Radiohalogenation of Organic Compounds: Practical Considerations and Challenges for Molecular Imaging

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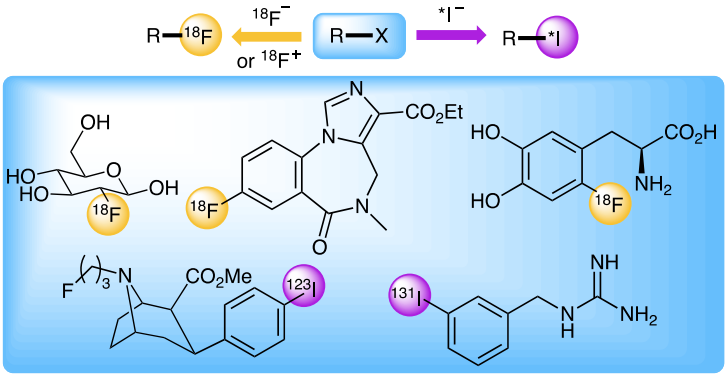
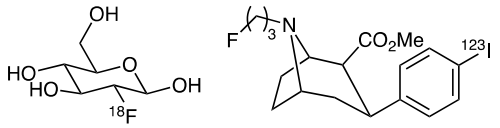


Abstract

In the last few decades, advances in molecular imaging technologies have had a major impact on many aspects of healthcare. In particular, radiohalogenated compounds have been used for non-invasive visualization of human anatomy, the diagnosis of disease and in drug development programs. As a consequence of these advances, a range of novel synthetic radiochemical methods have been reported that allow more effective and efficient radiohalogenation from a broader range of precursors. In developing new radiochemical methods, special requirements are required to optimize the incorporation of highly radioactive, short-lived, isotopically labelled reagents. This concept article highlights the key practical considerations and challenges required when utilizing the most commonly used radiohalogens in nuclear medicine.

1 Introduction

Molecular imaging technologies such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) in combination with radionuclide-labelled compounds have had a significant impact in the medical and life sciences.[1] The development of novel imaging agents have resulted in a wide range of healthcare applications such as clinical diagnosis and prognosis for diseases associated with neurology, oncology and cardiology.[1,2] Radionuclide based tracers have also been used in drug discovery programs and to monitor therapy. For example, 2-[^{18}F]fluoro-2-deoxyglucose (FDG) (**1**) is used worldwide in healthcare facilities for the detection and diagnosis of human malignancies, such as lung, breast and colorectal cancers, and lymphoma and melanoma (Figure 1).[3] The cocaine derivative, [^{123}I]FP-CIT (ioflupane), is used as a radiopharmaceutical for the detection of the dopamine transporter and the subsequent clinical diagnosis of dementia disorders,[4] such as Parkinson's disease.



1 2

Figure 1 Chemical structures of [^{18}F]FDG (**1**) and [^{123}I]FP-CIT (**2**).

The continued growth and importance of PET and SPECT imaging has driven the need for new molecular tracers and chemical methods for the radiolabelling of precursor compounds. In terms of radiohalogenated imaging agents, [^{18}F]-labelled compounds are most widely used in PET imaging, while [^{123}I]- and [^{125}I]-labelled compounds are commonly used for SPECT imaging and preclinical studies, respectively.[1,2] There are many well documented advantages for the incorporation of fluorine atoms in bioactive compounds.[5] In terms of PET imaging, fluorine-18 has many favorable nuclear properties, such as a relatively long half-life of 110 minutes that allows for more complex radiosynthesis and longer in vivo studies. Fluorine-18 also has a high percentage of β^+ emission (97%) and a relatively low positron energy. A consequence of the low positron energy is that the distance traveled by the positron (positron range) before it undergoes annihilation by an electron is relatively small. This ultimately leads to higher resolution spatial images. In contrast, although the use of radioiodine and SPECT imaging generates lower resolution images, the longer half-life of iodine-123 (13.2 h), allows a wider range of radiosynthesis reactions and imaging studies.[1] Furthermore, compounds can also be incorporated with [^{125}I]iodide or [^{131}I]iodide and used in preclinical development or radiotherapy applications, respectively.[1a] Isotopes of bromine (e.g. bromine-75 and -76) are positron emitting and so have been used for PET imaging.[1a] However, the production and isolation of these radionuclides is not trivial (e.g. isolation by dry distillation) and they possess non-ideal nuclear properties. For example, bromine-75 (half-life of 97 minutes) has high positron energy and a second-high energy gamma emission, both of which result in poor resolution for imaging. As a consequence, radionuclides of bromine are less commonly used for molecular imaging.

