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Rapid Iododeboronation with and without Gold Catalysis: Application to Radiolabelling of Arenes

Stacey Webster,[a] Kerry M. O'Rourke,[b] Conor Fletcher,[a] Sally L. Pimlott,[c] Andrew Sutherland*[b] and Ai-Lan Lee*[a]

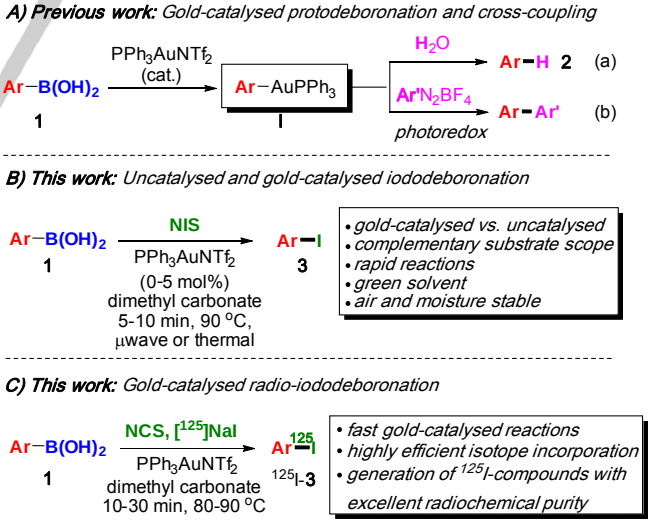
Abstract: Radiopharmaceuticals incorporating radioactive iodine in combination with SPECT imaging play a key role in nuclear medicine, with applications in drug development and disease diagnosis. Despite this importance, there are relatively few general methods for incorporating radioiodine into small molecules. Here we describe a rapid, air- and moisture-stable *ipso*-iododeboronation procedure using NIS, in the non-toxic and green solvent dimethyl carbonate. The fast reaction and mild conditions of the gold-catalysed method led to the development of a highly efficient process for radiolabelling of arenes, which constitutes the first example of an application of homogenous gold catalysis to selective radiosynthesis. This has been exemplified with an effective synthesis of radiolabelled *meta*-[^{125}I]iodobenzylguanidine, a radiopharmaceutical used for the imaging and therapy of human norepinephrine transporter-expressing tumours.

Introduction

Aryl iodides are versatile, key building blocks in organic synthesis and have found widespread applications in areas such as cross-coupling reactions and generation of free-radical intermediates.[1] In addition to their applications in synthesis, aryl iodides are also found in natural products and pharmaceutically important compounds.[2],[3] More recently, radiolabelled aryl and heteroaryl iodides are finding increasing medical application; in particular single photon emission computed tomography (SPECT) imaging for drug development and clinical diagnoses of disease, and in targeted radionuclide therapy.[4]

As a result of these applications, much effort has gone into developing methods for efficient synthesis of aryl iodides.[5] One such method is the *ipso*-substitution of arylboronic acids using *N*-iodosuccinimide (NIS) developed by Olah.[6] However, one limitation of this uncatalysed method is the substrate scope: deactivated arylboronic acids with electron withdrawing substituents perform poorly even after extended reaction times. For this reason, several base- or phase-transfer mediated[7] and Cu-catalysed[8],[9] *ipso*-iodination reactions of boronic acids have emerged in recent years. Despite the much-improved substrate scopes afforded by these recent developments, there are still limitations such as the need for base/additives, environmentally damaging solvents, or long reaction times.[10] Therefore, improvement is still required, especially if this transformation is to find widespread utility in fields such as total synthesis, material science and medical imaging.

