



Boron Reagents for Divergent Radiochemistry

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Radiolabelled (bio)molecules have advanced many areas of science from fundamental biology to human health including applications in molecular imaging and more generally nuclear medicine. Today, the field of radiochemistry is rapidly expanding, a trend resulting from the increasing demand for labelled molecules necessary for diagnosis and to accelerate pharmaceutical drug development. More often, the synthesis of labelled (bio)molecules employs a pre-functionalised precursor to allow for the chemoselective installation of a particular radioisotope-containing substituent. Among the array of precursors available, boron reagents occupy a prominent place because they are easy to handle, numerous possibilities exist for their preparation, and their reactivity has been well studied especially in cross-coupling chemistry. In this review, we discuss the value of boron-based precursors for the radiolabelling of (bio)molecules with the radionuclides carbon-11, fluorine-18, iodine-123, iodine-125 and iodine-131, and we illustrate how these radiosynthetic advances have opened the radiochemical space available for areas such as PET and SPECT imaging.

Introduction

Since their discovery and use in Suzuki-Miyaura cross-coupling reactions, boron reagents have gained significant attention throughout the scientific community due to their stability, ease of purification, broad functional group tolerance, and relatively low environmental toxicity. Boron reagents have been extensively modified through variation of the substituents on the boron, and insightful methods have been implemented to study their reactivity. To date, numerous reviews have discussed the synthesis and reactivity of boron reagents, and over 1500 boron containing molecules are available to purchase. The favorable properties of boron reagents have not gone unnoticed by radiochemists, especially since at present time, the growing field of molecular imaging requires access to increasingly complex labelled molecules, that can be prepared from readily available precursors and used for applications in therapy, diagnosis or pharmaceutical drugs discovery. Both metals and non-metal radioisotopes have been employed in RIT (Radioisotope Therapy),² PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography), and

scintigraphy.^{3,4,5} Non-metallic radionuclides can however, be advantageous when it is important not to, or minimally, disturb the structure and properties of the target (bio)molecule under consideration. As a result, a vast range of radiochemical transformations have been developed for these non-metallic radioisotopes, typically using pre-functionalised precursors, more rarely relying on C-H functionalisation strategies (Figure 1A). In this context, stannane and boron reagents stand out as divergent precursors for radiolabelling, and both classes of reagents have been studied for the installation of valuable radioisotopes. More recently, the lower toxicity of boron reagents has encouraged radiochemists to consider these precursors for the development of novel radiochemical transformations (Figure 1B).⁶ The aim of this review is to discuss the value of boron reagents in the context of radiochemistry. The panel of radionuclides covered herein will be contained to carbon-11, fluorine-18, iodine-123, iodine-125 and iodine-131, as these radioisotopes represent, to date, the most prevalent non-metallic radionuclides used in the field of human health. This discussion does not cover boron reagents in the context of prosthetics-based radiochemistry as this subject has been reviewed extensively.⁷

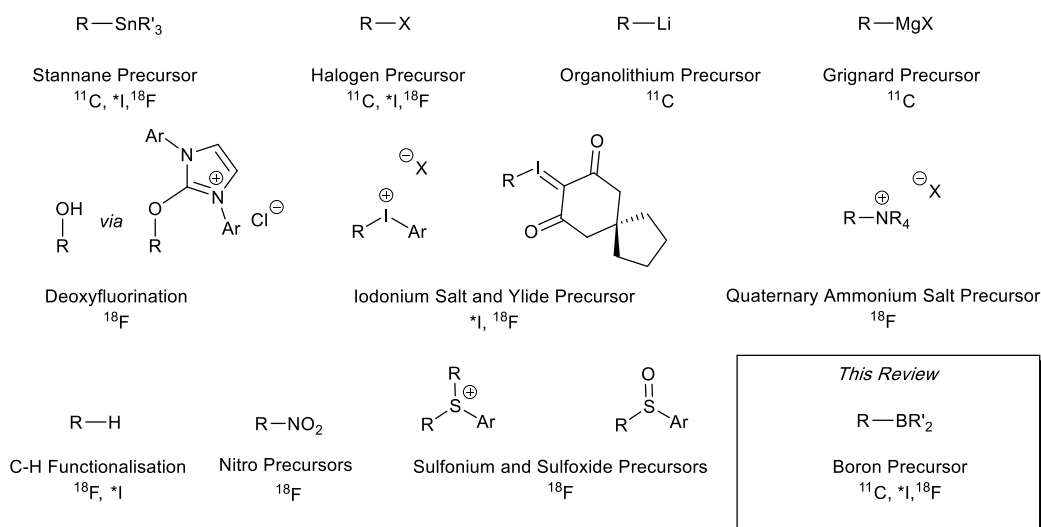
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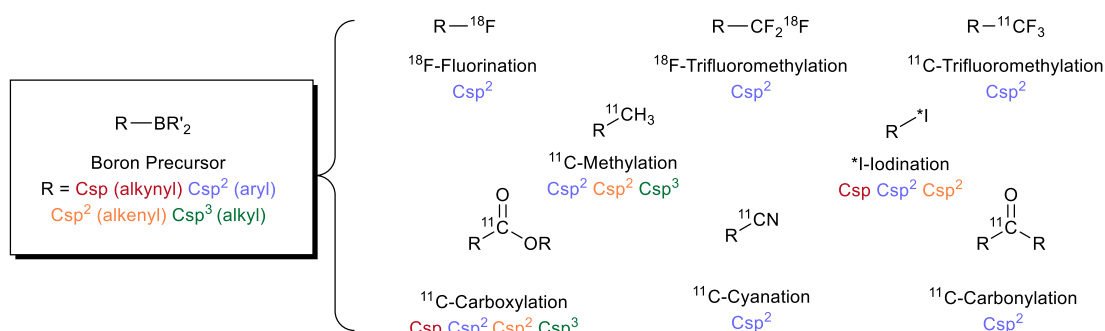


Figure 1 A) Summary of common precursors employed for radiochemistry. B) Divergent radiolabelling of boron reagents: state of the art.

I Synthesis and reactivity of boron reagents

Commonly used boron reagents for synthesis and catalysis include boronic acids, boronic esters and potassium trifluoroborate salts. The most efficient methods applied to obtain boronic acids are electrophile trapping of organomagnesium or organolithium derivatives with $B(OMe)_3$ or $B(OiPr)_3$ followed by hydrolysis,^{8,9} and Pd-catalysed borylation of C_{sp}^2 -LG (LG = leaving group) bonds using tetrahydroxyboron.^{10,11} Boronic esters such as pinacol derivatives for example, can be obtained through the same processes using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as electrophile or bis(pinacolato)diboron as the boron source, respectively.^{12,13} Alternatively, bis(pinacolato)diboron may be used for direct Ir-catalysed borylation of C_{sp}^2 -H bonds.¹⁴ Hydroboration of alkenes or alkynes provide access to a wide variety of alkyl or alkenyl boronic esters.^{15,16} Boronic esters can be easily hydrolysed to

boronic acids, and the reverse esterification of boronic acids is also possible.^{17,18} Potassium trifluoroborate salts are mainly produced through the reaction of boronic acids or esters with KHF_2 .^{19,20} For more detailed reports, the readers should consult several excellent reviews available within the literature.^{1,13} Within our own lab, the Pd-catalysed borylation of C_{sp}^2 -LG and Ir-catalysed borylation of C_{sp}^2 -H bonds have been most widely adopted. Boron reagents offer flexibility in terms of tailored reactivity. Mayr has developed electrophilicity and nucleophilicity scales that allow one to directly compare reagents, and thus predict the outcome of various nucleophile – electrophile combinations (Figure 2).²¹ For example, B_{sp}^2 -reagents such as boronic pinacol esters are less reactive towards carbocations, iminium ions or Michael acceptors than the benchmark compound 2-methylfuran. B_{sp}^3 -reagents, with an extra ligand on boron, are more nucleophilic as would be expected for a formally anionic species. The most nucleophilic boron reagents are the intramolecularly ligated trialkoxyboronate salts that react some ten orders of magnitude

faster than pinacol boronic esters with standard electrophilic benzhydrylium ions, a reactivity profile indicating that their nucleophilicity is comparable to that of ketene acetals and enamines. The high electronegativity of fluoride renders organotrifluoroborates less nucleophilic than trialkoxyboronate salts. Interestingly, MIDA (*N*-methyliminodiacetic acid) boronates are the least nucleophilic of all those studied. The electron withdrawing effect of the carbonyl groups out-competes the quaternisation by nitrogen, which is responsible of the increased nucleophilicity of the *N*-methyl diethanolamine adduct (Figure 2). Most radiochemical transformations make use of boronic acids or esters reagents.

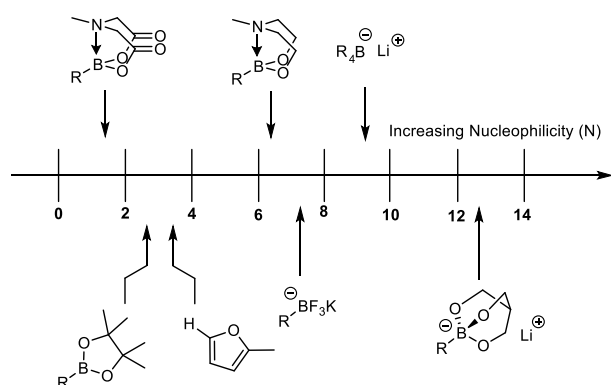


Figure 2 Relative reactivity of boron reagents according to Mayr's nucleophilicity scale; nucleophilicity of boron species determined by the rate of addition of 2-borylated furan moieties to an electrophilic benzhydrylium ion.⁹