With the growth and advances in PET and SPECT imaging, there have been significant efforts in developing new radiochemical methods for the synthesis of radiofluorinated and radioiodinated compounds.[6-8] However, the translation of non-radioactive halogenation methods for use with radioactive reagents often requires further development. New radiohalogenation reactions entail significant re-optimization when handling highly

radioactive, short-lived isotopically labelled reagents. This concept article describes the key challenges when developing radiohalogenation reactions for the preparation of radiopharmaceuticals or molecular imaging agents.

2 Synthetic Challenges for Radiohalogenation

As well as the safety issues when handling highly radioactive regents that are positron- or γ-ray emitters (use of lead-shielded fumehoods or hot-cells), there are a number of general factors to consider when developing radiohalogenation methods. One of the key objectives is the preparation of radiolabelled products with high specific radioactivity.[1] Achieving this aim allows radiotracers to be administered to humans in low enough doses that minimizes any toxic or pharmacological side-effects. This requires maximizing the short-lived radioisotope by late-stage introduction and fast reaction and purification times. In general, the reaction and purification timeframe should not exceed 2–3 times the half-life of the radionuclide. During most radiohalogenation reactions, the radiolabelled reagent is limiting, with an excess used of the substrate and other reagents. This has the combined effect of both driving the reaction of the radiolabelled reagent to completion and maximizing its use. The other major difference between non-radiohalogenation and radiohalogenation reactions is scale. As both PET and SPECT are highly sensitive techniques, radiotracers are administered in low amounts (<1–10 nmol).[1a] As a consequence of this and the safety issues with handling highly radioactive material, radiotracers are generally prepared on micromolar scale. Thus, following optimization of a halogenation reaction using typically milligram quantities of the precursor, translation to the sub-milligram radiolabelled version normally requires re-optimization. This is generally done in combination with the changes described above, such as using the radiohalogen as the limiting reagent. At this scale, the radiohalogenation reactions are monitored using (radio)-HPLC, where the production and purity of the radiohalogenated product can be assessed against a non-radioactive standard (Figure 2).[9]

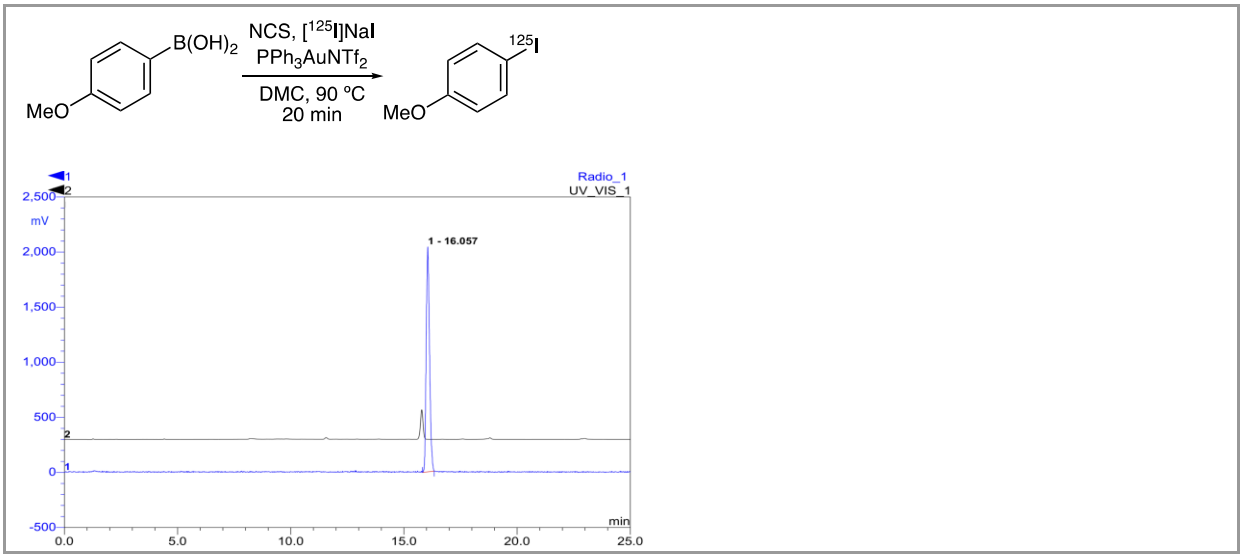
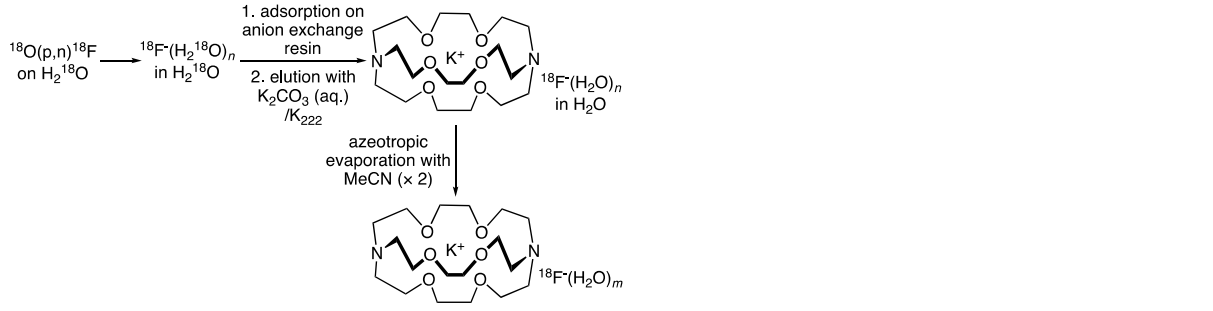


