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Chemistry for Positron Emission Tomography: Recent Advances in ^{11}C-, ^{18}F-, ^{13}N- and ^{15}O-labeling Reactions

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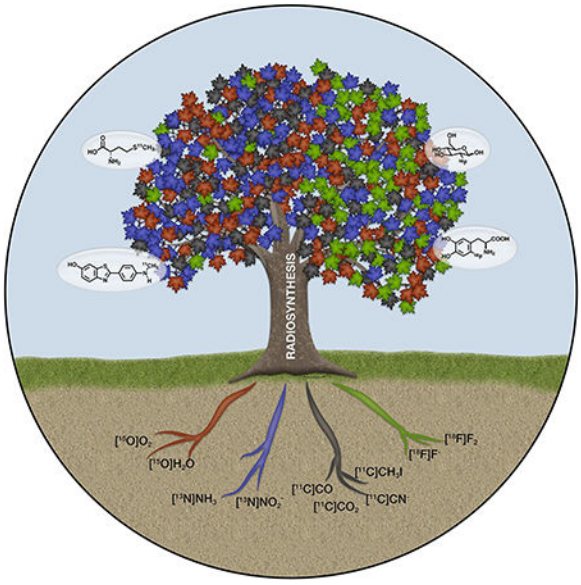
Abstract

Positron emission tomography (PET) is a molecular imaging technology that provides quantitative information about function and metabolism in biological processes *in vivo* for disease diagnosis and therapy assessment. The broad application and rapid advances of PET has led to an increased demand for new radiochemical methods to synthesize highly specific molecules bearing positron-emitting radionuclides. This article provides an overview of commonly-used labeling chemistry in the examples of clinically relevant PET tracers, and highlights most recent development and breakthroughs over the past decade with focus on ^{11}C, ^{18}F, ^{13}N, and ^{15}O.

Graphical Abstract



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Keywords

positron emission tomography; carbon-11; fluorine-18; nitrogen-13; oxygen-15

1. Introduction

Positron emission tomography (PET), a non-invasive molecular imaging technique, is capable of probing biological processes *in vivo*, monitoring the progression of disease states, and evaluating drug treatment efficacy.[1–4] Unlike structural and anatomical imaging techniques, including X-ray and ultrasound, PET offers functional information via the interaction between a targeted molecule bearing a positron-emitting radionuclide ('radiotracer') and biological system. Since only trace amounts of radioactive materials (10^{-6}–10^{-9} grams) are necessary to obey the 'tracer principle' in such diagnostic imaging studies, it is feasible to directly monitor the biological process via PET without eliciting pharmacological effects, particularly when radiotracers with high specific activity are employed. PET radiotracers possess desired binding and physiochemical properties to interact with biological targets of interest, including receptors, enzymes and ion channels.[5–7] The growing role of PET imaging in drug discovery efforts has prompted significant investment in novel PET ligand discovery from both industry and academic communities, yielding a steady flow of novel radioligands that showed requisite specificity toward intended biological targets to enable target engagement studies. PET imaging has also been used to examine whether the desired tissue partition of therapeutic agents are achieved and can also serve as a disease-state biomarker by detecting expression level changes in biological target between healthy and disease state, modulation of which by therapeutic agents can be used to monitor treatment efficacy in longitudinal studies.

The advance of PET is often paced by the availability and facile synthesis of targeted radiotracers.[5] To a considerable extent, the key for successful clinical translation depends not only on the biological characteristics of the PET tracer, but also the implementation of an efficient and practical radiolabeling method to enable widespread use. Such radiochemical methods are strongly influenced by the characteristics of the PET nuclides, including chemical reactivity and half-life. Numerous review articles have captured the basic principles of PET[1–6] and overviewed radiotracer development.[7, 8] Herein, we aim to emphasize the importance of commonly-used methods, and highlight recent advances and breakthroughs in the chemistry of carbon-11, fluorine-18, nitrogen-13 and oxygen-15 in the last decade (2008–2018). The proof-of-concept application and synthesis of a diverse range of representative and clinically relevant small molecule PET pharmaceuticals are discussed. We also present unsolved challenges in PET chemistry with these radionuclides and potential area for methodology development as a unified theme to stimulate discovery research in PET chemistry.

2. Labeling methods with carbon-11

Since carbon is the backbone element in the whole spectrum of pharmaceutical molecules, isotopologue labeling using carbon-11 (^{11}C, t½ = 20.4 min) presents a unique opportunity

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for radiochemistry and PET tracer development since no changes of structural, biological, and pharmacological properties are anticipated after the radiolabel is implemented. The short half-life of ^{11}C requires highly-efficient transformation which usually occurs on the ultimate or penultimate step to maximize the use of rapidly-decaying radioactivity. Complementary to previous ^{11}C reviews,[5, 9–14] we highlight some recent developments and breakthroughs in ^{11}C chemistry with an emphasis on commonly used synthons and novel building blocks (Scheme 1). The nuclear reactions and production of the respective synthons have been reviewed elsewhere.[5, 12]

2.1. [^{11}C]CH_3X (X = I or OTf) chemistry

[^{11}C]CH_3I is by far the most frequently used ^{11}C-labeling agent. Nucleophilic substitution of [^{11}C]CH_3X (X = I or OTf) can generate ^{11}C-methyl heteroatomic (N, O, or S) compounds or activated carbonic ^{11}C-methylated compounds under neutral or basic conditions. This simple and direct ^{11}C-methylating method has been well applied in the synthesis of many ^{11}C-labeled tracers, including [^{11}C]PIB, [^{11}C]DASB, [^{11}C]flumazenil, [^{11}C]DTBZ, [^{11}C]MET and [^{11}C]fenoprofen (Scheme 2, A). While [^{11}C]CH_3I is satisfactory for most ^{11}C-labeling reactions, the more reactive [^{11}C]CH_3OTf (produced from [^{11}C]CH_3I with silver triflate at 200 °C) may offer an alternative solution for improved radiochemical yield (RCY) and chemoselectivity, shorter reaction time, lower reaction temperature and less precursor loading. For example, ^{11}C-*N*-methylation could be selectively achieved with [^{11}C]CH_3OTf under neutral conditions in the synthesis of [^{11}C]PIB without the protection of hydroxyl group.[15] Pd-Mediated cross coupling reactions, particularly Stille and Suzuki-type, are often used to synthesize ^{11}C-labeled aryl or alkenyl tracers. Representative examples in each category include (15*R*)-[^{11}C]TIC, [^{11}C]MNQP and a ^{11}C-labeled mGlu1 ligand from tributylstannes,[16] [^{11}C]celecoxib, [^{11}C]cibbi-772, and [^{11}C]UCB-J from organoborates, respectively (Scheme 2, B1). Complementary to these major approaches, proof-of-concept ^{11}C-labeling methodology studies involving Negishi[17] / Sonogashira-type[18] reactions, and Schwartz's reagent,[19] were also reported. Recently, a novel ^{11}C-acetylation method was developed using transition metal-mediated cross coupling reactions via [^{11}C]CH_3I and a CO source (Scheme 2, B2–3).[20, 21]

2.2 [^{11}C]CO_2 chemistry

2.2.1 Formation of ^{11}C-carbonyl labeled carboxylic acids and derivatives via [^{11}C]CO_2—

[^{11}C]CO_2 is the feedstock virtually for all ^{11}C chemistry and can be readily converted to other synthons in high RCYs and high specific activity.[9, 12] Trapping [^{11}C]CO_2 with strongly basic organometallic reagents, such as Grignard and organolithium reagents, represents an early and conventional approach to generate ^{11}C-labeled carboxylic acids (Scheme 3, A1). ^{11}C-Labeled fatty acids, such as acetic, propionic, butyric and palmitic acids, have been prepared by this method.[12] The addition of [^{11}C]CO_2 to the lithium aldimine intermediate yielded ^{11}C-labeled α-keto acids, such as pyruvic acid.[22] A recent example entailed [^{11}C]CO_2 insertion into organolithium (from organostannane precursor), leading to an ^{11}C-labeled of RXR- partial agonist (Scheme 3, A1).[23]

[^{11}C]Carboxylic derivatives including ^{11}C-labeled esters and amides, as well as ^{11}C-labeled amines could also be produced from [^{11}C]carboxymagnesium halides depending on the

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nature of nucleophiles and proper reducing agents if necessary (Scheme 3, A2).[9, 12, 24] Representative examples include the preparation of [^{11}C]melatonin, and radiopharmaceuticals routinely used in clinical research including (+)-[^{11}C]PHNO and [^{11}C]WAY100635.

In addition, ^{11}C-labeled alkyl halides, for example, [^{11}C]benzyl iodide, can also be prepared by Grignard reaction, followed by reduction and halogenation.[25]

Grignard and organolithium reagents are reactive species which are unstable towards air and moisture, and technical challenges of such radiosyntheses have restricted their widespread use. In 2012, Riss and Pike *et al.* developed a novel strategy to synthesize ^{11}C-labeled carboxylic acids and derivatives from boronic esters in the presence of a copper catalyst in high RCYs and high specific activity (Scheme 3B).[26] The conversion was tolerant with diverse functional groups, such as halides, nitro and carbonyl groups, demonstrating a significantly broader substrate scope than that of organometallic reagents. In 2014, Vasdev and Liang *et al.* adopted this method to prepare [^{11}C]bexarotene under modified conditions and translated this ligand for PET-MR imaging studies in nonhuman primates.[27] Recently, Gee and Bongarzone *et al.* developed a method for synthesizing ^{11}C-labeled amides from primary amines using Grignard reagents (Scheme 3C). This work utilized DBU to trap [^{11}C]CO_2, followed by the formation of ^{11}C-oxyphosphonium or [^{11}C]isocyanate intermediates, to afford ^{11}C-labeled amides upon Grignard addition.[28]

2.2.2 Formation of ^{11}C-carbonyl labeled ureas and carbamates using [^{11}C]CO_2—

The first attempt to prepare ^{11}C-labeled urea from [^{11}C]CO_2 was carried out via ^{11}C-carbonylation reaction with amines in the presence of diphenylphosphite and pyridine albeit in low RCYs. Other methods[9, 12] including the use of lithium hexamethyldisilazide (LHMDS), and the formation of reactive intermediate [^{11}C]cyanamides or [^{11}C]isocyanates, offered diverse approaches to synthesize symmetrical ^{11}C-labeled ureas from [^{11}C]CO_2.

