isotopes, which can be distributed throughout the body.[4] Despite the clear advantages ^{211}At offers, synthetic methodologies that can provide access to astatinated compounds are exceedingly rare, mainly because of the absence of stable At isotopes, the scarcity of radioisotope production sites capable of making ^{211}At, and lack of understanding of the chemical behavior of the element.[6] An efficient late-stage astatination strategy would provide a much-needed platform for developing ^{211}At-based α-emitting therapeutics.

Traditional routes to astatinated compounds proceed through electrophilic destannylation of an organotin functional group, allowing rapid incorporation of ^{211}At (Scheme 1a).[1,7,8] However, handling of toxic alkyltin reagents is required to develop the aryl stannane precursors, and only modest yields of the ^{211}At-radiolabeled products are achieved. This is attributed to the multiple oxidation states astatine can adopt, which makes it difficult to obtain the desired, and nonstable, At^+ species for electrophilic substitution.[9,10] In 2016, Brechbiel and co-workers illustrated the use of aryl iodonium salts to access astatinated aryl compounds through an S_NAr mechanistic pathway (Scheme 1b).[11] This detailed report also demonstrated how the regioselectivity was driven by electronic effects, as ^{211}At product formation proceeded with high selectivity for the aryl ring containing the most electron-withdrawing substituent at the *para* position. Despite the high yields obtained using this method, astantination of the conjugate aryl group results in unwanted side-product formation.

On the basis of previous reports illustrating the versatility of the Chan−Evans−Lam reaction[12−14] to access radioiodinated and -fluorinated compounds via boronic reagents,[15−22] we

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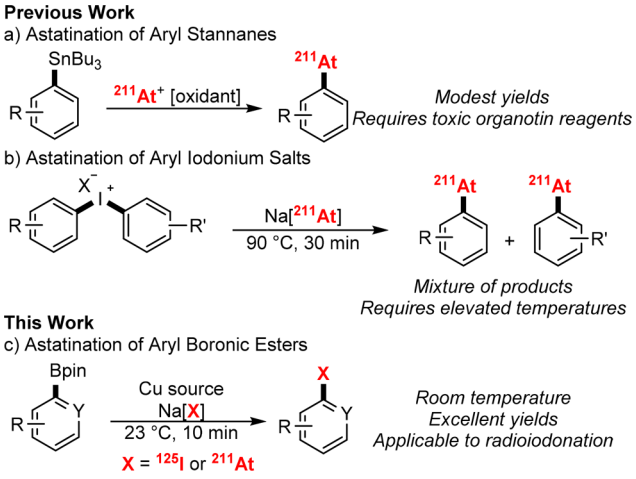
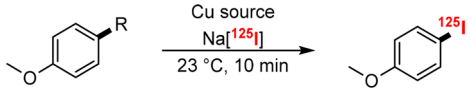
Scheme 1. Synthetic Routes to ^{211}At-Labeled Compounds



adapted a similar strategy to access ^{211}At-labeled hetero(aryl) synthons. This study complements those previous studies as well as the Cu-assisted halogenation reports by Sanford and Scott,[23−25] demonstrating facile access to versatile α-emitting synthetic building blocks.

In 2016, Zhang and co-workers outlined a Cu/ligand-catalyzed radioiodination methodology using boronic acid precursors, achieving good radiochemical conversions (RCCs) in 1 h at room temperature.[22] Therefore, we began our initial investigation by screening several Cu sources in order to identify an efficient catalyst for ^{125}I radiolabeling of aryl boronic esters that could be translated to astatination. Using the Cu(pyridine)$_4$OTf complex, we were able to obtain excellent RCCs of **2** (Table 1, entry 5) in just 10 min at room temperature with no ligand additives. Analogous boryl reagents of **1** (entries 9−11) were also compatible with the outlined ^{125}I radiolabeling protocol. We then investigated 4-methoxyphenylboronic *N*-methyliminodiacetic acid (MIDA) ester (entry 12), a pyramidalized class of boryl reagents, but low RCCs were obtained (entry 12).

