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Recent Advances in Synthetic Methods for Radioiodination

Emmanuelle Dubost, Holly McErlain, Victor Babin, Andrew Sutherland,* and Thomas Cailly*

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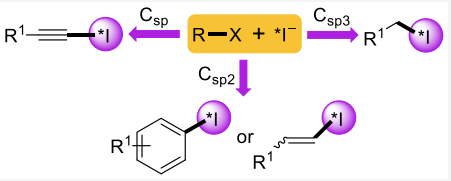
ABSTRACT: Organic compounds bearing radioisotopes of iodine are widely used for biological research, diagnostic imaging, and radiotherapy. Early reported synthetic methods for the incorporation of radioiodine have generally involved high temperature reactions or strongly oxidizing conditions. To overcome these limitations and to cope with the demand for novel radioiodinated probes, there has been a surge in the development of new synthetic methodology for radioiodination. This synopsis describes the key transformations developed recently.



Organic compounds bearing radioisotopes of iodine play a major role in nuclear medicine and molecular imaging.[1−3] As there are a number of radioactive iodine isotopes (Table 1), a single biologically or medicinally active iodinated compound can be labeled with different radioisotopes for a particular application. For example, compounds bearing iodine-123 or iodine-124 can be used for the diagnostic imaging of disease via single photon emission computed tomography (SPECT) or positron emission tomography (PET) techniques, respectively.[4−6] Radiopharmaceuticals bearing iodine-131 are used for radiotherapy, while iodine-125 labeled compounds are commonly used in preclinical, biological, and medicinal chemistry applications.

Table 1. Radioiodine Isotopes Most Commonly Used in Imaging and Therapy

isotope	half life	type of emission[a]	application
^{123}I	13.2 h	γ	SPECT imaging
^{124}I	4.18 days	β^+	PET imaging
^{125}I	59.4 days	Auger e$^-$	preclinical research and therapy
^{131}I	8.04 days	β^-	therapy

[a] γ: gamma ray emission, β^+: positron emission, β^-: electron emission.

The importance of radioiodinated probes and agents in nuclear medicine and imaging has required the development of efficient synthetic methods for the preparation of these compounds.[4−6] In a similar manner to conventional synthetic chemistry, the aim of these methods is to produce radioiodinated compounds as efficiently as possible. In radiochemistry, this is measured using RadioChemical Yield (RCY, the amount of activity in the isolated product expressed as a percentage of starting activity) or RadioChemical Conversion (RCC, the amount of activity in the nonisolated product, usually obtained from a radio-HPLC and expressed as a percentage of starting activity) and RadioChemical Purity (RCP, the percentage of activity of the radionuclide with respect to the total activity of all radionuclides in the sample).[7] The other important property of radioiodinated compounds is Molar Activity (A_m, the measured radioactivity per mole of compound, typically expressed as becquerels per micromole). For imaging applications, radiolabeled compounds with high molar activity are important to generate actual tracer conditions, where the biological target is mainly bound with radioactive compounds and not nonradioactive species. The level of molar activity required for imaging is highly dependent on the context and biological target. However, in developing radioiodination methods, final compounds with molar activities in the GBq.μmol^{-1} range of magnitude are considered suitable. Unlike the radioisotopes commonly used in PET imaging (e.g., ^{11}C, ^{18}F), the radioisotopes of iodine have relatively long half-lives and for this reason, synthetic methods for radioiodination are more varied.[4−6,8−11] As radioiodine isotopes are produced in iodide form,[12] early reported methods have involved nucleophilic substitution reactions, such as the use of high temperature and solid state halogen exchange reactions (e.g., Scheme 1).[13] Alternatively, radioactive iodide can be oxidized to iodine or iodine monochloride and used in electrophilic substitution reactions, such as the iododestannylation of aryltin compounds.[14]

Although these methods allow the iodination of various compounds with high RCY and RCP, the harsh reaction conditions, challenging purifications (such as the removal of organotin residues) and the need for more varied and sometimes complex targets have required the development of new radioiodination reactions. To meet this demand, a variety of new transformations for the incorporation of radioiodine

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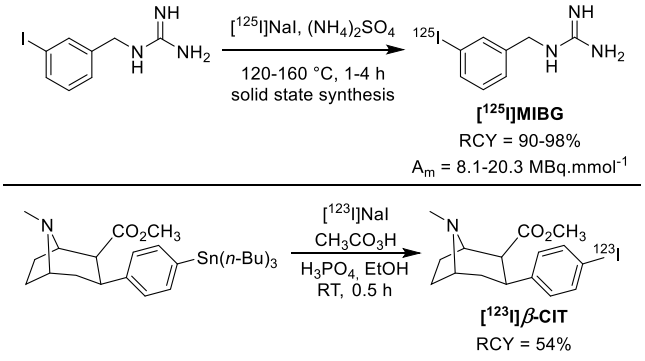
Scheme 1. Early Methods of Radioiodination[13,14]

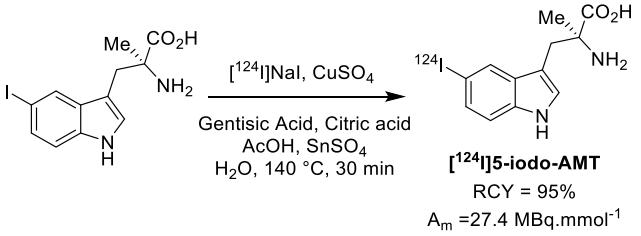


into organic compounds have been developed in recent years. This synopsis describes these key synthetic advances and in particular, the main transformations used for the preparation of radioiodine bonds with C_{sp}, C_{sp2}, and C_{sp3} centers.

1. RADIOIODINATION OF $C_{SP}{}^2$ CENTERS

1.1. Nucleophilic Aromatic Substitution Reactions. *Isotopic and Halogen Exchanges.* Direct replacement of stable iodine isotopes on organic molecules by a radioiodine isotope, also called isotopic exchange, is a well-known procedure. The reaction is usually performed neat, with the radioiodide ion, at very high temperature and most often in the presence of sulfate salts and oxidants such as dioxygen from the air (Scheme 1).[13] Isotopic exchange can also be realized in water at high temperature, but in this case, addition of copper sulfate as a reagent has been evidenced to both promote the radioiodination and shorten reaction times (Scheme 2).[13,15,16]

Scheme 2. General Isotopic Exchange Procedure[13,16]

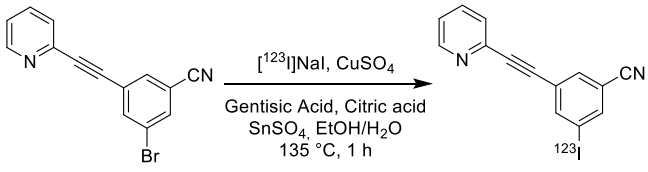


However, due to the impossible separation of nonradioactive and radioactive iodinated products, this method is not suitable to access radioiodinated molecules in the GBq·μmol^{-1} range of magnitude.

In order to restore optimal molar activities, bromine−iodine exchanges can be performed using the same conditions as isotopic exchanges. Thus, in 2014, Brownell et al. described the radioiodination of [^{123}I]IPEB, a metabotropic glutamate receptor subtype 5 radioligand, through bromine−iodine exchange at high temperature in the presence of copper and tin sulfate (Scheme 3).[17] Solid-state synthesis can also be used. For example, the radiosynthesis of a Matrix MetalloProteinase-12 (MMP-12) iodinated probe was described by Mukai in 2018.[18] Overall, bromine−iodine exchange appears to give comparable RCYs as isotopic exchange along with higher molar activities but in all cases at the cost of very harsh reaction conditions.

