ChemPubSoc Europe

DOI: 10.1002/chem.201604105

CHEMISTRY
A European Journal
Communication

Radiochemistry

A Highly Efficient Copper-Mediated Radioiodination Approach Using Aryl Boronic Acids

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Abstract: A convenient and quantitative radioiodination method by copper-mediated cross-coupling of aryl boronic acids was developed. The mild labeling conditions, ready availability of the boronic acid substrate, simple operation, broad functional group tolerance and excellent radiochemical yield (RCY) make this a practical strategy for radioiodine labeling without further purification.

Radiopharmaceuticals labeled with radioactive iodine isotopes (^{123}I, ^{124}I, ^{125}I, and ^{131}I) have always played a major role in nuclear medicine and molecular imaging, for disease therapy with β^- emission (^{131}I) and for in vivo non-invasive diagnosis and therapy response monitoring with positron emission tomography (PET) (^{124}I) or single photon emission computed tomography (SPECT) ($^{123/125/131}$I).[1] The availability and well-defined chemical properties of various radioactive iodine isotopes make radioiodine a cornerstone in nuclear medicine.[2] Correspondingly, the methods of labeling small molecules, peptides, proteins, and antibodies with radioiodine will have a significant impact on biomedical research and drug development.[3]

Although there have been a number of radioiodination methods reported, they are generally restricted to using oxidizing agents to generate electrophilic iodine species such as molecular iodine or iodine monochloride, which then react with an activated aromatic moiety or olefin group by electrophilic substitution reactions[4] (for example, radioiododestannylation[5] and radioiododeboronation[6]). Despite the wide use of these methods, there are some serious issues associated with them. Chloramine T, one of the most commonly used oxidant, exposes the compounds to harsh oxidizing conditions and may cause a number of undesirable side reactions.[7] The molecular iodine generated by the oxidant is volatile, thus limits the operation to avoid airborne release. Furthermore, the low yields of the precursor synthesis[8] and low radiochemical yields (RCY)[9] are also of concern. Radiodehalogenation, a straightforward radioiodination method of introducing radioiodine into aromatic compounds without an oxidant, is induced by nucleophilic substitution. As this is an energy demanding process, high temperature is required.[10] Another concern is the low specific activity, which is due to the difficult separation of the radiolabeled product from the precursor. Recently, Cant et al.[11] reported a nickel-mediated direct radioiodination of aryl and heteroaryl bromides with a single-step method, but this kind of halogen-exchange reaction is restricted by the steric hindrance effect and the requirement of harsh temperature conditions (180 °C). Considering the drawbacks of these methods, it is critical to develop a simple and practical new radioiodination method through a mild and efficient reaction with high RCY and specific activity for radiopharmaceutical applications.

The Chan–Evans–Lam reaction,[12] a copper-mediated oxidative cross-coupling of aryl boronic acids and heteroatom nucleophiles, is a major breakthrough in the C-heteroatom transformation for its mild reaction conditions and the ready availability of the boronic acid substrates. Significant progress has been made in expanding the scope and the application of this kind of reaction in the past two decades.[13] Motivated by this powerful synthetic methodology and the opportunity to develop a better radioiodination method, we report herein a copper mediated radioiodination using aryl boronic acids through a Chan–Evans–Lam cross-coupling reaction.

Phenylboronic acid served as a model substrate to optimize the labeling conditions. First, Cu_2O was chosen as the catalyst[14] and various ligands (Table 1) were examined to enhance the efficiency of the copper-mediated reaction. When using acetonitrile as the solvent, 1,10-phenanthroline was identified as the most efficient ligand, which gave excellent RCY (>98%; Table 1, Entry 1). Second, a series of Cu compounds were chosen as catalysts; the RCY results shown in Table 1 demonstrate that the catalytic efficiency of Cu^I compounds was much higher than those of Cu^{II} compounds. Considering that the iodine and chloride ions from the catalysts CuI and CuCl could interfere with the radioiodine labeling progress, Cu_2O was chosen as the catalyst to perform other reactions. Then, we

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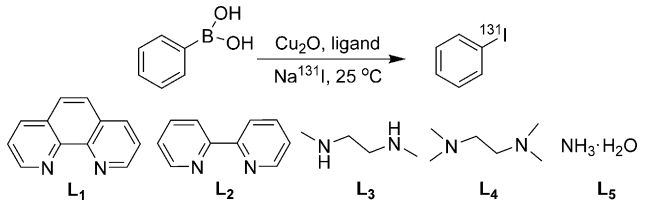
Supporting information for this article and ORCID(s) for the author(s) are available on the WWW under: http://dx.doi.org/10.1002/chem.201604105.