Our interest in this area arose from our previous work on gold catalysis,[11] in particular, the mild gold-catalysed[12] proto- and deutero-deboronations[13] [Scheme 1A(a)] and cross-couplings [Scheme 1A(b)].[14] We hypothesised that the organogold intermediate **I**[15] should react with NIS to rapidly form iodoarenes **3**. Our aims were therefore to: i) compare the gold-catalysed and uncatalysed reactions to ascertain whether gold-catalysis can be used to overcome some of the substrate scope limitations of the uncatalysed reaction, ii) develop a much faster iodination protocol, both catalysed and uncatalysed iii) utilise environmentally friendly solvents to significantly improve the practicality of the reaction (the original reaction times were 1.5 – 25 hours in acetonitrile),[6] and finally iv) to apply the methodology to radio-iododeboronations.



Scheme 1. Gold-catalysed protodeboronation/cross couplings, gold- and uncatalysed iododeboronation, and gold-catalysed radio-iododeboronation.

Although there are early isolated reports of unselective gold-mediated radioiodinations[16] and elegant recent use of stoichiometric gold substrates for radiofluorinations,[17] as far as the authors are aware, there are no examples of selective

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radioiodinations[5] or radiofluorinations[18] using homogenous gold catalysis. Therefore, one of the main aims of this work was to demonstrate the first such application of gold catalysis to radiosynthesis. To the best of our knowledge, gold-catalysis has never been used for iododeboronations, even in cold (non-radiolabelled) procedures.[19] However, the groups of Wang and Frontier have reported mechanistically distinct iodinations of arenes via gold-catalysed activation of NIS for electrophilic aromatic substitutions.[20],[21] Another challenge was therefore to develop the intended *ipso*-iododeboronation selectively, without any over-iodination caused by electrophilic aromatic substitutions.

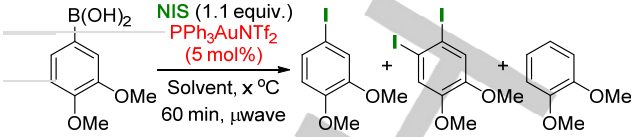
We herein report a rapid *ipso*-substitution of arylboronic acids using NIS in the environmentally friendly solvent dimethyl carbonate (DMC),[22] under microwave heating[23] or thermal heating (Scheme 1B). Both the gold-catalysed and uncatalysed reactions were investigated concurrently and we demonstrate that Au(I)-catalysis can be used to greatly improve the yields in cases where the uncatalysed reaction is poor. Conversely, the fast, uncatalysed reaction is often excellent in cases where gold-catalysis fails, so both protocols complement each other nicely. We also describe the use of this mild and general transformation for the radioiodination of arenes (Scheme 1C). Incorporation of the ^{125}I-radioisotope was fast and highly efficient, allowing the preparation of the radiopharmaceutical *meta*-[^{125}I]iodobenzylguanidine in high molar activity and excellent radiochemical purity.

Results and Discussion

We initiated our studies by carrying out a solvent screen on the gold-catalysed iododeboronation of arylboronic acid **1a** (Table 1). Pleasingly, the expected iododeboronation product **3a** was observed as the major product in various solvents, although the overiodination product **4a** (resulting from electrophilic aromatic substitution of gold-activated NIS)[20a] was also observed as a minor product. In addition, the protodeboronation product **2a** was also observed in toluene (entry 4) and is unsurprisingly the main product in water (entry 8). The two best results were obtained in chloroform (entry 2) and dimethyl carbonate (entry 3), and dimethyl carbonate was therefore taken forward for optimisation due to its "green" credentials.[22]

With an eco-friendly solvent in hand, our next aim was to significantly reduce the reaction times. To this end, the gold-catalysed iododeboronation of arylboronic acid **1b** was investigated under various times (2–5 min), temperatures (70–100 °C) and equivalents of NIS (Table 2). As shown in Table 2, higher temperatures (entry 1 vs. entry 2) and a lower equivalent of NIS (entry 3 vs. 5) reduces the amount of unwanted over-iodination product **4b**. The conditions shown in entry 6 (90 °C, 5 min, 1.0 equiv. NIS) produced the best compromise between yield and **3b**:**4b** selectivity, and it was therefore taken forward as optimal conditions.