Table 1. Optimization of ^{125}I Radiolabeling of 4-Methoxyphenyl Boryl Reagents[a]



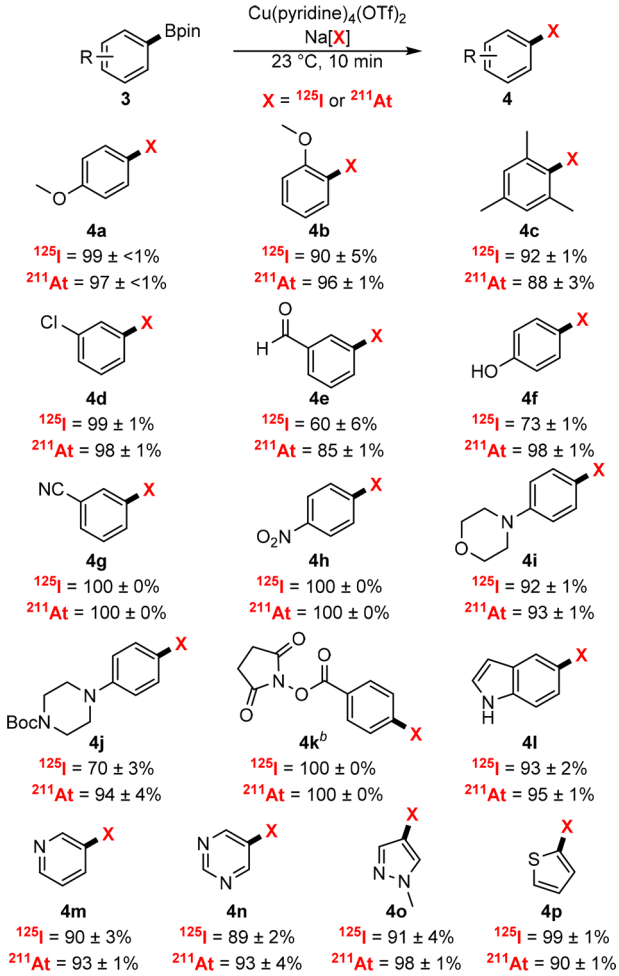
1 **2**

entry	R	Cu source	mol %	RCC (%)[b]
1	Bpin	none	0	NC[c]
2	Bpin	Cu_2O	5	NC[c]
3	Bpin	$Cu(CO_2CH_3)_2$	5	7 ± 1
4	Bpin	$Cu(OCOCF_3)_2{\cdot}H_2O$	5	50 ± 1
5	Bpin	$Cu(CH_3CN)_4OTf$	5	91 ± 2
6	Bpin	Cu(pyridine)$_4$(OTf)$_2$	5	95 ± 1
7	Bpin	Cu(pyridine)$_4$(OTf)$_2$	1	80 ± 8
8	none[d]	Cu(pyridine)$_4$(OTf)$_2$	5	NC[c]
9	$B(OH)_2$	Cu(pyridine)$_4$(OTf)$_2$	5	99 ± 1
10	BF_3K	Cu(pyridine)$_4$(OTf)$_2$	5	89 ± 4
11	Bnep[e]	Cu(pyridine)$_4$(OTf)$_2$	5	99 ± 1
12	MIDA[f]	Cu(pyridine)$_4$(OTf)$_2$	5	47 ± 14

[a]Standard conditions: **1** (15 μmol), Cu source (0.75 μmol), Na[^{125}I] solution (3−6 MBq) in 150 μL of MeOH/ACN (4:1). [b]Determined by radio-HPLC (average of $n \geq 2$ runs). Product identities were determined by HPLC using 4-iodoanisole as the reference standard. [c]NC = no conversion. [d]No substrate was used. [e]Bnep = boronic acid neopentylglycol ester. [f]MIDA = *N*-methyliminodiacetic acid.

The optimized conditions were then applied to radioiodination and -astatination of aryl boronic esters with varying functional groups (Scheme 2). The HPLC chromatograms of

Scheme 2. Scope of ^{125}I and ^{211}At Radiolabeling of Boronic Esters[a]



[a]Standard conditions: **1** (15 μmol), Cu(pyridine)$_4$(OTf)$_2$ (0.75 μmol), Na[^{125}I] or Na[^{211}At] solution (3−6 MBq) in 150 μL of MeOH/ACN (4:1). RCCs for ^{125}I- and ^{211}At-labeled compounds were determined by radio-TLC (n = 3). [b]RCCs for the ^{125}I- and ^{211}At-labeled compounds were determined by radio-HPLC (n = 3).

the respective nonradioactive ^{127}I standards were used to identify both the ^{125}I- and ^{211}At-labeled products because of the nearly identical retention times of the radiolabeled congeners resulting from the chemical similarities of iodine and astatine (see the Supporting Information).

