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Transition-metal-free Nucleophilic ^{211}At-astatination of Spirocyclic Aryliodonium Ylides

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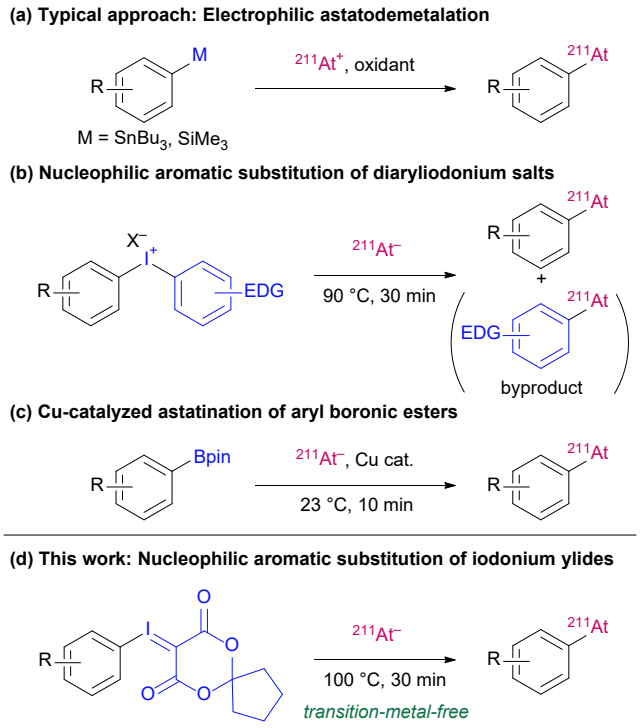
The transition-metal-free ^{211}At-astatination of spirocyclic aryliodonium ylides via a nucleophilic aromatic substitution reaction is described. This method enables the preparation of ^{211}At-radiolabeled compounds derived from multi-functionalized molecules and heteroarenes in good to excellent radiochemical yield.

Radionuclides have been widely applied in the fields of molecular imaging and diagnostics, and used as therapeutics in nuclear medicine.[1] Moreover, targeted alpha therapy (TAT) has recently attracted significant attention in cancer therapy.[2,3] In TAT, antibodies or small molecules that can recognize a targeted biomolecule are labelled with radionuclides that emit α-particles and introduced into the body. The labeled molecules are then localized in target tissues where the α-emissions selectively damage cancer cells. Due to the high linear energy transfer, α-emitters can, in contrast to β$^-$-emitters, efficiently induce cytotoxic DNA double-strand breaks in target cells. Short-path length of α-particles can cause site-selective radiation damage in malignant cells whilst sparing the surrounding normal cells from unwanted radiation exposure.[4] Several α-emitting radionuclides have been investigated as potential radiopharmaceuticals for TAT, and of these, astatine-211 (^{211}At) has attracted much attention because of its physical properties.[5,6] ^{211}At has a half-life of 7.2 h, which means it is suitable for labeling small molecules that quickly accumulate in tumor sites. The decay of ^{211}At results in almost 100% α-particle emissions with no production of long-lived α-particle-emitting daughters. Despite the favorable properties of ^{211}At and the recent increase in interest in nuclear medicine, the number of studies on the synthetic methodology of ^{211}At-labeled small molecules remains limited due to the absence of a stable astatine isotope and a limited understanding of the chemical behavior of ^{211}At.[7,8] To further expand preclinical and clinical studies of ^{211}At-based TAT, the development of operationally simple synthetic routes to ^{211}At-labeled compounds is essential.

A typical synthetic route to ^{211}At-labeled compounds is the electrophilic destannylation of aryl stannanes (Scheme 1a).[1,9] To avoid the use of toxic organotin reagents, the electrophilic desilylation of aryl silanes has also been reported.[10,11] However, these electrophilic substitution reactions often suffer from problems probably related to the control of unstable At$^+$ species under oxidative reaction conditions, as astatine can adopt multiple oxidation states (+I, +III, +V, and +VII).[12,13] In contrast,



Scheme 1 Synthetic approaches to ^{211}At-labeled compounds.