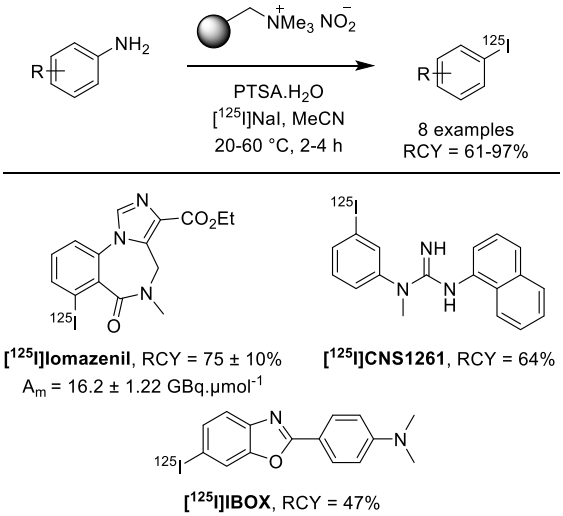
Diazo and Triazene Leaving Groups. In 2017, Sutherland et al. described an efficient methodology to radioiodinate aryl

Scheme 3. Typical Bromine−Radioiodine Exchange Procedure[17]



amines via stable diazonium salts (Scheme 4).[19] This methodology is based on the use of widely available starting

Scheme 4. Radioiodination of Aryl Amines through Diazotization by Sutherland[19]



materials and a polymer supported nitrite reagent, which allowed both the formation of diazonium salts and the subsequent Sandmeyer reaction to take place under mild conditions. The incorporation of the radioiodine atom was done thereafter using sodium iodide. This one-pot methodology was used on eight example substrates, demonstrating its functional tolerance, as well as generating several SPECT tracers, including [^{125}I]iomazenil, [^{125}I]CNS1261, and [^{125}I]IBOX with RCYs between 47 and 75%. Triazene derivatives can also be used in S_NAr reactions; however, even if these precursors are stable and can be isolated, they are usually less reactive than the corresponding diazonium salts.[20,21]

Iodonium Leaving Groups. In 2016, Gestin et al. published a systematic study aimed at comparing the reactivity of aryliodonium salts in radiolabeling using either sodium iodide or astatide.[22] Their investigations showed that the use of acetonitrile as solvent, at 90 °C, with iodonium sulfonate were the optimal conditions to perform efficient radioiodination from iodonium salts. The regioselectivity of the nucleophilic substitution of unsymmetrical iodoniums salts was found to be controlled by electronic and steric effects. The same authors have used this methodology to radiolabel activated esters acting as prosthetic groups able to bind biomolecules. Thus, *N*-[^{125}I]succinimidyl-3-iodobenzoate ([^{125}I]SIB) was obtained in 36−87% RCY, depending on the nature of the electron-rich

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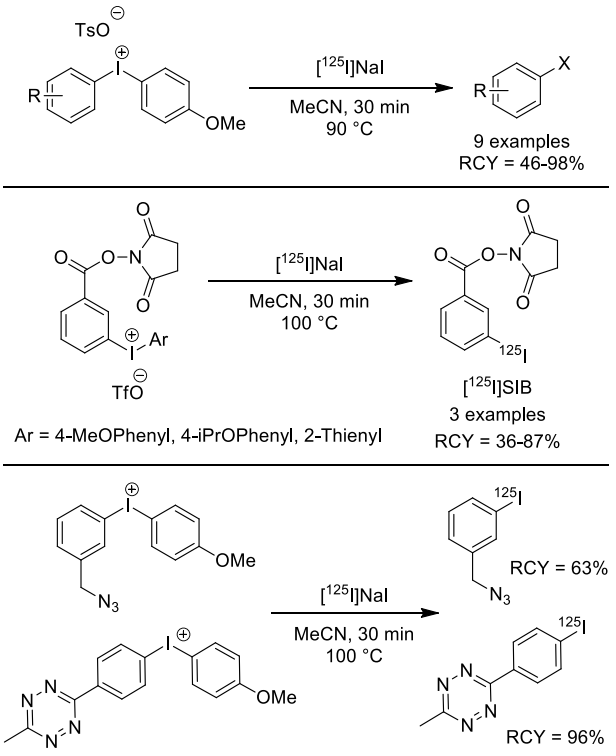
arene moiety (Scheme 5).[23] In 2019, this methodology was applied to the radiolabeling of two other prosthetic groups, for

Scheme 5. Radioiodination Using Iodonium Salts as Precursors by Gestin[11,22,23]

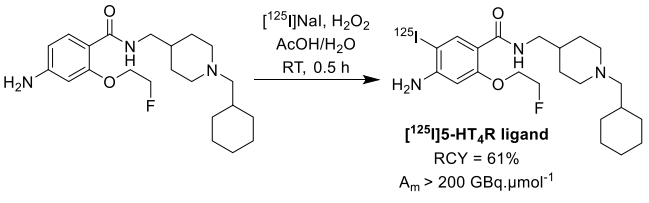


attachment to biomolecules by either click chemistry or inverse-electron-demand Diels–Alder reactions.[11]

1.2. Electrophilic Aromatic Substitution Reactions. Electrophilic aromatic substitution is a very popular strategy to perform radioiodination, which can be applied either directly with the compound of interest or using a prefunctionalized precursor. Nevertheless, this procedure requires the generation of an electrophilic iodine species, which is typically prepared from sodium iodide and a strong oxidant such as hydrogen peroxide, peracids, *N*-halosuccinimides, or *N*-chloroamides.

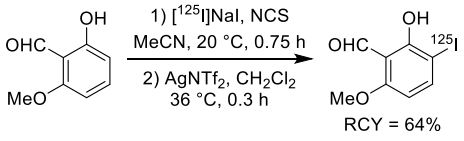
Direct S_EAr. Direct electrophilic aromatic substitution is a typical process to perform radioiodination of aromatic molecules.[24] Generally, this strategy exhibits low regioselectivity unless there has been careful choice of starting compound. In these cases, the reaction can lead to the radioiodinated compound with good RCY and high molar activity. For example, this approach has been used for the direct and regioselective radioiodination of the 4-aminobenzoic core found in numerous 5-HT_4 receptor ligands (Scheme 6).

Scheme 6. Typical Radioiodination through Direct Electrophilic Aromatic Substitution[24]



In 2016, a silver-catalyzed radioiodination was reported, which used the mild Lewis acid nature of a silver triflimide salt, avoiding the poly iodination of activated aromatic rings (Scheme 7).[25] The completely regioselective radioiodination

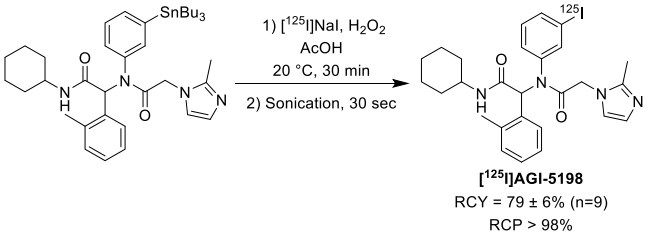
Scheme 7. Silver(I) Triflimide Mediated Electrophilic Radioiodination[25]



of electron-rich substrates (as observed by nonradioactive reactions) facilitated by this method has enlarged the panel of substrates accessible to direct S_EAr reactions. Nevertheless, to overcome the regioselectivity issues of other S_EAr strategies, the preparation of stannylated, silylated, or boronated precursors is generally required to perform *ipso* S_EAr.

Iododestannylation. Iododestannylation is the most used methodology to perform radioiodination in research facilities.[1−5] Starting from a stannane precursor, using an in situ generated iodinated reagent from NaI and an oxidant, the transformation proceeds smoothly and selectively to afford, via an *ipso* S_EAr reaction, the radiolabeled derivatives. Despite issues concerning their stability and toxicity, aryltrialkylstannanes are generally prepared from the corresponding halogenated precursor through metalation or palladium-mediated reactions. The major drawback of this reliable method, often hampering its use in clinics, is the contamination of the obtained radiotracer with organotin residues. Nevertheless, radioiododestannylation is currently the main method of choice to perform radioiodination and many small molecules used as radiotracers, such as [^{125}I]AGI-5198, have been prepared accordingly (Scheme 8).[26]

Scheme 8. Radioiodination of [^{125}I]AGI-5198 Using Radioiododestannylation[26]



Several approaches have been described recently to specifically address the purification issues inherent to iododestannylation. In 2006, the Valliant group employed fluorine-rich organostannane to perform radioiododestannylation in order to discard organotin residues through fluorous solid-phase extraction (Scheme 9). Thus, labeling with [^{125}I]NaI in the presence of the oxidant, iodogen allowed the quick formation of the radiolabeled derivatives with RCYs up to 85% and RCPs up to 98%.[27] This method was used by the same group to produce [^{125}I]iodoxuridine and [^{125}I]FIAU, with RCYs of 94 and 88%, respectively, while allowing the efficient removal of organotin precursors through a simple filtration technique as evidenced by a UV-HPLC technique.[28]

A similar approach was proposed by the Gestin group in 2016, using an ionic liquid supported stannylated precursor for

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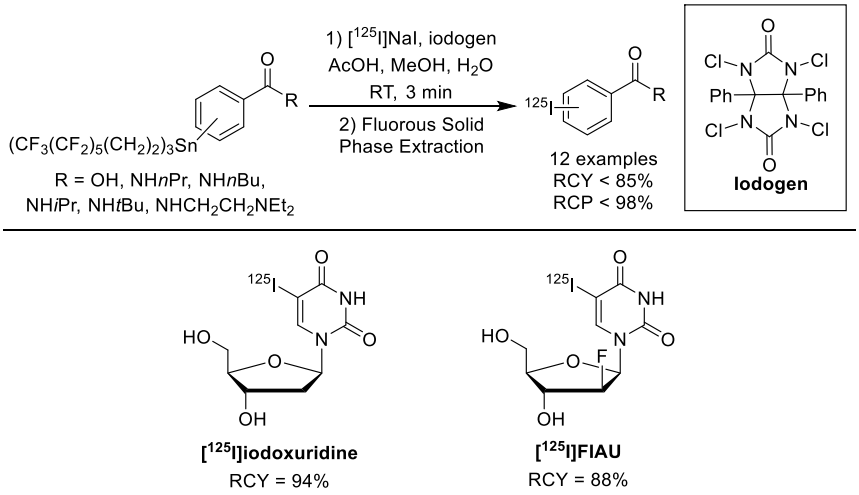
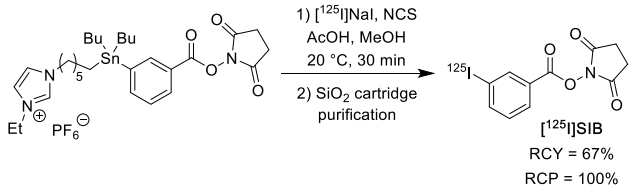
Scheme 9. Radioiododestannylation Using Fluorine-Rich Organostannanes by Valliant[27,28]



radiolabeling (Scheme 10).[29] This strategy significantly facilitated the formation and purification of the product,

Scheme 10. Radioiododestannylation Using Ionic Liquid Supported Organostannane by Gestin[29]



using a simple SiO_2 filtration to separate radio-iodinated product and organotin precursor, allowing the isolation of [^{125}I]SIB with 67% RCY and 100% RCP.

