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

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Abstract

Access to ^{211}At and ^{125}I -radiolabeled compounds in excellent RCCs and RCYs was achieved in just 10 minutes at room temperature using a Cu catalyst. 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 alpha-emitting radiotherapeutics.

Graphical Abstract

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 due to the 50–70 μm path-length of the alpha-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

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Notes

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General methods and radiolabeling protocol, synthesis, characterization, ^1H and ^{13}C Spectrum of boronic ester precursors and ^{127}I Standards, and UV-HPLC and radio-HPLC chromatograms. (PDF)

^{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 with fast targeting vectors that are retained in tumors such as small molecules. Although many groups have explored astatinated peptides and antibodies, a recent study has demonstrated oxidative lysosomal degradation of these targeting agents results in dehalogenation in vivo.⁵ While ^{225}Ac ($t_{1/2} = 10$ d), ^{223}Ra ($t_{1/2} = 11.4$ d), and ^{227}Th ($t_{1/2} = 18.7$ d) illustrate more favorable half-lives for antibodies, these α -emitters require ligand chelation in order to form stable chemical complexes that often escape the respective radiobio-conjugate. These radionuclides also emit unwanted decay products and are ineffective after a single alpha-decay, resulting in toxic daughter isotopes, which can distribute throughout the body.⁴ Despite the clear advantages ^{211}At offers, synthetic methodologies that can provide access to astatinated compounds are exceedingly rare, mainly due to At having no stable isotopes, the scarcity of radio-isotope production sites capable of making ^{211}At , and lack of understanding 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 for 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, therefore, making it difficult to obtain the desired, and non-stable, At^{+1} 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 $\text{S}_{\text{N}}\text{Ar}$ mechanistic pathway (Scheme 1b).¹¹ This detailed report also demonstrated how 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 in the *para*-position. Despite the high yields obtained using this method, astatination of the conjugate aryl group results in unwanted side-product formation.

Due to previous reports illustrating the versatility of the Chan–Evans–Lam reaction^{12–14} to access radio-iodinated and -fluorinated compounds via boronic reagents,^{15–22} we adapted a similar strategy to access ^{211}At -labeled hetero(aryl) synthons. This study will complement these previous studies, as well as the Cu-assisted halogenation reports illustrated by Sanford and Scott,^{23, 24, 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 one hour at room temp.²² Therefore, we began our initial investigation by screening several Cu-sources in order to identify an efficient catalyst for ^{125}I -radiolabelling aryl boronic esters that could be translated to astatination. Using $\text{Cu}(\text{pyridine})_4\text{OTf}$ complex, we were able to obtain excellent RCCs of **2** (Table 1, entry 5) in just 10 minutes at room temp 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, however, low RCC values were obtained (entry 12).

Optimized conditions were then applied to radiodination and astatination of aryl boronic esters with varying functional groups (Scheme 2). The HPLC chromatogram of each respective non-radioactive ^{127}I standard was used to identify both the ^{125}I - and ^{211}At -labelled products due to the near identical retention times of the radiolabeled congeners resulting from the chemical similarities of iodine and astatine (see Supporting Information).

We found reaction conditions to be well tolerant of both electron-rich and -poor substrates, **3a–c**, including sterically crowded substrates **3b–c**, which have been reported to slow down the transmetallation 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–j**, prevalent nitrogen heterocycles found in many bioactive compounds and FDA-approved drugs.²⁶ Quantitative ^{125}I and ^{211}At RCC was observed with **3k**, providing access to ^{125}I and ^{211}At -labelled benzoate *N*-hydroxysuccinimide esters, compounds commonly employed in radiolabeling proteins.^{1, 27, 28} Good RCCs continued with nitrogen and sulfur heterocycles, including 5-membered ring systems as well (**4l–p**).