Table 1. Optimization of copper-mediated radioiodination of phenylboronic acid.[a]

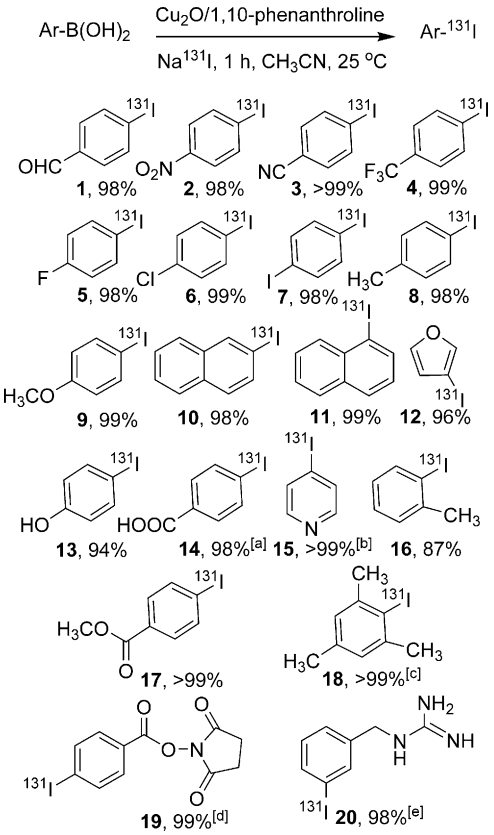


Entry	Ligand	Cu compound	RCY [%][b]
1	L_1	Cu_2O	>98
2	L_2	Cu_2O	37
3	L_3	Cu_2O	26
4	L_4	Cu_2O	5
5	L_5	Cu_2O	4
6	L_1	CuI	>98
7	L_1	CuCl	>98
8	L_1	$CuCl_2$	12
9	L_1	$CuBr_2$	5

[a] All reactions were performed using phenylboronic acid (2 μmol), acetonitrile as solvent, $Na^{131}I$ (18.5—20 MBq, 5 μL in water) at 25 °C for one hour. [b] Decay-corrected RCY determined by radio-HPLC.

turned our attention to the catalyst dosage (Supporting Information, Table S1). The RCY remained high when the catalyst concentration was as low as 5% (molar ratio) of the substrate (98%; Supporting Information, Table S1, Entry 1). Results of reaction time monitoring shown in the Supporting Information, Table S1, confirmed that this radioiodination method was time-dependent and the optimal reaction time was about 1 h, which is acceptable for radioiodination labeling. The labeling reactions under other commonly used solvents, such as methanol, dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO), were also tested. Except for DMF and DMSO, all the other solvents could be used and worked well for radioiodination (Supporting Information, Table S1). Finally, the optimized labeling conditions were as follows: substrate (2 μmol), Cu_2O (0.4 μmol), and 1,10-phenanthroline (0.8 μmol) dissolved in acetonitrile, $Na^{131}I$ (18.5–20 MBq, 5 μL in water), reacted for 1 h at 25 °C to give the final radio-product.

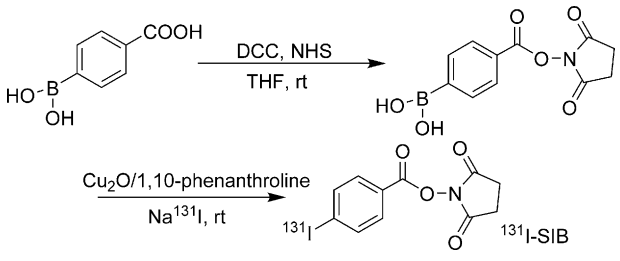
The above conditions were used to test a variety of substrates (Scheme 1) to explore the scope and limitation of this labeling method. Under the optimized standard labeling conditions, aryl boronic acids bearing different substituents including formyl, nitro, cyano, hydroxyl, and ester groups and heteroarenes, such a as 3-furanboronic acid and pyridine-4-boronic acid, were used as substrates and labeled with ^{131}I in high RCYs (Scheme 1). As illustrated in Scheme 1, in the presence of electron-withdrawing or electron-donating substituents, the substrates were all converted into the desired products with excellent RCYs. Unprotected carboxyl is a special substituent for this reaction because it can affect the coordination between the catalyst and aryl boronic acids; therefore, when labeling 4-carboxyphenylboronic acid (2 μmol), triethylamine (4 μmol) was added to the mixture and a high RCY (98%) was obtained (Scheme 1, product 14). Considering that the steric