In 2006, a practical protocol to prepare unsymmetrical ^{11}C-ureas from amines and phosphinimines was reported (Scheme 4A).[29] Phosphinimines derived from azides or primary amines generated ^{11}C-isocyanate intermediate, followed by second amine addition, to provide unsymmetrical ^{11}C-ureas in 8–49% RCYs. In 2009, Hooker and Fowler *et al.* reported a novel method using DBU as [^{11}C]CO_2 trapping base and carried out the synthesis of ^{11}C-labeled carbamate from amines and alkyl halides (Scheme 4B).[30] Several radioligands based on drug scaffolds including [^{11}C]metergoline and [^{11}C]MS-275,[31] were labeled in 25–40% RCYs. In 2011, Wilson and Vasdev *et al.* discovered a unified method using a phosphazene base, BEMP (as [^{11}C]CO_2 trapping base) and POCl3 (as dehydrating or chlorinating reagent) to achieve the formation of unsymmetrical ^{11}C-labeled ureas and carbamates (Scheme 4, C1).[32] This protocol was applied in the synthesis of a broad scope of bioactive molecules,[9, 12] including [^{11}C]CURB, [^{11}C]PF-04457845 and [^{11}C]SL25.1188. Recently, this process was automated by using an ‘in-loop’ synthesis module, and produced [^{11}C]SL25.1188 and [^{11}C]JNJ1661010 by flow chemistry.[33, 34] Another method to obtain unsymmetrical ^{11}C- labeled ureas was developed by Gee *et al.* in 2013 using Mitsunobu conditions (Scheme 4, C2).[35] Both aliphatic and less reactive

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aromatic amines proceeded well to offer unsymmetrical ^{11}C-labeled ureas in high RCYs of 69–94%. Most noteworthy is that these [^{11}C]CO_2 fixation reactions are simple, one-pot, generally require no heating or cooling, and are easily automated. Consequently, [^{11}C]CURB and [^{11}C]SL2511.88 have been translated for human use, thereby paving the way to numerous PET radiopharmaceuticals synthesized directly from [^{11}C]CO_2.[9, 12]

Different with ^{11}C-carbonylation, Billard *et al.* developed a simple method to achieve ^{11}C-methylation for amines from [^{11}C]CO_2 under reducing conditions.[36] This direct ^{11}C-labeling strategy was applied to the synthesis of [^{11}C]PIB in 45% RCY and 50 GBq/μmol molar activity.

2.3 [^{11}C]CO chemistry

2.3.1 Aromatic and activated alkyl ^{11}C-carbonylation via [^{11}C]CO—

[^{11}C]CO is an established building block for the synthesis of ^{11}C-carbonyl labeled carboxylic acids, esters, amides, ketones and aldehydes via transition-metal mediated carbonylation reactions[10–14] Pd-mediated cross coupling reaction between aryl/benzylic/methyl halides and [^{11}C]CO can provide ^{11}C-labeled carboxylic acids or esters in the presence of hydroxides or alcohols, respectively (Scheme 5, A1).[12, 37–39] For example, [^{11}C]eprosartan was synthesized in 54% RCY by using the corresponding aryl iodide and [^{11}C]CO in the presence of $Pd(PPh_3)_4$ and Bu_4NOH.[40] Similarly, aryl(mesityl)iodonium saltscould replace aryl halides to react with [^{11}C]CO and generate^{11}C-labeled carboxylic acids.[41] Aryl halides could also be converted into ^{11}C-labeled aryl formyl chlorides *in situ* in the presence of Bu4NCl, then transformed into ^{11}C-labeled amides, esters, acids, aldehydes, alcohols and ketones.[42, 43] In addition, boronate precursors via Pd-mediated transmetalation could proceed ^{11}C-carbonylation with [^{11}C]CO (Scheme 5, A2). Representative examples include a retinoid compound [^{11}C]Am80[44] and [^{11}C]aspirin[45] obtained from the corresponding boronates.

^{11}C-Labeled amides could also be obtained from appropriate primary or secondary amines in Pd-mediated cross coupling reactions between aryl halides and [^{11}C]CO.[10–14] Several representative radiotracers are shown in Scheme 5, B1. This is one of three primary methods to access ^{11}C-labeled amides, in addition to [^{11}C]CO_2 (via acylation and aminolysis) and [^{11}C]CN (via controlled hydrolysis) methods. Since [^{11}C]CO has limited solubility in organic solvents, efficient radioactive gas trapping in the reaction system is challenging. Several novel strategies were developed to address this problem,[11, 14] including use of a high-pressure reactor, continuous flow microreactor, gas-liquid segmented microfluidics, use of palladium dimer catalyst or NHC ligand, trapping [^{11}C]CO by Pd catalyst, NHC ligand, borane, and copper(I) complex, xenon gas carrier, and improved methods to produce [^{11}C]CO.[46–48] Among these methods, a recent example by Skrydstrup and Antoni *et al.* highlighted the use of [^{11}C]CO in a simple low-pressure vessel with pre-activated aryl-Pd species as stoichiometric reagents and produce well-functionalized radioligands in high RCYs (Scheme 5, B2).[49] The same authors also applied this strategy in the *N*-^{11}C-acetylation of peptides with [^{11}C]CO and bisphosphine-ligated Pd complexes (Scheme 5, B3).[50] Several representative *N*-^{11}C-acetylated bioactive peptides, such as

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[^{11}C]lacosamide, [^{11}C]acetyl LULUPhol and [^{11}C]acetyl cRGDfK were obtained in high RCYs of 33–46% and high molar activity of 281–404 GBq/μmol.[50]

The synthesis of ^{11}C-carbonyl labeled ketones can be accomplished by [^{11}C]CO-involved three-component Stille-type cross coupling reactions (Scheme 6A).[10–14, 5152] For example, a potential PET radioligand for histamine subtype 3 receptors, was ^{11}C-labeled by this method using the corresponding arylstannane, aryl iodide and [^{11}C]CO.[52] [^{11}C]Benzaldehyde could be obtained when Et_3SiH was employed instead of an organotin reagent.[51] Furthermore, Suzuki-type reactions were also capable of providing ^{11}C-carbonyl labeled ketones (Scheme 6B).[53] The products were obtained in the range of 10–70% RCYs and high molar activity (>150 GBq/μmol).

2.3.2 ^{11}C-Carbonylation of nonactivated aliphatic substrates via [^{11}C]CO—

Despite the exciting advances in the Pd-mediated ^{11}C- carbonylation reactions with [^{11}C]CO, the scope is commonly limited to aryl, alkenyl, methyl and benzyl substrates without liability of inclined *β-H* elimination from ensuing oxidative Pd(II) complex. To expand substrate chemotype, other transition metals or radical-mediated methods were used to activate alkyl halides containing *β*-hydrogen atoms. In 2016, Rahman *et al.* developed a Ni-mediated method for the synthesis of ^{11}C-carbonyl labeled alkyl amides starting from non-activated alkyl iodides (Scheme 7A).[54] Cyclic or acyclic alkyl iodides were converted to ^{11}C- carbonyl labeled amides in 33–90% RCYs. Alkyl iodides could also be utilized in free radical-mediated reactions with [^{11}C]CO, to generate ^{11}C-carbonyl labeled carboxylic acids, esters and amides in good RCYs (44–76%) with high molar activity (Scheme 7B).[55–57]

2.3.3 Synthesis of ^{11}C-carbonyl labeled urea and carbamate via [^{11}C]CO—

Complementary to [^{11}C]CO_2 and [^{11}C]$COCl_2$ chemistry, Rh-mediated ^{11}C-carbonylation reactions convert aryl azides and [^{11}C]CO into the corresponding Rh-coordinated ^{11}C-isocyanates, which subsequently form ^{11}C-carbonyl labeled ureas and carbamates, respectively (Scheme 8).[58] This method was applied in the preparation of a wide range of ^{11}C-compounds, including ^{11}C-labeled VEGFR-2/PDGFR-*β* dual inhibitors,[59]

[^{11}C]phenytoin,[60] ^{11}C-labeled sulfonyl ureas and carbamates,[61, 62] and ^{11}C-labeled hydroxyurea derivatives.[63] in addition, Se-mediated ^{11}C-carbonylation of amines and alcohols with [^{11}C]CO offered an alternative method for the preparation of ^{11}C-carbonyl labeled carbamoyl compounds.[64]

2.4 [^{11}C]CN chemistry

2.4.1 Synthesis of ^{11}C-labeled aliphatic nitriles and derivatives—

While aromatic nitriles are often found as key scaffolds and pharmacophores in drug molecules, aliphatic nitriles typically exist as intermediates for the preparation of carboxylic acids, amides, amines, and related derivatives. This principle is also applicable for chemistry with [^{11}C]CN. ^{11}C-Labeled alkyl nitriles are commonly prepared by nucleophilic substitution or addition reactions with H[^{11}C]CN as the reagent. The most frequent derivatization is to generate ^{11}C-carboxylic acids or derivatives (Scheme 9A). For example, [^{11}C]lactic acid was produced by [^{11}C]CN addition to acetaldehyde or substitution of aldehyde- bisulfite adduct,

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followed by hydrolysis. The same protocol could be also applied in the synthesis of [^{11}C]valine (via hydrolysis), [^{11}C]glutamine (via aminolysis) and [^{11}C]dopamine (via reduction). Another method to obtain ^{11}C-labeled amino acids involved the formation of [^{11}C]hydantoin, which was produced via the Bücherer-Bergs reaction from ketones or aldehydes (Scheme 9B). Then [^{11}C]hydantoin was converted to the corresponding ^{11}C-labeled amino acids via hydrolysis in basic conditions. Furthermore, ring-opening of aziridine with [^{11}C]CN also led to alkyl-^{11}CN compounds, which could be converted to ^{11}C-labeled carboxylic acids in 30–40% RCYs (Scheme 9C).[65]