In the challenging field of biomolecules radiolabeling, taking into account synthetic efficacy, half-lives and/or safety issues, the introduction of the radionuclide is preferred at the last step of the radio-synthesis. This late stage diversification is generally achieved using a prosthetic group strategy in order to reach selectivity toward the radio-labeling site. Several prosthetic groups have been radioiodinated using an iododestannylation approach (Scheme 11). For example, [^{125}I]1,2,4,5-tetrazines[30,31] and a [^{125}I]benzamide moiety[32] have been efficiently prepared using iododestannylation and then attached to the target biomolecules using inverse electron demand Diels–Alder and copper-catalyzed condensation reactions, respectively.

Iododesilylation. Silanes can be used as precursors for the labeling of molecules of interest. However, compared to iododestannylation, the obtained RCYs are generally lower due to the higher stability of the carbon–silicon bond. This methodology has nevertheless been used to label specific substrates with success, generally in acidic media, starting from an activated precursor and an electrophilic source of iodine. For example, in 1993, [^{131}I]MIBG was labeled in 85–90% RCY by Zalutsky,[33] starting from the corresponding aryltrimethylsilane in TFA, using trifluoroperacetic acid to generate [^{131}I]I_2 in situ (Scheme 12).

In 2016, Tanaka et al. described a polymer-supported version of the radioiododesilylation applied to the radio-iodination of iodometomidate (IMTO), a high affinity ligand of adrenal steroidogenic enzymes, from a polymethacrylamide-supported precursor (Scheme 13).[34] Solid-phase organic chemistry enabled reaction products to be purified rapidly and simply by filtration. In this work, the radioiododesilylation was performed in TFA and used *N*-chlorosuccinimide (NCS) to promote the formation of [^{125}I]NIS in situ. After 1 h at 40 °C, TFA was neutralized with a polymer supported amine, and the purification step of [^{123}I]IMTO was performed through elution on a Sep-Pak cartridge, while the unreacted polymethacrylamide-supported precursor was unable to be eluted. The radiotracer was obtained in 85% RCY and 94% RCP.

Iododeboronation. The use of boron derivatives to promote electrophilic radioiodination is well-known and was first described using boronic acids (Scheme 14). Initially, the reaction was used to radiolabel a barbituric acid analogue using chloramine-T to oxidize [^{125}I]NaI, with a 15% RCY.[35] Thereafter, the reaction was performed in aqueous HCl and substantial improvements of the RCYs were observed for the formation of an [^{131}I]amphetamine analogue[36] and 7-[^{123}I]-iodocognex obtained, respectively, with 86 and 66% RCYs.[37]

In 2019, iododeboronation from boronic acids was reinvestigated by the Sutherland and Watson groups (Scheme 15).[38] In this work, the role and positive contribution of a Lewis base was clearly evidenced. Thus, using NCS as an oxidant and a catalytic amount of KOAc to promote in situ formation of a boronate, the radioiodination of a variety of arenes bearing electron-donating or -withdrawing groups was achieved with RCYs between 49 and 99%. This was further employed for the radioiodination of biologically active targets, such as [^{125}I]5-iodouracil, which was generated with a molar activity of 0.53 GBq·μmol^{-1}.

Ipso-iododeboronation is also possible starting from boronate derivatives (Scheme 16). The reaction has been extensively investigated by Kabalka. Using chloramine-T as an oxidant and under very mild conditions, iododeboronation of electron rich-neopentylglycolboronic esters or aryltriolborates has led to the expected radioiodinated arenes.[39,40] A similar approach has been developed by the same authors using polymer supported organotrifluoroborates, which allowed easier purification of the radioiodinated compounds.[41] Nevertheless, poor RCYs are obtained when electron-poor arenes are used in these reactions.

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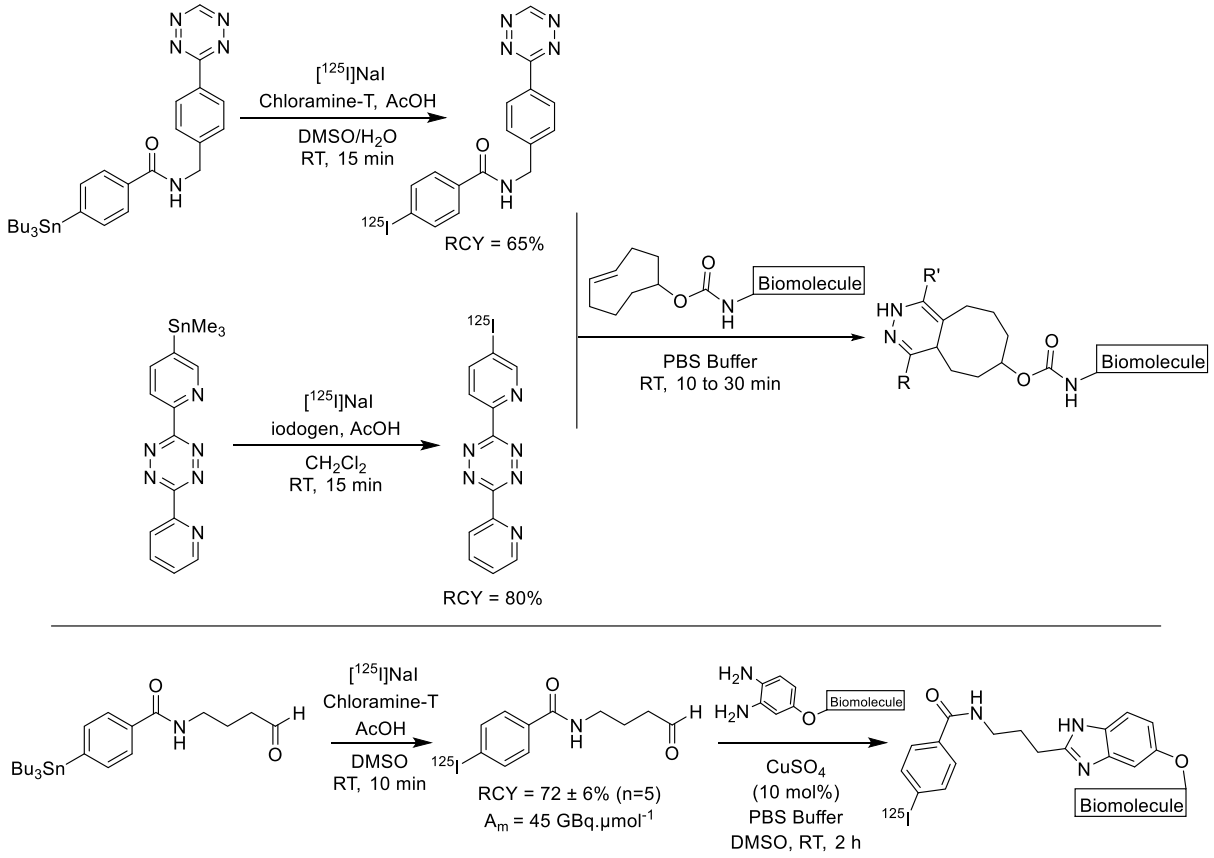
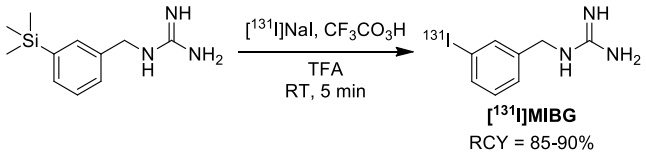
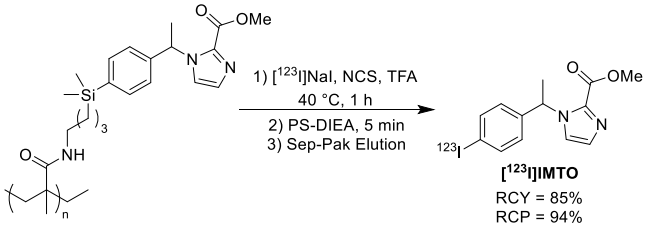
Scheme 11. Radioiodination of Biomolecules Using Prosthetic Groups and Iododestannylation[30−32]



