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Copper-Mediated Radiobromination of (Hetero)Aryl Boronic Pinacol Esters

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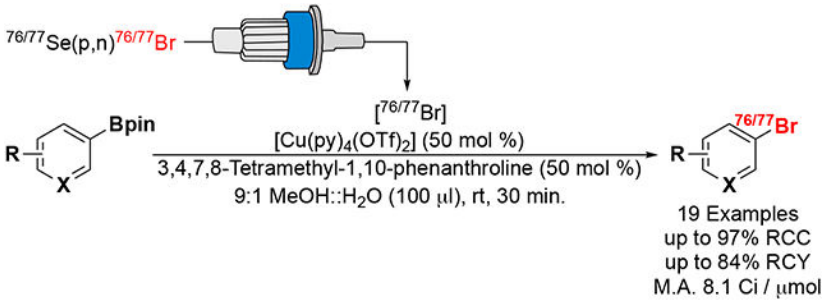
Abstract

A copper-mediated radiobromination of (hetero)aryl boronic pinacol esters is described. Cyclotron-produced [$^{76/77}$Br]bromide was isolated using an anion exchange cartridge, wherein the pre-equilibration and elution solutions played a critical role in downstream deboro-bromination. The bromination tolerates a broad range of functional groups, labeling molecules with ranging electronic and steric effects. Bologically active radiopharmaceuticals were synthesized, including two radiobrominated inhibitors of poly ADP ribose polymerase, a clinically relevant chemotherapeutic target for ovarian, breast, and prostate cancers.

Graphical Abstract



INTRODUCTION

Nuclear medicine is a multidisciplinary clinical specialty utilizing radiopharmaceuticals for the detection, assessment, and treatment of disease. A critical research area in the field focuses on the incorporation of radioactive isotopes into small and large

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Author Contributions

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Supporting Information

Supporting methods and reagents, analytical data, and figures. (PDF)

biological molecules for diagnostic and therapeutic purposes in neurology, cardiology, and oncology. Within nuclear medicine, the theranostic approach applies chemically matched diagnostic and therapeutic radiopharmaceuticals with interchangeable radioisotopes. This radiation oncology paradigm is becoming standard of care as highlighted by the recent FDA approvals of diagnostic/therapeutic radiopharmaceuticals Netspot[1]/Lutathera[2] for neuroendocrine tumors and Pylarify[3]/Ga 68 PSMA-11[4]/Pluvicto[5] for prostate cancer. The predominant methods for chemically labeling radiopharmaceuticals are through direct small molecule incorporation of organic radionuclides[6-8] or the incorporation of radiometals via chelators (DOTA, NOTA, etc.) coupled to targeting vectors.[9-11] Of the former of these methods, radiohalogenation has proven particularly useful, exemplified through the synthesis of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) used in positron emission tomography (PET) diagnosis, staging, and monitoring treatment response of various oncologic diseases.

Incorporation of halogens into (hetero)aryl structural motifs has become prevalent in recent years for utility in radiopharmaceuticals used for both diagnostic imaging (^{18}F, ^{76}Br, ^{124}I) and therapeutic treatment (^{77}Br, ^{82}Br, ^{123}I, ^{125}I, ^{131}I, ^{211}At).[7,12,13] Radiobromine is unique within the halides as it has several isotopes (^{76}Br, ^{77}Br, ^{82}Br) with suitable half-lives and radioactive decay pathways including positron emission (β^+) used in PET imaging (^{76}Br, $t_{1/2}$ = 16.2 h), electron capture (EC) leading to Meitner Auger electron emission (^{77}Br, $t_{1/2}$ = 57.0 h), and beta (β^-) emission (^{82}Br, $t_{1/2}$ = 35.3 h) for targeted radionuclide therapy (TRT).[14] Meitner Auger electrons are low energy (eV – keV) electrons that are produced in a cascade fashion following EC decay. These electrons are of significant interest due to their high linear energy transfer (LET), dissipating their energy within a short distance in tissue (nm – μm) and delivering low off-target radiation dose.[15] However, due to difficulty in the production/isolation or procurement of ^{76,77,82}Br, methods for incorporating radiobromine into medicinal chemical products have not seen the same explosive growth as that of radiofluorine and radioiodine to date. Recently, we reported the improved cyclotron production and nuclear chemical isolation of ^{76,77}Br resulting in the robust and reproducible production of clinical quantities of ^{76}Br and pre-clinical quantities of ^{77}Br.[16]