2.4.2 Formation of ^{11}C-labeled aromatic nitriles and derivatives—

Pioneered with the nucleophilic substitution of Cr(CO)3 complexes with [^{11}C]CN, aryl-^{11}CN formation was gradually replaced by Pd- or Cu-mediated cross coupling reactions attributed to more extensive substrate scope and higher reaction efficiency (Scheme 10, A1).[12] Representative examples of Pd- mediated reactions include [^{11}C]AZD9272, and compounds derived from aryl-^{11}CN, like [^{11}C]NAD-299. The recent discovery of biaryl phosphine ligands for Pd catalysts, such as *t*-BuXPhos, further advanced new aromatic ^{11}CN chemistry. In 2015, Hooker and Buchwald *et al.* developed a Pd-mediated ^{11}C-cyanation of aryl halides/triflates at ambient temperature with rapid reaction rate (<1 min; Scheme 10, A2).[66] These biaryl phosphine ligands, *e.g., t*-BuXPhos or BrettPhos, were the key to stabilize Pd-aryl complex and accelerate transmetalation and reductive elimination under mild reaction conditions. These authors further extended this concept to the labeling of cysteine-containing peptides via a sequential Pd-mediated C-S and C-^{11}CN bonding formation in one-pot.[67] The formal ‘nucleophile-nucleophile coupling’ provided ^{11}C-labeled peptides in high RCYs (10–50%). Arylboron

Alternative to Pd-mediated ^{11}C-cyanation, Ponchant *et al.* found that [^{11}C]CN could be trapped by copper to produce Cu[^{11}C]CN *in situ,* which was then reacted with aryl halides to synthesize ^{11}C-labeled aryl nitriles under high temperature (150250 °C).[68] compounds and arylstannanes can also be used as precursors in the Cu-mediated cyanation. In 2017, Liang and Vasdev *et al.* developed a ^{11}C-cyanation methodology that takes advantage of aryl boronic acids. This strategy could be realized in aqueous solutions and was compatible with a wide range of aryl boronic precursors, resulting in diverse radiolabeled compounds in 9–70% RCYs (Scheme 10, B2).[69] In 2018, Scott and Sanford *et al.* further extended labeling precursors to other arylboron compounds and arylstannanes using Cu(II)$(OTf)_2$. This method was compatible with a broad range of substrates. For example, [^{11}C]perampanel was prepared in 10% RCY and 70 GBq/μmol molar activity using an automated radiosynthesis module (Scheme 10, B2).[70]

2.5 Miscellaneous ^{11}C synthons and reagents

Some commonly used / recent developed ^{11}C synthons and reagents prepared by 1–4 step reactions from [^{11}C]CO_2 are highlighted in Scheme 11 to demonstrate the diversity and creativity of ^{11}C chemistry.

Selected examples of recent ^{11}C-labeled building blocks are described below. [^{11}C]HCHO, produced from [^{11}C]CH_3OH oxidation, has been applied in reductive methylations,

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ringclosure reactions, electrophilic aromatic substitutions and others.[12, 13] In 2008, Hooker *et al.* developed a new method to synthesize [^{11}C]HCHO from [^{11}C]CH_3I with trimethylamine N- oxide (Scheme 12A).[71] Several ^{11}C-labeled tracers including [^{11}C]vabicaserin and [^{11}C]WAY-163909, were efficiently synthesized via the Pictet-Spengler reaction using [^{11}C]HCHO.[72] [^{11}C]CS_2 was first prepared from [^{11}C]CO_2 and H_2S in low RCYs.[73] In 2012, Miller *et al.* developed a novel method to produce [^{11}C]CS_2 by gas phase reaction between [^{11}C]CH_3I and a thionating agent P_2S_5.[74] Then they improved the method by switching the thionating reagent from P_2O_5 to elemental sulfur (Scheme 12B).[75] [^{11}C]CS2 was found to rapidly react with a broad spectrum of primary amines to give ^{11}C-labeled thiocarbonyl thioureas, including [^{11}C]tanaproget, in high RCYs and high molar activity. In 2017, Pike *et al.* described a new type ^{11}C-labeled agent [^{11}C]CF_3H, based on the fluorination of [^{11}C]CH_4 with CoF_3 (Scheme 12C).[76] This ^{11}C-labeled reagent was applied to demonstrate a wide range of trifluoromethylations, including nucleophilic additions with ketones, cross-coupling reactions with aryl boronic acids, aryl iodides and aryl diazonium salts via Cu[^{11}C]CF_3 generated *in situ.* ^{11}C-Labeled trifluoromethyl arenes, including [^{11}C]flutamide and [^{11}C]lefunomide, exhibited high RCYs and high molar activity (>200 GBq/μmol). In particular, the molar activity of ^{11}C-labeled trifluoromethyl arenes far exceeded its ^{18}F- counterpart (aryl [^{18}F]CF_3), providing a viable access to radiolabel mutlifluoromethylated compounds in high molar activity. Diverse methods to prepare [^{11}C]$COCl_2$ from [^{11}C]CO_2 or [^{11}C]CH_4 have been developed since the 1970s. Among these methods, an efficient automated [^{11}C]$COCl_2$ synthesis with high RCYs (>80%) was reported in 2010.[77] [^{11}C]$COCl_2$ is an effective reagent to synthesize ^{11}C-labeled ureas and carbamates via [^{11}C]isocyanate or [^{11}C]carbamoyl chloride intermediates. A diverse range of ureas and carbamates, including ^{11}C-labeled 18-β-glycyrrhetinic acid derivative,[78] [^{11}C]MFTC,[79] [^{11}C]SAR127303[80] and [^{11}C]MAGL-0519,[81] were efficiently obtained via [^{11}C]$COCl_2$.

3. Labeling methods with fluorine-18

Fluorine-18 (^{18}F) is the most widely used PET nuclide attributed to the extensive clinical use of 2-deoxy-2-[^{18}F]fluoro-D- glucose ([^{18}F]FDG) in the diagnosis of cancers, cardiovascular and neurological diseases. Fluorine-18 (as [^{18}F]fluoride) is most commonly produced via the ^{18}O(p,n)^{18}F nuclear reaction in high radioquantity and high specific activity, and has a relatively long half-life (109.8 min) compared to ^{11}C, which allows for multi-step synthesis, extended imaging protocols, and off-site use in satellite PET facilities without a cyclotron. These favorable characteristics provide a strong stimulus to develop novel ^{18}F-labeled compounds, and efficient and translational radiofluorination methods. Complementary to previous fluorine-18 reviews,[16, 82–88] we focus on the recent development and breakthroughs in the nucleophilic and electrophilic reactions with ^{18}F (Scheme 13). Indirect ^{18}F-labeling methods, *i.e.,* reactions involved with ^{18}F- building blocks, are discussed elsewhere.[88, 89]

3.1 Aliphatic ^{18}F-fluorination with nucleophilic [^{18}F]fluoride

3.1.1 Aliphatic nucleophilic substitution—Aliphatic nucleophilic substitution with [^{18}F]fluoride is a reliable method that has been commonly used to generate Csp3- ^{18}F bonds

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in high RCYs and high specific activity. The most common reaction of this type involves the substitution of an adequate leaving group that is susceptible to displacement by [^{18}F]fluoride (Scheme 14A). These leaving groups include -triflate (-OTf), -tosylate (−OTs), -mesylate (−OMs) and halides, with a decreasing order of leaving ability (−OTf > −OTs ~ −OMs > −I > −Br > −Cl). Another type of aliphatic nucleophilic ^{18}F-fluorination entails the addition of [^{18}F]fluoride into strained cyclic substrates, for example, ring opening reactions of epoxides and aziridines (Scheme 14B). The potential regio- and stereo-genicity makes this method attractive for the radiosynthesis of PET tracers, including clinically-relevant [^{18}F]FES and [^{18}F]FLT. Complementary to one-step nucleophilic [^{18}F]fluoride displacement approaches, indirect methods are also widely used,[89–91] which typically involve the utilization of [^{18}F]fluoroalkyl prosthetic groups to conjugate with O, *N,* or S-nucleophiles, especially when the corresponding precursors are labile during ^{18}F-fluorination (Scheme 14C).

A large number of ^{18}F-labeled PET tracers are prepared through aliphatic nucleophilic ^{18}F-fluorination and can be categorized into four major chemotypes, including unbranched and branched acyclic alkyl-^{18}F, cyclic alkyl-^{18}F, and alkyl-^{18}F with [^{18}F]fluorine atom at activated positions (Scheme 15). The first common form is the unbranched acyclic alkyl-^{18}F. Representative examples include [^{18}F]FMeNER-D2, [^{18}F]FMISO, [^{18}F]FET, [^{18}F]fallypride and [^{18}F]florbetapir (Scheme 15A). The two deuterium (D) atoms in [^{18}F]FMeNER-D2 are introduced to improve metabolic stability and reduce the rate of *in vivo* defluorination during PET studies.[92] An rigorous overview of ^{18}F- tracer metabolism can be found elsewhere.[93] The second chemotype entails branched acyclic alkyl-^{18}F (Scheme 15B), which includes but is not limited to [^{18}F]iNOS-9, [^{18}F]FTHA, and [^{18}F]FDS. Cyclic alkyl-^{18}F is another common chemotype (Scheme 15C), including the most widely used PET radiopharmaceutical [^{18}F]FDG, and other tracers, like [^{18}F]FES, [^{18}F]FLT, [^{18}F]FACBC, and [^{18}F]FP. In the last category, ^{18}F- fluorination takes advantage of activated positions on the molecule, including the benzylic, allylic or α-position of the carbonyl group, to facilitate ^{18}F-incorporation (Scheme 15D). A few representative examples include [^{18}F]SP203, [^{18}F]AB5186, ^{18}F-labeled allyl, propargyl, and α-carbonyl compounds, such as 4-[^{18}F]fluoroglutamine and [^{18}F]PBR06.