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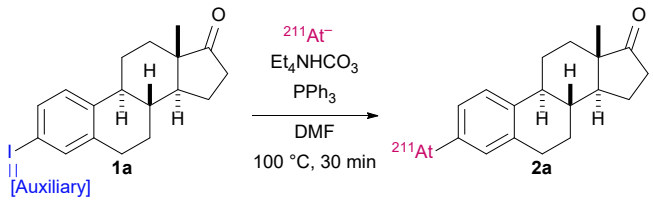
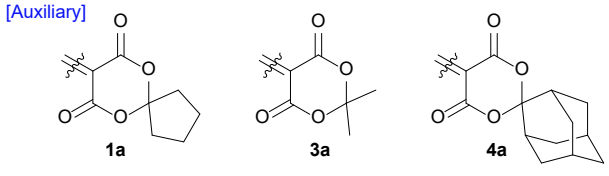
astatide (At^-) is known as a relatively stable oxidation state under reducing conditions, but its application in labeling reactions has been less explored systematically.[14-18] In 2016, Brechbiel, Guérard, and co-workers reported a nucleophilic aromatic substitution reaction of diaryliodinium salts using [^{211}At]NaAt under reducing conditions (Scheme 1b).[14] In this approach, the selectivity between the two aromatic rings is a potential problem when using unsymmetric diaryliodonium salts. Thus, the aromatic ring bearing electron-donating substituents is required as the leaving group to obtain the desired ^{211}At-labeled compounds with high regioselectivity. More recently, Mach, Makvandi, and co-workers have developed an efficient approach that gives ^{211}At-labeled compounds via the Cu-catalyzed astatination of aryl boronic esters (Scheme 1c), which rapidly furnishes ^{211}At-labeled compounds in excellent yield at room temperature.[17] These pioneering reports have motivated us to develop an alternative nucleophilic astatination reaction. Here, we report a transition-metal-free astatination of spirocyclic aryliodonium ylides with $^{211}At^-$ (Scheme 1d).

In 2014, Liang, Vasdev, and co-workers reported that spirocyclic aryliodonium ylides, which are stable solids and easily synthesized,[19,20] can serve as effective precursors for radiofluorination reactions with [^{18}F]fluoride.[21] This radiolabeling method is applicable to a broad range of non-activated arenes, including electron-rich arenes and radiopharmaceuticals used in positron-emission tomography.[22-26] We envisaged that by using an iodonium ylide, nucleophilic ^{211}At-astatination would also proceed in a similar manner. In our initial studies, we selected estrone derivative **1a**, which contains an electron-rich aromatic ring as the reaction site and would therefore be a challenging model substrate for the nucleophilic astatination (Table 1). After extensive optimization, we found that the reaction of $^{211}At^-$ with an iodonium ylide bearing a spirocyclopentyl-type auxiliary (**1a**), Et_4NHCO_3 as a phase-transfer agent, and PPh_3 as a reducing agent in dimethylformamide (DMF) at 100 °C for 30 minutes provided ^{211}At-labeled compound **2a** in 58% radiochemical yield (RCY), as determined using radio-thin layer chromatography (radio-TLC) analysis. The identity of **2a** was confirmed via radio high-performance liquid chromatography (radio-HPLC) analysis of a sample synthesized via astatodestannylation (for details, see the ESI). DMF is an optimal solvent for the reaction due to the solubility of the iodonium ylide. Replacement of the spirocyclopentyl-type auxiliary of the iodonium ylide with a standard Meldrum's acid (**3a**) or spiroadamantyl auxiliary (**4a**) resulted in lower RCYs (entries 2 and 3). This might be due to the lower stability of **3a** or the larger steric hindrance found in **4a**.[23] When Et_4NHCO_3 was removed from the reaction conditions, the RCY of **2a** decreased significantly (entry 4). It is possible that the formation of [^{211}At]Et_4NAt might enhance the nucleophilicity of $^{211}At^-$ and thus improve the RCY. Although the absence of PPh_3 from the reaction conditions only had a small effect on the RCY under the optimized conditions (entry 5), we maintained the use of PPh_3 for further investigations because we wanted to keep the reaction mixture under a reducing environment and thus retain the oxidation state of $^{211}At^-$.[12,26] When the reaction was carried out at a lower temperature (60 °C), **2a** was obtained only in 12% RCY.