Scheme 1. Copper-mediated radioiodination. [a] 4 μmol triethylamine added, [b] the precursor was dissolved in 10 μL pyridine, [c] reacted at 80 °C, [d] reacted under anhydrous conditions, [e] after deprotection of N-Boc with TFA.

hindrance effect may reduce the rate of this kind of cross-coupling radioiodination reaction, when 2,4,6-trimethylphenylboronic acid was chosen as the substrate, an increased reaction temperature (80 °C) was required to have quantitative radiolabeling (Scheme 1, product 18).

For the purpose of labeling peptides, proteins, or antibodies with radioiodine, the active ester of 4-carboxyphenylboronic acid (PB-NHS) was synthesized and then labeled with ^{131}I (^{131}I-SIB) (Scheme 1, product 19). The in vivo stability, versatility, and feasibility of radioiodination of monoclonal antibodies through succinimidyl *para*-iodobenzoate (SIB) has been demonstrated by Wilbur et al.[15] The new method was used for the radioiodination of the NHS ester (Scheme 2), which resulted in a higher RCY (Figure 1, 99%) than those previously reported (ca. 60–90%).[15] Furthermore, the peptide c(RGDyk) and the



Scheme 2. Synthesis of ^{131}I-SIB.

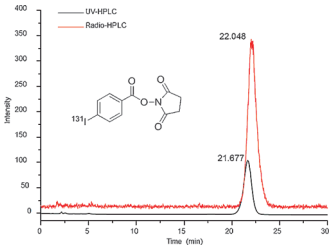


Figure 1. HPLC analysis of ^{131}I-SIB and non-radioactive reference with UV and radiometric detection.

protein bovine serum albumin (BSA) were successfully labeled with ^{125}I using ^{125}I-SIB, and the SPECT imaging results confirmed the good targeting ability and in vivo stability of the radiopharmaceuticals synthesized using this labeling method (Figure 2 and the Supporting Information, Figure S1).

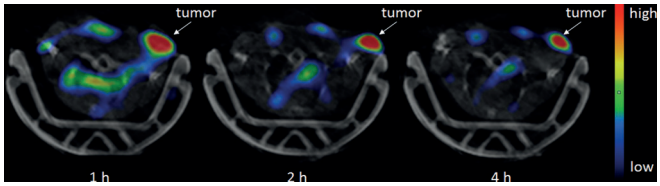
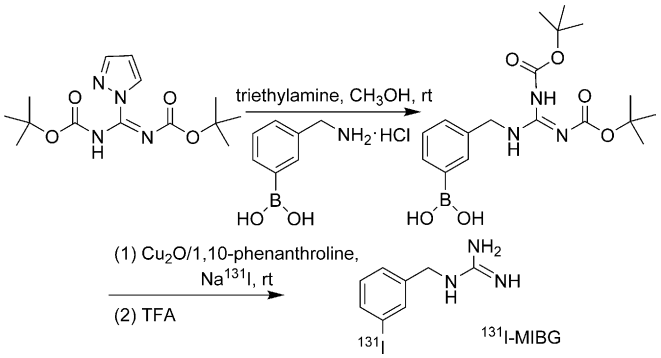


Figure 2. SPECT imaging of c(RGDyk) labeled with ^{125}I using ^{125}I-SIB.