We found the reaction conditions to be well-tolerant of both electron-rich and -poor substrates (**3a−c**), including sterically crowded substrates (**3b** and **3c**), which have been reported to slow down the transmetalation step in Cu-catalyzed radiolabeling protocols.[17,21,22] Excellent ^{125}I and ^{211}At RCCs were also obtained with morpholine and piperazine substrates (**3i** and **3j**), which are prevalent nitrogen heterocycles found in many bioactive compounds and FDA-approved drugs.[26] Quantitative ^{125}I and ^{211}At RCCs were observed with **3k**,

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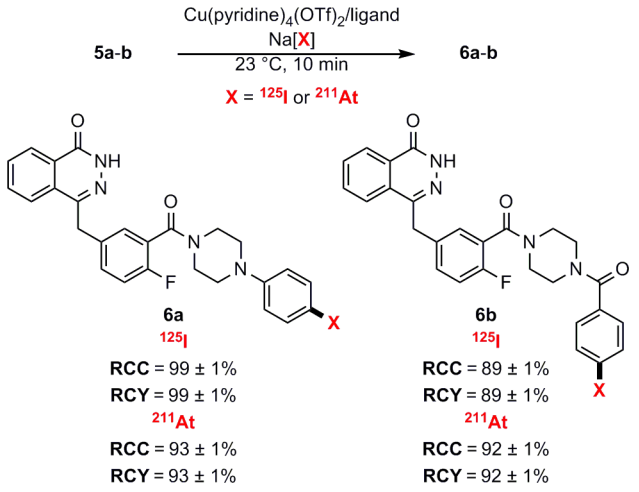
providing access to ^{125}I- and ^{211}At-labeled benzoate *N*-hydroxysuccinimide esters, compounds commonly employed in radiolabeling of proteins.[1,27,28] Good RCCs continued with nitrogen and sulfur heterocyles, including five-membered-ring systems as well (**4l**–**p**).

We next examined the efficiency of the method for ^{125}I and ^{211}At radiolabeling of molecules with potential clinical applications (Scheme 3). Thus, we applied this radiolabeling

Scheme 3. Access to ^{125}I- and ^{211}At-Labeled PARP-1 Inhibitor Compounds via Boronic Ester Precursors 5a and 5b[a]



[a]Standard conditions: **1** (15 μmol), Cu(pyridine)$_4$(OTf)$_2$ (0.75 μmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (0.75 μmol), Na[^{125}I] or Na[^{211}At] solution (3–6 MBq) in 150 μL of MeOH/ACN (4:1). RCCs and RCYs for ^{125}I- and ^{211}At-labeled compounds were determined by radio-HPLC (n = 3).

approach to poly(ADP–ribose) polymerase inhibitors (PARPi), effective cancer therapeutics for patients with BRCA mutations,[29] a current research focus in our laboratory. However, using the optimized conditions with PARPi precursors **5a** and **5b**, we achieved RCYs of only 61% and 69%, respectively. When utilizing a 1:1 ratio of Cu(pyridine)$_4$(OTf)$_2$ and the electron-rich ligand 3,4,7,8-tetramethyl-1,10-phenanthroline, we obtained excellent RCCs and RCYs of **6a** and **6b**.

The RCYs of **6b** obtained using our catalytic approach rival those in previous reports, outlined in Figure 1, which require reaction temperatures of 100 °C or greater[30,31] or reaction times of 2 to 4 h.[32,33] Although the astatinated analogue of **6b** was disclosed by Reiner and co-workers[34] (no RCY reported), they reported a 3 h synthetic procedure with ^{211}At, an unusual approach considering the 7.2 h half-life of the radionuclide.

Finally, we prepared **5c** to access our previously reported [^{125}I]KX1[35] and [^{211}At]MM4 using our Cu/ligand protocol (Scheme 4). Compared with tin precursor **5c′**, we were able to obtain greater RCCs and RCYs using **5c** with ^{125}I and ^{211}At under much milder reaction conditions.