II Boron reagents for radiolabelling with carbon-11

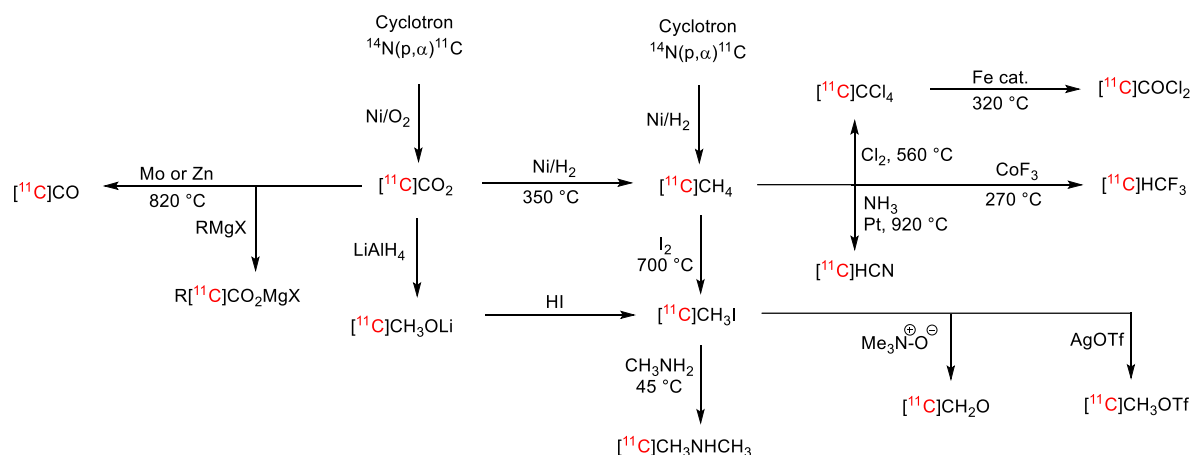
Radiolabelling procedures, more often than not, take inspiration from transformations already known for the corresponding abundant stable isotope. Therefore, it is of no surprise that this has led to a variety of elegant and efficient transformations with the radioactive isotope carbon-11. Of those radioisotopes discussed in this review, carbon-11 has the

shortest half-life (20.3 minutes), an important property when compared with much longer-lived isotopes such as iodine-123 (13.22 hours) for example; such time constraint will have a drastic influence on reaction parameters. Carbon-11 is cyclotron-produced *via* proton bombardment of nitrogen-14, and is collected either as [¹¹C]CO₂ or [¹¹C]CH₄ depending on the trace amounts of oxygen or hydrogen gas added to the target (Figure 3 and Scheme 1).^{22,23,24} These ¹¹C-reagents can be used directly or further transformed into other reactive ¹¹C-labelled species. For example, [¹¹C]CO₂ can be efficiently reduced to [¹¹C]CO, or [¹¹C]CH₃OLi, or can be directly employed for the carboxylation of Grignard reagents.^{25,26} Alternatively, starting from [¹¹C]CH₄, alkylating agents such as [¹¹C]CH₃I and [¹¹C]CH₃OTf can be obtained readily;^{27,28} other important reagents generated from [¹¹C]CH₄ include [¹¹C]HCN, [¹¹C]COCl₂ and [¹¹C]CH₃NHCH₃.^{22,29,30}

Carbon-11	Production	Source	Half-Life
	¹⁴ N(p,α) ¹¹ C	[¹¹ C]CO ₂	20.3 mins
	Decay Mode	[¹¹ C]CH ₄	Application
	β ⁺ (99.79%) EC (0.21%)		PET

Figure 3 Carbon-11 main properties. EC = Electron capture.

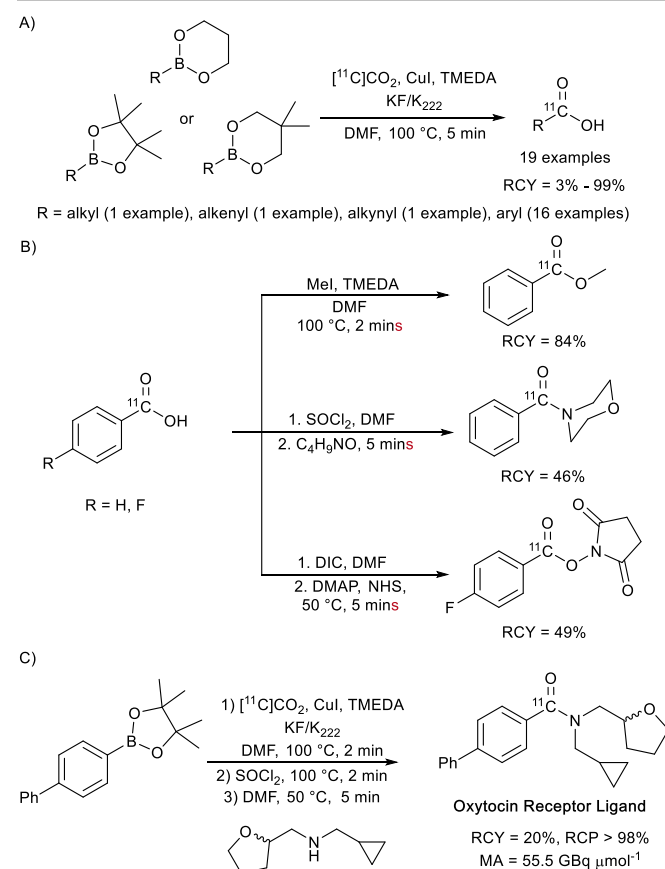
Whilst both [¹¹C]CH₃I and [¹¹C]CH₃OTf have been utilised widely for the labelling of heteroatoms,³¹ the stability of the resulting ¹¹C-labelled motifs to *in vivo* metabolism could be a drawback when compared to motifs arising from C_{sp2}-¹¹C bond forming processes. In this section, we describe the use of ¹¹C-reagents for the radiolabelling of aryl boron reagents *via* carboxylation, carbonylation, cyanation and methylation reactions.



Scheme 1 Formation of ¹¹C-containing reagents.

¹¹C-Carboxylation

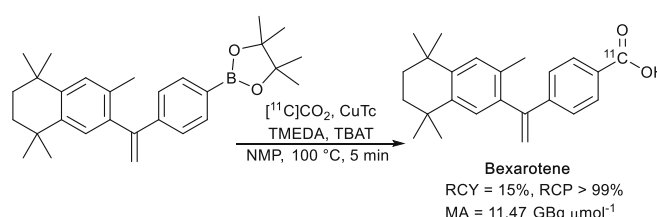
One commonality throughout radiochemistry is the sub-stoichiometric quantities of radiolabelled reagent, which is typically used in the order of nanomolar quantities. For ¹¹C-carboxylation reactions, this factor is problematic given the low solubility of [¹¹C]CO₂ in solution. Radiochemists have therefore developed methods to maximise [¹¹C]CO₂ concentration in solution to ensure reactivity. The first example of direct carboxylation of boronic esters using [¹¹C]CO₂ was reported by Pike and co-workers who sought to take advantage of the superior stability of the boron reagents compared to organolithium or Grignard reagents (Scheme 2).³² In this strategy, transmetalation of boronic esters is mediated by a copper(I) salt (CuI) in the presence of potassium fluoride (KF) and the cryptand K₂₂₂ (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane), thereby allowing efficient carboxylation to take place within 5 minutes at 100 °C through trapping with [¹¹C]CO₂. The addition of chelating agent tetramethylethylenediamine (TMEDA) was crucial to the success of this process, as this additive allowed for higher levels of [¹¹C]CO₂ to be retained in solution. This procedure was applied to a range of (hetero)aromatics as well as selected alkyl, alkenyl and alkynyl boronic esters leading to the corresponding ¹¹C-labelled carboxylic acids in low to moderate radiochemical yields and in molar activities (MA) up to 111 GBq μmol⁻¹ (Scheme 2A).



Scheme 2 Cu(I)-mediated carboxylation of boronic esters with [¹¹C]CO₂. DIC: *N,N*-diisopropylcarbodiimide. DMAP: 4-(dimethylamino)pyridine. NHS: *N*-hydroxysuccinimide.

Subsequently, the authors successfully derivatised the resulting carboxylic acids into methyl esters, amides or *N*-hydroxysuccinimide activated acids (Scheme 2B). The utility of this strategy was highlighted with the synthesis of a known oxytocin receptor radio-ligand produced in 20% radiochemical yield (RCY) and > 98% radiochemical purity (RCP) (Scheme 2C).³¹

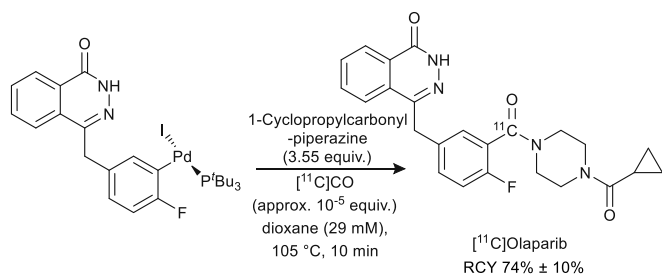
Recently, Vasdev and co-workers slightly modified this Cu(I)-mediated procedure for the radiosynthesis of the retinoid X receptor agonist, bexarotene in 15% RCY.³³ The process employs copper(I)-thiophene-2-carboxylate (CuTc) instead of copper iodide, a fluorosilicate instead of potassium fluoride source, but retains TMEDA as the critical chelating agent for [¹¹C]CO₂ (Scheme 3). This transformation was subsequently validated for pre-clinical translation with the neuroimaging of non-human primates.³⁴



Scheme 3 Copper(I)-mediated carboxylation of boronic esters for the synthesis of [¹¹C]bexarotene. TBAT: tetrabutylammonium difluorotriphenylsilicate.

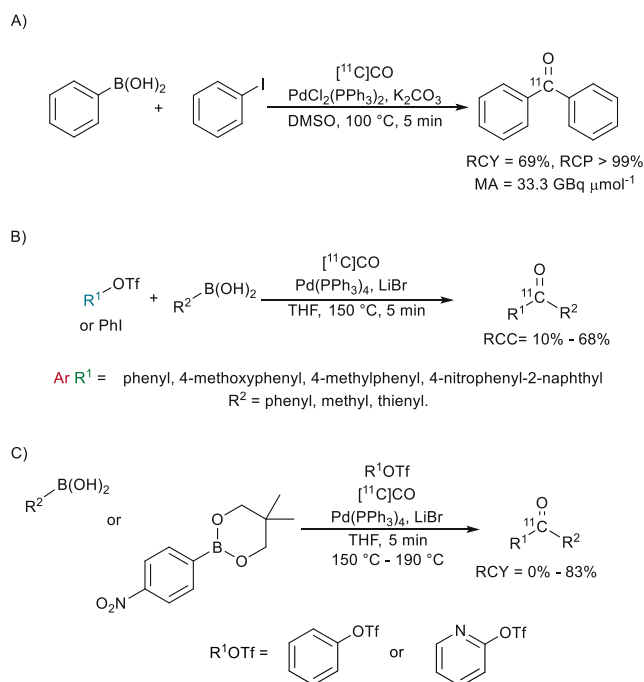
¹¹C-Carbonylation

[¹¹C]CO is generally produced by the gas phase reduction of cyclotron-produced [¹¹C]CO₂ on a metal surface (zinc or molybdenum) at high temperatures.³⁵ The unreacted [¹¹C]CO₂ is separated by trapping on soda lime and the remaining [¹¹C]CO collected on a silica trap cooled with liquid argon (Scheme 1). Once isolated, [¹¹C]CO can be warmed and captured in an isolation chamber to allow further manipulation as desired. To facilitate this manipulation, xenon is used as a carrier gas. Although [¹¹C]CO has shown synthetic utility, it has not gained broad adoption in the PET radiochemistry community. This could be attributed to the complexity of the autoclave system and the relatively high level of service needed to maintain the system operational. Moreover, the repeated use of an integrated stainless-steel reactor may infer issues related to transition metal build up over time, which is problematic in reaction development and system validation for GMP (good manufacturing practice).²² It is only recently that these low-pressure systems have been implemented for the incorporation of [¹¹C]CO into complex radiotracers. This is exemplified by the radiosynthesis of ¹¹C-Olaparib, a highly sought-after radiotracer for the imaging of PARP (poly(ADP-ribose)polymerase) (Scheme 4).³⁶



Scheme 4 ^{11}C -Carbonylation of a preformed aryl-palladium complex.