Table 1. Solvent and Temperature Screen.

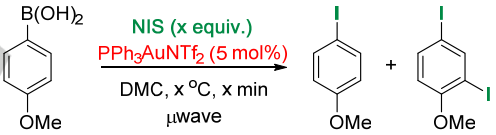


1a **3a** **4a** **2a**

Entry[a]	Solvent	Temp. (°C)	Yield (%)[b]	**3a:4a:2a**[c]
1	$CDCl_3$	70	60	86:14:0
2	$CDCl_3$	90	77	93:7:0
3	DMC[d]	90	80	93:7:0
4	Toluene	90	77	59:23:18
5	THF	90	50	93:7:0
6	Acetone	90	21	Complex mixture of products
7	Dioxane	90	80	87:13:0
8	Water	90	-	Mainly **2a**

[a] Reaction carried out on 0.1 mmol scale. Solvents are not anhydrous. [b] Combined yield of **3a**+**4a**+**2a**. [c] Determined by ^{1}H NMR analysis. [d] Dimethyl carbonate.

Table 2. Temperature, Time and Equivalents Screen.



1b **3b** **4b**

Entry[a]	Temp. (°C)	Time (min.)	NIS Equiv.	Yield (%)[b]	**3b:4b**[c]
1	70	10	1.1	93	75:25
2	90	10	1.1	100	86:14
3	100	5	1.1	91	91:9
4	100	2	1.1	99	90:10
5	100	5	1.0	88	95:5
6	**90**	**5**	**1.0**	**92**	**95:5**

[a] Reaction carried out on 0.1 mmol. [b] Combined yield of **3b**+**4b**. [c] Determined by ^{1}H NMR analysis.

It is worth noting that the reaction is not sensitive to air or moisture and is thus a very practical as well as fast procedure. In fact, wet solvent enhances the yields for the gold-catalysed reaction (see Supporting Information).[13]