With the advances in transition metal mediated couplings of ^{18}F, $^{12x/131}$I, and ^{211}At to (hetero)aryl electrophiles (Scheme 1) and the improvement in production and isolation of $^{76/77}$Br, we sought to investigate the translation of these radiochemical methods to bromination. Pioneered by the Gouverneur group, copper-mediated radiofluorination of (hetero)aryl boronic esters[17] / acids[18] has become a versatile method due to its efficiency, extensive functional group tolerance, and low toxicity of boronic esters / acids.[19] Furthermore, this work has been adapted for the incorporation of ^{123}I[20] and ^{211}At[13] by the Gouverneur and Mach groups respectively. While copper-mediated coupling of boronic pinacol esters[16,21,22] / acids[22,23] has facilitated incorporation of ^{77}Br into a small selection of molecules, a systematic investigation of a general procedure for labeling (hetero)aryl boronic pinacol esters with radiobromine has yet to be reported. One of the challenges of these methods has been highlighted in radiofluorination wherein the cyclotron-produced [^{18}F] fluoride (aq) must be concentrated through the use of a quaternary methyl ammonium (QMA) cartridge prior to deborylfluorination radiochemistry. It was observed that the presence of certain bases and phase transfer catalysts commonly used in liberating ^{18}F from the QMA cartridge had detrimental effects to downstream labeling, especially when

using transition metal mediated coupling methods.[24] This manuscript investigates the effect $^{76/77}$Br QMA cartridge trap / release conditions has on downstream copper-mediated deboro-bromination, the radiochemistry's tolerance to functional groups commonly found in medicinal compounds, the labeling of a wide substrate scope, and finally its application in the production of several theranostic radiopharmaceuticals.

RESULTS AND DISCUSSION

Recent advances in the production and isolation of ^{76,77}Br have also brought challenges, including the dilution of ^{76,77}Br in large volumes of water (~40 mL), requiring a QMA cartridge trap / release step prior to use in radiobromination reactions. Recent work investigating optimal QMA trapping and releasing conditions for aliphatic[25,26] and aryl[24] radiofluorination chemistry guided our studies with $^{76/77}$Br. Initially, $NaHCO_3$ (10 mL, 0.5 M aq) followed by deionized water (10 mL) was used to pre-equilibrate the QMA cartridge leading to near quantitative $^{76/77}$Br trapping (99 ± 0.5%). Subsequent $^{76/77}$Br elution with K_2CO_3 (0.8 mL, 0.1 mM) led to good recovery (> 95%); however, after solvent evaporation, the resulting $^{76/77}$Br demonstrated low radiochemical conversion (RCC) (3 ± 2%, n = 2) under our general copper-mediated deboro-bromination reaction conditions (see Scheme 2).

To circumvent the use of Na_2CO_3 as releasing agent and transition to a volatile base, NH_4OH (800 μL, 0.1 M) was used for elution (Table 1, entry 6); however, only 1% of the $^{76/77}$Br eluted from $NaHCO_3$-equilibrated QMA cartridges. With the recent report by Scott *et al.*[24] demonstrating greater ^{18}F elution from sulfate equilibrated QMA cartridges, we investigated Na_2SO_4 as equilibration agent. Equilibrating with Na_2SO_4 (10 mL, 0.5 M) and eluting with NH_4OH led to excellent $^{76/77}$Br trapping (96 ± 4%) and release (93 ± 7%) efficiencies (Table 1 entry 1). The $^{76/77}$Br eluted under these conditions led to improved but sporadic (5 – 80%) downstream deboro-bromination RCCs (reaction conditions in Scheme 3 forming compound **21**).

To determine if the releasing agent was causing the sporadic reaction yields, we screened a variety of volatile organic bases to elute ^{77}Br from Na_2SO_4 equilibrated cartridges (entries 2 – 5). High levels (> 98%) of release were seen in all cases, however labeling was challenging (<5% RCC, n = 1 for elution conditions of Table 1, entry 4, reaction conditions in Scheme 2). We hypothesize this is due small amounts of sulfate (SO_4^{2-}) being released off the QMA cartridge and complexing with the copper (Cu^{2+}), thereby inhibiting catalytic turnover. This phenomenon has also been observed in copper-mediated radiofluorination of aryl boronic pinacol esters.[24]