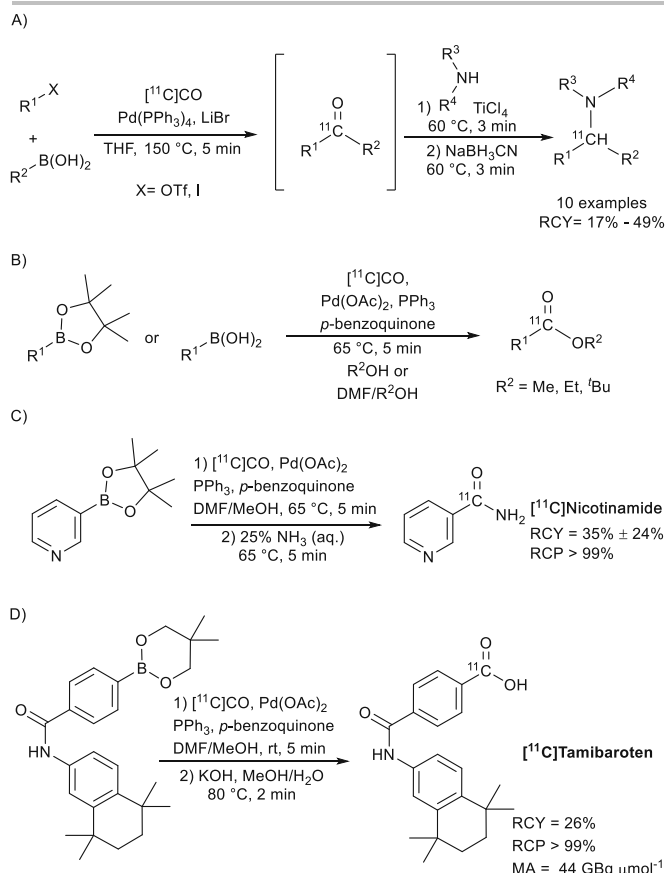
The first carbonylative Suzuki cross-coupling involving a boron reagent and ^{11}C CO was reported by Zeisler in 1997.³⁷ Using iodobenzene, phenylboronic acid and K_2CO_3 in DMSO, Zeisler was able to produce within 5 minutes ^{11}C -radiolabelled benzophenone in the presence of a palladium complex (Scheme 5A). Following this proof of concept, Långström reported two studies enhancing the scope of the reaction with the use of aryl triflates (Scheme 5B), and of boronic esters (Scheme 5C).^{38,39}



Scheme 5 A) Synthesis of radiolabelled benzophenone with ^{11}C CO. B) ^{11}C -Carbonylation of aryl triflate derivatives. C) ^{11}C -Carbonylation of aryl boronic ester derivatives.

Applying this radiochemistry, Långström and co-workers reported the synthesis of ^{11}C -labelled substituted amines in a two-step sequence involving ^{11}C CO-mediated synthesis of ketones from boronic acids followed by reductive amination (Scheme 6A).⁴⁰ Ishii later highlighted how boron reagents can be directly converted into esters upon treatment with ^{11}C CO in the presence of $\text{Pd}(\text{OAc})_2$, PPh_3 , benzoquinone and the required alcohol (Scheme 6B).⁴¹ Further broadening of this strategy was demonstrated with the synthesis of ^{11}C -amides (Scheme 6C), and ^{11}C -carboxylic acid derivatives (Scheme 6D),

as highlighted in the synthesis of ^{11}C nicotinamide and ^{11}C tamibaroten, respectively.^{41,42}



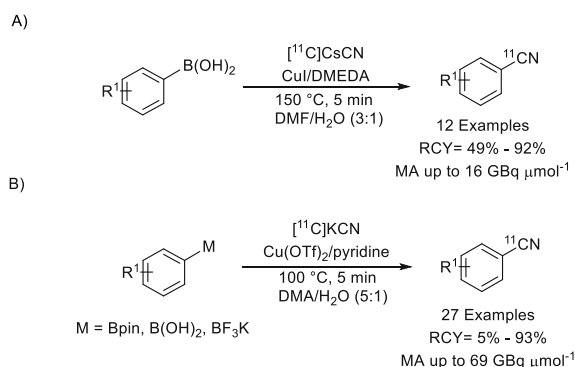
Scheme 6 A) ^{11}C -Carbonylation for the synthesis of ^{11}C -amines via reductive amination of ^{11}C -ketones. B) ^{11}C -Carbonylation of boronic esters and boronic acids for the synthesis of ^{11}C -esters. C) Synthesis of ^{11}C nicotinamide. D) Synthesis of ^{11}C tamibaroten.

^{11}C -Cyanation

The ^{11}C -cyanation of aryl boron reagents is an important transformation because of the prevalence of nitrile groups within biological molecules; moreover, the cyano group is amenable to a variety of transformations thereby providing a platform for further radiochemical space expansion. Taking cyclotron-produced ^{11}C CH₄, oxidation to ^{11}C HCN is achieved in the presence of anhydrous ammonia in a platinum oven at 950 °C.²⁹ Following removal of the excess ammonia, ^{11}C HCN can be used as a ^{11}C -cyanation reagent. Alternatively, ^{11}C HCN can be converted into the corresponding salt ^{11}C MCN ($\text{M}^+ = \text{K}^+$ or Cs^+) by eluting with water and the corresponding base (K_2CO_3 or Cs_2CO_3).

Liang and co-workers successfully subjected a range of (hetero)aryl boronic acids to cyanation with ^{11}C CsCN in the presence of CuI and *N,N'*-dimethylethylenediamine (DMEDA). The desired ^{11}C -labelled products were obtained in radiochemical conversions up to 70% with a molar activity of 16 GBq μmol^{-1} (Scheme 7a).⁴³ Recently, Scott and co-workers expanded the scope of this process by demonstrating that

boronic acids, boronic esters as well as trifluoroborate salts can be subjected to cyanation using [^{11}C]KCN in the presence of $\text{Cu}(\text{OTf})_2$ and pyridine (Scheme 7B).⁴⁴

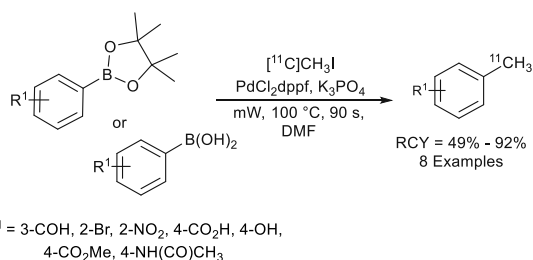


Scheme 7 Carbon-11 cyanation of aryl boron reagents.

^{11}C -Methylation

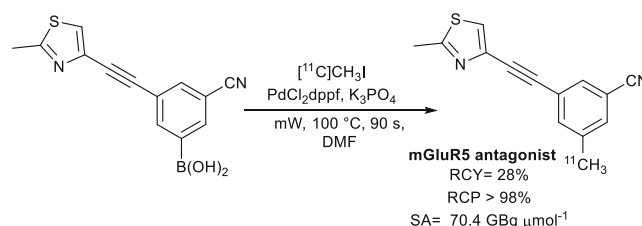
Both *N*- and *O*- ^{11}C -methylation are widespread transformations as many radiopharmaceuticals contain methylamine, aniline and/or anisole pharmacophores. These reactions are performed by nucleophilic substitution with [^{11}C]CH₃I or [^{11}C]CH₃OTf. However, with the use of PET imaging in diagnostic medicine growing rapidly, requests from physicians for more complex radiopharmaceuticals have led to the necessity to develop novel radiochemistry for the formation of C_{sp2}- ^{11}C CH₃ bonds.

To date, the coupling of [^{11}C]CH₃I and boron reagents has been accomplished in the presence of a palladium complex. The first Suzuki ^{11}C -methylation was reported by Burns and co-workers in 2005 with the synthesis of ^{11}C -tolyl derivatives from boronic acids or boronic esters using [^{11}C]CH₃I, K₃PO₄ and 1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl_2dppf) in DMF under microwave irradiation (Scheme 8).⁴⁵



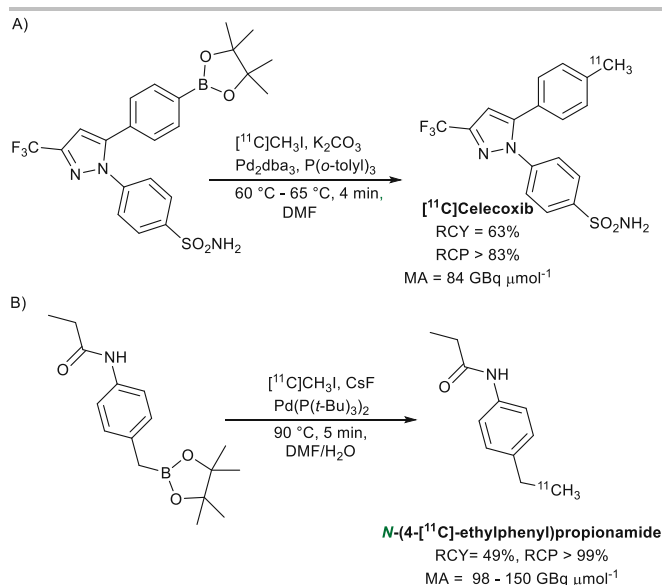
Scheme 8 [^{11}C]CH₃I-mediated methylation of arenes from boronic esters or acids. Dppf = 1,1'-bis(diphenylphosphino)ferrocene.