We next examined the efficiency of the method to radiolabel molecules with ^{125}I and ^{211}At that have potential clinical applications (Scheme 3). Thus, we applied this radiolabeling 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–b**, we only achieved RCYs of 61% and 69%, respectively. When utilizing a 1:1 ratio of $\text{Cu}(\text{pyridine})_4(\text{OTf})_2$ and electron-rich ligand 3,4,7,8-tetramethyl-1,10-phenanthroline, we obtained excellent RCCs and RCYs of **6a–b**.

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 2 to 4 hour reaction times.^{32, 33} Although the astatinated analogue of **6b** has been disclosed by Reiner and co-workers³⁴ (no RCY reported), they reported a three-hour synthetic procedure with ^{211}At , an unusual approach considering the 7.2 hour half-life of the radionuclide.

Finally, we prepared **5c** to access our previously reported [^{125}I]KX1³⁵ and [^{211}At]MM4 using our Cu/ligand protocol (Scheme 4). Compared to tin-precursor **5c'**, we were able to obtain greater RCCs and RCYs using **5c** with ^{125}I and ^{211}At , at much milder reaction conditions.

We have demonstrated the first approach to astatinated compounds using boronic ester precursors, providing an efficient and non-toxic 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 complex boronic ester precursors, allowing for late-stage radiolabeling with heavy halides.

This platform can be applied to other diverse and biologically relevant precursors, allowing for a more practical approach in developing α -emitting therapeutics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Previous Work**a) Astatination of Aryl Stannanes** **b) Astatination of Aryl Iodonium Salts** **This Work****c) Astatination of Aryl Boronic Esters**

Scheme 1.
Synthetic routes to ${}^{211}\text{At}$ -labeled compounds

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

^aStandard conditions: **1** (15 μmol), $\text{Cu}(\text{pyridine})_4(\text{OTf})_2$ (0.75 μmol), $\text{Na}[^{125}\text{I}]$ or $\text{Na}[^{211}\text{At}]$ solution (3–6 MBq) in 150 μL of $\text{MeOH}:\text{ACN}$ (4:1). RCC for ^{125}I - and ^{211}At -labeled compounds were each determined by radio-TLC ($n = 3$). ^bRCC for ^{125}I - and ^{211}At -labeled compounds were each determined by radio-HPLC ($n = 3$).

Scheme 3. Access to ${}^{125}\text{I}$ - and ${}^{211}\text{At}$ -PARP-1 Inhibitor Compounds via Boronic Ester Precursor 5a-b^a

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

^aStandard conditions: **1** (15 μmol), Cu(pyridine)₄(OTf)₂ (0.75 μmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (0.75 μmol), Na[¹²⁵I] or Na[²¹¹At] solution (3–6 MBq) in 150 μL of MeOH:ACN (4:1). RCC and RCY for ¹²⁵I- and ²¹¹At-labeled compounds were each determined by radio-HPLC (*n* = 3).

Table 1Optimization of ^{125}I -Radiolabelling of 4-Methoxyphenyl Boryl Reagents^a

entry	R	Cu source	mol %	RCC ^b (%)
1	Bpin	none	0	NC ^c
2	Bpin	Cu ₂ O	5	NC ^c
3	Bpin	Cu(CO ₂ CH ₃) ₂	5	7 ± 1
4	Bpin	Cu(OCOCF ₃) ₂ ·H ₂ O	5	50 ± 1
5	Bpin	Cu(CH ₃ CN) ₄ OTf	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 ₃ K	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

^aStandard conditions: **1** (15 μmol), Cu source (0.75 μmol), Na[^{125}I] solution (3–6 MBq) in 150 μL of MeOH:ACN (4:1).^bRCC determined by radio-HPLC (average of n = 2 runs). Identity of the product was determined by HPLC using 4-iodoanisole as the reference standard.^cNC = No Conversion.^dNo substrate was used.^eBnep = boronic acid neopentylglycol ester.^fMIDA = N-methyliminodiacetic acid.