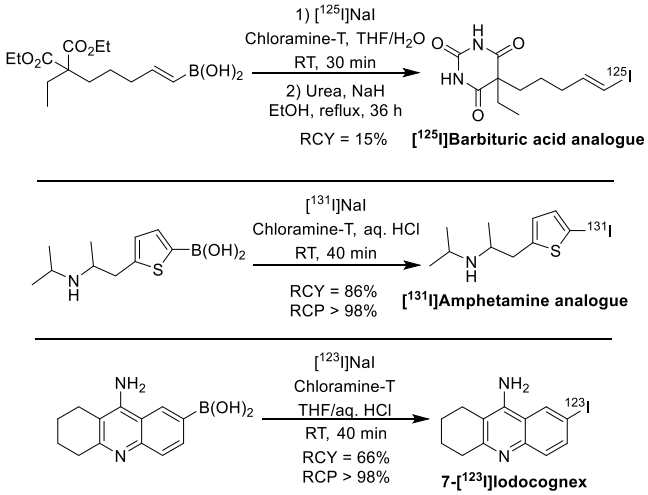
Scheme 12. Radioiododesilylation by Zalutsky[33]



Scheme 13. Radioiododesilylation and Polymer-Supported Radioiododesilylation by Tanaka[34]



Scheme 14. Electrophilic Iododeboronation from Boronic Acids[35−37]



1.3. Transition-Metal-Mediated Approaches. The purification issues associated with the common method of the radio-iododestannylation method have necessitated the development of other metal mediated processes for the radioiodination of aryl compounds. The main advantage of many of these methods is the more facile removement of "inorganic" metal complexes, compared to organotin residues.

Transition-Metal-Mediated Halogen Exchange. Bromine/iodine exchanges have been reinvestigated by Sutherland et al. in 2013 using a nickel(0) mediated approach (Scheme 17).[42] The reaction proceeded by oxidative addition of Ni(0) into the aryl C−Br bond, followed by radioiodide exchange of the resulting Ni(II)−Br species. Reductive elimination generated the new C−I* bond and allowed the preparation of various aryl and heteroaryl iodides with RCYs between 88 and 96%. The radiolabeling of SPECT tracers [^{125}I]iniparib and 5-[^{123}I]A85380 were also achieved with RCYs of 46 and 93%, respectively. In addition, the molar activity of 5-[^{123}I]A85380 was found to be 37 GBq·μmol^{-1}. The products of this method were analyzed by atomic absorption spectroscopy, demonstrating the absence of any nickel impurities and highlighting the advantage of using such an approach over more typical iododestannylation procedures.

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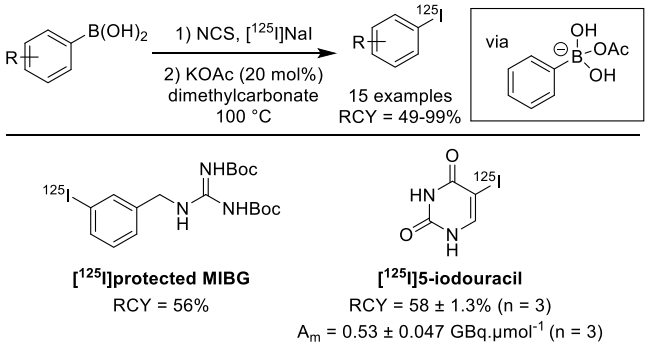
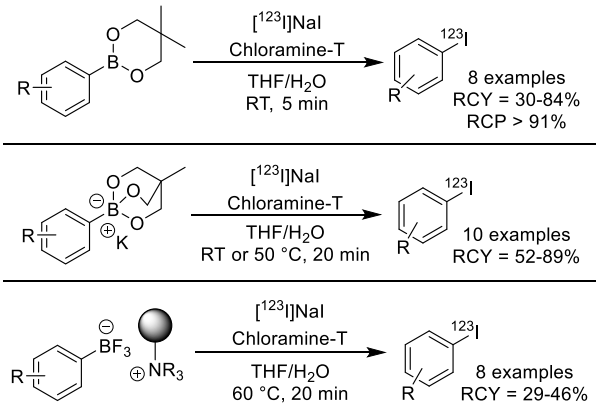
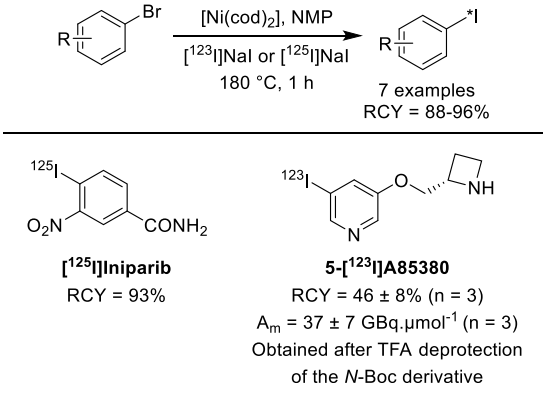
Scheme 15. KOAc-Catalyzed Iododeboronation by Sutherland and Watson[38]



Scheme 16. Electrophilic Iododeboronation from Boronic Esters and Boronates by Kabalka[39−41]

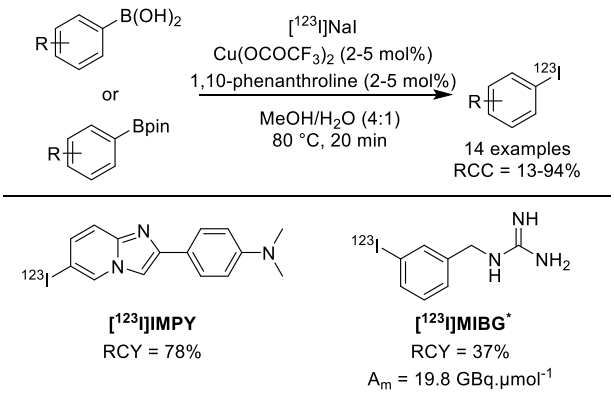


Scheme 17. Nickel-Mediated Halogen Exchange[42]



Copper-Mediated Iododeboronation. In 2016, Gouverneur and co-workers described the first copper(II)-mediated nucleophilic radioiodination of aryl boronic species following a Chan−Lam mechanism (Scheme 18).[43] Using conditions of 80 °C for 20 min in the presence of 1,10-phenanthroline as ligand, the reaction was tolerant of a broad scope of arenes bearing both electron-donating and -withdrawing groups, affording RCCs between 13 and 94%. The reaction was applicable to both boronic acids and esters, although the use of boronic acids led to a slightly lower RCC than with pinacol boronic esters. This methodology was also applied to the successful radiolabeling of various SPECT radiotracers with RCYs between 37 and 88%.

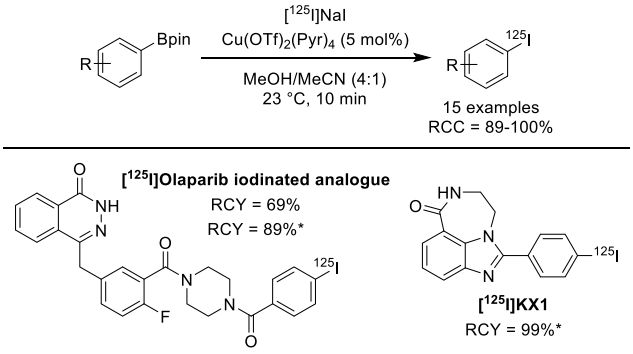
Scheme 18. Copper(II)-Mediated Iododeboronation by Gouverneur[43]



*Obtained after TFA deprotection of the *N*-Boc derivative

A similar approach was developed by Mach et al. in 2018 using a copper(II) catalyst (Scheme 19).[44] This procedure

Scheme 19. Copper(II)-Mediated Iododeboronation by Mach[44]



*3,4,7,8-Tetramethyl-1,10-phenanthroline (5 mol %) was added to the reaction.

allowed the efficient radioiodination of a variety of pinacol boronic esters under milder conditions (MeOH/MeCN 4:1, 23 °C for 10 min). The same mild reaction conditions were also successfully applied to boronic acids, neopentylglycolboronic esters, potassium trifluoroborate salts, as well as MIDA derivatives. Using pinacol boronates, this methodology was applied to the radiolabeling of iodinated olaparib analogues and for the preparation of [^{125}I]KX1 with RCYs between 61 and 99%.

Concomitantly to the Gouverneur work, Zhang et al. published an iododeboronation procedure starting from boronic acids using a copper(I) catalyst, Cu_2O (Scheme 20).[45] Using iodine-131 as the radioisotope, the reaction occurred smoothly at room temperature in one hour, achieving RCCs between 87 and 99%. This procedure was applied to the radiolabeling of MIBG as well as succinimidyl *p*-iodobenzoate (SIB).