A known metabotropic glutamate receptor subtype 5 (mGluR5) PET radiotracer was successfully synthesised applying this ^{11}C -methylation to the corresponding aryl boronic acid (Scheme 9).⁴⁶



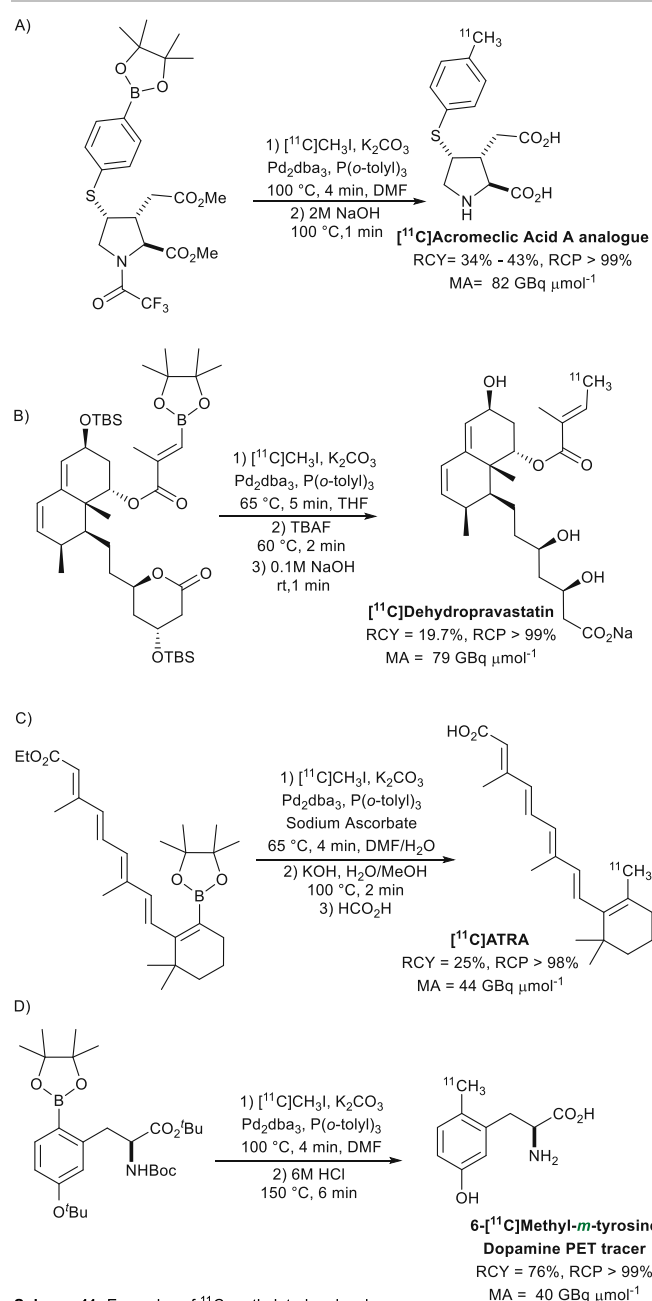
Scheme 9 Synthesis of a [^{11}C]mGluR5 antagonist.

In 2009, Suzuki improved the efficacy of ^{11}C -methylation by using K₂CO₃ instead of K₃PO₄, and replacing PdCl₂dppf with Pd₂dba₃/P(*o*-tolyl)₃ (dba = dibenzylideneacetone).⁴⁷ This modified protocol afforded [^{11}C]celecoxib in 63% RCY, > 83% RCP and MA of 84 GBq μmol⁻¹ (Scheme 10A).⁴⁸ More recently, these conditions were further modified for the ^{11}C -methylation of benzylic boronic esters. In this case, the use of fluoride ions to activate the boronic pinacol ester and tri-*tert*-butylphosphine as the palladium ligand was found to be highly effective for the radiosynthesis of *N*-(4-[^{11}C]-ethylphenyl)propionamide (Scheme 10B).⁴⁹

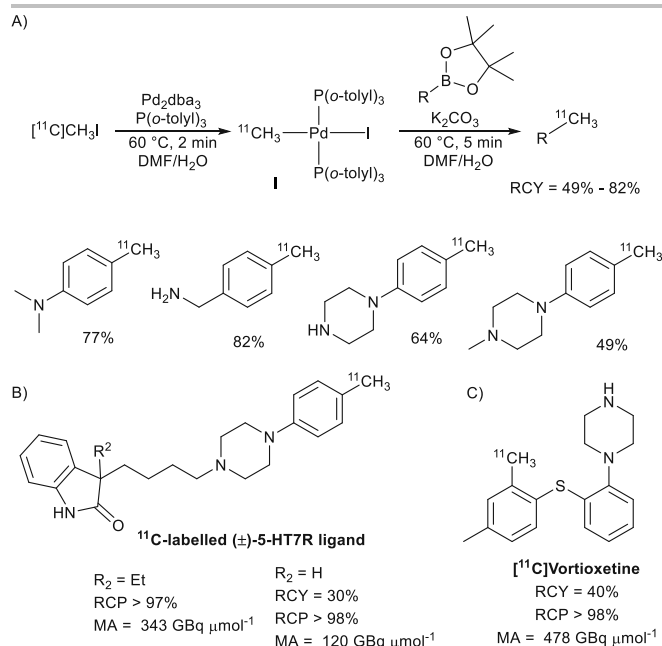


Scheme 10 Synthesis of A) [^{11}C]celecoxib. B) *N*-(4-[^{11}C]-ethylphenyl)propionamide using bulky phosphines.

The use of bulky phosphines to promote Pd-mediated ^{11}C -methylation from boronic esters has also been reported by other groups to access complex radioligands. With one or two steps post ^{11}C -methylation consisting of deprotection and/or hydrolysis, [^{11}C]acromelic acid analogue A (Scheme 11A),⁵⁰ [^{11}C]dehydropravastatin (Scheme 11B),⁵¹ ^{11}C -all *trans* retinoic acid (ATRA) (Scheme 11C), and the dopamine PET tracer 6-[^{11}C]methyl-*meta*-tyrosine (Scheme 11D) were all synthesised in good RCYs.^{52,53}

Scheme 11 Examples of ^{11}C -methylated molecules.

Interestingly, in 2013 Kristensen reported a procedure to selectively cross-couple aryl boronic esters bearing unprotected amine groups with $[^{11}\text{C}]\text{CH}_3\text{I}$. After initial formation of iodomethylpalladium(II) complex **I**, its subsequent reaction with boronic esters and K_2CO_3 afforded ^{11}C -toluene derivatives with no competing *N*- ^{11}C -methylation (Scheme 12A).⁵⁴ The same group applied this protocol to ^{11}C -label two serotonin 7 receptor (5-HT₇R) ligands (Scheme 12B),⁵⁵ and to the antidepressant drug Vortioxetine (Scheme 12C).⁵⁶

Scheme 12 $[^{11}\text{C}]\text{CH}_3\text{I}$ -mediated methylation A) *N*-unprotected pinacol-derived aryl boronic esters. B) ^{11}C -labelled (±)-5-HT₇R ligand. C) $[^{11}\text{C}]\text{Vortioxetine}$.

III Boron reagents for radiolabelling with iodine-123, -125 and -131

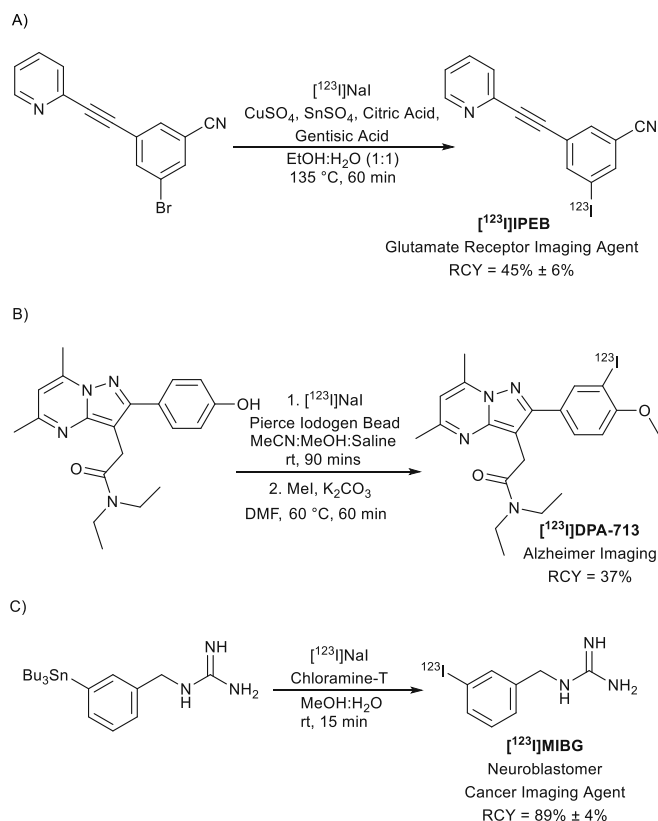
	Production	Source	Half-Life
^{123}I	$^{124}\text{Xe}(\text{p},\text{pn})^{123}\text{Xe} \rightarrow ^{123}\text{I}$	Na^{123}I in H_2O	13.2 h
Iodine-123	EC	Decay Mode	Application
		EC	SPECT
	Production	Source	Half-Life
^{125}I	$^{124}\text{Xe}(\text{n},\gamma)^{125}\text{Xe} \rightarrow ^{125}\text{I}$	Na^{125}I in H_2O	54.9 Days
Iodine-125	EC	Decay Mode	Application
		EC	RIA, Binding
	Production	Source	Half-Life
^{131}I	$^{130}\text{Te}(\text{n},\gamma)^{131}\text{Te} \rightarrow ^{131}\text{I}$	Na^{131}I in H_2O	8.02 Days
Iodine-131	β^-	Decay Mode	Application
		β^-	RIT, SPECT

Figure 4 Iodine-123, -125 and -131 main properties.

