Recent Advances in Synthetic Methods for Radioiodination

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

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

<table>
<thead>
<tr>
<th>isotope</th>
<th>half life</th>
<th>type of emission</th>
<th>application</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I</td>
<td>13.2 h</td>
<td>$\gamma$</td>
<td>SPECT imaging</td>
</tr>
<tr>
<td>$^{124}$I</td>
<td>4.18 days</td>
<td>$\beta^-$</td>
<td>PET imaging</td>
</tr>
<tr>
<td>$^{124}$I</td>
<td>59.4 days</td>
<td>Auger $e^-$</td>
<td>preclinical research and therapy</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>9.05 days</td>
<td>$\beta^-$</td>
<td>therapy</td>
</tr>
</tbody>
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Table 1. Radioiodine Isotopes Most Commonly Used in Imaging and Therapy

Organic compounds bearing radioisotopes of iodine play a major role in nuclear medicine and molecular imaging. As there are a number of radioactive iodine isotopes in 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. Radioisotopes bearing iodine-131 are used for radiotherapy, while iodine-125 labeled compounds are commonly used in preclinical, biological, and medicinal chemistry applications.

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. 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). 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. As radioiodine isotopes are produced in iodide form, early reported methods have involved nucleophilic substitution reactions, such as the iododestannylation of aryltin compounds. 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.

Although these methods allow the iodination of various compounds with high RY 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...
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 Csp,C sp2, and Csp3 centers.

1. RADIOIODINATION OF CSP2 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). 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).

However, due to the impossible separation of nonradioactive and radioactive i odinated 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 [123I]IPEB, a metabotropic glutamate receptor subtype 5 radioligand, through bromine—radioiodine exchange at high temperature in the presence of copper and tin sulfate (Scheme 3). 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. 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.

Diazoc and Triazene Leaving Groups. In 2017, Sutherland et al. described an efficient methodology to radioiodinate aryl amines via stable diazonium salts (Scheme 4). This methodology is based on the use of widely available starting 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 [125I]iomazenil, [125I]CNS1261, and [125I]IBOX with RCYs between 47 and 75%.

Iodonium Leaving Groups. In 2016, Gestin et al. published a systematic study aimed at comparing the reactivity of arylidonium salts in radiolabeling using either sodium iodide or astatide. 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 iodonium 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-[125I]succinimidyl-3-iodobenzoate ([125I]SIB) was obtained in 36–87% RCY, depending on the nature of the electron-rich...
arene moiety (Scheme 5). In 2019, this methodology was applied to the radiolabeling of two other prosthetic groups, for attachment to biomolecules by either click chemistry or inverse-electron-demand Diels–Alder reactions.\textsuperscript{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$_2$Ar. Direct electrophilic aromatic substitution is a typical process to perform radioiodination of aromatic molecules.\textsuperscript{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\textsuperscript{24}

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%.\textsuperscript{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.\textsuperscript{28}

A similar approach was proposed by the Gestin group in 2016, using an ionic liquid supported stannylated precursor for of electron-rich substrates (as observed by nonradioactive reactions) facilitated by this method has enlarged the panel of substrates accessible to direct S$_2$Ar reactions. Nevertheless, to overcome the regioselectivity issues of other S$_2$Ar strategies, the preparation of stannylated, silylated, or boronated precursors is generally required to perform ipso S$_2$Ar.

Iododestannylation. Iododestannylation is the most used methodology to perform radioiodination in research facilities.\textsuperscript{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$_2$Ar reaction, the radiolabeled derivatives. Despite issues concerning their stability and toxicity, aryltrialkylstannanes are generally prepared from the corresponding halogenated precursor through metatation 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).\textsuperscript{26}

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

In 2016, a silver-catalyzed radioiodination was reported, which used the mild Lewis acid nature of a silver triflimide salt, avoiding the polyiodination of activated aromatic rings (Scheme 7).\textsuperscript{25} The completely regioselective radioiodination
radiolabeling (Scheme 10).\textsuperscript{29} This strategy significantly facilitated the formation and purification of the product, using a simple SiO\textsubscript{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\textsuperscript{30,31} and a $^{125}$I-benzamide moiety\textsuperscript{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,\textsuperscript{33} starting from the corresponding aryltrimethylsilane in TFA, using trifluoroperacetic acid to generate $^{131}$I\textsubscript{2} in situ (Scheme 12).

In 2016, Tanaka et al. described a polymer-supported version of the radiiododesilylation applied to the radioiodination of iodometomidate (IMTO), a high affinity ligand of adrenal steroidogenic enzymes, from a polymethacrylamide-supported precursor (Scheme 13).\textsuperscript{34} Solid-phase organic chemistry enabled reaction products to be purified rapidly and simply by filtration. In this work, the radiiododesilylation 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.\textsuperscript{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\textsuperscript{36} and 7-$^{123}$I-iodocognex obtained, respectively, with 86 and 66% RCYs.\textsuperscript{37} In 2019, iododeboronation from boronic acids was reinvestigated by the Sutherland and Watson groups (Scheme 15).\textsuperscript{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\textsubscript{μ}mol\textsuperscript{−1}. Ipso-iododeboronation is also possible starting from boronate derivatives (Scheme 16).\textsuperscript{39} This 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.\textsuperscript{39,40} A similar approach has been developed by the same authors using polymer supported organotrifluoroborates, which allowed easier purification of the radioiodinated compounds.\textsuperscript{41} Nevertheless, poor RCYs are obtained when electron-poor arenes are used in these reactions.
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

**Scheme 11. Radioiodination of Biomolecules Using Prosthetic Groups and Iododestannylation**

**Scheme 12. Radioiododesilylation by Zalutsky**

**Scheme 13. Radioiododesilylation and Polymer-Supported Radioiododesilylation by Tanaka**

**Scheme 14. Electrophilic Iododeboronation from Boronic Acids**

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 [125I]iniparib and 5-[123I]A85380 were also achieved with RCYs of 46 and 93%, respectively. In addition, the molar activity of 5-[123I]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.
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). 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%.