We then screened the organic volatile base elution agents for releasing $^{76/77}$Br from $NaHCO_3$ equilibrated QMA cartridges (entries 7 – 11). Higher pKa releasing agents resulted in more effective elution of ^{77}Br, in agreement with radiofluoride trends observed by Scott *et al.*[24] Eluting the QMA cartridge with NMe_2H (0.8 mL) lead to good $^{76/77}$Br releasing efficiency (86 ± 18%) and increasing the amount of NMe_2H (0.8 to 1.6 mL) led to improved, more consistent elution (94 ± 6%). Following NMe_2H elution from $NaHCO_3$ equilibrated QMA cartridges, $^{76/77}$Br reacted with high, consistent copper-mediated deboro-bromination RCC (93 ± 5%, n = 3, reaction conditions in Scheme 2) of our standard benzaldehyde-Bpin

precursor. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was also an effective elution agent from $NaHCO_3$ equilibrated cartridges (100%, entry 11); however, the resulting $^{76/77}$Br was unreactive in copper- deboro-bromination reactions, likely due to the lack of volatility of the ~80 μmol of DBU elution agent. Thus, optimal QMA trap and release conditions are summarized by Table 1, entry 10, highlighted in red.

Upon determining optimal conditions for preparation of reactive [$^{76/77}$Br]bromide, we sought to investigate the tolerance of the copper-mediated deboro-bromination reaction to various functional groups that are found in a range of radiopharmaceutical targets using the catalyst system (i.e. $[Cu(py)_4(OTf)_2]$ / 3,4,7,8,-tetramethyl-1,10 phenanthroline) reported by Mach for radioiodination/astatination of aryl-boronic pinacol esters.[12] Inspired by Gouveneur *et al.*'s de-risking approach for radiofluorination,[27] we screened the functional groups in Scheme 2 by adding a 1:1 molar ratio of a functional-group-containing inhibitor molecule to our standard benzaldehyde **1** bromination reaction. It is hypothesized that if an inhibitor has an adverse effect on the standard radiolabeling, then radiopharmaceutical products containing this chemical functionality would similarly have low yield. Compared to radiofluorination, radiobromination is more tolerant to functional group variability.[27] Secondary amines **3a** and **3b** did not inhibit the reaction with $^{76/77}$Br RCCs of 94 ± 4% and 97 ± 3%, respectively, comparable with the RCC of the non-inhibited reaction (93 ± 5%).

Interestingly, a 1:1 molar ratio of DBU **3c** did not inhibit $^{76/77}$Br RCC (92.1 ± 0.2%) contradicting that when used as a QMA elution agent and present in an 80:1 molar ratio, DBU fully inhibits radiobromination (vide supra). **3e – 3h**, common functional groups in a variety of oncologic radiotracers, such as small molecule chemotherapeutic inhibitors of poly ADP ribose polymerase (PARP), did not inhibit the reaction leading to 87 – 90% RCC. Deboro-bromination was significantly inhibited by addition of 2-mercaptobenzoic acid (**3i,** 38 ± 10% RCC). We postulate this is due to bidentate coordination to copper through the carboxylic acid and aryl thiol thereby inhibiting catalytic turnover. Non-bidentate chelating thiols (**3j** and **3k**) did not significantly inhibit the radiobromination with (91.5 ± 0.3%) and (92.5 ± 2.5%), respectively.

To verify the inhibitor study, we labeled a range of substrates containing various structural motifs and electronic functional groups (Scheme 3). Initially, aryl-Bpin substrates were investigated (**4** – **13**), ^{77}Br-aryl esters **4** and **5** labeled efficiently suggesting that labeling the para or meta positions does not impact deboro-bromination. ^{77}Br-Benzoic acid **6** (97 ± 1%) was labeled in the para position with good RCC, however ^{77}Br-aniline **7** (54 ± 1%), ^{77}Br-ethynyl benzene **8** (67.5 ± 0.5%), and ^{77}Br-benzo-nitrile **9** (85.5 ± 0.5%) showed lower RCC's, which could be due to their coordination to the copper catalyst. Products **6** – **9** are important because they can be utilized in the subsequent aryl-radiobromination of amino acids and peptides via amide couplings (**6**, **7**) and click chemistry (**8** and **9**). The thiazole-based extended ^{77}Br-aryl system **11** labeled efficiently (90.5 ± 0.5% RCC) as predicted through the inhibitor study, but the similarly electron-rich ^{77}Br-benzo-oxazole **12** had mixed results with 75 ± 15% RCC. Surprisingly, ^{77}Br-phthalimide **13** only labeled in 17 ± 6%; we hypothesize this is due to the poor solubility of the precursor and subsequent product in the 9:1 MeOH/H_2O reaction solvent.