To date, radiolabelling with iodine from boronic species has been achieved with isotopes 123, 125 and 131 of iodine. These isotopes have significantly longer half-lives than carbon-11 and fluorine-18, and are available as aqueous solutions of sodium iodide containing sodium hydroxide. Iodine-123 is produced in a cyclotron through irradiation of xenon-124 with a proton beam. This isotope is the most used non-metal radioelement for SPECT imaging (the most common radioisotope used in diagnosis is technetium 99 (Tc-99)). The isotopologue iodine-125 is produced in a nuclear reactor from the bombardment of

xenon-124 with neutrons and is used daily in many research groups for binding studies/ RIA (radioimmunoassay), or autoradiography experiments. Iodine-131, produced in nuclear reactor from neutron bombardment of tellurium-130, was historically used for SPECT imaging. However, its high energy (971 keV) prompted the switch to iodine-123. As such, iodine-131 is mainly used in RIT, where its high energy is now advantageous (Figure 4).⁵⁷

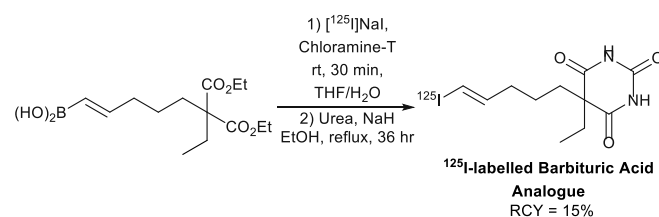
Common methods for forming C-*I bonds are shown in Scheme 13. One approach consists of applying a copper-mediated halogen exchange with [¹²³I]NaI as exemplified with the radiolabelling of 3-[¹²³I]iodo-5-(pyridine-2-ylethynyl)benzonitrile [¹²³I]PEB, an imaging agent for metabotropic glutamate receptor uptake subtype 5 (Scheme 13A).⁵⁸ An alternative approach involves an oxidative process affording iodonochloride from sodium iodide and a strong oxidant such as iodogen® and chloramine-T. This *in situ* formed reagent has been utilised for electrophilic aromatic substitution and iododestannylation for the radiolabelling of *N,N*-diethyl-2-(2-(3-[¹²³I]-iodo-4-methoxyphenyl)-5,7-dimethylpyrazolo [1,5-*a*]pyrimidin-3-yl) acetamide [¹²³I]DPA-713, an imaging agent for the translocator protein (TSPO), and *meta*-[¹²³I]iodobenzylguanidine [¹²³I]MIBG, a radiotracer for glioblastoma and pheochromocytoma imaging (Scheme 13B, 13C), respectively.^{59,60}



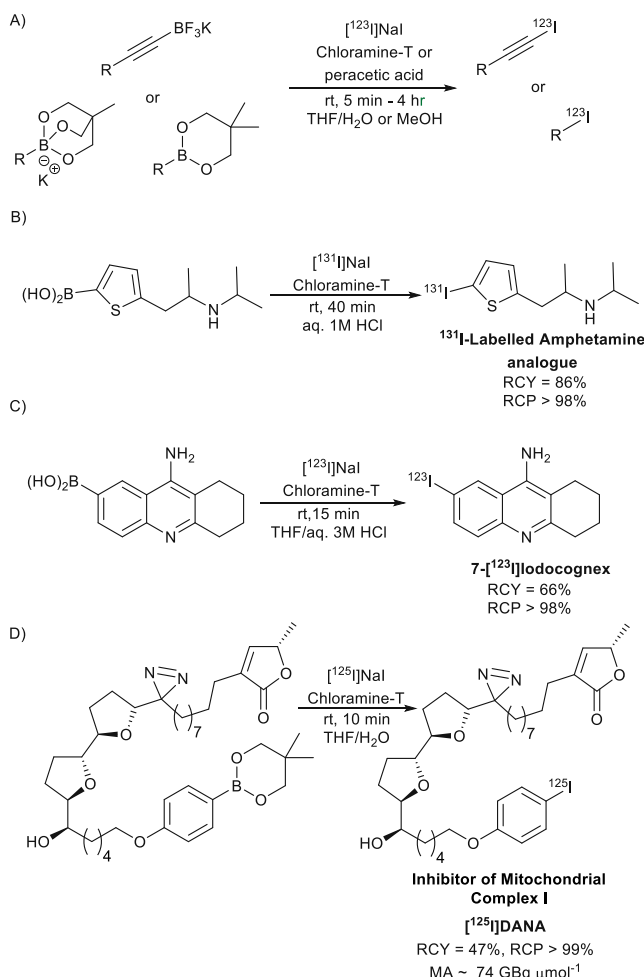
Scheme 13 Typical transformations for radiolodination. A) Halogen/Isotopic exchange: [¹²³I]PEB. B) Electrophilic aromatic substitution *I-iodination: [¹²³I]DPA-713. C) Iododestannylation: [¹²³I]MIBG.

Knapp and co-workers were the first to use boron reagents in radio-iodination to access an ¹²⁵I-tagged barbituric acid

analogue. Starting from an alkenyl boronic acid and *in situ* generated [¹²⁵I]ICl from chloramine-T and [¹²⁵I]NaI, radio-iodination occurred at room temperature in 15% RCY (Scheme 14).⁶¹ Following this proof of concept, Kabalka and co-workers demonstrated the adaptability of this reaction to a range of boron reagents (Scheme 15A).^{62,63,64} Subsequent efforts have been devoted to the radioiodination of various targets including ¹³¹I-amphetamine analogues (Scheme 15B),⁶⁵ 7-[¹²³I]iodocognex (Scheme 15C) and ¹²⁵I-tagged DANA, an inhibitor of mitochondrial complex I (Scheme 15D).^{66,67}



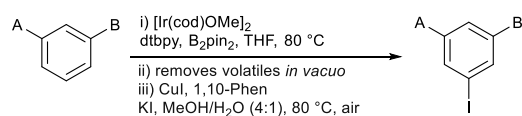
Scheme 14 ¹²⁵I-labelled barbituric acid analogue.



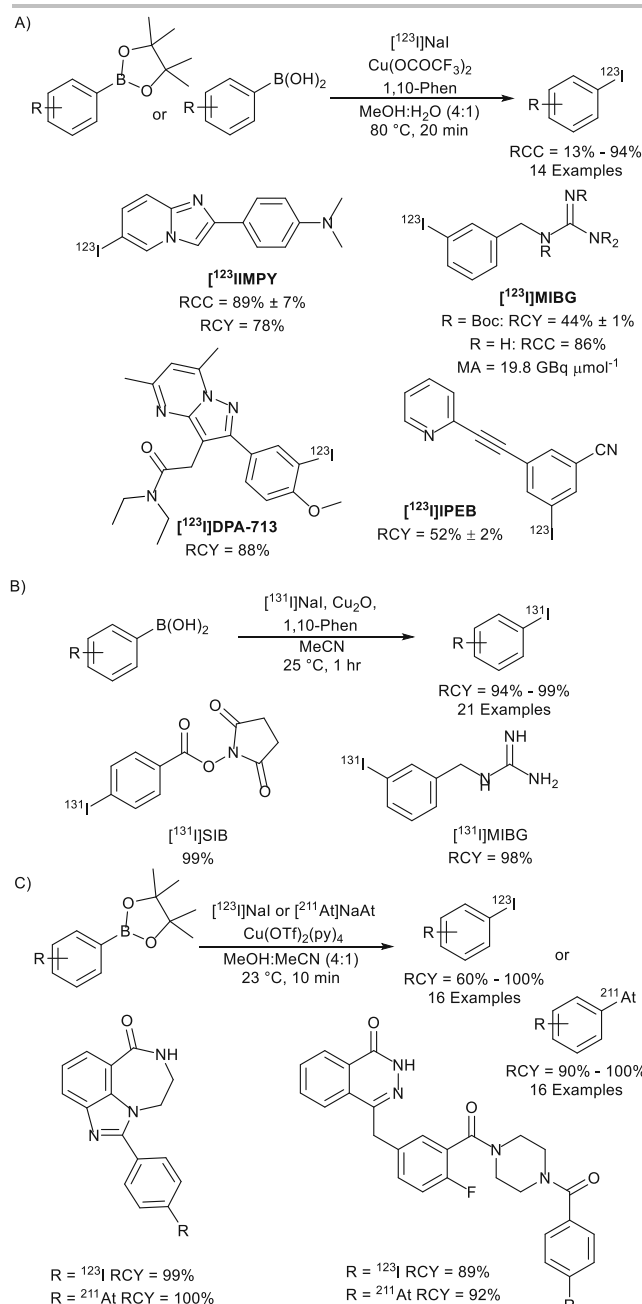
Scheme 15 Electrophilic *I-iodination of aryl boron reagents.

Whilst previous radioiodination protocols relied upon the formation of an electrophilic species, such as [^{*}I]ICl, more recent developments have sought to develop nucleophilic pathways using [^{*}I]NaI and a copper-based catalyst. Inspiration

for many of these transformations arose from studies carried out in Hartwig's laboratory. Specifically, the iridium catalyzed C-H borylation of (hetero)arenes followed by iodination of the resulting boronic ester intermediate using a copper(I) catalyst and potassium iodide proved to be a highly versatile process (Scheme 16).⁶⁸



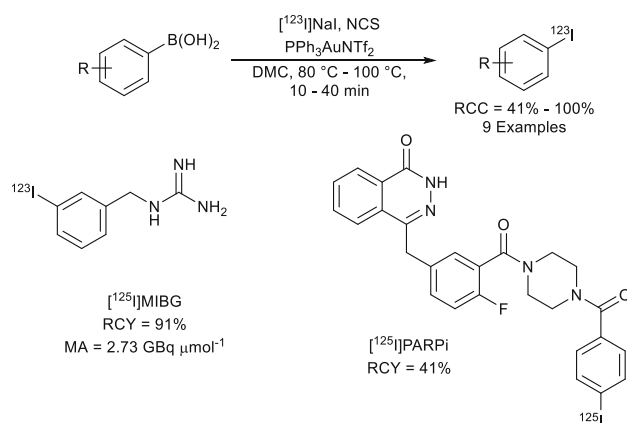
Scheme 16 Iodination of arenes via iridium catalyzed C-H borylation. 1,10-Phen: 1,10-Phenanthroline. dtbpy: 4,4'-di-tert-butyl-2,2'-dipyridyl



Scheme 17 Examples of copper mediated radioiodinations. 1,10-Phen: 1,10-Phenanthroline.

Adaptation of this chemistry to radioiodination was validated by Gouverneur and Zhang in 2016 with both groups reporting the nucleophilic radioiodination of boronic pinacol esters and boronic acids with [¹²³I]NaI under copper catalysis (Scheme 17A, 17B).^{69,70} The copper complex CuI used by Hartwig was replaced by Cu(OCOCF₃)₂ and Cu₂O respectively to prevent isotopic dilution. Using this protocol, Gouverneur successfully labelled four SPECT tracers from the corresponding aryl boronic pinacol esters. Zhang and co-workers were able to demonstrate the utility of this transformation with *in vivo* imaging studies of neuroblastoma and pheochromocytoma using [¹³¹I]MIBG. Further utility of this transformation was shown in 2018 with Mach and co-workers describing the ¹²⁵I-iodination and ²¹¹At-Astatination of boronic esters under mild conditions and fast reaction times (Scheme 17C).⁷¹

Sutherland reported that the gold(I) complex PPh₃AuNTf₂ can improve more demanding electrophilic ¹²⁵I-iodination of aryl boronic acids. Indeed, its presence was particularly beneficial for electron deficient and sterically hindered precursors. *Via* initial generation of [¹²⁵I]NIS *in situ* with [¹²⁵I]NaI and NCS, Sutherland was able to successfully carry out the necessary *ipso*-iododeboronation.⁷² This approach gave access to [¹²⁵I]MIBG and [¹²⁵I]PARPi (Scheme 18).



Scheme 18 Gold mediated ¹²⁵I-iododeboronation of aryl boronic acids.