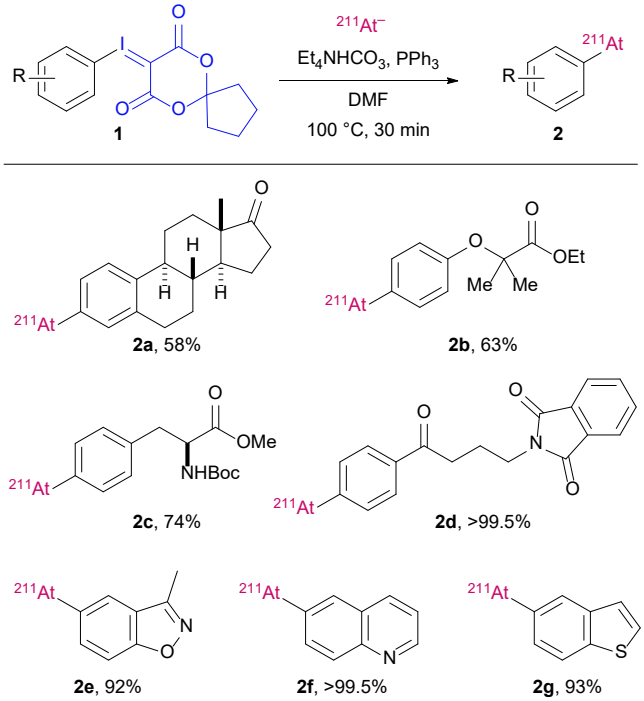
Table 1 Optimization of the reaction conditions[a]



Entry	Deviation from standard conditions	RCY (%)[b]
1	None	58
2	Meldrum's acid auxiliary **3a** instead of **1a**	32
3	Spiroadamantyl auxiliary **4a** instead of **1a**	12
4	Without Et_4NHCO_3	23
5	Without PPh_3	53
6	Performed at 60 °C	12



[a]Reaction conditions: **1a** (10 mg), Et_4NHCO_3 (7 mg), PPh_3 (5 mg), and $^{211}At^-$ (25-52 MBq) in DMF (500 µL) at 100 °C for 30 min, unless otherwise noted. [b]The identity of the products was confirmed using HPLC analysis of a reference sample synthesized via astatodestannylation. The radiochemical yields (RCYs) were determined by radio-TLC analysis.



Scheme 2 Substrate scope of the ^{211}At-astatination of aryliodonium ylides. Reaction conditions: **1** (10 mg), Et_4NHCO_3 (7 mg), PPh_3 (5 mg), and $^{211}At^-$ (16-43 MBq) in DMF (500 µL) at 100 °C for 30 min, unless otherwise noted. Product identities were confirmed by HPLC analysis of nonradioactive I-labeled analogues. RCYs were determined by radio-TLC analysis.