Hetero(aryl) substrates containing nitrogen were subsequently examined. The electronically stabilized heterocyclic systems: ^{77}Br-dimethylamino-pyrimidine **14** and ^{77}Br-isoquinoline **15** showed good labeling with RCC's of 89 ± 1% and 89.5 ± 0.5% respectively. The labeling position was significant when comparing ^{77}Br-chloro-pyridine products, with bromination at the meta (**17**, 85 ± 2%) position showing higher RCC than at the ortho (**18**, 9 ± 2%) position. Interestingly, electron deficient ^{77}Br-heterocycles (**16** – **18**) did not strictly follow radiofluorination trends where these radiofluorides often required higher quantities of catalyst loading to impart higher labeling efficiencies.[17]

We applied our optimized method to the preparation of three radiotracers with biological application for the diagnosis and therapy of prostate (**19**), ovarian, and other cancers (**20** and **21**), shown in Scheme 4. Initially our focus centered on synthesizing and labeling a derivative of the ^{18}F-DCFPyL (Pylarify) radioligand, used for the imaging of metastasis and recurrence in prostate cancer patients.[28] We successfully labeled the Bpin precursor of the radiotracer's tert-butyl ether-protected benzyl analogue with ^{77}Br under our optimized conditions with 31 ± 4% RCC and non-decay corrected isolated radiochemical yield (n.d.c. RCY) of 23 ± 2% (n = 2). We also focused on derivatives of clinical chemotherapeutic inhibitors of the nuclear PARP proteins, which are involved in the cellular single-stranded DNA damage response mechanism.[29] Pairing this biological mechanism with targeted Meitner-Auger electron emitting radionuclides is of significant interest because of its over-expression in a wide variety of cancers and the biological mechanism that brings, and in some cases traps,[30] the radiopharmaceutical within nanometers of the DNA.[31] Recent preclinical studies have investigated Meitner-Auger electron emitting radionuclide-labeled PARP inhibitors for the treatment of neuroblastoma,[32] glioblastoma,[33] ovarian,[34] breast,[35] and colon cancer.[36] The olaparib derivative **20** was successfully labeled from its Bpin precursor with RCC of 90 ± 3% and isolated RCY of 76 ± 1% (n = 2). A rucaparib derivative **21** was labeled from its Bpin precursor leading to high RCC (89 ± 4%, n = 7). Subsequent isolation and formulation of **21** was conducted leading to good RCY (74 ± 7%, n = 7) and high molar activity (350 ± 210 GBq / μmol for [^{77}Br]**21**, n = 6; ~700 GBq / μmol for [^{76}Br]**21**, n =1). Syntheses starting with ~400 MBq $^{76/77}$Br produced 300 MBq of [^{77}Br]**21** and 280 MBq of [^{76}Br]**21** at end of synthesis (EOS). This production scale is suitable for pre-clinical therapeutic (with ^{77}Br) and clinical diagnostic (with ^{76}Br) studies. Current investigations are underway to translate this method to an automated synthesis module for routine production. Preliminary data investigating the dependence of reactant concentration, time, and temperature on [$^{76/77}$Br]**21** optimized reaction conditions is shown in the supporting information (SI Figure S5 - S7) which we hope to use to streamline the translation of this work into an automated synthesis module.

CONCLUSION

In conclusion, this work presents a reproducible, high yielding QMA-cartridge based method for preparing reactive [$^{76/77}$Br]bromide for late-stage nucleophilic copper-mediated coupling to (hetero)aryl-boronic pinacol esters. This manuscript utilizes the approach to de-risking downstream labeling by conducting a competitive study of common functional groups seen in drug targets. The radiobromination method was observed to be amenable to

a variety of aryl and heteroaryl compounds with varying steric and electronic substituents. Compared with previous deboro-radiobromination reports[22,23], the method is effective with milder conditions, less precursor, and more radioactivity, as evidenced over a wide substrate scope. The utility of the developed methodology is demonstrated by synthesis of three radiobrominated medicinal targeted molecules with moderate to high yields and theranostic potential.