We have demonstrated the first approach to astatinated compounds using boronic ester precursors, providing an efficient and nontoxic protocol that eliminates the traditional need for toxic organotin reagents. This divergent synthesis delivers exceptional radionuclide incorporation for ^{125}I and ^{211}At at room temperature and is applicable to simple and

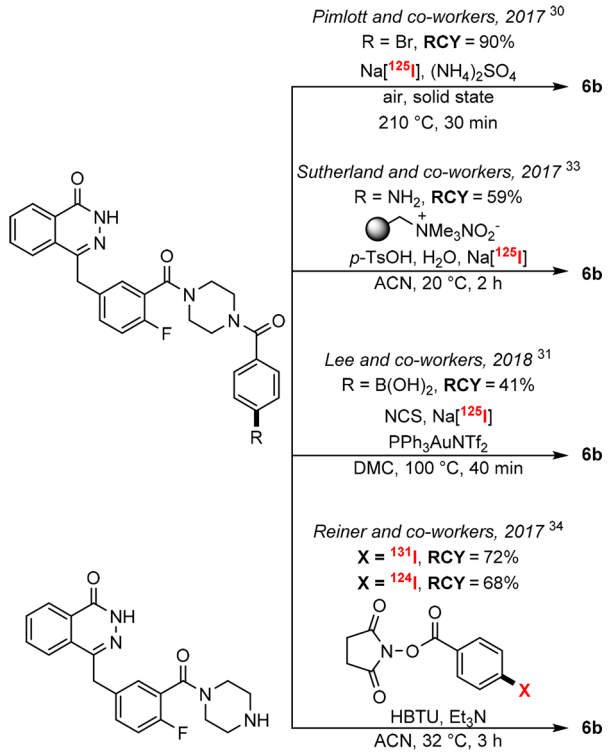
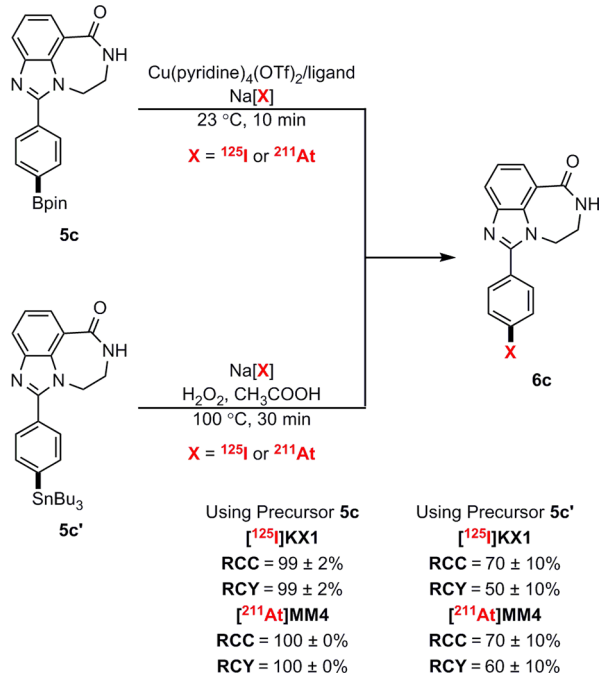


Figure 1. Current synthetic radiolabeling routes of **6b**.

Scheme 4. Access to ^{125}I- and ^{211}At-Labeled PARP-1 Inhibitor Compounds via Boronic Ester Precursor 5c[a]



[a]Standard conditions: **1** (15 μmol), Cu(pyridine)$_4$(OTf)$_2$ (0.75 μmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (0.75 μmol), Na[^{125}I] or Na[^{211}At] solution (3–6 MBq) in 150 μL of MeOH/ACN (4:1). RCCs and RCYs for ^{125}I- and ^{211}At-labeled compounds were determined by radio-HPLC (n = 3).

complex boronic ester precursors, allowing late-stage radiolabeling with heavy halides. This platform can be applied to

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other diverse and biologically relevant precursors, providing a more practical approach for developing α-emitting therapeutics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00232.

General methods and radiolabeling protocol; synthesis, characterization, and ^{1}H and ^{13}C spectra of boronic ester precursors and ^{127}I standards; and UV-HPLC and radio-HPLC chromatograms; and radio-TLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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