Having demonstrated the generality of this radioiodination method, the preparation of a clinically used imaging agent was also investigated. Iodine-123- and iodine-131-labeled meta-iodobenzyl-guanidine (^{123}I-MIBG and ^{131}I-MIBG) have been used clinically for diagnosis and therapy of neuroectodermally derived tumors like pheochromocytoma, carcinoid tumors, and neuroblastoma for decades.[16] $^{123/131}$I-MIBG are generally synthesized from the precursor of non-radioactive iodinated MIBG (^{127}I-MIBG) using a halogen exchange reaction. Consequently, the radiolabeled product can't be separated from the precursor, which resulted in rather low specific activity. For $^{123/131}$I-MIBG, about one molecule in 2000 was radiolabeled.[17] The non-radiolabeled precursors competing against $^{123/131}$I-MIBG for the norepinephrine transporter have a negative effect on diagnosis and therapy and may cause side-effects when the patient is given escalation doses. Therefore, there is an unmet pressing need for no-carrier-added radioiodinated MIBG for clinical applications. To address this challenge, we synthesized ^{131}I-MIBG (Scheme 1, product 20) using this newly developed radioiodination method (Scheme 3), with very high RCY (Figure 3, 98%). Furthermore, the radiolabeled product ^{131}I-Boc-MIBG could be separated well from the labeling precursor by high performance liquid chromatography (HPLC) as illustrated in Figure 3 and the Supporting Information, Figure S2, which could improve the specific activity significantly.

In conclusion, a highly efficient new copper-mediated radioiodination method using Cu_2O/1,10-phenanthroline as a catalyst was developed for the facile radioiodination of aromatic and heteroaromatic boronic acid systems. This kind of cross-coupling radioiodination is efficient, low-cost, technically simple, and unlike other electrophilic labeling methods, requires no oxidizing agents to produce molecular iodine and iodine monochloride. Most importantly, the reaction conditions are quite mild and most of the substrates were converted into the desired products with excellent RCYs at room temperature. The radioiodinated NHS ester (^{131}I-SIB) was also obtained in high RCY as an intermediate for a versatile radiolabeling process with good in vivo stability and feasibility, which has been demonstrated in the literature. All of these advantages make this new radioiodination method attractive for clinical applications.



Scheme 3. Synthesis of ^{131}I-MIBG.

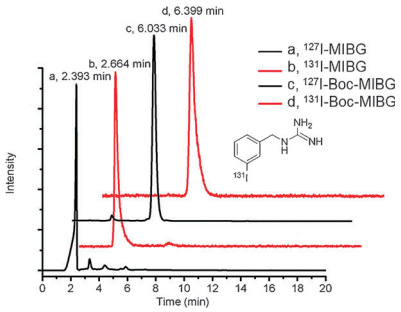


Figure 3. HPLC analysis of ^{131}I-MIBG and non-radioactive references with UV and radiometric detection.

Experimental Section

General radioiodination procedure: Precursor (2 μmol) was added into one 1.5 mL reaction vial; 50 μL of a solution of Cu_2O/1,10-phenanthroline in acetonitrile, which contained Cu_2O (0.4 μmol) and 1,10-phenanthroline (0.8 μmol), was then added to the vial. Na^{131}I (18.5–20 MBq) in 5 μL of water was added to the preceding mixture and reacted for 1 h at 25 °C.

Acknowledgements

This study was financially supported by the National Key Basic Research Program of China (2014CB744503) and the National Natural Science Foundation of China (21271030, 81471707)

and partially by the Fundamental Research Funds for the Central Universities (20720150063, 2013SH009).

Keywords: copper catalysts · molecular imaging · radiochemistry · radioiodination · radiopharmaceuticals

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Received: August 30, 2016
Published online on ■■ ▮▮, 0000

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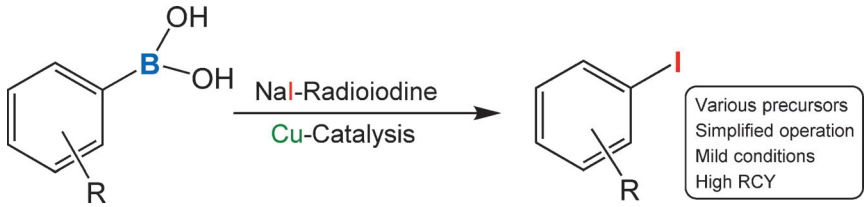

A convenient and quantitative radioiodination method was developed by using a copper-mediated cross-coupling of aryl boronic acids with high radiochemical yields (RCY) under mild labeling conditions. The variety of precursors, simple operation, and broad functional-group tolerance make it practical for radioiodine labeling without further purification.

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