Gold-Mediated Iododeboronation. In 2018, Sutherland et al. described the first homogeneous gold catalysis procedure for the radio-iododeboronation of aryl boronic acids (Scheme 21).[46] The air tolerant method was performed using a gold(I) complex, an electrophilic source of iodine, generated from NCS and [^{125}I]NaI, in the eco-friendly solvent dimethyl carbonate. The transformation allowed the radiolabeling of

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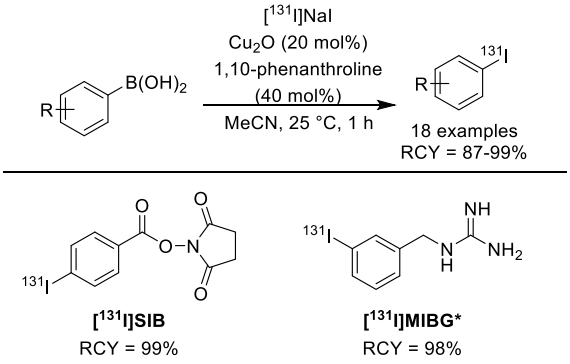
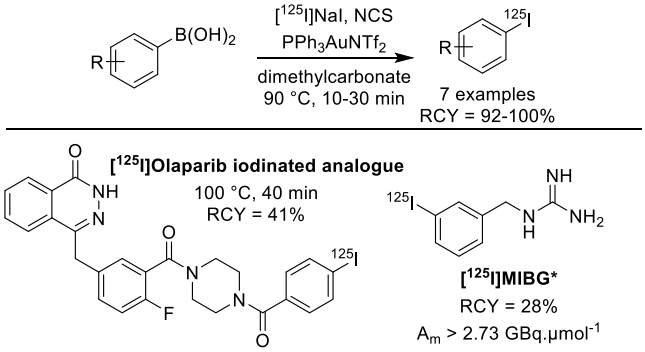
Scheme 20. Copper(I)-Mediated Iododeboronation by Zhang[45]



*Obtained after TFA deprotection of the *N*-Boc derivative.

Scheme 21. Gold(I)-Mediated Iododeboronation by Sutherland and Lee[46]



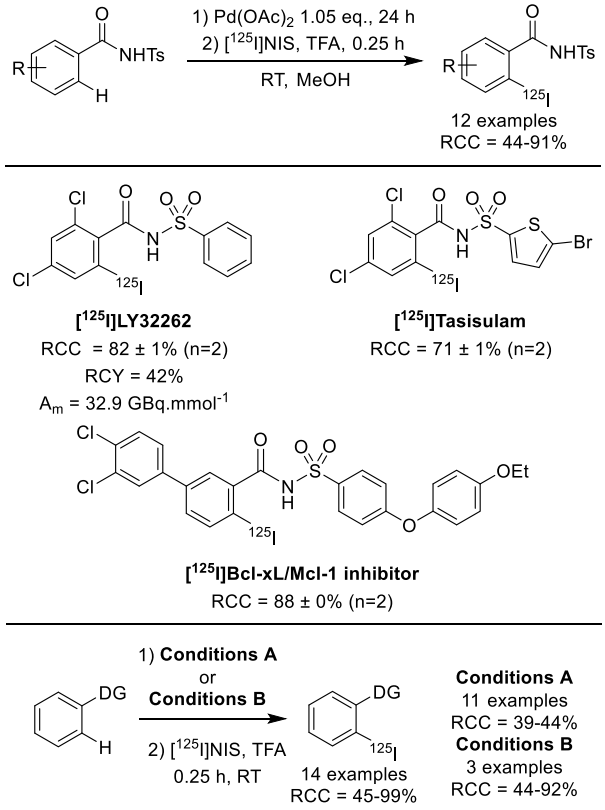
*Obtained after HCl deprotection of the *N*-Boc derivative.

electron donating and electron withdrawing substituted arenes with RCYs between 92 and 100%. Two radiotracers, [^{125}I]MIBG and a radioiodinated olaparib analogue were prepared following this procedure, with RCYs of 28 and 41%, respectively. The molar activity of [^{125}I]MIBG was up to 2.73 GBq·μmol^{-1}.

Click Chemistry. In 2013, Yan and Årstad proposed a one-pot radioiodination of 1,2,3-triazoles using copper(I)-mediated click chemistry (Scheme 22).[47] Their protocol promoted the formation of highly functionalized radioiodinated triazoles through 1,3-dipolar cycloaddition, generating a vinyl copper intermediate that underwent iododecupration. In 2018, this strategy was applied to the synthesis of a multimodal triazole imaging probe decorated with a fluorophore and incorporating iodine-124.[48]

C−H Radioiodination. In 2018, the group of Cailly applied palladium-mediated C−H activation processes to the field of radioiodination.[49] Their first efforts were focused on the use of *N*-acylsulfonamide as a directing group with palladium acetate to promote the formation of palladacycles (Scheme 23). Thus,

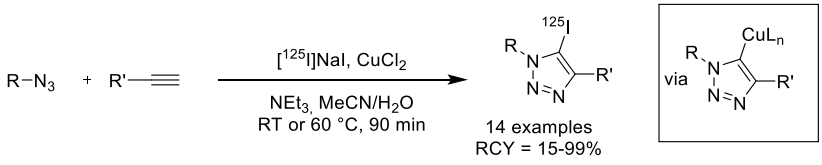
Scheme 23. C−H Radioiodination by Cailly[49,50,a]



[a]Conditions and directing groups (DG). Conditions A: $Pd(OAc)_2$ 1.05 equiv, PTSA 2 equiv, MeOH, 24 h, rt with DG = −NHAc, −NHCOPh, −NMeCOPh, −NHBoc, $-CONH_2$, $-CONMe_2$ −CON(OMe)Me, −CN, $-CH_2CN$, −*N*-pyrrolidin-2-one, and −NHCONH(*iso*Bu). Conditions B: $PdCl_2$ 1.05 equiv, MeCN, 24 h, 80 °C with DG = $-CO_2H$, $-CH_2CO_2H$, and −*N*-pyrrazolyl.

crude palladacycle solutions were prepared and reacted with an [^{125}I]NIS solution obtained from NCS and [^{125}I]NaI. Radioiodination was carried out smoothly at room temperature in 15 min after mixing of the two solutions and afforded RCCs between 44 and 91%. This strategy was also applied to the labeling of antitumoral *N*-acylsulfonamides and radioiodinated analogues of LY32262, tasisulam, and a Bcl-xL/Mcl-1 inhibitor. The reaction was then extended to other directing groups such as anilides and carboxamides derivatives, *N*-Boc-protected anilines, urea, pyrrazolyl, carboxylic acids, and nitriles. In 2019, an improvement of this methodology was reported,[50] allowing reduced amounts of palladium acetate (2 mol %) and PTSA (3 mol %), while maintaining RCCs. This new protocol led to an improvement in the purity of the crude mixture through abolition of nonradioactive side reactions, as well as an easier implementation, with palladacycle formation in several minutes instead of 24 h.

Scheme 22. One-Pot Radioiodinated 1,2,3-Triazole Synthesis by Yan and Årstad[47]



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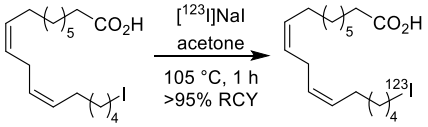
2. RADIOIODINATION OF C_{SP}^3 CENTERS

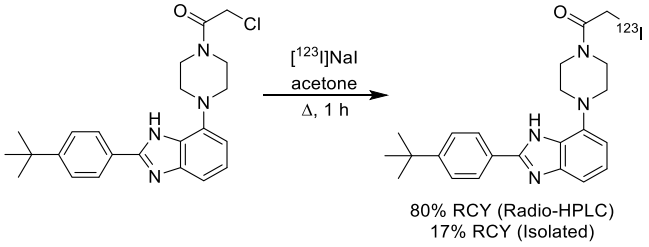
Radioiodine can be introduced into aliphatic groups using nucleophilic substitution reactions involving the displacement of typical leaving groups with radioiodide under Finkelstein conditions.[51] While the lability of the Csp^3–I bond has restricted the widespread use of these types of compounds for in vivo imaging, probes have been synthesized via Finkelstein-type reactions for specific applications.[51] Early methods involving direct exchange of nonradioactive iodide with radioiodide were employed for this type of process. Generally, isotopic exchange reactions produce radiolabeled compounds in modest molar activity due to competition between the radioactive and nonradioactive species.[52] Despite this issue, this approach was used in 2013 for the preparation of ^{123}I-labeled fatty acids (Scheme 24).[52] Reaction of the iodinated fatty acids in acetone with [^{123}I]iodide gave the corresponding ^{123}I-labeled compound with a RCY higher than 95%.