Figure 2 Gold-catalyzed radio-iododeboronation reaction (0.6 mg scale reaction). Chromatogram shows an overlay of the radio-HPLC trace of reaction mixture (blue) and UV/Vis trace of non-radioactive product (black).

2.1 Radiofluorination

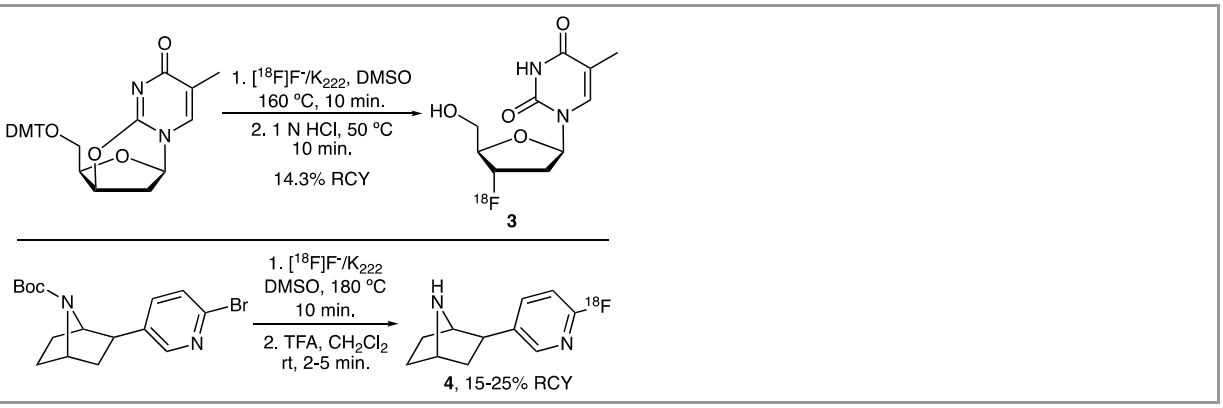
Radiofluorination reactions can be performed directly using nucleophilic [^{18}F]fluoride or with electrophilic [^{18}F]fluorine gas ([^{18}F]F_2) or fluorine-18 derived reagents.[1,2] Fluorine-18 (half-life

of 109.7 minutes) is most commonly produced using a cyclotron by proton irradiation of ^{18}O-enriched water.[10] This produces the [^{18}F]fluoride ion as a solution in the irradiated target water. As a consequence of this approach, the first stage of any radiofluorination reaction with [^{18}F]fluoride is a drying step, as hydrated fluoride has significantly diminished nucleophilicity.[11] This is typically done by adsorption of the [^{18}F]fluoride ion onto an ion exchange resin.[12] This also allows recovery of the expensive [^{18}O]water. The [^{18}F]fluoride ion is then eluted in a small volume of an aqueous base in the presence of a cryptand such as the aminopolyether K_{222} (Scheme 1) or as a tetraalkylammonium salt. Azeotropic evaporation with acetonitrile then provides a reagent that can be used for a wide-range of nucleophilic transformations.