IV Boron targets for radiolabelling with fluorine-18

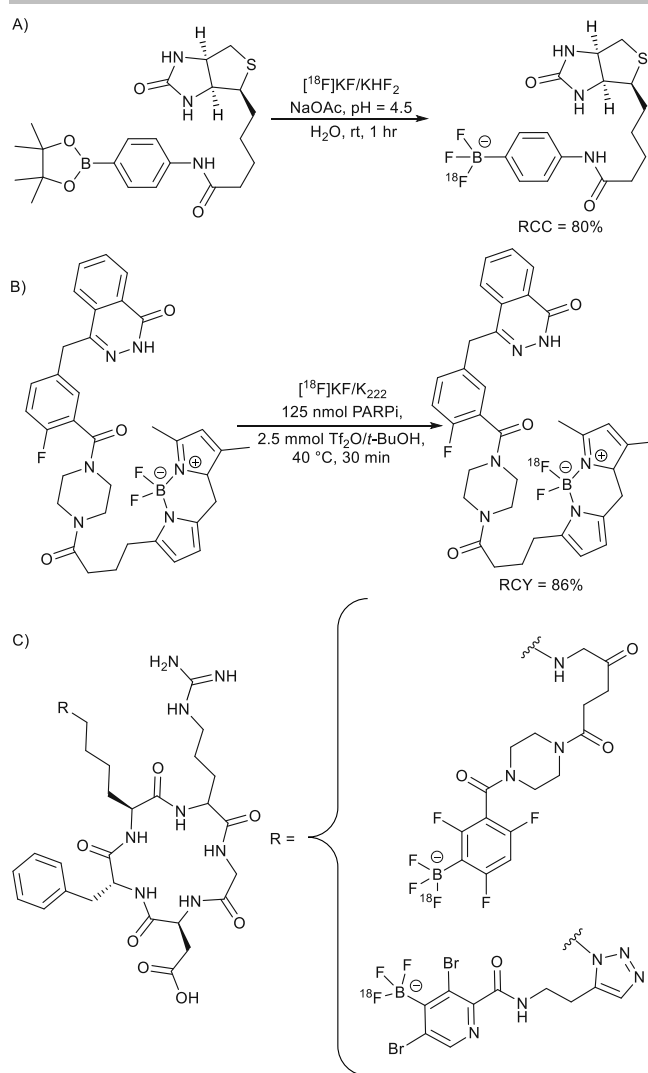
Production	Source	Half-Life
¹⁸ O(p,n) ¹⁸ F	Aqueous [¹⁸ F]Fluoride [¹⁸ F]F ₂	109.7 mins
Decay Mode	Application	
β ⁺ (97%)	PET	
EC (3%)		

Figure 5 Fluorine-18 main properties.

Of those isotopes used in PET, fluorine-18 has the lowest emission energy (511 keV) and therefore has the lowest range (2.4 mm in water), resulting in the highest resolution images.⁷³ Furthermore, the relatively long half-life (109.7 min) offers greater flexibility compared to other radionuclides in PET (Figure 5). In addition to these two favorable properties, its popularity is also due to the small radius of fluorine (Van der Waals radius is 1.47 Å), the strength of the C-F bond (~480 kJ mol⁻¹), and its prevalence in drug discovery.⁷⁴ This isotope is cyclotron-produced by irradiating [¹⁸O]H₂O with a proton beam to give [¹⁸F]fluoride ions in high molar activity. In the vast majority of cases, the resulting [¹⁸F]fluoride aqueous solution requires a drying step prior to labelling. Whilst production of highly reactive [¹⁸F]F₂ by targeting [¹⁸O]O₂ is also possible, this approach is less used because much lower molar activities are obtained due to the use of [¹⁹F]F₂ as a carrier gas (Figure 5).⁷⁵ Fluorine-18 radiochemistry has benefited from the greatest expansion in terms of the number of precursors amenable to C-¹⁸F bond formation, particularly for the ¹⁸F-fluorination of (hetero)arenes. Each class of precursors holds an advantage over the other for a particular purpose, such as stability, ease of purification or facile access to the starting material required for radiolabelling. In this context, boron reagents have however become increasingly popular as precursors of choice for the development of new methods of ¹⁸F-labelling.

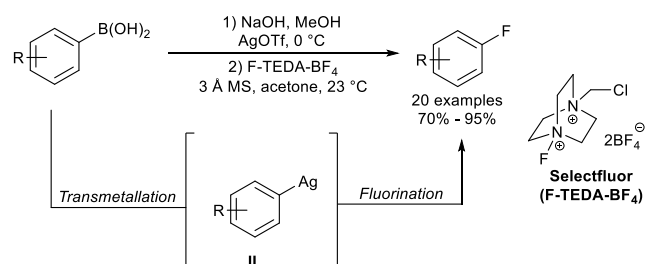
The [¹⁸F]BF₃K motif is well worth noting for the ¹⁸F-labelling of small molecules and biomolecules.^{76,77} The high stability of the B-F bond has been exploited in organic chemistry to convert aryl boronic acids and esters into the corresponding aryltrifluoroborates.⁷⁷ These reactions are rapid and can be carried out in the presence of water, making them attractive for ¹⁸F-radiochemistry. The preferred method for the radiofluorination of boron compound is by ¹⁸F/¹⁹F isotopic exchange despite consequential isotopic dilution. Perrin and co-workers demonstrated proof-of-concept in 2005 with the conversion of a biotinylated boronic ester into the corresponding trifluoroborate using an aqueous [¹⁸F]fluoride anion solution and KHF₂ as a carrier-added fluoride anion source (Scheme 19A).⁷⁸ This facile transformation has been widely employed to ¹⁸F-label drug molecules and biologically relevant targets (Scheme 19B, 19C).^{76,79,80} Specifically, application of this radiochemistry to BODIPY dyes, led to a new class of PET-fluorescence dual imaging agents.^{76,81}

With the view to develop radiochemistry that does not lead to prosthetic-modified labelled molecules, more recent studies have focused on structurally less invasive C_{sp2}-¹⁸F bond construction from aryl boron reagents. These advances build on the progress made in recent years in late stage catalytic fluorination.



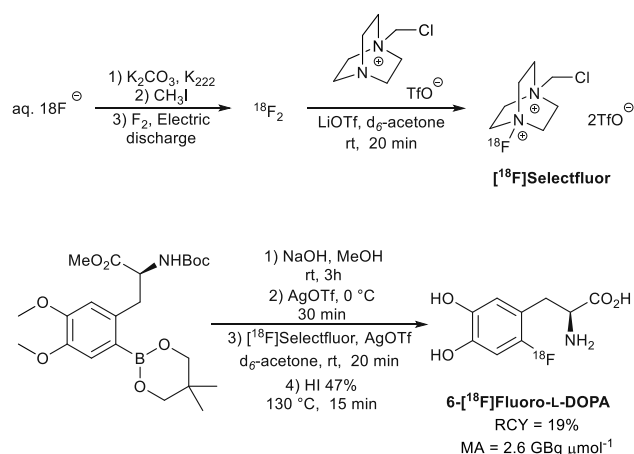
Scheme 19 A) First synthesis of the [¹⁸F]BF₃K motif. B) Application of [¹⁸F]BF₃K motifs within radiolabeling of drug like molecules. C) Application of [¹⁸F]BF₃K motifs within radiolabeling of biomolecules.

For the electrophilic fluorination of boron species, inspiration came from studies by Ritter and co-workers (Scheme 20).⁸² Using the fluorination reagent, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane (Selectfluor), the electrophilic fluorination of aryl boronates, activated using AgOTf and NaOH, was accomplished. The use of hydroxide was found to be critical to the reaction, likely due to the need to form a highly reactive boronate species enabling transmetalation into an active silver complex **II**. Upon treatment with Selectfluor, a range of fluorine-substituted (hetero)aromatics were obtained.



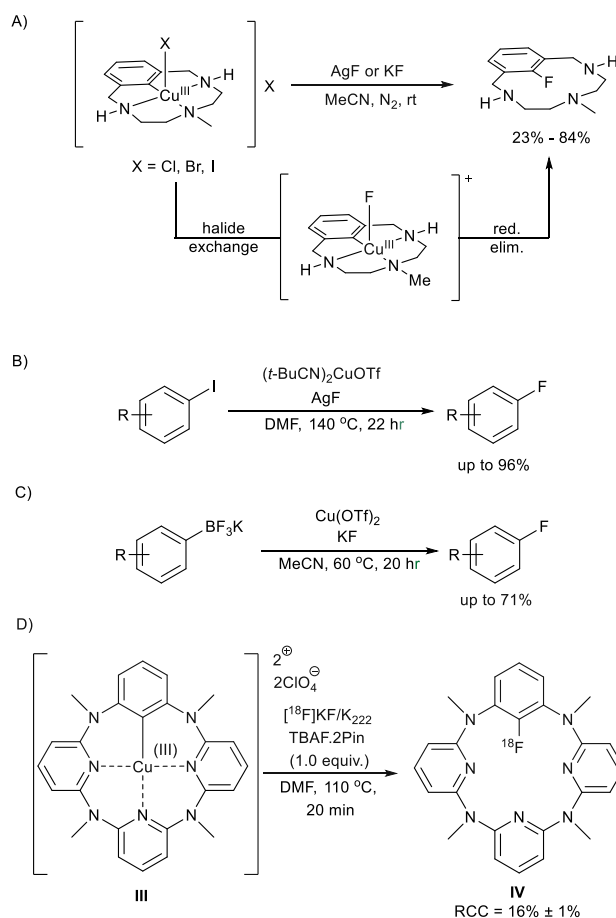
Scheme 20 Silver-mediated fluorination of aryl boronic acids.

Inspired by this work, Solin and Gouverneur described the first electrophilic ¹⁸F-fluorination of aryl boronic neopentyl glycol esters with [¹⁸F]Selectfluor bis(triflate),⁸³ a reagent prepared from [¹⁸F]₂ (Scheme 21).⁸⁴ For this study, the production of [¹⁸F]₂ was achieved with molar activity up to 55 GBq μmol⁻¹ applying the protocol developed by Solin and Bergman.⁵¹ The technique involved the formation of [¹⁸F]CH₃F from aqueous [¹⁸F]fluoride, which is then subjected to electric discharge in the presence of [¹⁹F]₂ to give [¹⁸F]₂. Subsequently, [¹⁸F]₂ was reacted with 1-chloromethyl-4-aza-1-azoniabicyclo [2.2.2]octane triflate to afford the electrophilic reagent [¹⁸F]selectfluor (bis)triflate.⁸³ Following the principles outlined for ¹⁹F-fluorination, transmetallation of the aryl boronic neopentyl glycol ester under basic conditions to form the corresponding silver complex was undertaken prior to ¹⁸F-fluorination.⁸³ ¹⁸F-Labeling with [¹⁸F]selectfluor (bis)triflate led to 6-[¹⁸F]fluoro-L-DOPA, an imaging agent for the dopaminergic pathways and associated diseases such as Alzheimer's (Scheme 21).