Scheme 24. Aliphatic Radioiodination Using Isotopic Exchange[52]



To overcome molar activity issues and aid separation of starting materials and products, sulfonate[53] or halogenated precursors are more commonly used.[51] Simple halogen exchange, through reaction of an alkyl bromide with [^{123}I]iodide, was used to prepare radioiodinated rhenacarborane complexes as potential drug delivery agents for the central nervous system.[54] Accelerated radioiodination via nucleophilic substitution of an alkyl chloride by amide group anchimeric assistance has also been recently studied.[55] Biologically active amines were initially acylated with chloroacetyl chlorides. Various approaches were then used to study the rates and mechanism of iodination, with 5-membered and 6-membered intermediates generated from the corresponding chloroamides benefiting from amide group anchimeric assistance. Nevertheless, shorter chain acyl chlorides were also rapidly radioiodinated (Scheme 25).

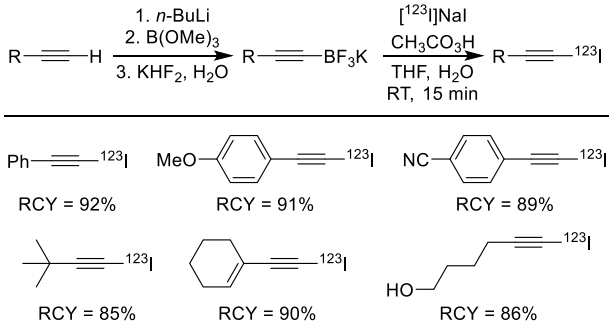
Scheme 25. Radioiodination of a Chloroamide via a Finkelstein-Type Reaction[55]



3. RADIOIODINATION OF C_{SP} CENTERS

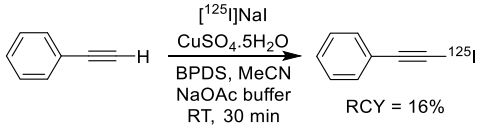
Methods for the radioiodination of C_{sp} centers and, in particular, alkynes are rare. Nonetheless, the relative metabolic stability of alkynes compared to various aryl groups and the highly chemoselective reactions that can be achieved with terminal alkynes have led to the development of radioiodination methods for the preparation of iodinated alkynes. Kabalka and Mereddy showed the efficient radioiodination of alkynyltrifluoroborates using [^{123}I]iodide under oxidative conditions.[56] Initially, the alkynyltrifluoroborates were prepared by lithiation of terminal alkynes followed by reaction with trimethylborate and then KHF_2 (Scheme 26). Radioiodination was achieved by peracetic acid in situ oxidation of sodium [^{123}I]iodide and subsequent iododeboronation of the alkynyltrifluoroborates. This gave a range of radioiodinated alkynes with RCY between 85 and 92%.

Scheme 26. Radioiodination of Alkynyltrifluoroborates under Oxidative Conditions[56]



Direct radioiodination of terminal alkynes has been achieved using stoichiometric amounts of copper(II) salts (Scheme 27).[57] The method which used bathophenanthrolinedisulfonic acid (BPDS) to solubilize the copper species was proposed to involve copper(II) oxidation of sodium [^{123}I]iodide. The resulting electrophilic iodine species then underwent an iododehydrogenation of the alkyne via a copper acetylide intermediate. In a proof of concept study, this allowed radioiodination of phenylacetylene after 30 min in 16% RCY.

Scheme 27. Direct Radioiodination of Phenylacetylene Using Copper(II) Salts[57]



4. CONCLUSION

Radioiodinated compounds are widely used for a range of applications across various fields of medicinal and biological sciences. In combination with PET and SPECT technologies, these compounds are now well established for the noninvasive in vivo visualization and diagnosis of disease. Despite this importance, the preparation of these compounds has relied traditionally on the use of harsh conditions, strong oxidants, and toxic precursors. However, in the last two decades, significant progress has been made in developing a wide range of alternative synthetic methodology for the efficient radioiodination of organic compounds, under milder conditions. The development of these novel transformations and the radiochemical translation of existing reactions has allowed rapid and effective radioiodination of a diverse range of structural analogues, particularly aryl systems, which are commonly found in radiopharmaceuticals. This methodology can now be used to facilitate the development of novel

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radiotracers, leading to new applications in radiotherapy, the imaging of disease and the drug discovery process. Efforts are now focused on the application of these novel methods for clinical production of radioiodinated imaging agents.

AUTHOR INFORMATION

Corresponding Authors

Andrew Sutherland − *WestCHEM, School of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, United Kingdom;* orcid.org/0000-0001-7907-5766; Email: andrew.sutherland@glasgow.ac.uk

Thomas Cailly − *Normandie Univ, UNICAEN, Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), 14000 Caen, France; Normandie Univ, UNICAEN, IMOGERE, 14000 Caen, France; Department of Nuclear Medicine, CHU Côte de Nacre, 14000 Caen, France;* orcid.org/0000-0002-5262-4494; Email: thomas.cailly@unicaen.fr

Authors

Emmanuelle Dubost − *Normandie Univ, UNICAEN, Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), 14000 Caen, France*

Holly McErlain − *WestCHEM, School of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, United Kingdom*

Victor Babin − *Normandie Univ, UNICAEN, Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), 14000 Caen, France*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c00644

Notes

The authors declare no competing financial interest.

Biographies

Dr. Emmanuelle Dubost received her Ph.D. degree at the University of Caen in 2010. She then moved to CEA, Saclay where she worked as postdoctoral fellow in the Rousseau group on the synthesis and the evaluation of molecular hosts as biosensors for ^{129}Xe MRI. In 2014, she obtained a Marie Curie fellowship to join the Gouverneur's group in Oxford, UK, to undertake radiofluorination of biomarkers of hypoxia. Then she moved back to CERMN, in Caen, when she is employed as senior postdoctoral fellow. Her main research area is focused on radio-iodination and the development of biosensors for MRI applications.

Holly McErlain graduated with a 1st class MChem degree in Chemistry with Drug Discovery from the University of Strathclyde in 2017. During her undergraduate studies, she undertook an industrial placement with Sosei Heptares and a masters research project with Dr. Craig Jamieson on the synthesis of novel autotaxin inhibitors. Since 2017, she has been a Ph.D. student in the Sutherland research group, and her research is focused on the development of new methodologies for the synthesis of radio-halogenated PET and SPECT imaging agents targeting the PARP-1 and SV2A proteins.

Victor Babin received his Ph.D. from Caen-Normandy University in 2018 under the guidance of Pr. Fabis, Pr. Bouillon, and Dr. Cailly. His work was focused on the synthesis of new iodinated 5-HT$_4$ receptors radioligands and the development of new radio-iodination methodologies. In 2019, he joined the group of Dr. Taran and Dr. Audisio in CEA Paris-Saclay for a postdoctoral position where he worked on the implementation of new synthetic methodologies for carbon isotopes labeling of biologically active small molecules.

Dr. Andrew Sutherland obtained his B.Sc. Honours degree in chemistry from the University of Edinburgh. He then undertook a

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Ph.D. at the University of Bristol under the supervision of Professor Christine Willis. This was followed by postdoctoral studies with Professor John Vederas at the University of Alberta and Professor Timothy Gallagher at the University of Bristol. In January 2003, he was appointed to a lectureship in the School of Chemistry at the University of Glasgow and currently holds the position of Reader. His research group's interests are on the discovery of new radionuclide-based molecular imaging agents and the development of new radiohalogenation methodology.

Dr. Thomas Cailly obtained his Ph.D. from the University of Caen (2006) under the supervision of Pr. Sylvain Rault. In 2008, he joined the group of Pr. M. Begtrup at the University of Copenhagen (Denmark) as a postdoctoral fellow. In 2009, he was appointed maître de conférences in bioinorganic chemistry at the University of Caen and joined the Gouverneur group in Oxford for one year as a visiting scientist in 2014. He is now the diagnostic tool group leader in the Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN) in Caen.