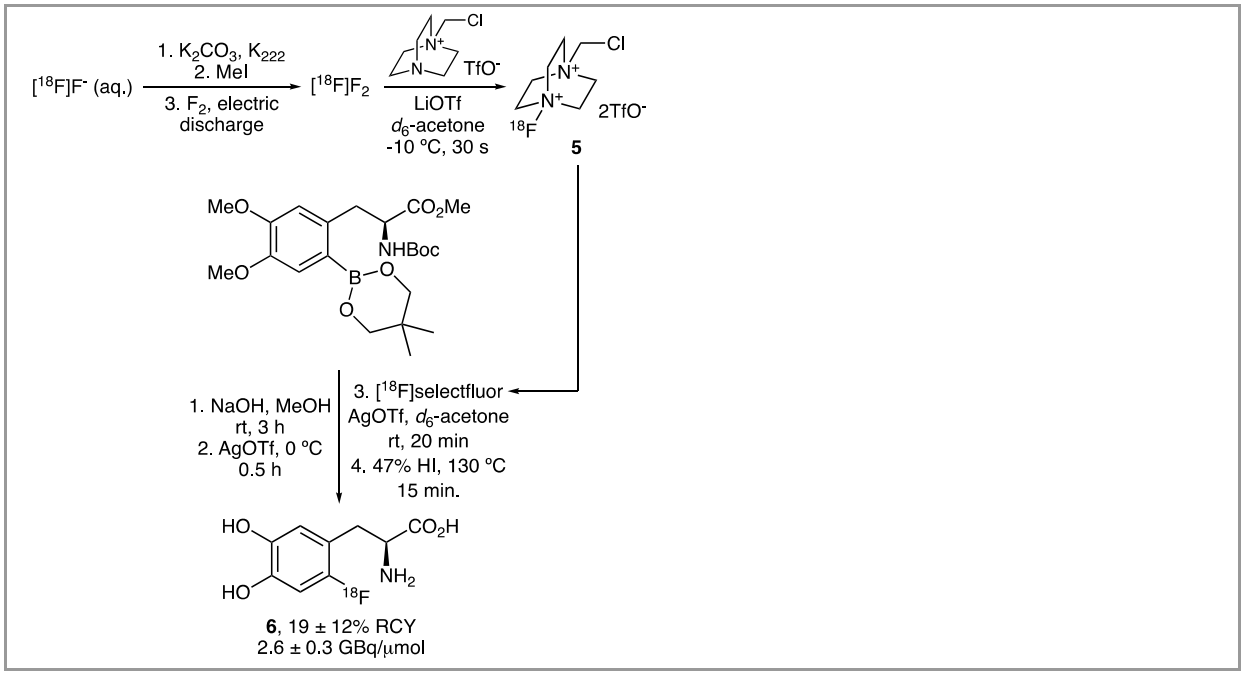
Scheme 1 Preparation of [^{18}F]fluoride ion from cyclotron-irradiated [^{18}O]water.

The effort of achieving dehydrated [^{18}F]fluoride ion has to be balanced with the time required to do this and completely dry fluoride may not always be necessary. For example, while a high degree of dryness is important for difficult nucleophilic aromatic substitution reactions, less rigorous drying can be used for less demanding nucleophilic aliphatic substitution reactions.[13] In recent years, alternative methods to azeotropic drying, such as eluting [^{18}F]fluoride from modified solid-phase extraction (SPE) cartridges[14] or from ion-exchange resins using organic bases have provided dry fluoride ion with high recovery of activity.[15] It should also be noted that the [^{18}F]fluoride ion can "stick" to reaction vessel walls. This can be minimized with the use of pyrex vessels, rather than those composed of glassy carbon or platinum.[12] When all of these conditions are met, [^{18}F]fluoride/K_{222} solutions can then be used for radiolabeling using typical organic reactions. In the standard examples shown in scheme 2, nucleophilic aliphatic fluorination for the preparation of the tumor proliferation imaging agent 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT) (**3**)[16] and nucleophilic aromatic fluorination generating the nicotinic acetylcholine receptor imaging agent [^{18}F]norchlorofluoroepibatidine (**4**),[17] the reactions with [^{18}F]fluoride/K_{222} solutions were performed at high temperatures, resulting in short reaction times. The work up and purification of these reactions are also typical, with a dilution step, initial purification by passing the reaction mixture through a C-18 cartridge, followed by a final purification by HPLC.



Scheme 2 Radiosynthesis of [^{18}F]FLT (**3**) and [^{18}F]norchlorofluoroepibatidine (**4**). DMT: 4,4'-dimethoxytriphenylmethyl; RCY: radiochemical yield.

