Radiochemistry

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C(sp^3)—^{18}F Bond Formation by Transition-Metal-Based [^{18}F]Fluorination

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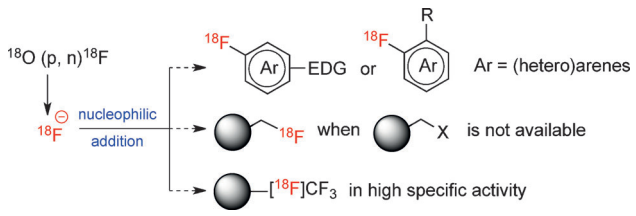
Fluorine-18 · imaging agents · positron emission tomography · radiochemistry · transition metals

Fluorine-18 (^{18}F; $t_{1/2}$ = 109.7 min) is the most commonly used isotope to prepare radiopharmaceuticals for molecular imaging by positron emission tomography (PET).[1] Nucleophilic displacement reactions of suitably activated precursors with no-carried-added [^{18}F]fluoride ions are routinely performed in the radiosynthesis of PET radiotracers, including clinically approved radiotracers: 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), the most widely used PET radiotracer used primarily for oncology imaging, and (*E*)-4-(2-(6-(2-(2-(2-([^{18}F]-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methyl)benzenamine (AMYViD), for visualizing β-amyloid plaques in Alzheimer's disease and related dementias. Despite extensive efforts to develop a general solution of introducing ^{18}F into non-activated precursor molecules there are several challenges to achieving this goal. Scheme 1 lists



Scheme 1. Some challenges in fluorine-18 radiochemistry. EDG = electron-donating group.

some urgent and unmet needs in ^{18}F-radiochemistry development, including the introduction of this short-lived radionuclide into non-activated arenes (not easily achieved by traditional S_NAr reactions), nucleophilic displacement reactions in the absence of adequate leaving groups (partially attributed to instability under labeling conditions), the preparation of the [^{18}F]trifluoromethyl group from readily available [^{18}F]fluoride ion in high specific activity, etc.

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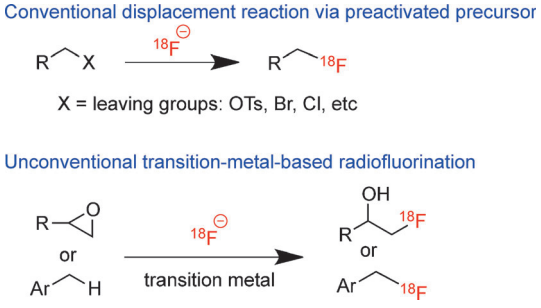
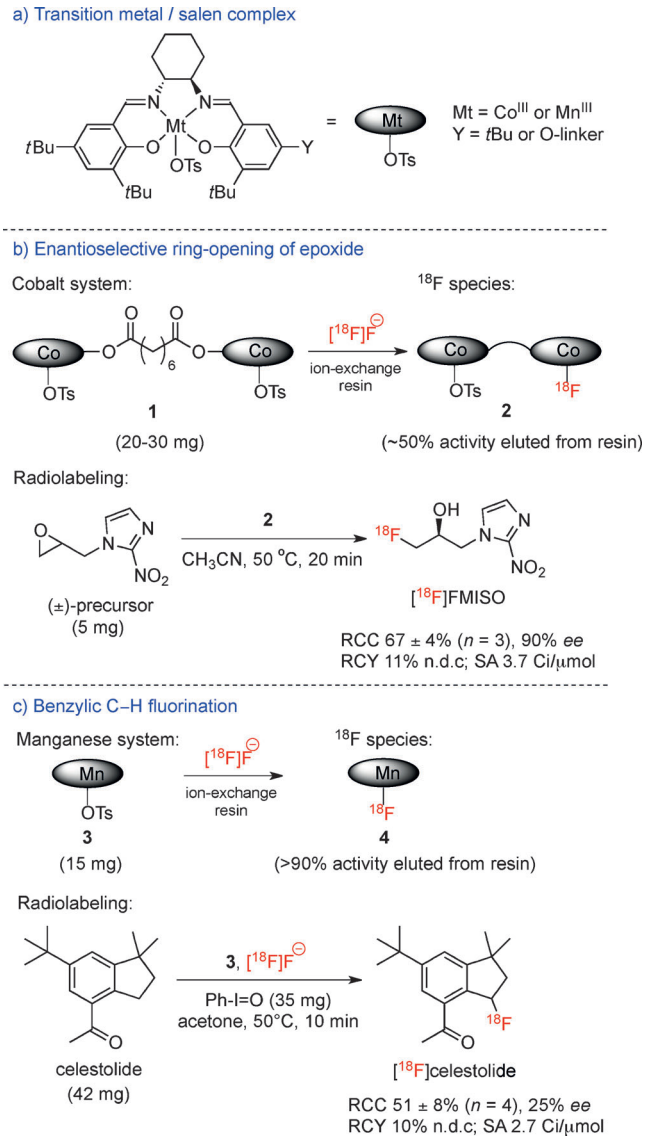
Recent breakthroughs for novel radiofluorination methods to address these challenges can be classified into two main categories, that is, the bond formation between C(sp^2)—^{18}F and C(sp^3)—^{18}F. For the former class, there are several new ^{18}F-radiochemistry methods involving palladium-,[2] nickel-,[3] or copper-mediated transformations,[4] strategies based on a phenolic precursors,[5] hypervalent iodine(III) methods,[6] and renewed interests in diaryliodonium salts[7] or aryl iodonium ylides,[8] all of which showcase a comprehensive collection of new technologies which could translate into the production of PET tracers and radiopharmaceuticals.