Scheme 21 Synthesis of 6-[¹⁸F]fluoro-L-DOPA using [¹⁸F]selectfluor bis(triflate).

A nucleophilic variant of this process emerged in 2014 building on advances made in the field of copper-mediated ¹⁹F-fluorination. Ribas followed by Wang demonstrated that Cu(III) intermediates in geometrically-constrained systems are amenable to nucleophilic fluorination (Scheme 22A).^{85,86} Following these studies, Hartwig reported the fluorination of aryl iodides with [Cu(OTf)(*t*-BuCN)₂] and AgF evoking a

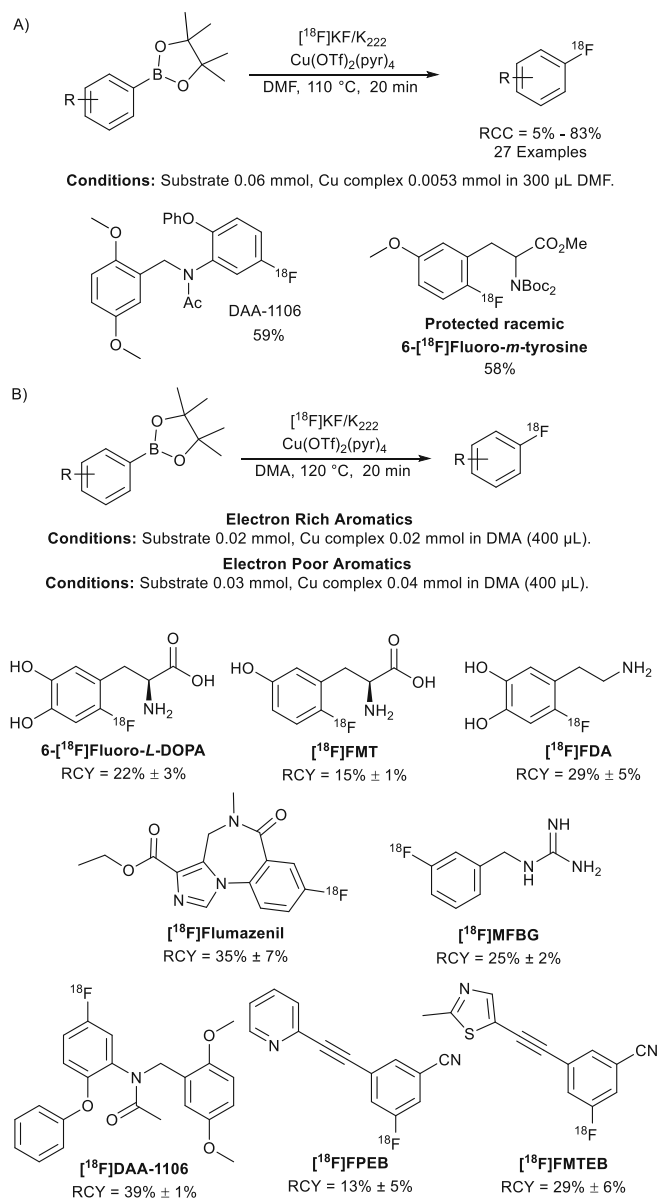
mechanism involving a Cu(III) intermediate and C-F reductive elimination pathway (Scheme 22B).⁸⁷ Sanford and co-workers later on reported the reaction of (hetero)aryl trifluoroborate salts with KF and Cu(OTf)₂ (Scheme 22C).⁸⁸ Bridging the gap between ¹⁹F and ¹⁸F-fluorination, Gouverneur and co-workers demonstrated that the pre-formed Cu(III) complex **III** is responsive to nucleophilic ¹⁸F-fluorination in the presence of carrier-added [¹⁸F]fluoride (Scheme 22D).⁸⁹ This experiment paved the way for a general procedure to access ¹⁸F-(hetero)arenes from boron species using nucleophilic [¹⁸F]fluoride.



Scheme 22 Nucleophilic fluorinations of (hetero)aromatics via Cu(III) intermediates.

In 2014, the Gouverneur group demonstrated that the direct labelling of aryl boronic esters *via* a nucleophilic source of fluorine-18, [¹⁸F]KF/K₂₂₂, is feasible. Starting from aqueous [¹⁸F]fluoride and after a conventional drying step, [¹⁸F]KF was reacted with boronic pinacol esters in the presence of tetrakis pyridine copper(II) triflate to give a variety of ¹⁸F-labelled (hetero)arenes (Scheme 23).⁹⁰ This method allows labelling of electron poor and electron rich arenes, and more functionalised molecules such as DAA-1106 and protected racemic 6-[¹⁸F]Fluoro-*m*-tyrosine. Of note, the method provides direct access to 6-[¹⁸F]Fluoro-L-DOPA from [¹⁸F]fluoride with a protocol requiring a single deprotection step post-labelling. Further optimisation tailored for either electron-rich or

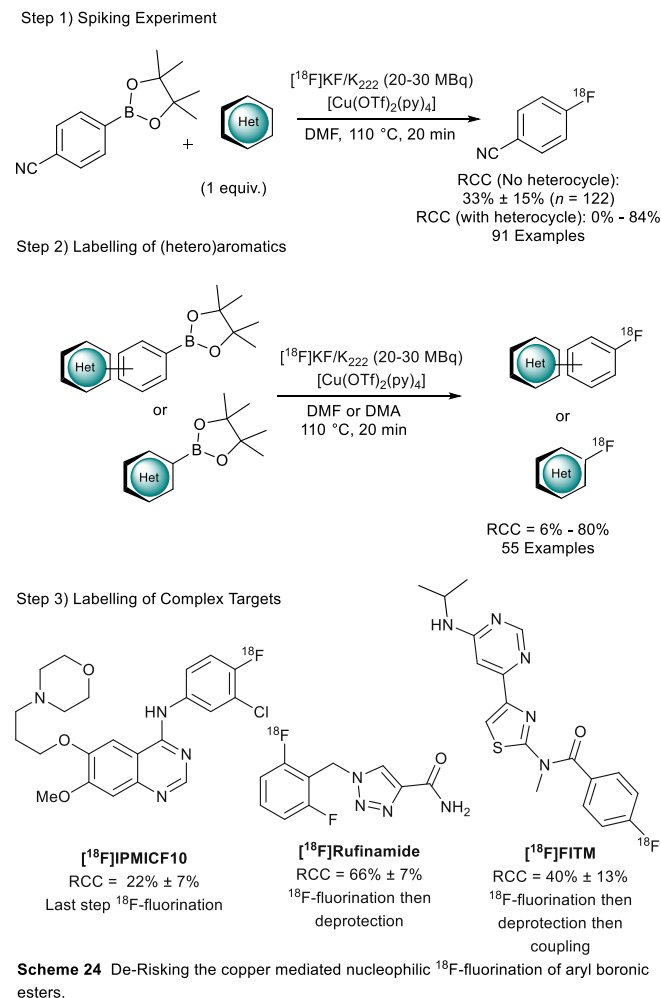
electron-poor boron reagents enabled access to eight clinically relevant PET tracers using up to 26 GBq [^{18}F]fluoride.⁹¹ Key optimisation parameters include change of solvent (DMA instead of DMF), the ratio between the boron reagent and the copper complex, and/or cartridge pre-conditioning ($\text{K}_2\text{C}_2\text{O}_4$ instead of K_2CO_3).



Scheme 23 A) Nucleophilic ^{18}F -fluorination of boronic esters. B) Copper mediated ^{18}F -fluorination of eight clinically relevant PET tracers. DMA: *N,N*-dimethylacetamide.

In 2017, an in-depth evaluation of the scope and limitation of the copper-mediated ^{18}F -fluorination of (hetero)aryl boronic species was accomplished.⁸⁹ The approach inspired by the robustness screening technique of Collins and Glorius,⁹² consisted of assessing the compatibility of the methodology with close to 100 heterocycles and carrying out the ^{18}F -labelling of over 50 small molecules all containing at least one heterocyclic ring. The large data set arising from this study proved extremely useful for designing low-risk retro-

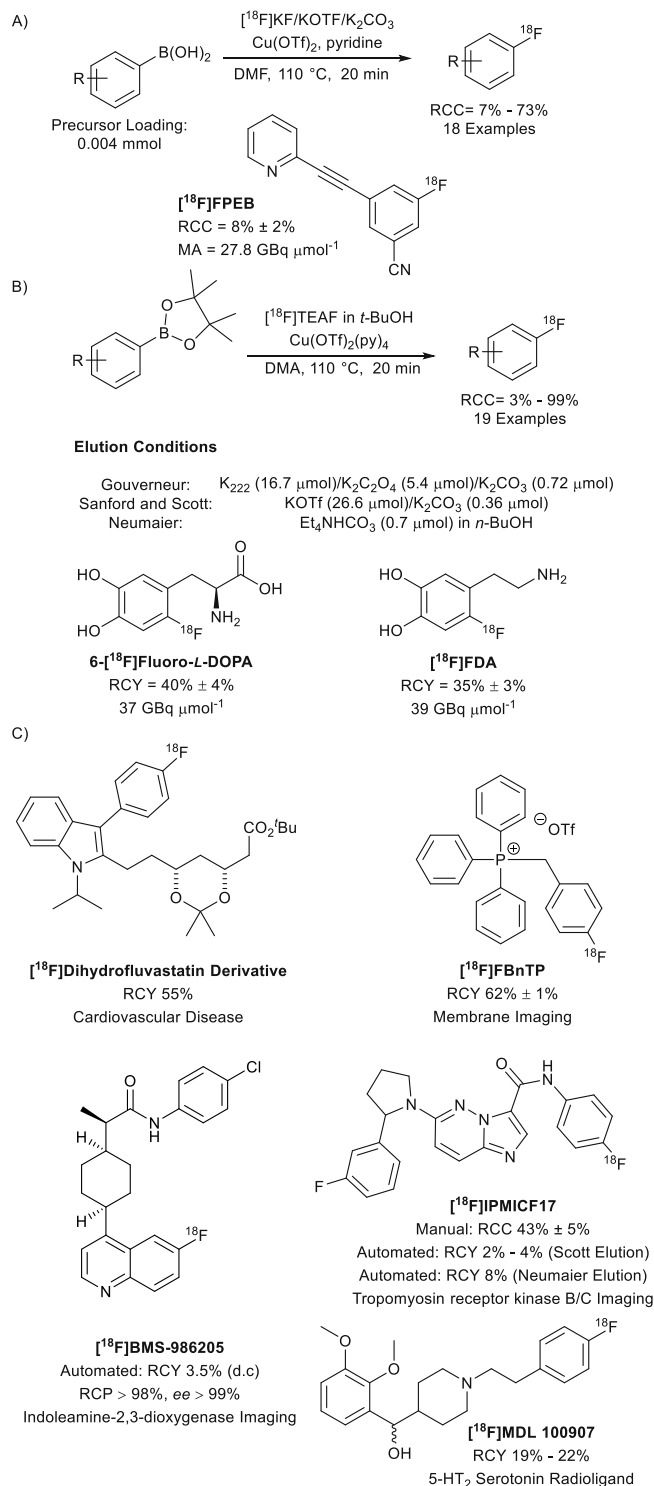
radiosynthetic routes for complex targets. Rewardingly, this rational approach culminated in the successful radiosynthesis of seven complex targets labelled applying one of three strategies: 1) last step ^{18}F -fluorination, 2) ^{18}F -fluorination followed by a single conventional deprotection step, and 3) more than one step post ^{18}F -labelling (Scheme 24).⁸⁹