Electrophilic radiofluorination can be achieved using highly reactive [^{18}F]fluorine gas. [^{18}F]F_2 is produced by targeting [^{18}O]oxygen.[6a] However, the specific activity of the [^{18}F]F_2 is compromised by the use of [^{19}F]F_2 as a carrier gas and the enriched [^{18}F]F_2 requires cryogenic trapping. While [^{18}F]F_2 is widely used for radiofluorination reactions and the preparation of less reactive electrophilic radiofluorinating reagents, such as acetyl [^{18}F]hypofluorite, [^{18}F]XeF_2 or *N*-[^{18}F]fluorosulfonamide, [^{18}F]fluoride is often used as a more active, indirect source of electrophilic fluorine-18. An example of this approach has been described by Solin, Gouverneur and co-workers for the preparation of [^{18}F]selectfluor (bis)triflate (**5**) (Scheme 3).[18] This method generated [^{18}F]F_2 from [^{18}F]fluoride with high specific activity in an electrical discharge chamber using [^{18}F]fluoromethane as an intermediate. The resulting [^{18}F]selectfluor reagent was used for a range of reactions, including aryl fluorodeboronation and the radiosynthesis of 6-[^{18}F]fluoro-L-DOPA (**6**), a PET imaging agent for the dopaminergic pathways.[19] Although involving several steps, electrophilic approaches such as this allow the preparation of radiofluorinated compounds with high specific activity via a [^{18}F]F_2 source. While such advances have expanded methods for electrophilic fluorination in research, the specialized equipment needed (e.g. discharge chamber) has restricted widespread use in nuclear medicine facilities. As a consequence, nucleophilic fluorination or the use of [^{18}F]F_2 are still the most common approaches for the production of clinically used radiofluorinated tracers.[20]

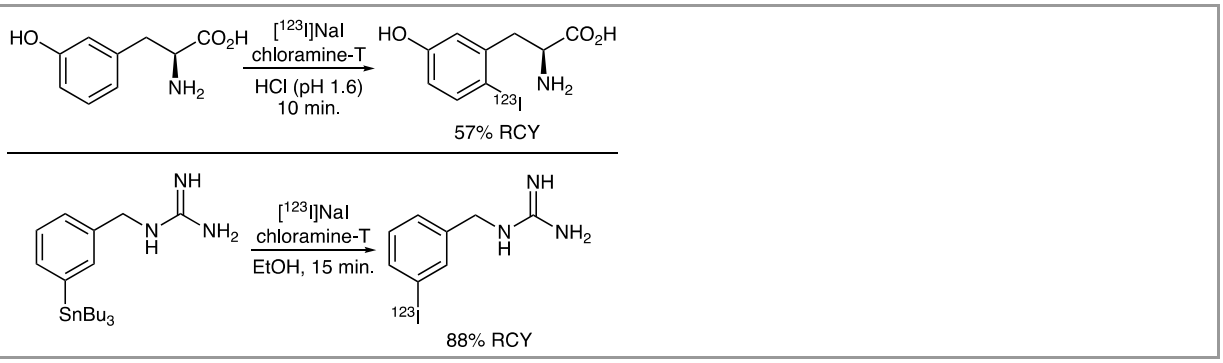


Scheme 3 Radiosynthesis of high activity $[^{18}F]F_2$ and [^{18}F]selectfluor **5** and application in the preparation of 6-[^{18}F]fluoro-L-DOPA (**6**).

2.2 Radioiodination

The most commonly used radioisotopes of iodine are 123, 125 and 131.[1,7] Iodine-123 which is a gamma emitter and has a half-life of 13.2 hours is the most used non-metal radionuclide for SPECT imaging. Iodine-125 has a half-life of 59.4 days and is used in preclinical research, such as radioimmunoassay techniques, binding studies and autoradiography, while the high energy iodine-131 radionuclide (half-life of 8.02 days) is mainly used in radiotherapy. Iodine-124, which is a positron-emitting radionuclide, with a half-life of 4.2 days has been less commonly used due to its complex radioactive decay process. However, more recently, this radionuclide is finding greater application for PET imaging.[21] As a consequence of the significantly longer half-lives, local nuclear facilities are not necessary. The radioisotopes of iodine can be made in central commercial facilities and transported to where they are required.