A similar approach was developed by Mach et al. in 2018 using a copper(II) catalyst (Scheme 19). This procedure allowed the efficient iododeboronation 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 [125I]KX1 with RCYs between 61 and 99%.

Gold-Mediated Iododeboronation. In 2018, Sutherland et al. described the first homogeneous gold catalysis procedure for the radio-iododeboronation of aryl boronic species starting from a Chan−Lam mechanism (Scheme 18). 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%.

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). The air tolerant method was performed using a gold(I) complex, CuPr (Scheme 19). 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).

Concomitantly to the Gouverneur work, Zhang et al. published an iododeboronation procedure starting from boronic acids using a copper(I) catalyst, Cu2O (Scheme 20). 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).
electron donating and electron withdrawing substituted arenes with RCYs between 92 and 100%. Two radiotracers, $[^{125}\text{I}]$MIBG and a radioiodinated olaparib analogue were prepared following this procedure, with RCYs of 28 and 41%, respectively. The molar activity of $[^{125}\text{I}]$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$\text{–H}$. Radioiodination.** 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

Crude palladacycle solutions were prepared and reacted with an $[^{125}\text{I}]$NIS solution obtained from NCS and $[^{125}\text{I}]$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, tassulisum, 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, pyrazolyl, 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 20. Copper(I)-Mediated Iododeboronation by Zhang.**

![Scheme 20](https://example.com/scheme20)

$[^{125}\text{I}]$NISb

RCY = 99%

Obtained after TFA deprotection of the N-Boc derivative.

**Scheme 21. Gold(I)-Mediated Iododeboronation by Sutherland and Lee**

![Scheme 21](https://example.com/scheme21)

$[^{125}\text{I}]$Olaparib iodinated analogue

RCY = 41%

100 °C, 40 min

Obtained after HCl deprotection of the N-Boc derivative.

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

![Scheme 22](https://example.com/scheme22)

$[^{125}\text{I}]$MIBG

RCY = 87-99%

18 examples

Obtained after TFA deprotection of the N-Boc derivative.

$[^{125}\text{I}]$MIBG

RCY = 98%

Obtained after HCl deprotection of the N-Boc derivative.

1. 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$_2$CN, $-$N-pyrrolidin-2-one, and $-$NHCONH(isoBu). Conditions B: PdCl$_2$ 1.05 equiv, MeCN, 24 h, 80 °C with DG = $-$CO$_2$H, $-$CH$_2$CO$_2$H, and $-$N-pyrazolyl.
2. RADIOIODINATION OF C₆SP³ CENTERS

Radioiodine can be introduced into aliphatic groups using nucleophilic substitution reactions involving the displacement of typical leaving groups with radioiodide under Finkelstein conditions. While the lability of the C₆sp³−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. 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. Despite this issue, this approach was used in 2013 for the preparation of ¹²³I-labeled fatty acids (Scheme 24). Reaction of the iodinated fatty acids in acetone with [¹²³I]iodide gave the corresponding ¹²³I-labeled compound with a RCY higher than 95%.

To overcome molar activity issues and aid separation of starting materials and products, sulfonate or halogenated precursors are more commonly used. Simple halogen exchange, through reaction of an alkyl bromide with [¹²³I]iodide, was used to prepare radioiodinated rhenacarborane complexes as potential drug delivery agents for the central nervous system. Accelerated radioiodination via nucleophilic substitution of an alkyl chloride by amide group anchimeric assistance has also been recently studied. 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).

3. RADIOIODINATION OF C₆SP CENTERS

Methods for the radioiodination of C₆ centers and, in particular, alkenes are rare. Nonetheless, the relative metabolic stability of alkenes compared to various aryl groups and the highly chemoselective reactions that can be achieved with terminal alkenes have led to the development of radioiodination methods for the preparation of iodinated alkenes. Kabalka and Mereddy showed the efficient radioiodination of alkynyltrifluoroborates using [¹²³I]iodide under oxidative conditions. Initially, the alkynyltrifluoroborates were prepared by lithiation of terminal alkynes followed by reaction with trimethylborate and then KH₂F₂ (Scheme 26). Radioiodination was achieved by peracetic acid in situ oxidation of sodium [¹²³I]iodide and subsequent iododeboronation of the alkynyltrifluoroborates. This gave a range of radioiodinated alkenes with RCY between 85 and 92%.

Direct radioiodination of terminal alkenes has been achieved using stoichiometric amounts of copper(II) salts (Scheme 27). The method which used bathophenanthroline disulfonic acid (BPDS) to solubilize the copper species was proposed to involve copper(II) oxidation of sodium [¹²³I]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.

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
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.

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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 MRL. 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 radioiodination 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
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 radiohalogenation-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 (2006) under the supervision of Pr. Sylvain Rault. In 2008, he joined Dr. Thomas Cailly obtained his Ph.D. from the University of Caen (Denmark) as a postdoctoral fellow. In 2009, he was appointed maître de conferences 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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