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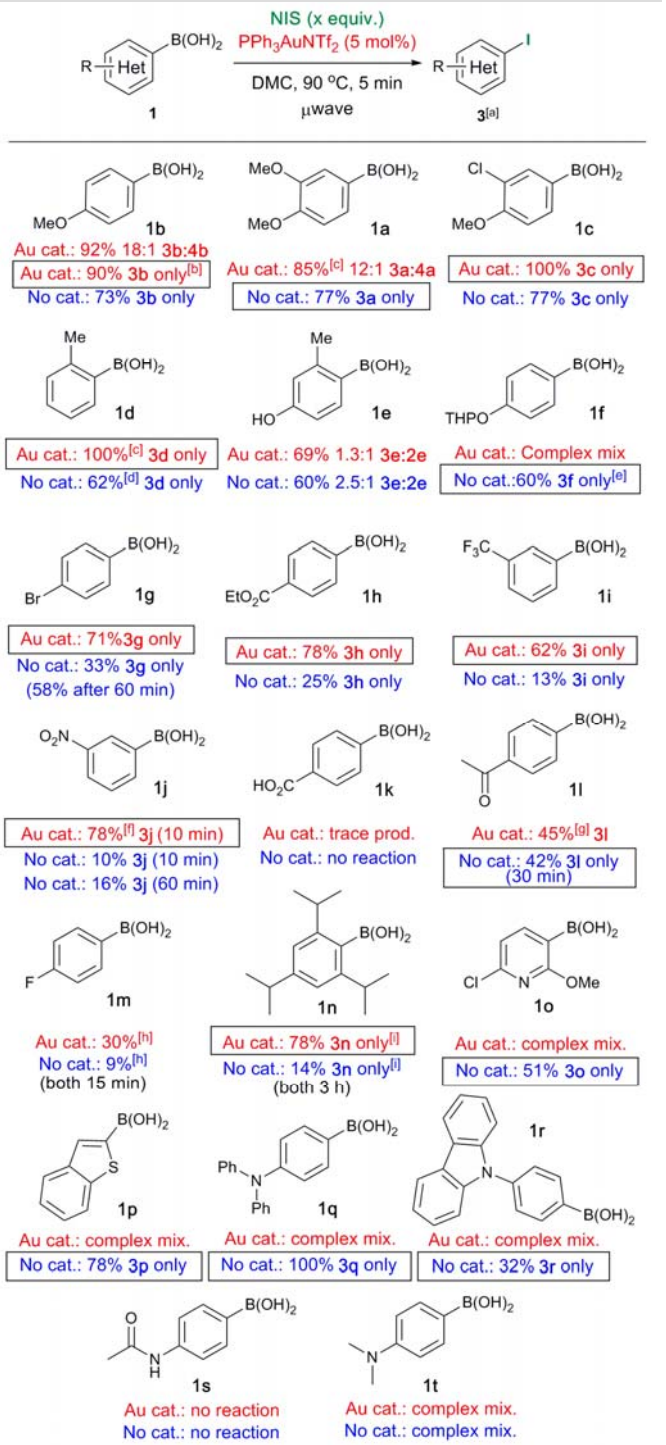
Next, the substrate scope of the gold-catalysed reaction as well as the uncatalysed reaction was investigated using these new conditions (Table 3). Both the catalysed and uncatalysed reactions were run concurrently for all substrates to ascertain whether there are situations where gold catalysis offers advantages over the uncatalysed reaction and vice versa. For strongly electron-rich arylboronic acids **1a**–**1b**, the catalysed reaction gives a better yield but often poorer selectivity (18:1, 12:1 for **1a** and **1b** *vs.* >20:1 uncatalysed) for the desired *ipso*-iodination (**3**) *vs.* overiodination (**4**) products. However, note that thermal heating can be used to improve the selectivity (>20:1 **3b**:**4b**). Over-iodination is not a problem with less electron-rich substrates (**1c**–**1l**). This trend is as expected, as very electron-rich aryls are more likely to undergo competitive electrophilic aromatic substitution than the less electron-rich counterparts. With mildly electron-rich arylboronic acid **1d**, the gold-catalysed reaction is significantly more efficient (100% vs. 62%) and clean (inseparable side-product observed in uncatalysed reaction). However, the presence of a phenolic proton (**1e**) causes both catalysed and uncatalysed reactions to produce a significant amount of protodeboronated side-product (**2e**).[24] THP protected phenol **1f**, however, is tolerated in the uncatalysed reaction with the acid-sensitive THP left untouched during the iododeboronation reaction to yield **3f** (60%). Therefore, for electron-rich boronic acids, the gold-catalysed reaction generally provides higher yields, but the lower yielding uncatalysed reaction may arguably still be preferred due to cheaper cost.

A different pattern, however, emerges for electron poor and sterically demanding arylboronic acids (Table 3, **1g**–**1l**). These deactivated substrates react extremely sluggishly in the uncatalysed reaction and provide poor yields even after extended reaction times. To our delight, gold catalysis provides a significant improvement in yields as well as reaction times. For example, **3g**, **3h** and **3i** are formed in 71%, 78% and 62% respectively, after 5 min in the presence of PPh_3AuNTf_2, whereas only 33%, 25% and 13% yields are obtained without catalyst. The comparison is even starker with the nitro-substituted substrate **1j**: product **3j** is furnished in 78% yield after 10 min under gold catalysis, whereas the uncatalysed reaction provided a poor 10% yield. Extending the reaction time to 60 min does not significantly improve the yield of **3j** without catalyst (16%). The free carboxylic acid, however, is not tolerated (**1k**) and it appears that acidic protons (e.g. **1e**, **1k**) are generally detrimental to the reaction. While acetyl functionality in **1l** is tolerated in the uncatalysed reaction (albeit yielding **3l** in a modest 42% after 30 min), the faster gold-catalysed reaction yields a 1:1 ratio of the desired **3l** as well as undesired α-iodination product. The fluoro-substituted arylboronic acid **1m** reacts sluggishly and produces a significant amount of homocoupling product (4,4'-difluoro-1,1'-biphenyl) in both the gold-catalysed and uncatalysed reactions. Pleasingly, the extremely sterically demanding substrate **1n** iododeboronates smoothly under gold catalysis to produce **3n** in a good 78% yield (vs. 14% uncatalysed), albeit with a longer 3 h reaction time to account for the steric hindrance. For electron-poor and sterically hindered arylboronic acids, the uncatalysed reaction is generally