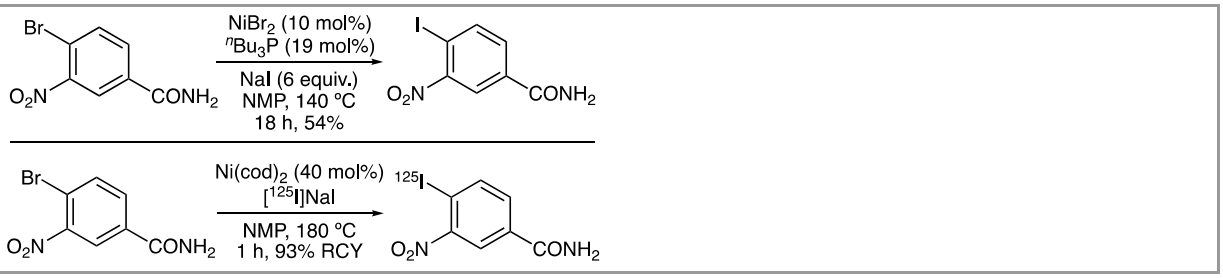
All radioiodine isotopes are produced in iodide form, commonly as sodium iodide in solutions of sodium hydroxide (0.01–0.1 M). In a similar manner to aqueous solutions of [^{18}F]fluoride, enriched iodide requires drying before most applications, however, the time required to do this is less of an issue. Traditional nucleophilic reactions of iodide can be used directly to incorporate radioiodine into organic compounds.[1,7] Alternatively, iodide can be oxidized to iodine or iodine monochloride and subjected to electrophilic reactions. For the preparation of many aryl-based SPECT tracers this can be done by direct electrophilic aromatic substitution or by use of a leaving group, such as in iodo-destannylation reactions (Scheme 4).[22,23] In common with radiofluorination reactions, minimal work up is involved with these processes, typically requiring dilution and purification by prep-HPLC. Validation of the correct product using analytical-HPLC is performed by co-injection with a non-radioactive standard.



Scheme 4 Examples of electrophilic radioiodination.

These types of transformations are commonly used in healthcare facilities for the preparation of iodine-123 SPECT imaging agents, mainly as they are fast and produce the tracer in high specific activity.[1,7] However, strong oxidizing agents such as chloramine-T, peracetic acid and iodogen are not compatible with a wide range of organic compounds and organotin precursors are highly toxic and can be unstable.

For these reasons, in recent years, a wide range of radioiodination methods, mainly involving transition metal mediated processes have been developed.[8] Like the more traditional transformations, these processes have required further development on translation from the non-radioactive version. A good example of this is a nickel(0)-catalyzed halogen exchange process reported by Sutherland and co-workers.[24] A general iodination process of aryl bromides was developed using in situ generation of nickel(0) and an excess of sodium iodide (Scheme 5). In a radioactive version, which used radioiodide as the limiting reagent, higher loadings of the nickel(II) bromide pre-catalyst were required for reaction.[8a] However, the increased concentration of bromide ion interfered with the equilibrium of halogen exchange, resulting in moderate conversion to the radioiodine products (<29%). As a consequence, the nickel(0)-mediated radioiodination of aryl bromides had to be re-developed using a non-bromide source of nickel(0). The use of $Ni(cod)_2$ was found to be optimal under the conditions for radioiodination and was compatible with incorporation of either iodine-123 or -125 (Scheme 5). While this required 40 mol% of the catalyst, on typical micromolar scale used for radioiodination reactions, this equates to a relatively small amount of the nickel complex (<0.5 mg).



Scheme 5 Non-radioactive versus radioactive nickel(0)-mediated iodination for the preparation of [125I]iniparib.

3 Conclusions and Future Outlook

In summary, typical fluorine and iodine-based reactions can be performed for radiohalogenation of organic compounds. However, the highly radioactive material and short

half-lives require the radiohalogenation step to be fast, easy to purify and usually the last step in the synthetic route. Translation from a previously developed non-radioactive method generally requires re-optimization, particularly as the radiohalogen source is normally the limiting reagent during these transformations. Due to these changes of scale and stoichiometry, some radiohalogenation reactions have been developed and optimized directly, without prior investigation with a non-radioactive method.[1,6,7] For general application in clinical and nuclear medical facilities, methods should be operationally simple and avoid highly toxic precursors and reagents.