EXPERIMENTAL SECTION

Dry [$^{76/77}$Br]bromide was dissolved in a mixture of [$Cu(py)_4OTf_2$] / 3,4,7,8-tetramethyl-1,10-phenanthroline (50 mol%, prepared fresh as 50 mM stock in MeOH) and an aryl Bpin precursor (1 μmol, prepared fresh as 12.5 mM stock in MeOH) in 9:1 MeOH/H_2O (100 μL). The solution was stirred for 30 min at room temperature. Upon completion the solution was diluted in water (10 mL) and passed through a preconditioned C18 Sep-Pak to trap the radiolabeled compound. The cartridge was rinsed with water (10 mL) and the radio labeled compound was eluted from the C18 Sep-Pak with subsequent additions of pure ethanol (0.5 mL) and water (0.5 mL). The combined load/rinse solution (~20 mL), elution solution (~1 mL), and eluted C18 cartridge were assayed with a radioactive dose calibrator (CRC-15R setting #120 for ^{77}Br, #690÷2 for ^{76}Br, Capintec). A crude radiochemical conversion (RCC) was calculated by dividing the activity of the elution solution by the total summed activity. The elution solution was then injected onto a preparative high performance liquid chromatography (HPLC, Kinetix XB-C18, 5 μm, 100 Å, 10 x 250 mm) using the elution conditions detailed in the supporting information. Purified RCC was calculated by multiplying the crude RCC by the radiochemical purity of the product peak determined by integration of radioactivity peak areas of the HPLC chromatogram. Non-decay corrected radiochemical yield (RCY) was determined by the quantity of radiolabeled product isolated from the preparative HPLC divided by the starting activity in the reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

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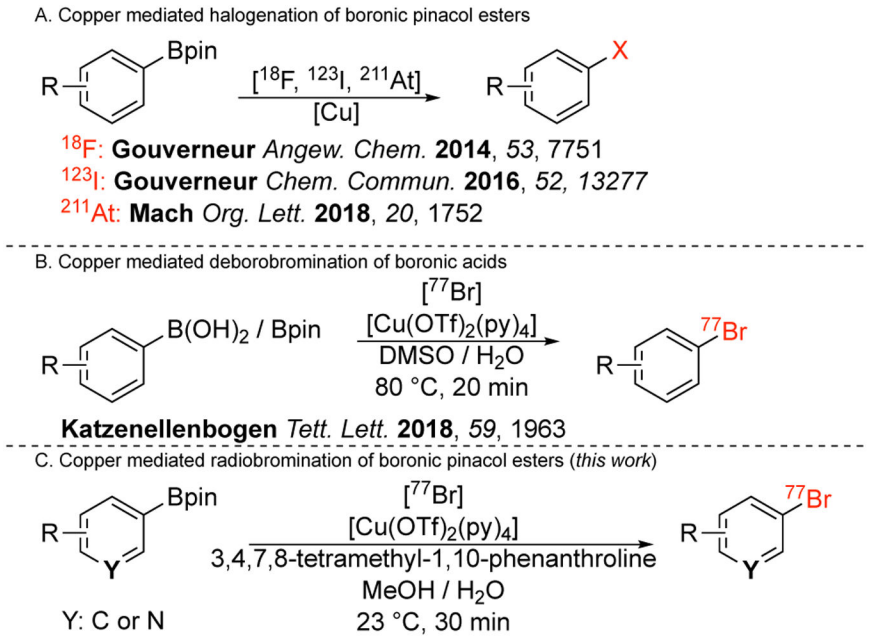
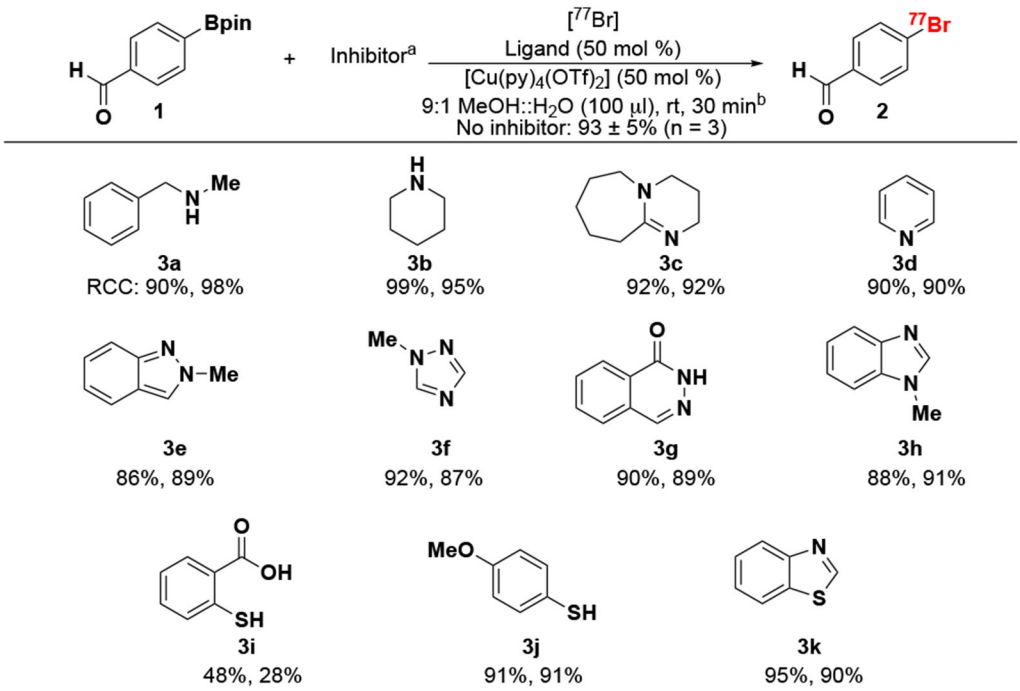