Compared with nucleophilic ^{18}F-fluorination reactions which are often conducted in polar aprotic solvents, Chi and co-workers used ionic liquids[94] and unusual protic solvents[95] to improve ^{18}F- labeling efficiency (Scheme 16, A1). These conditions could not only dramatically increase ^{18}F reactivity and reaction rate, but also decrease the formation of undesired products, such as alkenes, alcohols or ethers. For instance, [^{18}F]FP-CIT was synthesized in 36% RCY under new conditions containing *t*BuOH, in contrast to only 3% RCY using CH_3CN as a solvent (Scheme 16, A2).[96] These new labeling conditions were also applied in the synthesis of several radioligands, including [^{18}F]FP-CIT, [^{18}F]FLT and [^{18}F]PF05270430 (Scheme 16, A3).[97] The conversion of alcohols to alkyl-^{18}F typically involve a two-step sequence, namely, the formation of alcohol-derived leaving groups, such as -OTs or - OMs, and the subsequent aliphatic ^{18}F-fluorination. In 2015, Doyle *et al.* reported a ‘one-pot’ direct synthesis of alkyl fluorides from the corresponding alcohols with 2-pyridinesulfonyl fluoride (PyFluor), a new deoxyfluorination reagent (Scheme 16B).[98] As proof of concept, [^{18}F]FDG was achieved by ^{18}F-deoxyfluorination of O-protected carbohydrate in 15% radiochemical conversion (RCC).

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An azeotropic [^{18}F]fluoride drying is nearly always employed to ensure high reactivity of ^{18}F under anhydrous conditions. However, this process may lead to decreased RCY/molar activity attributed to prolonged reaction and/or surface adsorption. In 2015, van Dam and Sergeev *et al.* developed TiO_2-catalyzed ^{18}F- fluorination of tosylated precursors in highly aqueous medium without the need of [^{18}F]fluoride drying (Scheme 16C).[99] TiO_2 was the key in the ^{18}F-fluorination. First, solvated [^{18}F]fluoride in water was adsorbed at the active surface of TiO_2, thus enhancing fluorine-18 reactivity. Synergistically, TiO_2 also activated the tosylate precursor via Ti-O coordination with two oxygen atoms of the sulfonyl group.

^{18}F-Fluorination was not merely limited to organic reactions. O'Hagan *et al.* developed a novel ^{18}F-labeling protocol using enzymatic biosynthesis (Scheme 16D). ^{18}F-Fluorination of (*S*)- adenosyl-L-methionine (SAM) to 5'-[^{18}F]fluoro-5'-deoxyadenosine (5'-[^{18}F]FDA) was carried out smoothly by fluorinase with up to 95% RCY.[100] Recently, they further extended this enzymatic ^{18}F- fluorination to obtain 5'-[^{18}F]fluorodeoxy-2-ethynyladenosine labeled RGD peptides in 12% RCY and no radiodefluorination was observed in PET imaging studies.[101]

3.1.2 Transition metal-mediated aliphatic ^{18}F-fluorination—Aliphatic nucleophilic ^{18}F-fluorination is usually performed in basic conditions at high temperature; however, these conditions may not be compatible with well-functionalized molecules, resulting in the formation of undesired side products. Transition metal-mediated aliphatic ^{18}F-fluorination may thus provide an alternative to generate alkyl-^{18}F bonds under mild conditions. In 2011, Gouverneur and Brown *et al.* reported Pd-catalyzed fluorination of highly active allyl *p*-nitrobenzoates with TBAF at room temperature.[102] Allylic ^{18}F-fluorination was also achieved using [^{18}F]TBAF (Scheme 17, A1). In the same year, Nguyen *et al.* developed Ir-catalyzed allylic fluorination of trichloroacetimidates.[103] The ^{18}F-labeling reaction was conducted with K[^{18}F]F/K_{222}, and the ensuing allyl [^{18}F]fluoride was achieved in 38% RCY (Scheme 17, A2). In 2013, Gouverneur and Brown *et al.* reported another Ir-catalyzed fluorination of allyl carbonates,[104] in which a wide range of branched, linear (*E*)- and (*Z*)- allyl substrates were labeled with [^{18}F]Et4NF in 8–76% RCYs (Scheme 17, A3).

Ring-opening of epoxides with [^{18}F]fluoride is a stereogenic method to prepare ^{18}F-tracers. In 2014, Doyle *et al.* developed an enantioselective ^{18}F-fluorination of epoxides with chiral [^{18}F](salen)CoF (Scheme 17B).[105] The group also developed a dimeric chiral cobalt catalyst to overcome the challenges associated with epoxide substrates bearing Lewis basic nitrogen or α-branching substituents. Several PET tracers were synthesized by this method, including [^{18}F]THK-5105 (85% ee) and [^{18}F]FMISO (90% *ee*).

Groves and Hooker *et al.* developed a novel Mn-catalyzed benzylic C-H ^{18}F-fluorination method (Scheme 17C).[106] Several fluorinated drug moieties, including a [^{18}F]celecoxib analog and a ^{18}F-labeled fingolimod, were efficiently labeled. The authors also extended this method to non-activated aliphatic substrates.[107] The use of a more reactive Mn-porphyrin complex Mn(TPFPP)OTs was essential to enable efficient transformation. A diverse range of bioactive molecules was efficiently labeled, including [^{18}F]ACPC (48% RCC) and a [^{18}F]flutamide analog.

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Lu and Li *et al.* recently reported Ag-promoted intramolecular cyclization of unsaturated carbamates using [^{18}F]fluorobenziodoxole.[108] A range of ^{18}F-labeled heterocycles were achieved by using this method but the efficiency of ^{18}F-labeling needs to be further improved (RCYs < 10%). Szabó *et al.* also reported a metal-free intramolecular cyclization of unsaturated amides with isolated [^{18}F]fluorobenziodoxole.[109] ^{18}F-Fluorocyclization of a wide range of *o*-styrilamides were performed with high RCCs (54–90%).

3.2 Aromatic ^{18}F-fluorination with nucleophilic [^{18}F]fluoride

3.2.1 Aromatic nucleophilic substitution—

Aromatic nucleophilic substitution (S_NAr) with [^{18}F]fluoride represents a direct and commonly used method to form C_{Sp2}-^{18}F bonds (Scheme 18A). An optimal precursor will generally bear both a leaving group and an activating group (usually electron- withdrawing) in the *ortho* or *para* position to facilitate the S_NAr reaction by stabilizing the Meisenheimer complex. Representative PET tracers are shown in Scheme 18B. Alternatively, molecules with non-activating substituents could also be synthesized through S_NAr conversion of arenes with electron-withdrawing groups, followed by post-S_NAr functional group manipulations.[110, 111] Nitrogenous heteroarene, such as pyridine, is electron-deficient than its homoarenes counterpart, which provides a unique opportunity for ^{18}F-labeling via S_NAr without the need of activating groups. A wide range of ^{18}F-heteroarenes (particularly 2- [^{18}F]fluoropyridine), were synthesized by this approach (Scheme 18C).

Efficient ^{18}F-labeling via S_NAr requires the presence of an activating group and a leaving group on the arene, which significantly limits the substrate scope. To overcome this challenge, the search for novel precursors carrying new activating and/or leaving groups continues. Recently, research efforts have been made in the development of novel sulfur-based precursors. The first example was demonstrated by Maeda *et al.* using aryldimethylsulfonium salts in 1987.[112] However, the formation of undesired methyl [^{18}F]fluoride made this method unfavorable for labeling arenes. In 2012, Ametamey *et al.* developed triarylsulfonium salts as a new class of precursors for ^{18}F-labeling arenes (Scheme 19, A1).[113] ^{18}F-fluorination preferred to occur on the relatively electron-deficient aryl group and the remaining diarylsulfonium group served as the leaving group. In 2015, Arstad *et al.* extended the substrate scope to electron-rich arenes by using diarylsulfonium bearing para-methoxyphenyl groups as the leaving group (Scheme 19, A2).[114] Besides triarylsulfonium salts, diaryl sulfoxides were also potential precursors for ^{18}F- labeling reactions discovered by Pike *et al.* in 2016.[115] A higher reaction temperature (150–200 °C) was required probably attributed to low reactivity of diaryl sulfoxides. Electron-deficient diaryl sulfoxides offered products in high RCCs, such as 1-[^{18}F]fluoro-4-nitrobenzene (78%), whereas the labeling of electron-rich diaryl sulfoxides remained a challenge.

Murphy *et al.* developed *N*-arylsydnones as novel precursors for ^{18}F-labeling of arenes bearing electron-deficient substituents (Scheme 19B).[116] It was found that the sydnone was not only inductively more electron-withdrawing than the nitro group, but also positioned away from the aryl plane and limited full resonance with the arene. This makes the sydnone a weak anion stabilizer as an excellent activating group for ^{18}F-incorporation.

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Phenols are common building blocks in organic synthesis, which makes ^{18}F-deoxyfluorination an attractive strategy to achieve ^{18}F-labeled arenes. Ritter and Hooker *et al.* developed a novel ^{18}F-fluorination method of phenols based on a concerted nucleophilic aromatic substitution (CS_NAr) mechanism (Scheme 20A).[117] This reaction involved the formation of a uronium intermediate, which was distinct from the Meisenheimer complex in the conventional S_NAr. Electron-deficient phenols were efficiently converted to aryl-^{18}F in high RCCs (>80%). Recently, Ritter and Hooker *et al.* further utilized a ruthenium catalyst via η^6 π-complex for ^{18}F-deoxyfluorination of electron-rich phenols (Scheme 20B).[118]

Different with ^{18}F-deoxyfluorination, Gouverneur *et al.* reported a novel method for *ipso* ^{18}F-substitution of t-butyl group at the *para* position of phenols.[119] As an alternative S_NAr-type pathway, this reaction involved two steps, *i.e.,* de- aromatization/fluorination under oxidative conditions, and re- aromatization under acidic conditions. A series of 4-*tert*-butylphenols were converted to 4-[^{18}F]fluorophenols using $PhI(OAc)_2$ as the oxidant with 7–20% RCYs.