As with other areas of organic synthesis, radiochemical methods for halogenation continue to embrace new technologies that facilitate fast reactions and allow simple purification. For example, reactions have been accelerated using microwave irradiation,[25] flow- and micro-reactors,[26] while purification has been simplified using solid-supported substrates or reagents.[1,2,27] It should also be noted that while the development of many radiohalogenation methods is still performed manually, commercial production of tracers used in medical imaging is done using automatic synthesizer modules in which components of the reaction are supplied by cassettes, with minimal contact with the human operator. New radiohalogenation chemistry continues to be discovered. A notable example is from the O'Hagan laboratory where a biocatalytic radiofluorination using the fluorinase enzyme has allowed the preparation of 5'-[^{18}F]fluoro-5'-deoxyadenosine and other biomolecules in high radiochemical yield.[28] Methods that allow the incorporation of other radiohalogens are also being reported. These include the preparation of small molecules bearing astatine-211, an α-particle emitting radionuclide that has potential for targeted radiotherapy.[1a,29] All of these new technologies continue to expand the limits of radiohalogenation reactions, producing labelled compounds with high specific activity. This of course underpins the subsequent development of the highly important applications of these compounds in medical imaging of disease and as radiopharmaceuticals.

Acknowledgment

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References

(1) For reviews, see: (a) Adam, M. J.; Wilbur, D. S. *Chem. Soc. Rev*. **2005**, *34*, 153. (b) Pimlott, S. L.; Sutherland, A. *Chem. Soc. Rev*. **2011**, *40*, 149.

(2) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev*. **2008**, *108*, 1501.

(3) (a) Kelloff, G. J.; Hoffman, J. M.; Johnson, B.; Scher, H. I.; Siegel, B. A.; Cheng, E. Y.; Cheson, B. D.; O'Shaughnessy, J.; Guyton, K. Z.; Mankoff, D. A.; Shankar, L.; Larson, S. M.; Sigman, C. C.; Schilsky, R. L.; Sulliven, D. C. *Clin. Cancer. Res*., **2005**, *11*, 2785. (b) Ido, T.; Wan, C.-N.; Casella, V.; Fowler, J. S.; Wolf, A. P.; Reivich, M.; Kuhl, D. E. *J. Labelled Compds Radiopharm*. **1978**, *14*, 175.

(4) (a) McKeith, I.; O'Brien, J.; Walker, Z.; Tatsch, K.; Booij, J.; Darcourt, J.; Padovani, A.; Giubbini, R.; Bonuccelli, U.; Volterrani, D.; Holmes, C.; Kemp, P.; Tabet, N.; Meyer, I.;

Reininger, C. *Lancet Neurol*. **2007**, *6*, 305. (b) Bajaj, N.; Hauser, R. A.; Grachev, I. D. *J. Neurol. Neurosurg. Psychiatry* **2013**, *84*, 1288.

(5) For example, see: (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) O'Hagan, D. *J. Fluor. Chem*. **2010**, *131*, 1071. (c) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev*. **2016**, *116*, 422.

(6) (a) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev*. **2016**, *116*, 719. (b) Wilson, T. C.; Cailly, T.; Gouverneur, V. *Chem. Soc. Rev*. **2018**, *47*, 6990.

(7) Seevers, R. H.; Counsell, R. E. *Chem. Soc. Rev*. **1982**, *82*, 575.

(8) For examples of some recently developed radioiodination methods, see: (a) Cant, A. A.; Champion, S.; Bhalla, R.; Pimlott, S. L.; Sutherland, A. *Angew. Chem. Int. Ed*. **2013**, *52*, 7829. (b) Zhang, P.; Zhuang, R.; Guo, Z.; Su, X.; Chen, X.; Zhang, X. *Chem. Eur. J*. **2016**, *22*, 16783. (c) Wilson, T. C.; McSweeney, G.; Preshlock, S.; Verhoog, S.; Tredwell, M.; Cailly, T.; Gouverneur, V. *Chem. Commun*. **2016**, *52*, 13277. (d) Dubost, E.; Babin, V.; Benoist, F.; Hébert, A.; Barbey, P.; Chollet, C.; Bouillon, J.-P.; Manrique, A.; Pieters, G.; Fabis, F.; Cailly, T. *Org. Lett*. **2018**, *20*, 6302. (e) 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. *Org. Lett*. **2019**, *21*, 2488.

(9) Webster, S.; O'Rourke, K. M.; Fletcher, C.; Pimlott, S. L.; Sutherland, A.; Lee, A.-L. *Chem. Eur. J*. **2018**, *24*, 937.

(10) Ruth, T. J.; Wolf, A. P. *Radiochim. Acta* **1979**, *26*, 21.

(11) Campbell, M. G.; Ritter, T. *Chem. Rev*. **2015**, *115*, 612.

(12) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem*. **2008**, 2853.