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■ REFERENCES

(1) Adam, M. J.; Wilbur, D. S. Radiohalogens for Imaging and Therapy. *Chem. Soc. Rev.* **2005**, *34* (2), 153−163.
(2) Pimlott, S. L.; Sutherland, A. Molecular Tracers for the PET and SPECT Imaging of Disease. *Chem. Soc. Rev.* **2011**, *40* (1), 149−162.
(3) Zhu, L.; Ploessl, K.; Kung, H. F. PET/SPECT Imaging Agents for Neurodegenerative Diseases. *Chem. Soc. Rev.* **2014**, *43* (19), 6683−6691.
(4) Seevers, R. H.; Counsell, R. E. Radioiodination Techniques for Small Organic Molecules. *Chem. Rev.* **1982**, *82* (6), 575−590.
(5) Wager, K. M.; Jones, G. B. Radio-Iodination Methods for the Production of SPECT Imaging Agents. *Curr. Radiopharm.* **2010**, *3* (1), 37−45.
(6) Mushtaq, S.; Jeon, J.; Shaheen, A.; Jang, B. S.; Park, S. H. Critical Analysis of Radioiodination Techniques for Micro and Macro Organic Molecules. *J. Radioanal. Nucl. Chem.* **2016**, *309* (2), 859−889.
(7) Coenen, H. H.; Gee, A. D.; Adam, M.; Antoni, G.; Cutler, C. S.; Fujibayashi, Y.; Jeong, J. M.; Mach, R. H.; Mindt, T. L.; Pike, V. W.; Windhorst, A. D. Consensus Nomenclature Rules for Radiopharmaceutical Chemistry — Setting the Record Straight. *Nucl. Med. Biol.* **2017**, *55*, v−xi.
(8) Kabalka, G. W.; Varma, R. S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates. *Tetrahedron* **1989**, *45* (21), 6601−6621.
(9) Kabalka, G. W. Isotope Incorporation via Organoboranes. *J. Labelled Compd. Radiopharm.* **2007**, *50* (9−10), 888−894.
(10) Wilson, T. C.; Cailly, T.; Gouverneur, V. Boron Reagents for Divergent Radiochemistry. *Chem. Soc. Rev.* **2018**, *47* (18), 6990−7005.
(11) Navarro, L.; Berdal, M.; Chérel, M.; Pecorari, F.; Gestin, J. F.; Guérard, F. Prosthetic Groups for Radioiodination and Astatination of Peptides and Proteins: A Comparative Study of Five Potential Bioorthogonal Labeling Strategies. *Bioorg. Med. Chem.* **2019**, *27* (1), 167−174.
(12) Sutherland, A. Radiohalogenation of Organic Compounds: Practical Considerations and Challenges for Molecular Imaging. *Synthesis* **2019**, *51* (23), 4368−4373.
(13) Mangner, T. J.; Wu, J. l.; Wieland, D. M. Solid-Phase Exchange Radioiodination of Aryl Iodides. Facilitation by Ammonium Sulfate. *J. Org. Chem.* **1982**, *47* (8), 1484−1488.
(14) Baldwin, R. M.; Zea-Ponce, Y.; Zoghbi, S. S.; Laurelle, M.; Al-Tikriti, M. S.; Sybirska, E. H.; Malison, R. T.; Neumeyer, J. L.; Milius, R. A.; Wang, S.; Stabin, M.; Smith, E. O.; Charney, D. S.; Hoffer, P. B.; Innis, R. B. Evaluation of the Monoamine Uptake Site Ligand [^{123}I]Methyl 3β-(4-Iodophenyl)-Tropane-2β-Carboxylate ([123I]β-CIT) in Non-Human Primates: Pharmacokinetics, Biodistribution and SPECT Brain Imaging Coregistered with MRI. *Nucl. Med. Biol.* **1993**, *20* (5), 597−606.
(15) Chezal, J. M.; Papon, J.; Labarre, P.; Lartigue, C.; Galmier, M. J.; Decombat, C.; Chavignon, O.; Maublant, J.; Teulade, J. C.; Madelmont, J. C.; Moins, N. Evaluation of Radiolabeled (Hetero)-Aromatic Analogues of *N*-(2-Diethylaminoethyl)-4-Iodobenzamide for Imaging and Targeted Radionuclide Therapy of Melanoma. *J. Med. Chem.* **2008**, *51* (11), 3133−3144.
(16) Giglio, B. C.; Wang, H.; Yan, X.; Li, Z. Synthesis and Initial Evaluation of Radioactive 5-I-α-Methyl-Tryptophan: A Trp Based Agent Targeting IDO-1. *MedChemComm* **2019**, *10* (5), 814−816.
(17) Kil, K. E.; Zhu, A.; Zhang, Z.; Choi, J. K.; Kura, S.; Gong, C.; Brownell, A. L. Development of [^{123}I]IPEB and [^{123}I]IMPEB as SPECT Radioligands for Metabotropic Glutamate Receptor Subtype 5. *ACS Med. Chem. Lett.* **2014**, *5* (6), 652−656.
(18) Hagimori, M.; Temma, T.; Kudo, S.; Sano, K.; Kondo, N.; Mukai, T. Synthesis of Radioiodinated Probes Targeted toward Matrix Metalloproteinase-12. *Bioorg. Med. Chem. Lett.* **2018**, *28* (2), 193−195.
(19) Sloan, N. L.; Luthra, S. K.; McRobbie, G.; Pimlott, S. L.; Sutherland, A. A One-Pot Radioiodination of Aryl Amines via Stable Diazonium Salts: Preparation of ^{125}I-Imaging Agents. *Chem. Commun.* **2017**, *53* (80), 11008−11011.
(20) Khalaj, A.; Beiki, D.; Rafiee, H.; Najafi, R. A New and Simple Synthesis of *N*-Succinimidyl-4-[$^{127/125}$I]Iodobenzoate Involving a Microwave - Accelerated Iodination Step. *J. Labelled Compd. Radiopharm.* **2001**, *44* (3), 235−240.
(21) Vivier, M.; Rapp, M.; Papon, J.; Labarre, P.; Galmier, M.-J.; Sauzière, J.; Madelmont, J.-C. Synthesis, Radiosynthesis, and Biological Evaluation of New Proteasome Inhibitors in a Tumor Targeting Approach. *J. Med. Chem.* **2008**, *51* (4), 1043−1047.
(22) Guérard, F.; Lee, Y. S.; Baidoo, K.; Gestin, J. F.; Brechbiel, M. W. Unexpected Behavior of the Heaviest Halogen Astatine in the Nucleophilic Substitution of Aryliodonium Salts. *Chem. - Eur. J.* **2016**, *22* (35), 12332−12339.
(23) Guérard, F.; Navarro, L.; Lee, Y. S.; Roumesy, A.; Alliot, C.; Chérel, M.; Brechbiel, M. W.; Gestin, J. F. Bifunctional Aryliodonium Salts for Highly Efficient Radioiodination and Astatination of Antibodies. *Bioorg. Med. Chem.* **2017**, *25* (21), 5975−5980.
(24) Lalut, J.; Tournier, B. B.; Cailly, T.; Lecoutey, C.; Corvaisier, S.; Davis, A.; Ballandonne, C.; Since, M.; Millet, P.; Fabis, F.; Dallemagne, P.; Rochais, C. Synthesis and Evaluation of Novel

