Published in final edited form as:

Angew Chem Int Ed Engl. 2014 October 20; 53(43): 11416–11418. doi:10.1002/anie.201407065.

Aliphatic ^{18}F Bond Formation via Transition Metal Based $[^{18}\text{F}]$ Fluorination

Prof. Steven H. Liang* and Prof. Neil Vasdev*

*Division of Nuclear Medicine and Molecular Imaging, CAMIS, Massachusetts General Hospital; Department of Radiology, Harvard Medical School 55 Fruit St., White 427, Boston, MA 02114 (USA)

Graphical abstract

Recent advances in aliphatic radiofluorinations enabled by transition metals, specifically Co- and Mn-salen complexes, have been unveiled. These new approaches operate in a unique way that obviates the need of highly activated substrates for radiolabeling and offers a new synthetic strategy to prepare ^{18}F -labeled radiotracers.

Keywords

Fluorine-18; transition metal; nucleophilic displacement; positron emission tomography; PET radiochemistry

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 $[^{18}\text{F}]$ fluoride ion are routinely performed in the radiosynthesis of PET radiotracers, *i.e.*, clinically approved radiotracers: 2- $[^{18}\text{F}]$ fluoro-2-deoxy-D-glucose ($[^{18}\text{F}]$ FDG), the most widely used PET radiotracer used primarily for oncology imaging and (*E*)-4-(2-(6-(2-(2-($[^{18}\text{F}]$ -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 to introduce ^{18}F into non-activated precursor molecules there are several challenges to achieve this goal. Scheme 1 lists 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 $\text{S}_{\text{N}}\text{Ar}$ reactions), nucleophilic displacement reactions in the absence of adequate leaving groups (partially attributed to instability under labeling conditions), the preparation of $[^{18}\text{F}]$ trifluoromethyl group from readily available $[^{18}\text{F}]$ fluoride ion in high specific activity, etc.

Recent breakthroughs for novel radiofluorination methods to address these challenges can be classified into two main categories, *i.e.*, the bond formation between C(sp²)-¹⁸F and C(sp³)-¹⁸F. For the former class, there are several new ¹⁸F radiochemistry methods involving Pd-,^[2] Ni-^[3] or Cu-mediated transformations,^[4] strategies based on a phenolic precursors,^[5] and hypervalent iodine(III) methods,^[6] with renewed interests in diaryliodonium salts^[7] or aryl iodonium ylides,^[8] all of which showcase a comprehensive collection of new technologies that could translate into the production of PET tracers and radiopharmaceuticals.

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

The Doyle group recently described an enantioselective aliphatic fluorination using ¹⁸F-cobalt-salen complex (Scheme 3A and B) to generate [¹⁸F]fluorohydrins.^[10] [¹⁸F]fluoride in target water was first trapped on an ion exchange resin, then rinsed by either monomeric or dimeric air-stable cobalt salen complex **1** (*ca.* 20–30 mg in MeOH) to generate a (salen)Co(III)-¹⁸F intermediate **2** with about 50% trapping and release efficiency. The radiofluorination between **2** and racemic epoxides were carried out at 50 °C in MTBE or CH₃CN for 20 min with *ca.* 20–70% radiochemical incorporation yield with >90% *ee*. Several radiotracers, including an experimental radiotracer for imaging tau protein, [¹⁸F]THK5105, as well as [¹⁸F]FETNIM, N-Cbz [¹⁸F]fluoro-theronine were successfully prepared by this method.

In order to demonstrate the potential application of this methodology for use in PET radiopharmaceutical production, a semi-automated radiosynthesis of a nitroimidazole-based hypoxia imaging agent, [¹⁸F]FMISO, was carried out to produce 12 mCi isolated product in a 10% non-decay corrected yield with a specific activity of 3.7 Ci/μmol 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 that can produce labeled compounds and clinically useful PET radiotracers under mild conditions.

The Groves and Hooker groups have discovered another class of radiochemical transformations that can directly replace sp³ hydrogen with [¹⁸F]fluoride at the benzylic position, obviating the need of pre-activated precursors and also enabling a rapid functionalization of parent molecule with ¹⁸F.^[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) to generate the ^{18}F -transfer catalyst **4** with >90% trapping and release efficiency (Scheme 3A and 3C). 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 *ca.* 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 position by replacing H by ^{18}F . For example, [^{18}F]celestolide was isolated in 10% non-decay corrected yield with a specific activity of 2.7 Ci/ μmol , which allows a “late-stage” labeling strategy for a variety of organic molecules bearing benzylic C–H functionalities.