Table 3. Substrate scope.



[a] Isolated yields. [b] Thermal heating. [c] Temperature increased to 100 °C. [d] Inseparable unidentified side product observed. [e] 4 Å molecular sieves added. [f] 50% yield after 5 mins. [g] 1:1 ratio of **3l** and α-iodination product. [h] 1:1 **3k**:homocoupled product 4,4'-difluoro-1,1'-biphenyl. [i] Carried out with 1.1 equiv. of NIS.

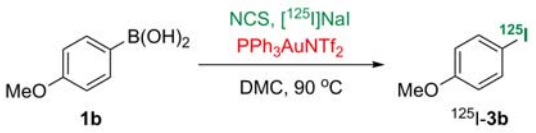
poor yielding and extremely sluggish, and gold-catalysis can be used to significantly improve the reaction times and yields.

The opposite pattern emerges for heterocyclic and *N*-containing arylboronic acids (Table 3, **1o**–**1r**). Both heterocyclic boronic acids **1o** and **1p** produced a complex mixture of products under gold-catalysis, but iododeboronated cleanly under uncatalysed conditions in 51% and 78% respectively. Similarly, amine substituted arylboronic acids **1q** and **1r** provided a complex mixture under gold catalysis, but iododeboronated under uncatalysed conditions (100% **3q** and 32% **3r**). The complex mixture under gold catalysis is most likely due to over-iodination[20a] of these highly electron-rich aryls. Unsurprisingly, therefore, the more electron rich amine in **1t** results in a complex mixture, but this time under both the catalysed and uncatalysed procedures. The amide functionality in **1s** seems to shut the reaction down under both conditions. Although there are some limitations to the type of *N*-substituents that are tolerated, in general, the uncatalysed procedure is preferred for heterocyclic and *N*-substituted arylboronic acids.

As our studies demonstrated that gold-catalysed *ipso*-substitution of arylboronic acids using NIS could be performed rapidly and efficiently under mild conditions, we were interested in investigating the application of this method for the radioiodination of arenes. Radioactive iodine is normally supplied in the form of NaI, and so initial studies involved the iodination of 4-methoxybenzeneboronic acid (**1b**) using NIS, prepared *in situ* by pre-stirring NaI and *N*-chlorosuccinimide (NCS).[25] Under the standard gold-catalysed conditions this gave **3b** in 80% yield. These general conditions were then investigated for the radioiodination of **1b**, where radiochemical yields (RCY) were determined by radio-HPLC analysis of the crude product.[26] At micromole scale, the gold-catalysed *ipso*-substitution reaction was easily modified for radioiodination. Using [^{125}I]NaI (4–6 MBq solution in water) as the limiting reagent, gave ^{125}I-**3b** in 63% RCY (Table 4, entry 1). On extending the reaction time, 20 minutes was found to be optimal and gave a quantitative RCY of ^{125}I-**3b** (entry 3). The corresponding radio-HPLC for this transformation showed a particularly clean reaction with no other radiolabelled by-products (Figure 1). It should be noted that radioiodination can be done without the use of PPh_3AuNTf_2. However, in parallel with the cold studies, the thermally-mediated reaction is less efficient and gave only 47% RCY after 20 minutes (entry 4).