3.2.2 ^{18}F-Fluorination of hypervalent iodine(III) compounds—Despite significant advances in the ^{18}F-labeling of arenes via the S_NAr method, there is an unmet need for efficient ^{18}F- fluorination methods of non-activated arenes. The low efficiency of using Balz-Schiemann and Wallach reactions in the ^{18}F- labeling shifted the research focus initially towards the application of trimethylammonium triflates[120] and more recently major advances have been made with hypervalent iodine(III) based precursors. The first example of diaryliodonium salts as precursors in the synthesis of aryl-^{18}F was reported by Pike *et al.* (Scheme 21A),[121] in which arenes with electron-deficient or -rich substituents showed high ^{18}F-labeling efficiency. The relatively electron-deficient aryl moiety of the corresponding salt was preferrably labeled by fluorine-18. To achieve high regioselectivity of unsymmetrical diaryliodonium salts, Coenen *et al.* developed a novel class of aryl(2-thienyl)iodonium salts and demonstrated ^{18}F- labeling in a highly regioselective manner (Scheme 21B).[122] Specifically, ^{18}F-fluorination of aryl(2-thienyl)iodonium salts preferred to occur on the counterpart. An *ortho* substitution on the aryl group of diaryliodonium salts has substantial effects on the regioselectivity, with the preference of radiofluorination occurs on the ortho-substituted arene (Scheme 21C).[123] Mechanistically, a trigonal bipyramidal iodine intermediate was proposed during ^{18}F- fluorination of diaryliodonium salts (Scheme 21D). While the two aryl groups could rapidly exchange their positions via Berry pseudorotation process, steric bulky *ortho*-substituted aryl group was situated in an equatorial position to minimize the steric repulsion, leading to a favored reductive elimination pathway to form an Csp^2-^{18}F bond on the equatorial arene in both monomeric and oligomeric state. [123, 124]

Recent optimization of reaction conditions and involvement of transition metal catalysts have advanced diaryliodonium salts based radiofluorinations. In 2012, DiMagno and Snyder *et al.* reported a new method for ^{18}F-fluorination of diaryliodonium salts in nonpolar solvents with high RCYs.[125] In particular, diaryliodonium triflate and [^{18}F]fluoride were first dissolved in a polar aprotic solvent (e.g., MeCN) to facilitate ion exchange between OTf and ^{18}F. After solvent removal, a nonpolar medium (e.g., toluene) was then added for reductive radiofluorination, which was beneficial to inhibit side reactions, including internal

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electron transfer and disproportionation of diaryliodonium salts. The new method has been used in the synthesis of several ^{18}F- pharmaceuticals,[126] including [^{18}F]FDOPA, [^{18}F]mFBG, [^{18}F]FDA, and [^{18}F]flutemetamol.

In 2014, Scott and Sanford *et al.* reported Cu-mediated ^{18}F- fluorination of mesityl(aryl)iodonium salts (Scheme 22A).[127] Contrary to the *"ortho* effect", ^{18}F-Csp^2 reductive elimination occurred on the counterpart of steric bulky mesityl group to allow access to a variety of electron-rich, -neutral and -deficient ^{18}F- arenes. Recently, the same authors improved their method by the formation of electron-rich mesityl(aryl)iodonium salts *in situ,* which offers a potential solution to synthesize electron-rich aryl-^{18}F bonds without the need of isolation for certain unstable electron- rich diaryliodonium salts.[128]

The traditional method for the preparation of diaryliodonium salts was limited to oxidation of aryl iodides, followed by ligand exchange. In 2016, Liang and Liu *et al.* developed a new one-pot method to synthesize aryl(isoquinoline)iodonium salts via the mesoionic carbene silver complex (Scheme 22B).[129] Radiofluorination of a board range of aryl(isoquinoline)iodonium salts were achieved with [^{18}F]Et_4NF in 25–65% RCYs. As proof of concept, a ^{18}F-labeled natural product, [^{18}F]fluoroaspergillitine, was achieved in 10% RCY with molar activity of 37 GBq/μmol.

In all, attributed to its high efficiency in the ^{18}F-labeling of arenes, particularly for the substrates without proper activating substituents, diaryliodonium salts method has been well applied in the synthesis of a wide range of clinically relevant PET tracers (Scheme 22C).[126]

Among the methods for ^{18}F-labeling of hypervalent iodine(III) species, little attention was paid to other type λ^3-iodine compounds until radiofluorination of (diacetoxyiodo)arenes[130] and aryliodonium ylides were developed in recent years. Notably, the latter method has shown excellent progress to achieve unprecedented radiofluorination of non-activated arenes.

In an early report by Ermert *et al.* in 2014, aryliodonium ylides with Meldrum acid auxiliaries were developed for ^{18}F-labeling of arenes.[131] In the same year, Liang and Vasdev *et al.* independently developed a novel class of spirocyclic iodonium ylides (SCIDY) and demonstrated regioselective radiofluorination of non-activated arenes (Scheme 23A).[132] SCIDY with cyclopentyl auxiliary gave the highest 85% RCC in the ^{18}F- fluorination of biphenyl iodonium ylides. Using this auxiliary, a wide range of [^{18}F]fluoroarenes were readily achieved via SCIDY in high RCYs. Thermal stability of aryliodonium ylides highly depended on auxiliary substitution, which showed a positive correlation with ^{18}F-incorporation efficiency. A second generation auxiliary, namely SPIAd (spiroadamantyl-1,3-dioxane-4,6-dione), developed by the same authors, outperformed all the other auxiliaries of aryliodonium ylides in stability tests and exhibited highly efficient ^{18}F-labeling capability (Scheme 23B).[133] In addition, Riss *et al.* reported an improved PPh_3-assisted ^{18}F-fluorination of aryliodonium ylides, which showed increased fluorination yield and reaction rate.[134]

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^{18}F-Labeling of aryliodonium ylides demonstrated substantially improved regioselectivity over diaryliodonium salts method.[133] The auxiliary group has a preference for the axial position and aryl group takes the equatorial position. The calculation results showed that undesired Csp^3-F reductive elimination had *ca.* 25 kcal/mol higher barrier than favorable Csp^2- F pathway, which explained the unique regioselectivity in the ^{18}F- labeling of aryliodonium ylides (Scheme 23C).

As radiofluorination of aryliodonium ylides is an efficient and metal-free method for non-activated arenes, a diverse range of clinically relevant radiopharmaceuticals and ^{18}F-labeled drug scaffolds were obtained by this route (Scheme 24).[81, 132, 133, 135–143] It is noteworthy that [^{18}F]FPEB synthesized via SCIDY technology was fully automated, resulting in a substantial improvement (3–10 fold) in RCYs and molar activity compared with the traditional S_NAr method, and has been validated for human use.[144]

3.2.3 Transition metal-mediated aromatic ^{18}F-fluorination—Significant advances have been achieved in the aromatic radiofluorination using transition metals with enhanced reactivity, selectivity and tolerance towards functional groups, which may provide an alternative approach to access [^{18}F]fluoroarenes. In 2011, Ritter and Hooker *et al.* developed a novel aromatic ^{18}F- fluorination method based on Pd(IV) complex (Scheme 25A).[145] The highly fluorophilic Pd species **1** and [^{18}F]fluoride generated Pd-^{18}F complex **2**, which not only served as an electrophilic ^{18}F- fluorination reagent but also oxidized aryl-Pd(II) complex **3** to aryl- Pd(IV)-^{18}F complex, to afford [^{18}F]fluoroarenes after reductive elimination. This method was applied in the synthesis of [^{18}F]fluoroestrone, [^{18}F]paroxetine and a ^{18}F-labeled 5-HT_{2C} agonist (> 1% RCYs).[145, 146] In 2012, Ritter *et al.* developed another oxidative ^{18}F-fluorination by using aryl-Ni(II) complexes (Scheme 25B).[147] The ^{18}F-Ni(II) complex occurred directly with aqueous [^{18}F]fluoride at room temperature. Both aryl and alkenyl [^{18}F]fluoride could be obtained in high RCYs and representative examples include 3-[^{18}F]fluorobenzamide, [^{18}F]fluorophenylalanine, 5-[^{18}F]fluorouracil and [^{18}F]MDL100907, as well as several ^{18}F-labeled aromatic amino acids, 6-[^{18}F]FDA, 6-[^{18}F]FDOPA, 6-[^{18}F]FMT under an improved ‘low base’ protocol.[148–150]

Copper catalysts are widely used in the aromatic fluorination reactions with aryl boronates and arylstannanes. In 2014, Gouverneur *et al.* developed Cu-mediated ^{18}F-fluorination of aryl boronic esters (e.g., aryl-BPin) with [^{18}F]fluoride (Scheme 26A). The reaction with aryl-BPin precursors was performed in the presence of Cu(OTf)2Py4 and O_2, the latter of which was necessary and beneficial for ^{18}F-incorporation.[151, 152] Besides aryl-BPin and copper triflate pyridine system, Sanford and Scott *et al.* independently developed Cu-mediated ^{18}F-fluorination from aryl boronic acid precursors (Scheme 26B).[153] The reaction was mediated by $Cu(OTf)_2$ in the presence of pyridine with high ^{18}F- labeling efficiency.

Arylstannanes are excellent arylating reagents in transmetalation processes, leading them as potential labeling precursors for Cu-based radiofluorinations. In 2016, Murphy *et al.* reported copper-mediated oxidative fluorination of arylstannanes with fluoride using TBAT and copper(II) triflate.[154] In the same year, Sanford and Scott *et al.* independently developed Cu- mediated radiofluorination of arylstannanes (Scheme 26C).[155] The reaction

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was performed with [^{18}F]fluoride in the presence of pyridine, and compatible with electron-rich and -deficient arylstannanes, as well as vinyl substrates.

These Cu-mediated ^{18}F-labeling methods from boron or tin precursors have been applied in the synthesis of a number of clinical relevant PET ligands under original or improved 'low base' conditions.[156] Representative examples from boron esters, boronic acids and arylstannanes are shown in Scheme 27, respectively[151–153, 155, 157]

3.3 Formation of ^{18}F-labeled multifluoromethyl motifs from nucleophilic [^{18}F]fluoride

3.3.1 ^{18}F-Labeled aryl-CF_3/CF_2H/OCF_3/OCF_2H groups via halogen-^{18}F exchange—

Continuous development of CF_3/CF_2H-containing pharmaceuticals provides a strong impetus to develop novel radiochemical methods to label these groups that were previously not accessible to drug discovery and PET tracer development. Halogen exchange of CF_2X (X = F, Cl, Br) with [^{18}F]fluoride represents a traditional way to access ^{18}F-labeled trifluoromethyl motifs. For example, ^{18}F-labeled aryl-CF_3 could be obtained by either ^{19}F/^{18}F isotope exchange, or halogen-^{18}F exchange with aryl-ClF_2 or -BrF_2 as shown in the synthesis of ^{18}F-celecoxib (Scheme 28).[158] Since the presence of two α-fluorine severely inhibits displacement reactions with [^{18}F]fluoride, harsh conditions including corrosive reagents and high temperature, are usually employed, thus limiting the compatibility with well-functionalized groups.