The mechanism of the aforementioned 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 the racemic epoxide coordinated to cobalt center, is displaced by a [^{18}F]fluoride ion in an enantioselective manner. The manganese(IV)– ^{18}F complex, generated via 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 ($^{12}\text{C}(\text{sp}^3)$ - ^{18}F) bond formations, including enantioselective reactions. Further application in the ring-opening of multi-substituted epoxides, selective functionalization of relatively inactive C–H bond 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- or Mn-salen- ^{18}F species, in conjunction with mechanistic studies offers an exciting new methodology for unconventional aliphatic radiofluorinations.

References

1. a) Fowler JS, Wolf AP. Accounts of Chemical Research. 1997; 30:181–188. b) Phelps ME. Proc Natl Acad Sci. 2000; 97:9226–9223. [PubMed: 10922074] c) Miller PW, Long NJ, Vilar R, Gee AD. Angew Chem Int Ed. 2008; 47:8998–9033. d) Ametamey SM, Honer M, Schubiger PA. Chemical Reviews. 2008; 108:1501–1516. [PubMed: 18426240] e) Cai L, Lu S, Pike VW. Eur J Org Chem. 2008; 2008:2853–2873.
2. Lee E, Kamlet AS, Powers DC, Neumann CN, Boursalian GB, Furuya T, Choi DC, Hooker JM, Ritter T. Science. 2011; 334:639–642. [PubMed: 22053044]
3. Lee E, Hooker JM, Ritter T. J Am Chem Soc. 2012; 134:17456–17458. [PubMed: 23061667]
4. Tredwell M, Preshlock SM, Taylor NJ, Gruber S, Huiban M, Passchier J, Mercier J, Génicot C, Gouverneur V. Angew Chem Int Ed. 2014; 53:7751–7755.

5. Gao Z, Lim YH, Tredwell M, Li L, Verhoog S, Hopkinson M, Kaluza W, Collier TL, Passchier J, Huiban M, Gouverneur V. *Angew Chem Int Ed*. 2012; 51:6733–6737.
6. a) Pike VW, Aigbirhio FI. *J Chem Soc, Chem Commun*. 1995:2215–2216. b) Carroll MA, Nairne J, Smith G, Widdowson DA. *J Fluorine Chem*. 2007; 128:127–132. c) Ross TL, Ermert J, Hocke C, Coenen HH. *J Am Chem Soc*. 2007; 129:8018–8025. [PubMed: 17536798] d) Wang B, Graskemper JW, Qin L, DiMagno SG. *Angew Chem Int Ed*. 2010; 49:4079–4083.
7. Ichiishi N, Canty AJ, Yates BF, Sanford MS. *Org Lett*. 2013; 15:5134–5137. [PubMed: 24063629]
b) Ichiishi N, Brooks AF, Topczewski JJ, Rodnick ME, Sanford MS, Scott PJH. *Org Lett*. 2014; 16:3224–3227. [PubMed: 24890658]
8. a) Rotstein B, Stephenson N, Vasdev N, Liang SH. *Nat Commun*. 2014; 5:4365.doi: 10.1038/ncomms5365 [PubMed: 25007318] b) Cardinale J, Ermert J, Humpert S, Coenen HH. *RSC Advances*. 2014; 4:17293–17299.
9. Aerts J, Voccia S, Lemaire C, Giacomelli F, Goblet D, Thonon D, Plenevaux A, Warnock G, Luxen A. *Tetrahedron Lett*. 2010; 51:64–66. and references therein.
10. Graham TJA, Lambert RF, Ploessl K, Kung HF, Doyle AG. *J Am Chem Soc*. 2014; 136:5291–5294. [PubMed: 24628021]
11. Huang X, Liu W, Ren H, Neelamegam R, Hooker JM, Groves JT. *J Am Chem Soc*. 2014; 136:6842–6845. [PubMed: 24766544]

Scheme 1.

Some challenges in fluorine-18 radiochemistry.

Conventional displacement reaction via pre-activated precursor **Unconventional transition metal based radiofluorination** **Scheme 2.**

Conventional and unconventional transition metal based radiofluorinations on aliphatic carbons.

Scheme 3. Cobalt or manganese-mediated fluorine-18 PET chemistry. RCC = radiochemical conversion by chromatograph; RCY = isolated radiochemical yield; n.d.c. = non-decay corrected; SA = specific activity

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