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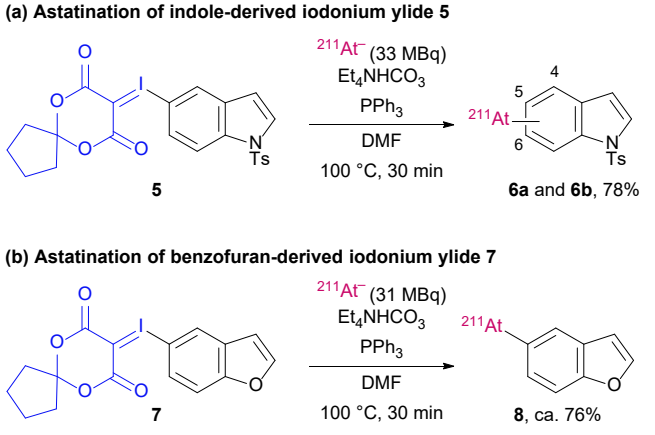
We applied the optimized conditions (Table 1, entry 1) to various aryliodonium ylides, including those derived from multi-functionalized molecules (Scheme 2). These iodonium ylides (**1**) were synthesized using our previously developed protocols that enable the direct preparation of polyfunctionalized iodonium ylides.[27-29] As iodine and astatine are chemically similar, the identities of the ^{211}At-labeled compounds **2** could be confirmed by the comparison of the HPLC retention times of **2** with those of the corresponding nonradioactive I-labeled analogues. The RCYs of the ^{211}At-labeled compounds **2** were determined via radio-TLC analysis. In addition to estrone derivative **2a**, ^{211}At-labeled compound **2b** was obtained in a good RCY. A fibrate core structure of **2b** acts as peroxisome proliferator-activated receptor alpha (PPARα) agonist. An iodonium ylide derived from phenylalanine afforded the labeled compound **2c** in 74% RCY. Astatination of the electron-deficient aryl ring in butyrophenone fragment **1d** proceeded efficiently to afford the labeled compound **2d** in an almost quantitative RCY. These results demonstrate the functional-group tolerance of our method. Furthermore, this protocol can also be applied to several heteroarenes. An isoxazole, found in the structure of risperidone, was radiolabeled with ^{211}At$^-$ using iodonium ylide **1e**, which generated **2e** in 92% RCY. Astatination of an electron-deficient quinoline ring and an electron-rich benzothiophene ring proceeded regardless of their electronic properties to afford labeled compounds **2f** and **2g** in almost quantitative RCYs. During the investigation of the heteroarene substrates, the astatination of indole-derived iodonium ylide **5** afforded two labeled compounds (**6a** and **6b**) with similar polarities, which were detected in the radio-TLC analysis (Scheme 3a). Although their characterization proved difficult, we speculated that these compounds might be regioisomers of ^{211}At-labeled indole. In addition to the desired nucleophilic aromatic substitution reaction at the C-5 position of the indole, radiolabeling at the C-4 or C-6 position might be feasible through the formation of an aryne. The formation of regioisomers via aryne intermediates has also been reported in the radiofluorination of highly electron-rich aryliodonium ylides.[25] However, while the reaction proceeded in a reducing environment containing PPh_3, we cannot fully exclude the possibility that At$^-$ is oxidized to At$^+$ and astatination occurs at the C-2 or C-3 position via an electrophilic aromatic substitution reaction. We also examined the astatination of benzofuran-derived iodonium ylide **7** (Scheme 3b). The treatment of **7** with ^{211}At$^-$, Et_4NHCO_3, and PPh_3 at 100 °C gave the corresponding ^{211}At-labeled compound **8**, as confirmed using radio-HPLC analysis. However, the observed product was unstable on silica gel and gradually decomposed during the TLC analysis. Although an accurate analysis was difficult due to the instability of the product, the RCY was estimated to be ca. 76% based on the radio-TLC analysis (for details, see the ESI).



Scheme 3 Effect of the heteroaromatic ring on the ^{211}At-astatination reaction.

In summary, we have developed a transition-metal-free ^{211}At-astatination of spirocyclopentyl aryliodonium ylides **1** using nucleophilic ^{211}At$^-$ under reducing reaction conditions. Multi-functionalized molecules and heteroarenes were efficiently radiolabeled avoiding the use of toxic organotin reagents and the difficult to control electrophilic ^{211}At$^+$. Our methods can be expected to facilitate further studies on the development of ^{211}At-based targeted alpha therapy.

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Conflicts of interest

There are no conflicts to declare.

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