In recent years, Ag(I) was found to be an accelerant for halogen-^{18}F exchange under mild reaction conditions. In 2015, Gouverneur *et al.* found aryl-SCF_2Br, -OCF_2Br, -OCHFCl precursors could be converted to ^{18}F-labeled aryl-SCF_3, -OCF_3 and -$OCHF_2$ groups, respectively, in the presence of AgOTf (Scheme 29A).[159] Subsequently, they also found AgOTf could promote the formation of a broad array of ^{18}F-labeled aryl-CF_3 and aryl-CF_2H from the corresponding aryl-CF_2Br and aryl-CHFCl precursors, respectively (Scheme 29A).[160] Another Ag(I) application entailed the synthesis of ^{18}F-labeled Umemoto reagent for trifluoromethylthiolation by Gouverneur *et al.* (Scheme 29B).[161] The reagent was synthesized from an oxidative ring closure of ^{18}F-labeled [1,1'-biphenyl]-4-yl(trifluoromethyl)-sulfane. ^{18}F-Trifluoromethylthiolation was tolerated with various functional groups and exhibited high chemoselectivity for the radiolabeling of the cysteine residue of unmodified peptides. An $\alpha_v\beta_3$ integrin-targeted peptide (cRGDfC- [^{18}F]SCF_3) was prepared in 19% RCY with 0.15 GBq/μmol molar activity.

Metal-free halogen-^{18}F approaches via activating groups have also been developed in recent years. In 2016, a practical method for ^{18}F-labeled aryl-CF_2H compounds was developed by the Ritter, Vasdev and Liang groups (Scheme 29C).[162] The desired product was generated in a highly efficient 'one-pot' sequence, including C-H bromination to generate α-Br-α-F-acetophenone *in situ,* followed by facilitated ^{18}F/Br-exchange at the α position of the carbonyl group and subsequent benzophenone cleavage. A number of well-functionalized ^{18}F- difluoromethylarene analogs including fenofibrate, Claritin and fluoxetine was efficiently synthesized. In the same year, Liang *et al.* developed another metal-free oxidative C-H activation method for ^{18}F-labeled aryl-CF_2H compounds (Scheme 29D).[163] The procedure involved the conversion of benzyl halides into aryl- [^{18}F]CFH_2, followed by oxidative C-H activation and fluorination. The method was well tolerated with a diverse

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range of electron- donating and -neutral functional groups with 10–45% RCCs, and achieved the highest molar activity of 22 GBq/μmol for aryl- [^{18}F]CF_2H compounds to date.

3.3.2 ^{18}F-Labeled aryl-CF_3 groups via transition metal-mediated cross coupling—The preparation of aryl-CF_2X (X = Cl or Br) as labeling precursors is challenging and involves multi-step synthesis in most cases, which limits the substrate scope of halogen-^{18}F exchange method. In 2013, Passchier and Gouverneur *et al.* introduced an efficient method for aromatic ^{18}F- trifluoromethylation of aryl iodides with Cu(I) catalyst (Scheme 30, A1).[164] [^{18}F]$CuCF_3$ was proposed to generate *in situ* from CuI, $ClCF_2CO_2Me$ (a difluorocarbene reagent) and [^{18}F]fluoride in the presence of TMEDA. This procedure was operationally simple and tolerated with a variety of functional groups with high RCYs. Another Cu(I)-mediated ^{18}F-trifluoromethylation using CHF_2I to generate [^{18}F]$CuCF_3$ was reported by Riss *et al.* in 2014.[165] Several representative ^{18}F-labeled CF_3 molecules, including [^{18}F]flutamide, [^{18}F]trifluorothymine and ^{18}F-labeled Boc-protected piperazine were synthesized by these methods (Scheme 30, A2).

Other than the ‘one-pot’ protocol, a stepwise procedure for [^{18}F]$CuCF_3$ formation with isolated [^{18}F]HCF_3 was also viable. In 2014, Vugts *et al.* employed cross coupling reactions between [^{18}F]$CuCF_3$ and aryl iodides or boronic acids, to generate ^{18}F- labeled CF_3 motifs (Scheme 30, B1).[166] Et3N· 3HF was added to stabilize [^{18}F]$CuCF_3$[167] so that this method could offer an increased molar activity of ^{18}F-labeled products to 25 GBq/μmol. The [^{18}F]HCF_3 was also used in the reactions with ketones and aldehydes.[168] Using a difluoromethyl sulfonium salt as difluorocarbene regent, Jubault and Labar *et al.* developed an alternative method to generate [^{18}F]HCF_3 (Scheme 30, B2), which was used for the formation of [^{18}F]$CuCF_3$ and subsequent ^{18}F- trifluoromethylation in high RCYs (78–88%).[169]

Other than Cu-mediated cross coupling reactions, Carroll *et al.* developed site-selective oxidative fluorination of benzylic difluoromethyl groups with Mn(salen)Cl.[170] Based on the mechanism of ^{18}F-transfer with Mn catalyst,[106] ^{18}F-labeled CF_3 groups could be obtained in 16–61% RCYs except for a few electron-deficient derivatives.

3.3.3 ^{18}F-Labeled alkyl-CF_3 compounds—^{18}F-Labeled trifluoroethyl tosylate can be obtained either by ^{19}F/^{18}F exchange[171] or ^{18}F-addition of 2,2-difluorovinyl tosylate (Scheme 31A-B).[172, 173] Using the protocol in Scheme 31B, ^{18}F- labeled trifluoroethyl tosylate could further react with nucleophiles, including phenols, carboxylic acids and amines, in 77–93% RCYs. As PET imaging application, Scott *et al.* used this strategy to produce [^{18}F]lansoprazole in 4–14% RCYs with 37 GBq/μmol molar activity.[174]

In 2017, Toste and O’Neil *et al.* reported a novel method for borane-catalyzed ^{18}F-labeled alkyl-CF_3 compound formation from Au(III) complex (Scheme 31C).[175] Treatment with [^{18}F]KF and $B(C_6F_5)_3$, Au(III)-OAc complex was converted to alkyl-[^{18}F]CF_3 compound via ligand exchange and reductive elimination. Three representative alkyl-CF_3 analogs were labeled in reasonable RCCs, and [^{18}F]BAY 59–3074 was isolated with 6% RCY and 0.3 GBq/μmol molar activity.

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3.3.4 ^{18}F-Labeled alkyl- and aryl-SCF_3/$SeCF_3$ groups via difluorocarbene—

Complementary to Ag(I)-accelerated exchange method of aryl-SCF_2X, Jubault and Labar *et al.* prepared ^{18}F-labeled aryl- SCF_3 or -$SeCF_3$ from disulfides or diphenyl diselenides with [^{18}F]fluoroform, respectively (Scheme 32A).[176] Different sulfur- containing derivatives including 2-(phenylthio)isoindoline-1,3- dione and *S*-phenyl benzenesulfonothioate could also produce the desired product in 84–99% RCYs.

Despite impressive progress has been achieved in synthesis of ^{18}F-labeled aromatic-SCF_3 compounds, ^{18}F- trifluoromethylthiolation on aliphatic carbon was challenging until Liang and Xiao *et al.* reported an effective method in 2015.[177] ^{18}F- Labeled SCF_3 anion generated *in situ* from [^{18}F]fluoride, S_8 and $Ph_3P^+CF_2CO_2^-$ (PDFA, a novel difluorocarbene reagent[178]), was reported to enable ^{18}F-trifluoromethylthiolation of alkyl electrophiles (Scheme 32, B1). The method was compatible with aliphatic substrates bearing electron-withdrawing or -donating groups in 22–83% RCCs. Subsequently, the authors found α-bromo carbonyls could also be converted to α-[^{18}F]SCF_3 carbonyls (Scheme 32, B2).[179] An unconventional reaction mechanism was discovered in the formation of alkyl-SCF_3 compounds by the identification of a key intermediate, thiocarbonyl fluoride.

3.4 Non-canonical ^{18}F-labelings via bond formations with B, Si, Al, Ga and S

A diverse array of noncanonical ^{18}F-labelings via bond formations with B, Si, Al, Ga and S have been established in the past decades.[86, 88] In 2005, Perrin *et al.* reported the first example of ^{18}F-labeling of biomolecules via ^{18}F-B bond formation (Scheme 33A).[180] A board range of ^{18}F-labeled arylfluoroborates, generated from pinacol boronate esters, borimidines and trifluoroborates, were utilized.[180–182] Recently, a new aliphatic trifluoroborates stabilized by adjacent ammonium groups (in a zwitterionic form) developed by Perrin *et al.* was demonstrted in the synthesis of a number of clinically relevant peptides.[183] Other labeled molecules via B-^{18}F bond formation have been showcased in the synthesis of [^{18}F]BODIPY,[184, 185] NHC-[^{18}F]BF_3 adduct[186] and [^{18}F]tetrafluoroborate through halogen-^{18}F exchange.[187] Recently Chen and Liu *et al.* reported several ^{18}F-labeled boramino acids (replacement of COO^- in amino acids with BF_3^-), synthesized by the ^{18}F-B method, for imaging amino acid transporters.[188]

In 2006, Jurkschat and Schirrmacher *et al.* reported the synthesis of stable [^{18}F]fluorosilanes via ^{19}F/^{18}F exchange (Scheme 33, B1).[189] Their silicon-based fluoride acceptor (SiFA) methodology took advantage of two bulky *teri*-butyl groups to shield Si-^{18}F bond and showed excellent *in vitro* stability. To further reduce high lipophilicity of silicon building blocks, structural modifications including PEGylation and/or zwitterion scaffold were further developed.[190] In parallel, Klar and Ametamey *et al.* reported the synthesis of [^{18}F]fluorosilanes via H/^{18}F or OH/^{18}F exchange of dialkylsilane precursors (Scheme 33, B2).[191] These ^{18}F-Si bond formation methods were successfully applied in the ^{18}F-labeling peptides, including Tyr^3-octreotate and bombesin derivatives, with high efficiency.