(13) Blair, A.; Zmuda, F.; Malviya, G.; Tavares, A. A. S.; Tamagnan, G. D.; Chalmers, A. J.; Dewar, D.; Pimlott, S. L.; Sutherland, A. *Chem. Sci*. **2015**, *6*, 4772.

(14) Aerts, J.; Voccia, S.; Lemaire, C.; Giacomelli, F.; Goblet, D.; Thonon, D.; Plenevaux, A.; Warnock, G.; Luxen, A. *Tetrahedron Lett*. **2010**, *51*, 64.

(15) Lemaire, C. F.; Aerts, J. J.; Voccia, S.; Libert, L. C.; Mercier, F.; Goblet, D.; Plenevaux, A. R.; Luxen, A. J. *Angew. Chem. Int. Ed*. **2010**, *49*, 3161.

(16) Machulla, H.-J.; Blocher, A.; Kuntzsch, M.; Piert, M.; Wei, R.; Grierson, J. R. *J. Radioanal. Nucl. Chem*. **2000**, *243*, 843.

(17) Dolci, L.; Dolle, F.; Valette, H.; Vaufrey, F.; Fuseau, C.; Bottlaender, M.; Crouzel, C. *Bioorg. Med. Chem*. **1999**, *7*, 467.

(18) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem. Int. Ed*. **2010**, *49*, 6821.

(19) Stenhagen, I. S. R.; Kirjavainen, A. K.; Forsback, S. J.; Jørgensen, C. G.; Robins, E. G.; Luthra, S. K.; Solin, O.; Gouverneur, V. *Chem. Commun*. **2013**, *49*, 1386.

(20) Jacobson, O.; Kiesewetter, D. O.; Chen, X. *Bioconjugate Chem*. **2015**, *26*, 1.

(21) Braghirolli, A. M. S.; Waissmann, W.; da Silva, J. B.; dos Santos, G. R. *Appl. Radiat. Isot*. **2014**, *90*, 138.

(22) Adam, M. J.; Ponce, Y. Z.; Berry, J. M. *J. Labelled Compd. Radiopharm*. **1990**, *28*, 1065.

(23) Samnick, S.; Bader, J. B.; Müller, M.; Chapot, C.; Richter, S.; Schaefer, A.; Sax, B.; Kirsch, C.-M. *Nucl. Med. Commun*., **1990**, *20*, 537.

(24) Cant, A. A.; Bhalla, R.; Pimlott, S. L.; Sutherland, A. *Chem. Commun*. **2012**, *48*, 3993.

(25) (a) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev*. **2000**, *29*, 239. (b) Stone-Elander, S.; Elander, N. *J. Labelled Compd. Radiopharm*. **2002**, *45*, 715.

(26) (a) Lucignani, G. *Eur. J. Nucl. Med. Mol. Imaging* **2006**, *33*, 849. (b) Lu, S. Y.; Pike, V. W., in *PET Chemistry-The Driving Force in Molecular Imaging*, Eds. Schubiger, P. A.; Lehmann, L.; Friebe, M. Springer-Verlag, Heidelberg, **2007**, pp271-287.

(27) For example, see: (a) Brown, L. J.; Bouvet, D. R.; Champion, S.; Gibson, A. M.; Hu, Y.; Jackson, A.; Khan, I.; Ma, N.; Millot, N.; Wadsworth, H.; Brown, R. C. D. *Angew. Chem. Int. Ed*. **2007**, *46*, 941. (b) Tang, G.; Wang, M.; Tang, X.; Luo, L.; Gan, M. *Nucl. Med. Biol*. **2003**, *30*, 509. (c) Sloan, N. L.; Luthra, S. K.; McRobbie, G.; Pimlott, S. L.; Sutherland, A. *Chem. Commun*. **2017**, *53*, 11008.

(28) For example, see: (a) Deng, H.; Cobb, S. L.; Gee, A. D.; Lockhart, A.; Martarello, L.; McGlinchey, R. P.; O'Hagan, D.; Onega, M. *Chem. Commun*. **2006**, 652. (b) Zhang, Q.; Dall'Angelo, S.; Fleming, I. N.; Schweiger, L. F.; Zanda, M.; O'Hagan, D. *Chem. Eur. J*. **2016**, *22*, 10998. (c) Lowe, P. T.; Dall'Angelo, S.; Devine, A.; Zanda, M.; O'Hagan, D. *ChemBioChem* **2018**, *19*, 1969.

(29) Reilly, S. W.; Makvandi, M.; Xu, K.; Mach, R. H. *Org. Lett*. **2018**, *20*, 1752.