In performing radioiodination reactions, a rapid transformation that produces the product cleanly is crucial for generating the target radiolabelled compound in high radiochemical purity, radioactive yield and molar activity. Therefore, the use of gold-catalysis for these radioiodinations rather than the thermally-mediated reaction is particularly advantageous, as the reactions are faster, more efficient and easier to purify.

Table 4. Optimisation of gold-mediated radioiodination of **1b**.[a]



Entry	Time (mins)	PPh_3AuNTf_2 (mol%)	RCY (%)
1	5	50	63
2	15	50	96
3	20	50	100
4	20	0	47

[a] All reactions were performed using a 4–6 MBq solution of [^{125}I]NaI in water (0.01 mL). Reactions were performed under thermal heating conditions in a sealed tube.

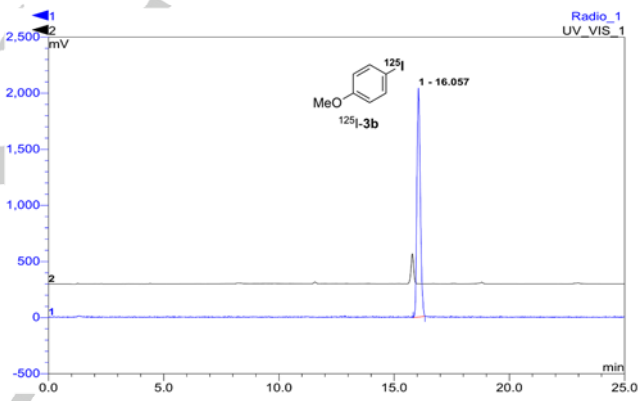
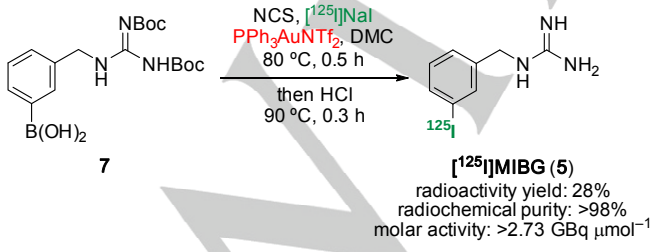


Figure 1. Chromatograph obtained by analytical radio-HPLC (blue) of the reaction mixture from the radioiodination of **1b**, showing a quantitative yield of radioiodide incorporation. An overlay of the UV-Vis HPLC trace (black) of **3b** is also shown.

The scope of the optimised gold-mediated radioiodination reaction was next examined for a selection of arylboronic acids (Table 5). Under these conditions, electron-rich and electron-deficient arenes with various substitution patterns were found to be substrates for the reaction and gave the ^{125}I-labelled products in excellent RCY (92–100%). Only two arylboronic acids required further optimisation. Initial reaction of ethyl ester and trifluoromethyl analogues **1h** and **1i** under the optimised conditions (90 °C, 20 mins) produced radio-HPLC traces with several radiolabelled by-products. Repeating the reactions at a lower temperature of 80 °C allowed a cleaner transformation and while a slightly longer reaction time was required (30 mins), this gave the products ^{125}I-**3h** and ^{125}I-**3i** in excellent RCY. Only sterically hindered boronic acid **1n** showed no reaction under these conditions, even after 30 mins. As observed for the cold iododeborination of this compound, a significantly longer reaction time is likely required for this substrate.