PET tracers with aliphatic ^{18}F motifs are typically synthesized through a nucleophilic substitution reaction between activated leaving groups, for instance, halides or aryl/alkyl sulfonates and a [^{18}F]fluoride ion in the presence of base. These traditional methods generally necessitate a stable precursor molecule which can survive at high temperatures (> 100 °C) and in basic environments, show tolerance in elimination pathways, and resist racemization/epimerization in chiral molecules. Exploration of milder reaction conditions, including avoiding azeotropic drying of [^{18}F]fluoride,[9] remains active areas of exploration. In this Highlight, we focus on two recent advances for the construction of aliphatic carbon–^{18}F bonds, namely the ring-opening of epoxides and reaction of benzylic C–H bonds by [^{18}F]fluoride with [(salen)Co^{III}X] and [(salen)Mn^{IV}X] (X = anionic counterions) precursors, respectively (Scheme 2). Such chiral transition-metal-based radiofluorination methodologies provide a new strategy to prepare ^{18}F-labeled aliphatics beyond conventional methodologies and enable novel functionalities to be explored in PET radiopharmaceutical design.



Scheme 2. Conventional and unconventional transition-metal-based radiofluorinations on aliphatic carbons. Ts = 4-toluenesulfonyl.



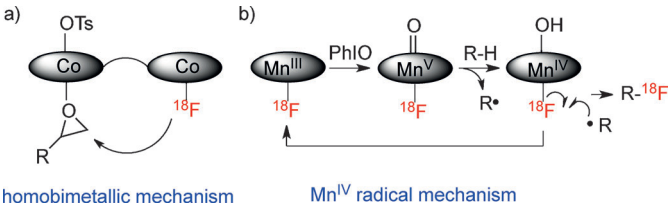
Scheme 3. Cobalt- or manganese-mediated fluorine-18 chemistry. RCC = radiochemical conversion, calculated from chromatographic profiles; n.d.c. = non-decay corrected; RCY = isolated radiochemical yield; SA = specific activity.

The group of Doyle recently described an enantioselective aliphatic fluorination using an ^{18}F/cobalt/salen complex (Scheme 3a and b) to generate [^{18}F]fluorohydrins.[10] [^{18}F]fluoride in target water was first trapped on an ion-exchange resin, then rinsed with either the monomeric or dimeric air-stable cobalt salen complex **1** (ca. 20–30 mg in MeOH) to generate the (salen)Co^{III}/^{18}F intermediate **2** with about 50% trapping and release efficiency. The radiofluorination between **2** and racemic epoxides was carried out at 50 °C in MTBE (methyl *tert*-butyl ether) or CH_3CN for 20 minutes with about a 20–70% radiochemical incorporation yield and greater than 90% *ee*. Several radiotracers, including an experimental radiotracer for imaging tau protein, [^{18}F]THK5105, as well as [^{18}F]FETNIM, and N-Cbz [^{18}F]fluoro-theronine were successfully prepared by this method.

To demonstrate the potential application of this methodology for use in PET radiopharmaceutical production, a semi-automated radiosynthesis of a nitroimidizole-based hypoxia imaging agent, [^{18}F]FMISO, was carried out to produce 12 mCi of the isolated product in a 10% non-decay-corrected yield with a specific activity of 3.7 Ci μmol^{-1} within 40 minutes. ICP-MS analysis showed only trace residues (5 ppb) of cobalt in the product. As a result, the method provides an operationally simple procedure which can produce labeled compounds and clinically useful PET radiotracers under in mild reaction conditions.