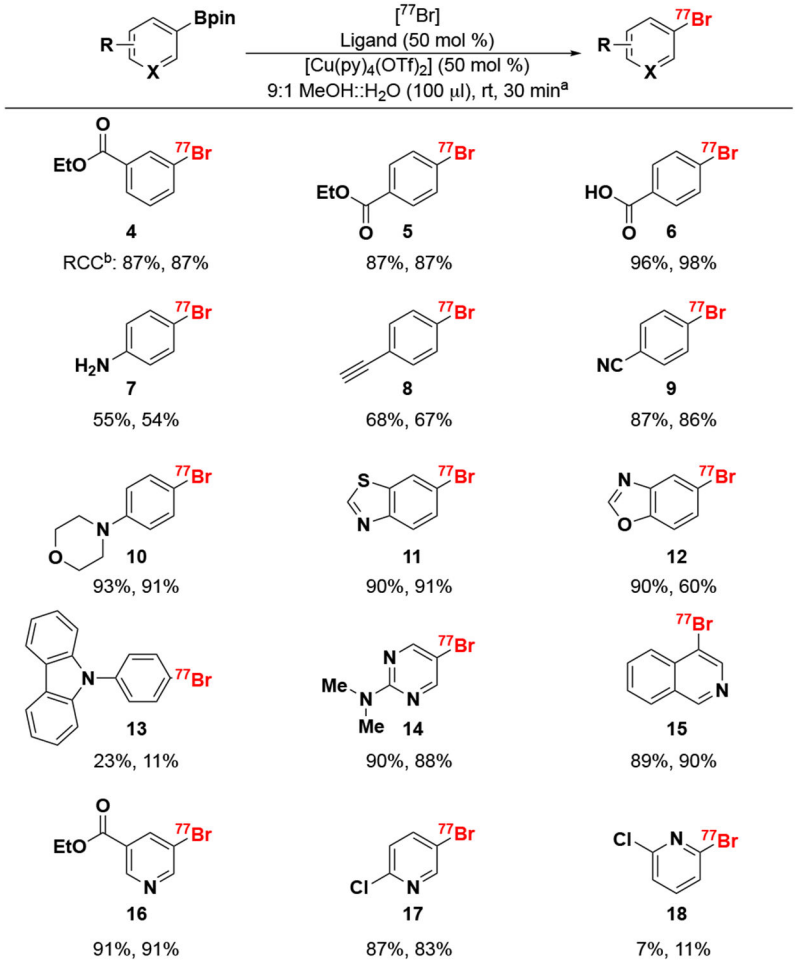
Scheme 1. Copper-mediated (hetero)aryl deboro-radiohalogenation reactions and references.



Scheme 2. Structural dependence of radiobromination on boronic pinacol esters via copper mediation

[a]Inhibitors were added 1:1 vs Bpin (1 μmol).