In 2015, the groups of Sanford and Scott reported a similar copper mediated ^{18}F -fluorodeboronation of aryl boronic acid precursors. The authors noted the sensitivity of the reaction to high levels of base, their optimized conditions for the elution of ^{18}F -fluoride using a 73:1 molar ratio of $\text{KOTf}:\text{K}_2\text{CO}_3$.⁹³ Following azeotropic drying, the pre-formed tetrakis pyridine copper(II) triflate could be conveniently replaced by $\text{Cu}(\text{OTf})_2$ in the presence of pyridine. Whilst this study had a similar substrate scope to that of Gouverneur,⁹⁰ the lower precursor loading is advantageous, particularly for complex, expensive precursors.

In 2017, both Scott and Neumaier disclosed in-depth studies for the optimisation of the ^{18}F -fluoride elution for the ^{18}F -fluorodeboronation of aryl pinacol boronic esters and boronic acids.^{94,95} In the latter case, Neumaier and co-workers demonstrated that a solution of tetraethylammonium bicarbonate in alcohol solvents, ideally *n*-butanol, could be used

to elute the ^{18}F -fluoride. Applying this elution procedure, 6- ^{18}F fluoro-*L*-DOPA and ^{18}F FDA could be isolated in good radiochemical yields.



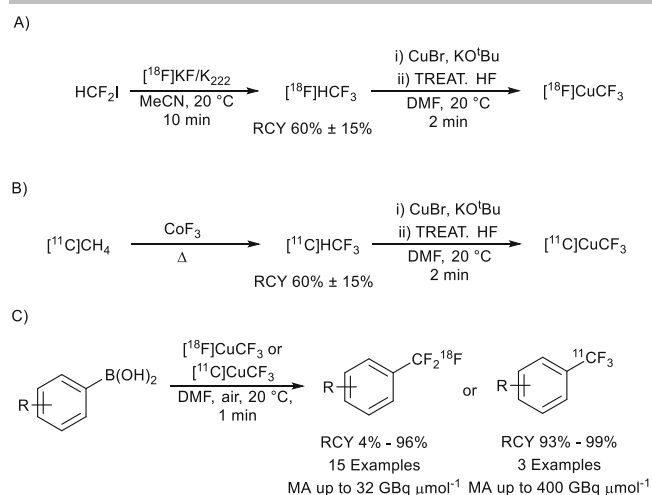
Scheme 25 A) Copper mediated nucleophilic ^{18}F -fluorination of boronic acids B) Elution studies for the copper mediated nucleophilic ^{18}F -fluorination C) Selected examples for the application of the copper mediated nucleophilic ^{18}F -fluorination.

illustrated by its successful implementation and application in laboratories worldwide (Scheme 25C). Selected examples include the ^{18}F -fluorination of ^{18}F dihydrofluvastatin analogue,⁹⁶ ^{18}F fluorobenzyl triphenylphosphonium triflate,⁹⁷ ^{18}F volinanserine ([^{18}F]MDL100907) and [^{18}F]IPMICF17.^{98,99} Subsequently, using elution conditions reported by Neumaier and co-workers,⁹⁵ Scott and Schirmacher described an improved automated synthesis of [^{18}F]IPMICF17 for the imaging of Trk receptors and oncogenic Trk fusion proteins in non-human primates.¹⁰⁰ Most recently, Bonacorsi and co-workers reported the synthesis of [^{18}F]BMS-986205 in high radiochemical purity, high enantiomeric excess and suitable for clinical imaging studies. This is rapid progress for a reaction only reported as recently as 2014!¹⁰¹

^{18}F -Trifluoromethylation

The trifluoromethyl group is frequently seen in pharmaceutical drugs due to its ability to improve binding selectivity, lipophilicity and metabolic stability.^{74,102} As a result, methods have appeared to install a ^{18}F -trifluoromethyl group onto (hetero)arenes, such as for example the reaction of (hetero)aryl iodides with [^{18}F]CuCF₃ *in situ* generated from a combination of CuI, ClCF₂CO₂Me and [^{18}F]fluoride.¹⁰³ In 2014, Vugts and co-workers reported that the ^{18}F -trifluoromethylation of aryl boronic acids can be accomplished at room temperature in DMF within one minute using [^{18}F]CuCF₃ a reagent that they generated from ^{18}F -fluoroform ([^{18}F]HCF₃) (Scheme 26A).¹⁰⁴ This method affords ^{18}F -trifluoromethylated (hetero)arenes with molar activities in the range of 30 GBq μmol^{-1} (scheme 26C). Pike and co-workers pursue alternative strategies with a focus on [^{11}C]CuCF₃ as an alternative to [^{18}F]CuCF₃ aiming at increasing molar activities (Scheme 26B). Specifically, [^{11}C]HCF₃ was produced upon treatment of cyclotron-produced [^{11}C]CH₄ with CoF₃ in radiochemical yields up to 60%, and was subsequently converted to [^{11}C]CuCF₃.¹⁰⁵ Cross-coupling of this reagent with three representative aryl boronic acids gave the desired [^{11}C]CF₃-labelled products in high RCYs and vastly improved MAs (400 GBq μmol^{-1}) (Schemes 26B, 26C).

Arguably, the value of Cu-mediated ^{18}F -fluorination of aryl boron reagents as a route to access ^{18}F -(hetero)arenes is best



Scheme 26 Trifluoromethylation of boron precursors with $[^{18}\text{F}]\text{CuCF}_3$ or $[^{11}\text{C}]\text{CuCF}_3$.

Conclusion and Future Outlook

The field of radiochemistry has progressed tremendously in recent years and huge strides are being made for the labelling of small molecules as well as biomolecules. The use of boron reagents to access radiolabelled molecules has undergone a rapid expansion. Given their synthetic and commercial availabilities, it is clear as to why scientists have pursued them as precursors for radiolabelling. Nonetheless, challenges remain of which there are two clear areas that remain open to further investigations.

The first is the continued development of new radiolabelling reactions from boron reagents. Specifically for ^{18}F -labelling, whilst ^{18}F -fluorodeboronation, and ^{18}F -trifluoromethyl-deboronation transformations are well described, direct access to motifs including aryl- $[^{18}\text{F}]\text{CF}_2\text{H}$, aryl- $[^{18}\text{F}]\text{OCF}_3$, aryl- $[^{18}\text{F}]\text{SCF}_3$ would be beneficial.^{106,107,108,109} Furthermore, whilst the use of boron reagents for the construction of stereogenic $\text{C}_{\text{sp}^3}\text{-}^{19}\text{F}$ bond is well established,^{110,111} we are yet to see this transformation explored within the field of fluorine-18.

The second challenge, and arguably the more pressing one, is the need to translate those already established methodologies to molecules for pre-clinical and clinical imaging. Much effort is currently invested in developing methodologies with broad scope, high in molar activity and/or applicable to complex targets previously inaccessible. Many methodologies will require further development to be routinely adopted for GMP production.^{112,113} Although the use of metals for cross coupling with boron reagents may be seen as a drawback (Pd <1.2 ppm, Cu <17 ppm), the translation work highlighted in this review should persuade the readers of its value within the field of radiochemistry. Given the versatility of boron reagents for radiolabelling, there is no doubt that this class of precursors offer a huge opportunity for scientists looking to develop complex radiotracers for clinical imaging studies.

Notes and references

There are no conflicts to declare.

Acknowledgements

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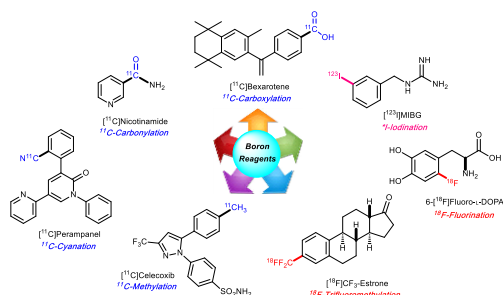
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Graphical Abstract



This review discusses boron reagents as precursors for divergent radiolabelling with a focus on carbon-11, fluorine-18 and iodine-123,-125,-131.

Biographies

Thomas Wilson:

Thomas Wilson graduated with an MChem degree from the University of York in 2014, completing his research project under the supervision of Dr William Unsworth. He is currently carrying out his DPhil at the University of Oxford under the supervision of Prof. Véronique Gouverneur. His research is focused on the development and application of novel fluorine-18 methodologies for cancer PET imaging.

Thomas Cailly:

Dr Thomas Cailly obtained his PhD from the University of Caen in 2006 under the supervision of Pr. Sylvain Rault. In 2006, he was appointed as a teaching and research assistant at the University of Caen and in 2007, a research engineer. In 2008, he joined the group of Pr. M. Begtrup at the University of Copenhagen. In 2009, he was appointed maître de conférences in bio-inorganic chemistry at the University of Caen and joined the Gouverneur group in Oxford for one year in 2014. His research interests in the Centre d'Etudes et de Recherche sur le Médicament de Normandie include: medicinal chemistry for application in diagnostics, radio-iodination methodologies and C-H activation processes.

Véronique Gouverneur:

Véronique Gouverneur secured a PhD in Chemistry at the Université Catholique de Louvain (Belgium). In 1992, she moved to a postdoctoral position at the Scripps Research Institute (California, USA). After four years as Maître de Conférence at the University Louis Pasteur in Strasbourg (France), she started her independent research career at the University of Oxford in the Chemistry Faculty and was promoted to Professor in 2008. Since her appointment in

Oxford, she holds a tutorial fellowship at Merton College. Her research published to date in > 175 peer-reviewed publications focuses on addressing long-standing problems in the synthesis of fluorinated molecules including pharmaceutical drugs and probes for imaging (Positron Emission Tomography). She has received numerous prizes and distinctions for her contribution to fluorine (radio)chemistry.