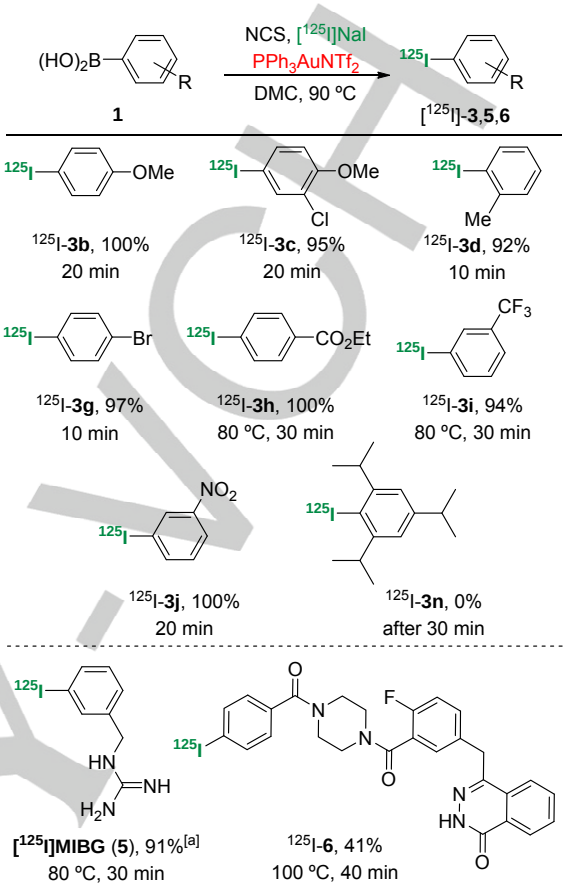
Having shown that this transformation could be used for the radio-iododeboronation of simple arylboronic acids, application of the method for radiolabelling of biologically active compounds and the generation of imaging agents was next investigated (Table 5). The first target was *meta*-[^{125}I]iodobenzylguanidine (MIBG, **5**). In ^{123}I-form, MIBG is a commercially available radiopharmaceutical used for the SPECT imaging of human norepinephrine transporter-expressing cancers.[27] In the ^{131}I-form, MIBG is used for targeted radionuclide therapy.[28] A di-Boc-protected boronic acid analogue of MIBG was efficiently prepared in one-step by coupling of 3-(aminomethyl)benzeneboronic acid with di-Boc-protected 1*H*-pyrazole-1-carboxamidine.[29] After some optimisation, gold-mediated *ipso*-substitution of this arylboronic acid was found to be most effective at 80 °C and a reaction time of 30 min. This produced the corresponding ^{125}I-labelled compound in quantitative RCY. The reaction mixture was then treated with hydrochloric acid to remove the Boc-protecting groups and this gave [^{125}I]MIBG (**5**) in 91% RCY over the two-steps. Gold-mediated radio-iododeboronation was also effective for the preparation of phthalazinone **6**, a nanomolar inhibitor and SPECT imaging agent of poly(ADP-ribose) polymerase-1 (PARP-1), a diagnostic and therapeutic target for cancer.[30] Despite the complex structure of this substrate, containing amide and *N*-heterocycle moieties, gold-mediated radio-iododeborination was achieved using a reaction temperature of 100 °C and gave ^{125}I-**6** in 41% RCY.[31]

Following these results, we decided to validate the radio-iododeboronation method with the synthesis and purification of [^{125}I]MIBG (Scheme 2). Boronic acid **7** was treated with [^{125}I]NaI (10.16 MBq) using the previously optimised gold-mediated *ipso*-radioiodination reaction. Following removal of the Boc-protecting groups under acidic conditons and HPLC purification, [^{125}I]MIBG (**5**) was isolated in 28% radioactivity yield. The radiochemical purity of **5** was measured as >98%, with a molar activity of >2.73 GBq μmol^{-1}. Identification of the product was confirmed by HPLC, with co-elution of a sample of unlabelled MIBG. These results compare favourably with other approaches for the preparation of radiolabelled MIBG and thus, demonstrates the potential of this methodology for widespread use in generating radioiodine labelled tracers.[9a, 9b, 27a, 32]



Scheme 2. Radiosynthesis of [^{125}I]MIBG (**5**).

Table 5. Scope of gold-mediated radio-iododeboronation.



[a] After ^{125}I-iododeborination, a second step involving HCl-mediated removal of the Boc-protecting groups was performed to generate [^{125}I]MIBG.