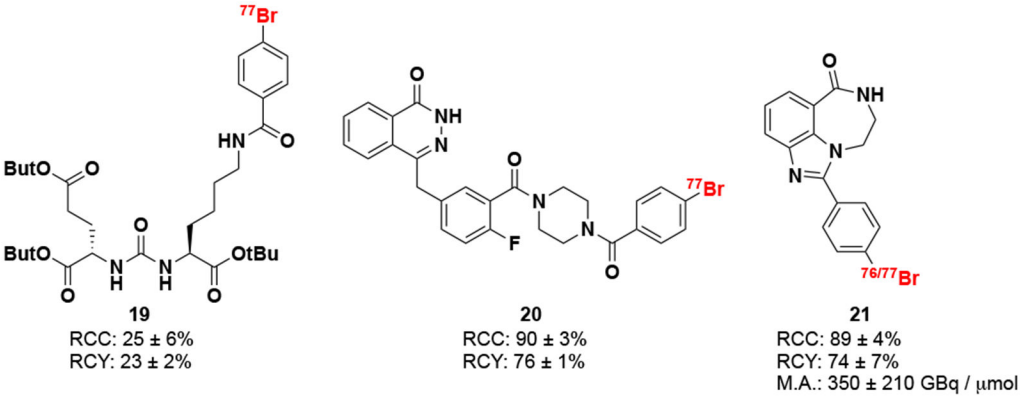
[b]Reactions were performed on a 7.5 MBq [^{77}Br]bromide with 1 μmol of **1**, 0.5 μmol of $[Cu(py)_4(OTf)_2]$ and 3,4,7,8-Tetramethyl-1,10-phenanthroline (Ligand) stirred in 100 μL of 9:1 MeOH::H_2O for 30 minutes at room temperature (rt). All reactions were conducted in duplicate and RCC's were calculated by activity trapped on C18 vs starting activity scaled by HPLC chromaogram rad peak integration to account for impurities.



Scheme 3. Substrate scope of copper-mediated deboro-bromination

[a]Reactions were performed with 7.5 MBq [^{77}Br]bromide, 1 μmol of boronic pinacol ester precursor, 0.5 μmol of [Cu(py)$_4$(OTf)$_2$], and 3,4,7,8-Tetramethyl-1,10-phenanthroline (Ligand) stirred in 100 μL of 9:1 MeOH::H_2O for 30 minutes at room temperature (rt).

[b]All reactions were conducted in duplicate and RCC calculated as activity trapped on C18 cartridge versus starting activity scaled by HPLC radioactivity detector chromatogram product peak area versus all peak areas to account for impurities.



Scheme 4. Radiobrominated biological targeting vectors

Reactions were performed on a 7.5 - 400 MBq scale with 1 μmol of boronic pinacol ester precursor, 0.5 μmol of $[Cu(py)_4(OTf)_2]$ and 3,4,7,8-Tetramethyl-1,10-phenanthroline stirred in 100 μL of 9:1 MeOH::H_2O for 30 minutes at room temperature. RCC's were calculated by activity trapped on C18 vs starting activity scaled by HPLC chromaogram radioactivity peak integration to account for impurities. RCY was calculated based on activity isolated from preperatory HPLC versus starting activtiy of the reaction.

Table 1.

QMA equilibration and elution solution investigation

QMA Equilibration Agent	$^{76/77}$Br Trapping (%)	Entry	QMA Elution Agent	pKa[a]	$^{76/77}$Br Eluted (%)	n
Na_2SO_4 (0.5 M)	96 ± 4 % n = 11	1	NH_4OH	9.23	93 ± 7	9
		2	Me_3N	9.8	99	1
		3	$MeNH_2$	10.66	98	1
		4	Me_2NH	10.73	100	1
		5	DBU	13.5	99	1
$NaHCO_3$ (0.5 M)	99 ± 0.5 % n = 9	6	NH_4OH	9.23	1	1
		7	Me_3N	9.8	5 ± 1	2
		8	$MeNH_2$	10.66	55	1
		9	Me_2NH	10.73	86 ± 18	8
		10	Me_2NH[b]	10.73	94 ± 6	6
		11	DBU	13.5	100	1

[a] pKa values in aqueous solution from CRC Handbook of Chemistry and Physics Online except DBU from Kaupmees *et al. Croat. Chem. Acta* 87(4): 385–395 (2014).

[b] Eluted with 1.6 mL of QMA releasing agent instead of the standard 800 μL. 0.1 M 1:1 MeCN / H_2O