https://dx.doi.org/10.1021/acs.joc.0c00644
J. Org. Chem. 2020, 85, 8300−8310

Serotonin 4 Receptor Radiotracers for Single Photon Emission Computed Tomography. *Eur. J. Med. Chem.* **2016**, *116*, 90−101.
(25) Racys, D. T.; Sharif, S. A. I.; Pimlott, S. L.; Sutherland, A. Silver(I)-Catalyzed Iodination of Arenes: Tuning the Lewis Acidity of *N*-Iodosuccinimide Activation. *J. Org. Chem.* **2016**, *81* (3), 772−780.
(26) Chitneni, S. K.; Reitman, Z. J.; Spicehandler, R.; Gooden, D. M.; Yan, H.; Zalutsky, M. R. Synthesis and Evaluation of Radiolabeled AGI-5198 Analogues as Candidate Radiotracers for Imaging Mutant IDH1 Expression in Tumors. *Bioorg. Med. Chem. Lett.* **2018**, *28* (4), 694−699.
(27) Donovan, A.; Forbes, J.; Dorff, P.; Schaffer, P.; Babich, J.; Valliant, J. F. A New Strategy for Preparing Molecular Imaging and Therapy Agents Using Fluorine-Rich (Fluorous) Soluble Supports. *J. Am. Chem. Soc.* **2006**, *128* (11), 3536−3537.
(28) McIntee, J. W.; Sundararajan, C.; Donovan, A. C.; Kovacs, M. S.; Capretta, A.; Valliant, J. F. A Convenient Method for the Preparation of Fluorous Tin Derivatives for the Fluorous Labeling Strategy. *J. Org. Chem.* **2008**, *73* (21), 8236−8243.
(29) Rajerison, H.; Faye, D.; Roumesy, A.; Louaisil, N.; Boeda, F.; Faivre-Chauvet, A.; Gestin, J. F.; Legoupy, S. Ionic Liquid Supported Organotin Reagents to Prepare Molecular Imaging and Therapy Agents. *Org. Biomol. Chem.* **2016**, *14* (6), 2121−2126.
(30) Albu, S. A.; Al-Karmi, S. A.; Vito, A.; Dzandzi, J. P. K.; Zlitni, A.; Beckford-Vera, D.; Blacker, M.; Janzen, N.; Patel, R. M.; Capretta, A.; Valliant, J. F. ^{125}I-Tetrazines and Inverse-Electron-Demand Diels-Alder Chemistry: A Convenient Radioiodination Strategy for Biomolecule Labeling, Screening, and Biodistribution Studies. *Bioconjugate Chem.* **2016**, *27* (1), 207−216.
(31) Choi, M. H.; Shim, H. E.; Yun, S. J.; Kim, H. R.; Mushtaq, S.; Lee, C. H.; Park, S. H.; Choi, D. S.; Lee, D. E.; Byun, E. B.; Jang, B. S.; Jeon, J. Highly Efficient Method for ^{125}I-Radiolabeling of Biomolecules Using Inverse-Electron-Demand Diels-Alder Reaction. *Bioorg. Med. Chem.* **2016**, *24* (11), 2589−2594.
(32) Mushtaq, S.; Nam, Y. R.; Kang, J. A.; Choi, D. S.; Park, S. H. Efficient and Site-Specific ^{125}I-Radioiodination of Bioactive Molecules Using Oxidative Condensation Reaction. *ACS Omega* **2018**, *3* (6), 6903−6911.
(33) Vaidyanathan, G.; Zalutsky, M. R. No-Carrier-Added Synthesis of *meta*-[^{131}I]Iodobenzylguanidine. *Appl. Radiat. Isot.* **1993**, *44* (3), 621−628.
(34) Nakagawa, C.; Toyama, M.; Takeuchi, R.; Takahashi, T.; Tanaka, H. Synthesis of [^{123}I]-Iodometomidate from a Polymer-Supported Precursor with a Large Excluded Volume. *RSC Adv.* **2016**, *6* (15), 12215−12218.
(35) Srivastava, P. C.; Callahan, a P.; Cunningham, E. B.; Knapp, F. F. Potential Cerebral Perfusion Agents: Synthesis and Evaluation of a Radioiodinated Vinylalkylbarbituric Acid Analogue. *J. Med. Chem.* **1983**, *26* (5), 742−746.
(36) Goodman, M. M.; Kabalka, G. W.; Marks, R. C.; Knapp, F. F.; Lee, J.; Liang, Y. Synthesis and Evaluation of Radioiodinated 2-(2(*RS*)-Aminopropyl)-5- Iodothiophenes as Brain Imaging Agents. *J. Med. Chem.* **1992**, *35* (2), 280−285.
(37) Akula, M. R.; Zhang, J. H.; Kabalka, G. W. [^{123}I]Iodocognex, a Potent SPECT Agent to Map Acetylcholinesterase *via* a Boronic Acid Precursor. *J. Labelled Compd. Radiopharm.* **2001**, *44* (S1), S260−S261.
(38) Molloy, J. J.; O'rourke, K. M.; Frias, C. P.; Sloan, N. L.; West, M. J.; Pimlott, S. L.; Sutherland, A.; Watson, A. J. B. Mechanism of Cu-Catalyzed Aryl Boronic Acid Halodeboronation Using Electrophilic Halogen: Development of a Base-Catalyzed Iododeboronation for Radiolabeling Applications. *Org. Lett.* **2019**, *21* (7), 2488−2492.
(39) Kabalka, G. W.; Akula, M. R.; Zhang, J. Synthesis of Radioiodinated Aryl Iodides via Boronate Precursors. *Nucl. Med. Biol.* **2002**, *29* (8), 841−843.
(40) Akula, M. R.; Yao, M.-L.; Kabalka, G. W. Triolborates: Water-Soluble Complexes of Arylboronic Acids as Precursors to Iodoarenes. *Tetrahedron Lett.* **2010**, *51* (8), 1170−1171.
(41) Yong, L.; Yao, M.-L.; Green, J. F.; Kelly, H.; Kabalka, G. W. Syntheses and Characterization of Polymer-Supported Organotrifluoroborates: Applications in Radioiodination Reactions. *Chem. Commun.* **2010**, *46* (15), 2623−2625.
(42) Cant, A. A.; Champion, S.; Bhalla, R.; Pimlott, S. L.; Sutherland, A. Nickel-Mediated Radioiodination of Aryl and Heteroaryl Bromides: Rapid Synthesis of Tracers for SPECT Imaging. *Angew. Chem., Int. Ed.* **2013**, *52* (30), 7829−7832.
(43) Wilson, T. C.; McSweeney, G.; Preshlock, S.; Verhoog, S.; Tredwell, M.; Cailly, T.; Gouverneur, V. Radiosynthesis of SPECT Tracers *via* a Copper Mediated ^{123}I Iodination of (Hetero)Aryl Boron Reagents. *Chem. Commun.* **2016**, *52* (90), 13277−13280.
(44) Reilly, S. W.; Makvandi, M.; Xu, K.; Mach, R. H. Rapid Cu-Catalyzed [^{211}At]Astatination and [^{125}I]Iodination of Boronic Esters at Room Temperature. *Org. Lett.* **2018**, *20* (7), 1752−1755.
(45) Zhang, P.; Zhuang, R.; Guo, Z.; Su, X.; Chen, X.; Zhang, X. A Highly Efficient Copper-Mediated Radioiodination Approach Using Aryl Boronic Acids. *Chem. - Eur. J.* **2016**, *22* (47), 16783−16786.
(46) Webster, S.; O'Rourke, K. M.; Fletcher, C.; Pimlott, S. L.; Sutherland, A.; Lee, A. Rapid Iododeboronation with and without Gold Catalysis: Application to Radiolabelling of Arenes. *Chem. - Eur. J.* **2018**, *24* (4), 937−943.
(47) Yan, R.; Sander, K.; Galante, E.; Rajkumar, V.; Badar, A.; Robson, M.; El-Emir, E.; Lythgoe, M. F.; Pedley, R. B.; Årstad, E. A One-Pot Three-Component Radiochemical Reaction for Rapid Assembly of ^{125}I-Labeled Molecular Probes. *J. Am. Chem. Soc.* **2013**, *135* (2), 703−709.
(48) Lu, Z.; Pham, T. T.; Rajkumar, V.; Yu, Z.; Pedley, R. B.; Årstad, E.; Maher, J.; Yan, R. A Dual Reporter Iodinated Labeling Reagent for Cancer Positron Emission Tomography Imaging and Fluorescence-Guided Surgery. *J. Med. Chem.* **2018**, *61* (4), 1636−1645.
(49) Dubost, E.; Babin, V.; Benoist, F.; Hébert, A.; Barbey, P.; Chollet, C.; Bouillon, J.-P.; Manrique, A.; Pieters, G.; Fabis, F.; Cailly, T. Palladium-Mediated Site-Selective C-H Radio-Iodination. *Org. Lett.* **2018**, *20* (19), 6302−6305.
(50) Dubost, E.; Babin, V.; Benoist, F.; Hébert, A.; Pigrée, G.; Bouillon, J.-P.; Fabis, F.; Cailly, T. Improvements of C-H Radio-Iodination of *N*-Acylsulfonamides toward Implementation in Clinics. *Synthesis* **2019**, *51* (23), 4393−4400.
(51) Cavina, L.; van der Born, D.; Klaren, P. H. M.; Feiters, M. C.; Boerman, O. C.; Rutjes, F. P. J. T. Design of Radioiodinated Pharmaceuticals: Structural Features Affecting Metabolic Stability towards in Vivo Deiodination. *Eur. J. Org. Chem.* **2017**, *2017* (24), 3387−3414.
(52) Ouadi, A.; Habold, C.; Keller, M.; Bekaert, V.; Brasse, D. Synthesis of New ^{123}I-Labeled Free Fatty Acids Analogues and First Evaluation as Potential Tracers for SPECT Imaging to Elucidate Fatty Acid Flux in Mouse. *RSC Adv.* **2013**, *3* (41), 19040.
(53) Wyffels, L.; De Bruyne, S.; Blanckaert, P.; Lambert, D. M.; De Vos, F. Radiosynthesis, in Vitro and in Vivo Evaluation of ^{123}I-Labeled Anandamide Analogues for Mapping Brain FAAH. *Bioorg. Med. Chem.* **2009**, *17* (1), 49−56.
(54) Pruitt, D. G.; Bullock, K. M.; Banks, W. A.; Jelliss, P. A. Development of Rhenacarborane Complexes as Central Nervous System (CNS) Drug Delivery Agents. *Inorg. Chim. Acta* **2017**, *466*, 139−144.
(55) Fjellaksel, R.; Dugalic, D.; Demissie, T. B.; Riss, P. J.; Hjelstuen, O. K.; Sundset, R.; Hansen, J. H. An Acylation-Finkelstein Approach to Radioiodination of Bioactives: The Role of Amide Group Anchimeric Assistance. *J. Phys. Org. Chem.* **2018**, *31* (7), No. e3835.
(56) Kabalka, G. W.; Mereddy, A. R. A Facile Synthesis of Radioiodinated Alkynyl Iodides Using Potassium Alkynyltrifluoroborates. *J. Labelled Compd. Radiopharm.* **2005**, *48* (5), 359−362.
(57) Ferris, T.; Carroll, L.; Mease, R. C.; Spivey, A. C.; Aboagye, E. O. Iodination of Terminal Alkynes Using KI/$CuSO_4$ - A Facile Method with Potential for Radio-Iodination. *Tetrahedron Lett.* **2019**, *60* (13), 936−939.

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