The groups of Groves and Hooker have discovered another class of radiochemical transformations which can direcly replace and sp^3-carbon-bonded hydrogen with [^{18}F]fluoride at the benzylic position, thus obviating the need of preactivated precursors and also enabling rapid functionalization of the parent molecule with ^{18}F.[11] Analogous to the previously described cobalt system, aqueous [^{18}F]fluoride was trapped on an ion-exchange resin, and subsequently released by the addition of [Mn^{III}(salen)OTs] (**3**; 15 mg in acetone; Scheme 1) to generate the ^{18}F-transfer catalyst **4** with greater than 90% trapping and release efficiency (Scheme 3a and c). It is worthy of mention that this method requires no azeotropic drying of ^{18}F and is tolerant of both moisture and air. The reaction was carried out in the presence of a precursor molecule and an oxidant (PhIO; 35–60 mg) in acetone at 50 °C for 10 minutes. The radiochemical incorporations of a variety of organic molecules and building blocks ranged from about 20 to 70% and several bioactive molecules, including inhibitors of cyclooxygenase (COX), monoamine oxidase B (MAO-B), phosphodiesterase (PDE), angiotensin-converting-enzyme (ACE) etc., were successfully functionalized at the benzylic postion by replacing H with ^{18}F. For example, [^{18}F]celestolide was isolated in 10% non-decay-corrected yield with a specific activity of 2.7 Ci μmol^{-1}, and allows a "late-stage" labeling strategy for a variety of organic molecules bearing benzylic C–H functionalities.

The mechanism of the aforemention reactions depend on the nature of the transition metal and reaction conditions. For the formation of [^{18}F]fluorohydrin, a homobimetallic mechanism was proposed (Scheme 4a). The authors propose that



Scheme 4. Plausible mechanisms of radiolabeling reactions of with fluorine-18.

the racemic epoxide coordinated to the cobalt center, is displaced by a [^{18}F]fluoride ion in an enantioselective manner. The manganese(IV)/^{18}F complex, generated by PhIO oxidation and H abstraction from R-H, is postulated to be involved in the catalytic cycle, and is supported by DFT calculations (Scheme 4b). Followed by the reaction between a benzylic

radical and the $^{18}F/Mn^{IV}/OH$ complex, the product is likely generated as a thermodynamically favored outcome.

The examples presented herein illustrate the continued enthusiasm for novel radiofluorination methods and unconventional aliphatic [$^{12}C(sp^3)$–^{18}F] bond formations, including enantioselective reactions. Further application in the ring-opening of multi-substituted epoxides, selective functionalization of relatively inactive C–H bonds beyond benzylic positions, and reduced amount of catalyst and/or substrate during the reactions are areas of further development. Scale-up of these reactions and quality control validation would be required prior to clinical translation of these methodologies. Nevertheless, mastery of the factors that affect the design of chiral-transition-metal catalysis with Co/salen/^{18}F or Mn/salen/^{18}F species, in conjunction with mechanistic studies offers an exciting new methodology for aliphatic radiofluorinations.

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[1] a) J. S. Fowler, A. P. Wolf, *Acc. Chem. Res.* **1997**, *30*, 181–188; b) M. E. Phelps, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9226–9233; c) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem. Int. Ed.* **2008**, *47*, 8998–9033; *Angew. Chem.* **2008**, *120*, 9136–9172; d) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501–1516; e) L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* **2008**, 2853–2873.

[2] E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, *334*, 639–642.

[3] E. Lee, J. M. Hooker, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 17456–17458.

[4] M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot, V. Gouverneur, *Angew. Chem. Int. Ed.* **2014**, *53*, 7751–7755; *Angew. Chem.* **2014**, *126*, 7885–7889.

[5] Z. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban, V. Gouverneur, *Angew. Chem. Int. Ed.* **2012**, *51*, 6733–6737; *Angew. Chem.* **2012**, *124*, 6837–6841.

[6] a) V. W. Pike, F. I. Aigbirhio, *J. Chem. Soc. Chem. Commun.* **1995**, 2215–2216; b) M. A. Carroll, J. Nairne, G. Smith, D. A. Widdowson, *J. Fluorine Chem.* **2007**, *128*, 127–132; c) T. L. Ross, J. Ermert, C. Hocke, H. H. Coenen, *J. Am. Chem. Soc.* **2007**, *129*, 8018–8025; d) B. Wang, J. W. Graskemper, L. Qin, S. G. DiMagno, *Angew. Chem. Int. Ed.* **2010**, *49*, 4079–4083; *Angew. Chem.* **2010**, *122*, 4173–4177.

[7] a) N. Ichiishi, A. J. Canty, B. F. Yates, M. S. Sanford, *Org. Lett.* **2013**, *15*, 5134–5137; b) N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford, P. J. H. Scott, *Org. Lett.* **2014**, *16*, 3224–3227.

[8] a) B. Rotstein, N. Stephenson, N. Vasdev, S. H. Liang, *Nat. Commun.* **2014**, *5*, 5365; b) J. Cardinale, J. Ermert, S. Humpert, H. H. Coenen, *RSC Adv.* **2014**, *4*, 17293–17299.

[9] J. Aerts, S. Voccia, C. Lemaire, F. Giacomelli, D. Goblet, D. Thonon, A. Plenevaux, G. Warnock, A. Luxen, *Tetrahedron Lett.* **2010**, *51*, 64–66, and references therein.

[10] T. J. A. Graham, R. F. Lambert, K. Ploessl, H. F. Kung, A. G. Doyle, *J. Am. Chem. Soc.* **2014**, *136*, 5291–5294.

[11] X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc.* **2014**, *136*, 6842–6845.