In 2009, McBride *et al.* reported the first method utilizing ^{18}F- Al bond formation to access radiolabeled peptides, where the Al-F complex was stabilized by a hexadentate chelating ligand, NOTA (Scheme 33, C1).[192] The Al-^{18}F chelation strategy has enriched the landscape for biomolecule labeling and showcased in the labeling of many thermostable

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peptides, including IMP467, dimeric RGDyK and folate receptor-targeting peptides.[88] Recently, new chelators for ^{18}F-Al complex formation were developed by Bormans *et al.* to tackle with heat-sensitive biologics. The new acyclic polydentate ligands possessed less rigid structure than macrocyclic NOTA, which substantially reduced activation energy for Al-F complexation, and exhibited rapid and efficient labeling with a diverse range of peptides and antibodies (including affibody & nanobody type) at 20–40°C (Scheme 33, C2&C3).[193, 194]

Recently Reid *et al.* developed a chelating strategy for the preparation of a series of ^{18}F-labeled Ga compounds via halogen- ^{18}F exchange.[195–197] For example, [^{18}F]GaF_3($BnMe_2$-tacn) could be obtained by $^{19}_{F/}{}^{18}$F exchange in high RCYs (81 ± 1%; Scheme 33D). ^{18}F-Labeled sulfur-containing molecules are also important building blocks and imaging agents,[198] such as [^{18}F]FS-PTAD prepared from chlorosulfonyl intermediate for bioconjugation with tyrosine residues,[199] and [^{18}F]SF_6, a ^{18}F-labeled gas prepared via isotopic exchange for PET imaging assessment of lung ventilation (Scheme 33E).[200]

3.5 Electrophilic ^{18}F-fluorination with [^{18}F]F_2 and [^{18}F]F_2-derived reagents

3.5.1 Preparation of electrophilic [^{18}F]F_2 reagents—

The first and simplest electrophilic ^{18}F-fluorination reagent is [^{18}F]F_2, which can be produced via ^{20}Ne(d,α)^{18}F or ^{18}O(p,n)^{18}F nuclear reaction using F_2 as carrier (Scheme 34). Molar activity of [^{18}F]F_2 is usually in the range of 0.04–0.4 GBq/μmol. An improved preparation of [^{18}F]F_2 was reported using [^{18}F]CH_3F and a low amount of F_2, to (produce high molar activity up to 55 GBq/μmol).[201] Attributed to high chemical reactivity of [^{18}F]F_2, poor chemo- and regio-selectivity was often observed, resulting in low RCYs and technical challenges in purification. These limitations have stimulated the recent development of novel electrophilic ^{18}F-fluorination reagents aimed for milder reactivity and higher selectivity. A range of electrophilic ^{18}F-reagents were prepared from [^{18}F]F_2 (Scheme 34), including previously reviewed[5] [^{18}F]XeF_2, [^{18}F]CF_3OF, [^{18}F]CH_3COOF, [^{18}F]$FClO_3$, *N*- [^{18}F]fluoropyridinium triflate, 1-[^{18}F]fluoro-2-pyridone, and most recent [^{18}F]NFSI[202] and [^{18}F]Selectfluor.[203, 204]

3.5.2 Electrophilic [^{18}F]fluoroalkyl group formation—

The original synthesis of [^{18}F]FDG was conducted via electrophilic ^{18}F-fluorination, albeit in low RCY and accompanied with undesired regioisomers (Scheme 35, A1).[205] The analogous reaction was also applied in the electrophilic ^{18}F-fluorination of electron-deficient fluorinated alkenes, such as [^{18}F]EF5 (Scheme 35, A2).[206] The recent development of [^{18}F]F_2-derived reagents, such as [^{18}F]NFSI, provided a new opportunity for enantio- and diastereo-selective ^{18}F-fluorination. In 2015, Gouverneur *et al.* developed an organocatalyst-mediated enantioselective ^{18}F- fluorination of aldehydes with [^{18}F]NFSI (Scheme 35B).[207] The ‘one-pot’ reaction was commenced with a chiral imidazolidinone and [^{18}F]NFSI, followed by oxidation of CHO to COOH and deprotection, to provide ^{18}F-labeled amino acids. For instance, (2S,4S)-4-[^{18}F]fluoroglutamic acid was synthesized in 62% RCC with high enantioselectivity (>99% ee) and high diastereoselectivity (19:1 d.r). In 2017, Britton, Schaffer, Bénard and Martin *et al.* reported a selective photocatalytic ^{18}F- fluorination of nonactivated C-H bonds with [^{18}F]NFSI (Scheme 35C).[208] The reaction was initiated by abstracting H from the aliphatic chain using photoactivated decatungstate catalyst, followed

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by [^{18}F]fluorine atom transfer from [^{18}F]NFSI. As proof of concept, branched aliphatic amino acids 4-[^{18}F]fluoroleucine (4- [^{18}F]FL) and 5-[^{18}F]fluorohomoleucine (5-[^{18}F]FHL) were synthesized in 23% and 28% RCYs, respectively.

3.5.3 Electrophilic [^{18}F]fluoroarene formation—The most representative electrophilic aromatic ^{18}F- fluorination entails the synthesis of 6-[^{18}F]FDOPA. It was first synthesized from electrophilic aromatic substitution of 3,4- dihydroxy-phenyl-L-alanine with [^{18}F]F_2 in low RCYs and low regioselectivity. Electrophilic ^{18}F-fluorination of aryl organometallic reagents was regioselective compared with direct electrophilic ^{18}F-fluorination. As a result, the synthesis was improved to 25% RCY by a regioselective radiofluorodestannylation (Scheme 36A).[209] Another direction to improve regioselectivity of electrophilic ^{18}F-fluorination involved the use of milder electrophilic ^{18}F-fluorinating reagents, such as [^{18}F]NFSI[207][206] and more recently, [^{18}F]Selectfluor in the Ag- mediated ^{18}F-fluorination of arylstannanes or arylboronic esters precursors for [^{18}F]FDOPA synthesis reported by Gouverneur *et al.* (Scheme 36B-C).[203, 204]

4. Labeling methods with nitrogen-13 and oxygen-15

Considering the extremely short half-lives of ^{15}O ($t_{1/2}$ = 2.04 min) and ^{13}N ($t_{1/2}$ = 9.97 min), it is challenging to perform multiple- step radiochemical synthesis of complex molecules compared to ^{18}F. Automated inline production of ^{15}O and ^{13}N agents is often used to improve the synthesis efficiency and quality, so that repetitive PET studies can be conducted on the same subject within a short study period. Together with previous ^{13}N and ^{15}O reviews,[210, 211] we highlight the recent development of major synthons and transformations.

4.1 ^{13}N chemistry

Nitrogen-13 is routinely produced by nuclear reactions ^{16}O(p,α)^{13}N, ^{12}C(p,n)^{13}N or ^{13}C(p,n)^{13}N in the cyclotron (Scheme 37A).[212] [^{13}N]NH_3, widely used in clinical PET imaging for cardiovascular diseases[213] and glutamate metabolism,[214] was produced by proton irradiation of water.[212] [^{13}N]NH_3 could also serve as a building block for ^{13}N transformations including enzymatic reaction, Hofmann rearrangement, amide or imine reduction, amination of organoboranes, substitution or amidation. These reactions were used to prepare ^{13}N-labeled amino acids, primary amines, amides, ureas, carbamates and metal complexes (Scheme 37B).[212, 215–217]

[^{13}N]NO_2^- is another commonly used synthon for ^{13}N chemistry, which can be prepared by proton irradiation of water, oxidation of [^{13}N]NH_3 using gallium or cobalt oxides, or reduction of [^{13}N]NO_3^- through metals or eukaryotic nitrate reductase (Scheme 37A).[212, 218, 219] ^{13}N-Nitrosation of ureas, secondary amines and thiols could be realized via [^{13}N]NO_2^-.[218, 220] For example, GSNO, a most widely studied S-nitrosothiol, was synthesized in 24% RCY.[218] [^{13}N]NO_2^- is also used to prepare ^{13}N-labeled diazo[221, 222] and azido[223] compounds via diazonium intermediate. The ensuing ^{13}N-labeled azido compounds can be further used in the cyclization reactions to form [^{13}N]triazoles,[224] [^{13}N]tetrazoles,[225] and a furaxan analog [^{13}N]PRG150 (Scheme 37C).[226] Other ^{13}N-labeling agents, such as [^{13}N]N_2 and [^{13}N]N_2O, were reported as well. [212, 227]

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4.2 ^{15}O chemistry

The short half-life of ^{15}O necessitates rapid and single-step- preferred radiosynthetic process. [^{15}O]O_2 gas, produced from ^{14}N(*d,n*)^{15}O nuclear reaction, is the feedstock virtually for all ^{15}O- labeled tracers. The synthetic routes and PET imaging applications are depicted in Scheme 38. The [^{15}O]O_2 was converted to other ^{15}O gases including [^{15}O]CO_2, [^{15}O]CO and [^{15}O]N_2O under appropriate reductive or oxidative conditions at high temperature.[228, 229] Other essential tracers, for example, [^{15}O]H_2O_2, [^{15}O]butanol and 6-[^{15}O]-2-deoxy-D-glucose, were also efficiently prepared by the one-step reaction.[230–232]

The most important ^{15}O-labeled PET tracer is [^{15}O]H_2O, commonly used for the study of regional cerebral blood flow and metabolism.[233] Several methods for the production of [^{15}O]H_2O have been reported,[5] including direct bombardment of water using ^{16}O(*p,pn*)^{15}O reaction, reaction of [^{15}O]O_2 with H_2 over Pt or Pd at high temperature, and *in vivo* ^{15}O exchange of [^{15}O]CO_2 by carbonic anhydrase.