Conclusions

Fast, air and water stable *ipso*-iododeboronation reactions in the presence of NIS and the green solvent dimethylcarbonate have been developed. The gold-catalysed reaction is significantly preferred for electron-deficient and sterically hindered arylboronic acid substrates, where the uncatalysed reaction provides very poor yields. For electron-rich boronic acids, the gold-catalysed reaction also provides much higher yields. Heterocyclic and *N*-containing arylboronic acids, however, react more favourably under uncatalysed conditions. Moreover, the reaction is tolerant of halogens (Br and Cl), and is therefore complementary to the commonly used halogen exchange method to form aryl iodides.[33] The gold-catalysed iododeboronation reaction was highly amenable for ^{125}I-labelling of arenes, which constitutes the first example of an application of homogenous gold catalysis to selective radiosynthesis. Under optimised radiochemistry conditions, both electron-rich and electron-poor aryl boronic acids were rapidly converted to the radioiodinated products in excellent RCY. This general method was validated with the effective synthesis and isolation of

radioiodinated MIBG, a tracer used for the imaging of cancer. Current studies are investigating the extension of this methodology for the preparation of existing and novel SPECT imaging agents.

Experimental Section

General procedure A: Gold(I)-catalysed reactions

Boronic acid **1** (0.10 mmol, 1.0 equiv.), NIS (0.10 mmol, 1.0 equiv.), PPh_3AuNTf_2 (3.7 mg, 5 mol%) and DMC (0.4 mL) were added to a microwave tube and heated under microwave irradiation at 90 °C for 5 minutes. The resulting solution was passed through a silica plug and washed with 20:1 hexane/ether to yield product **3**. The crude product was purified by column chromatography as needed.

General procedure B: No catalyst

Boronic acid **1** (0.10 mmol, 1.0 equiv.), NIS (0.10 mmol, 1.0 equiv.) and DMC (0.4 ml) were added to a microwave tube and heated under microwave irradiation at 90 °C for 5 minutes. The resulting solution was passed through a silica plug and washed with 20:1 hexane/ether to yield product **3**. The crude product was purified by column chromatography as needed.

General procedure C: Radioiodination

To a solution of *N*-chlorosuccinimide (0.50 mg, 3.9 µmol) in DMC (0.1 mL) was added a 4–6 MBq solution of [^{125}I]NaI in water (0.01 mL). A solution of 4-methoxybenzeneboronic acid **1b** (0.60 mg, 3.9 µmol) and $Ph_3PAuNTf_2$ (3.0 mg, 2.0 µmol) in dimethylcarbonate (0.1 mL) was added and the reaction mixture heated to 90 °C for 20 minutes. The reaction mixture was then removed by syringe and diluted with a 1:1 mixture of acetonitrile and water (0.5 mL). Analysis of this solution by analytical radio-HPLC showed a radiochemical yield of 100%.

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Keywords: gold catalysis • iodination • radiochemistry • radioiodination • radiopharmaceuticals

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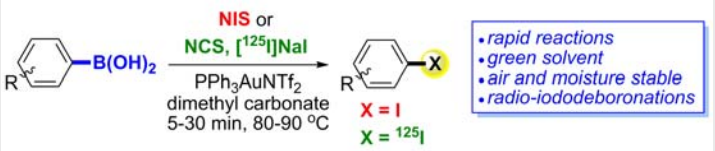

Dr. Stacey Webster, Kerry M. O'Rourke, Conor Fletcher, Dr. Sally L. Pimlott, Dr. Andrew Sutherland and Dr. Ai-Lan Lee**

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Rapid Iododeboronation with and without Gold Catalysis: Application to Radiolabelling of Arenes

A rapid, air- and moisture-stable *ipso*-iododeboronation procedure using NIS has been developed in the non-toxic and green solvent dimethyl carbonate. The procedure was utilised for the rapid and highly efficient gold-catalysed radio-iododeboronation of arenes.