5. Summary and Outlook

Small molecule PET ligand discovery has long been hampered by the stringent constraints imparted by challenges in working with the short-lived radionuclides, ^{11}C, ^{18}F, ^{13}N and ^{15}O. Over the last decade, we have observed a rapid growth in PET radiochemistry, partially driven by the growing importance of PET imaging in pharmaceutical research, yielding a plethora of exciting new methodologies that equipped researchers with not only greater synthetic options, but also a broader scope of functional groups. These advances provide greater flexibility when designing new PET ligands, with optimized pharmacological, physicochemical and ADME properties. Among several new ^{18}F-fluorination methods for labeling non-activated arenes, the most advanced for human use at this time are the hypervalent iodine(III) methods (diaryl iodonium salts and iodonium ylides). Copper-mediated radiofluorination using boron/tin precursors is also promising for clinical translation. In ^{11}C chemistry, carbonylation via [^{11}C]CO_2 fixation has advanced to human use and has been useful for ^{11}C-labeled carbamates, unsymmetrical ureas, carboxylic acids, amides and oxazolidinones. More advanced methods and board substrate scope for ^{11}C-labeled amides and nitriles have been seen in the transition metal mediated cross coupling reactions with [^{11}C]CO.

It is important, however, to realize that many emerging methodologies were established primarily using simple substrates with minimal functionalizations. Broad functional group toleration and robustness of a given methodology need to be rigorously assessed to gain a realistic understanding on its suitability in PET labeling of fully elaborated drug-like molecules. Other promising but underdeveloped areas may also include electrophilic fluorination and multifluoromethylation in high specific activity, electrochemical or light-induced reactions, radiolabeling of unmodified biologics under physiological conditions. Although it may be unrealistic to think of ^{13}N and ^{15}O as substitutes for ^{11}C or ^{18}F, these radionuclides are rarely considered by PET chemists and have potential for generating an arsenal of new radiotracers. Furthermore, with any new labeling methodology, amenability to simple purification, automation, quality control, and most importantly GMP practice needs to be considered upfront to ensure a clear pathway into the clinic. Finally, efforts

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toward expansion of functional groups that are amenable to radiolabeling with PET nuclides will increase the probability of successfully identifying PET ligands to guide the development of life-saving therapeutics.

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Biography

Steven H. Liang obtained his B.S. at Tianjin University, followed by his Ph.D. in Chemistry with Professor Marco Ciufolini in the University of British Columbia. Then he started as a NSERC fellow with Professor EJ Corey at Harvard University. Dr. Liang is currently the Director of Radiochemistry and Biomarker Development Program, Nuclear Medicine and Molecular Imaging at Massachusetts General Hospital and Assistant Professor of Radiology at Harvard Medical School.

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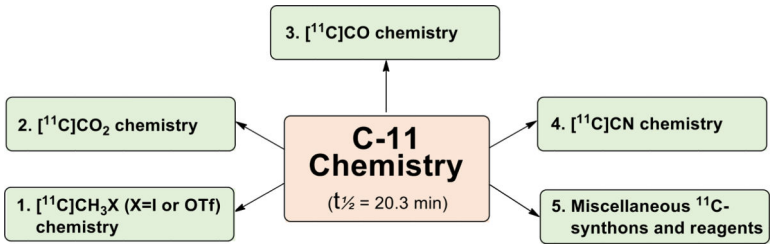

Scheme 1.
Overview of ^{11}C chemistry

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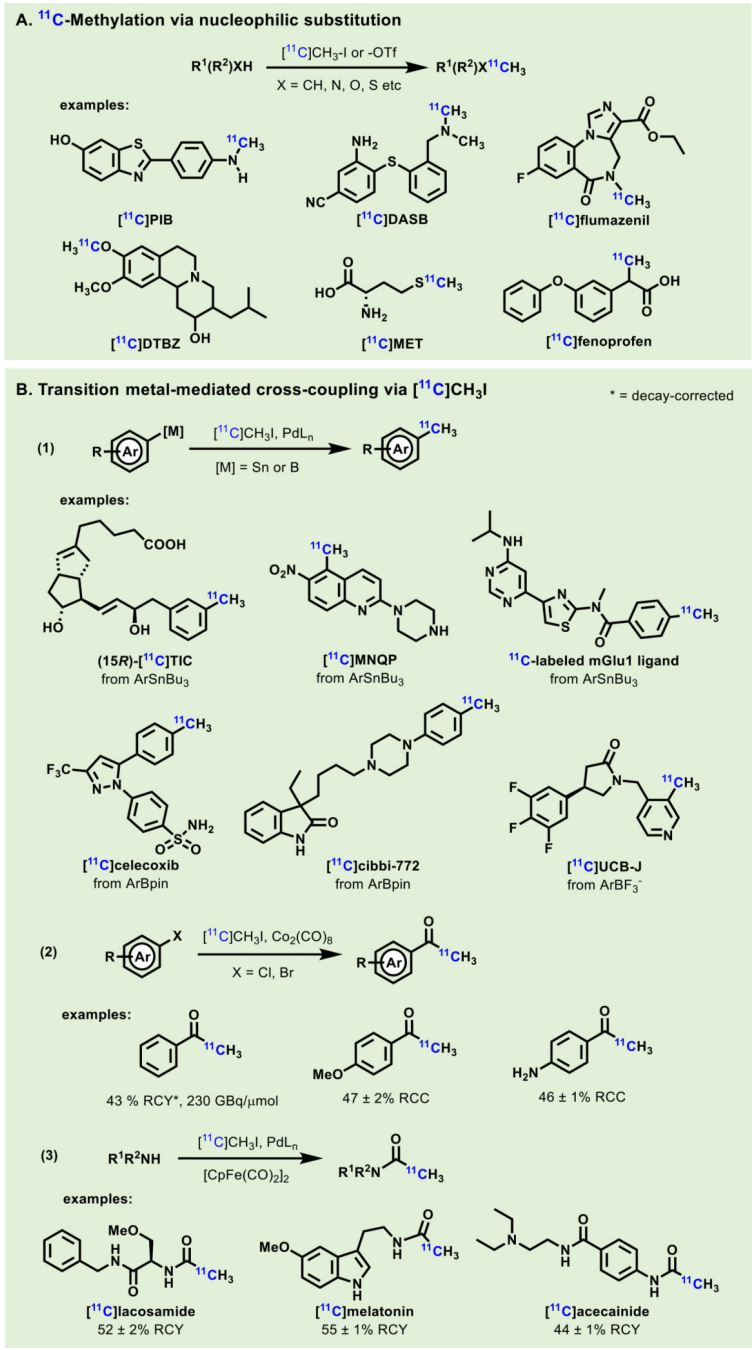

Scheme 2.
$[^{11}C]CH_3X$ (X=I or OTf) chemistry

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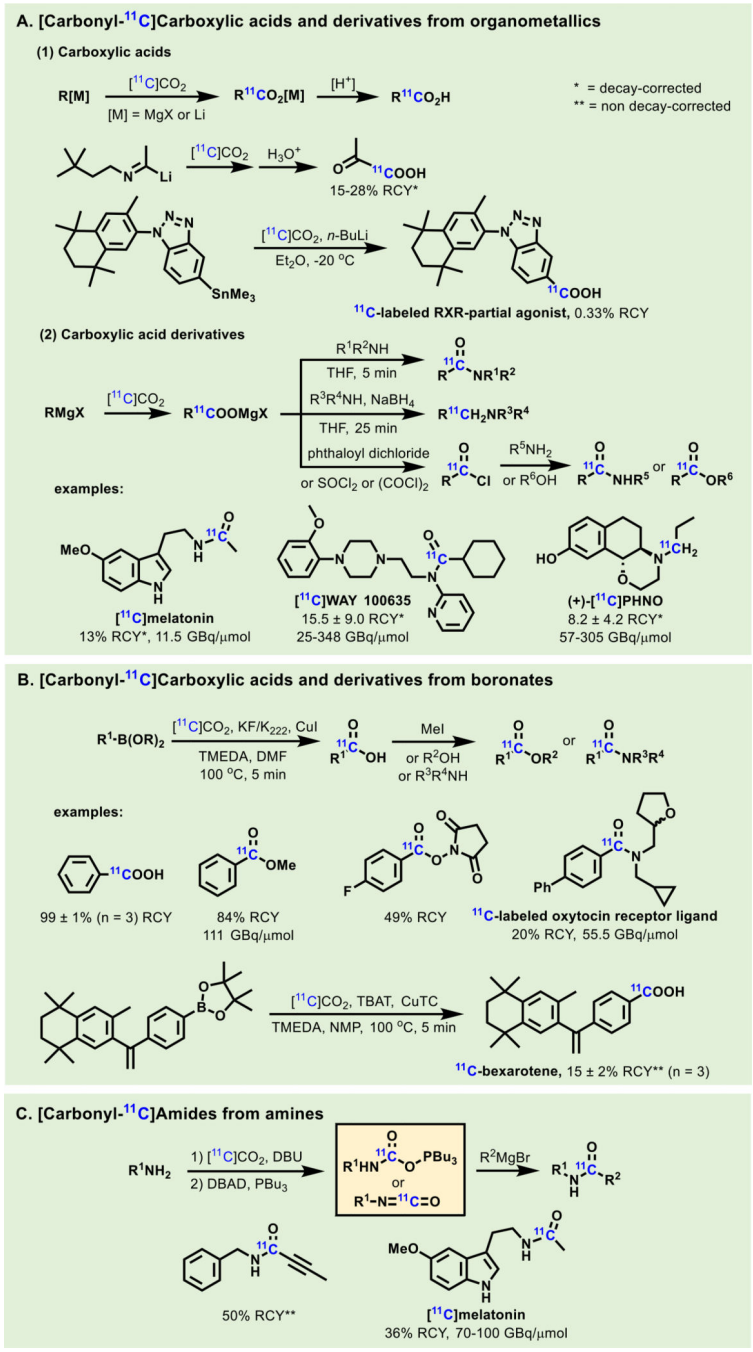

Scheme 3.

Synthesis of ^{11}C-labeled carboxylic acids and derivatives via [^{11}C]CO_2

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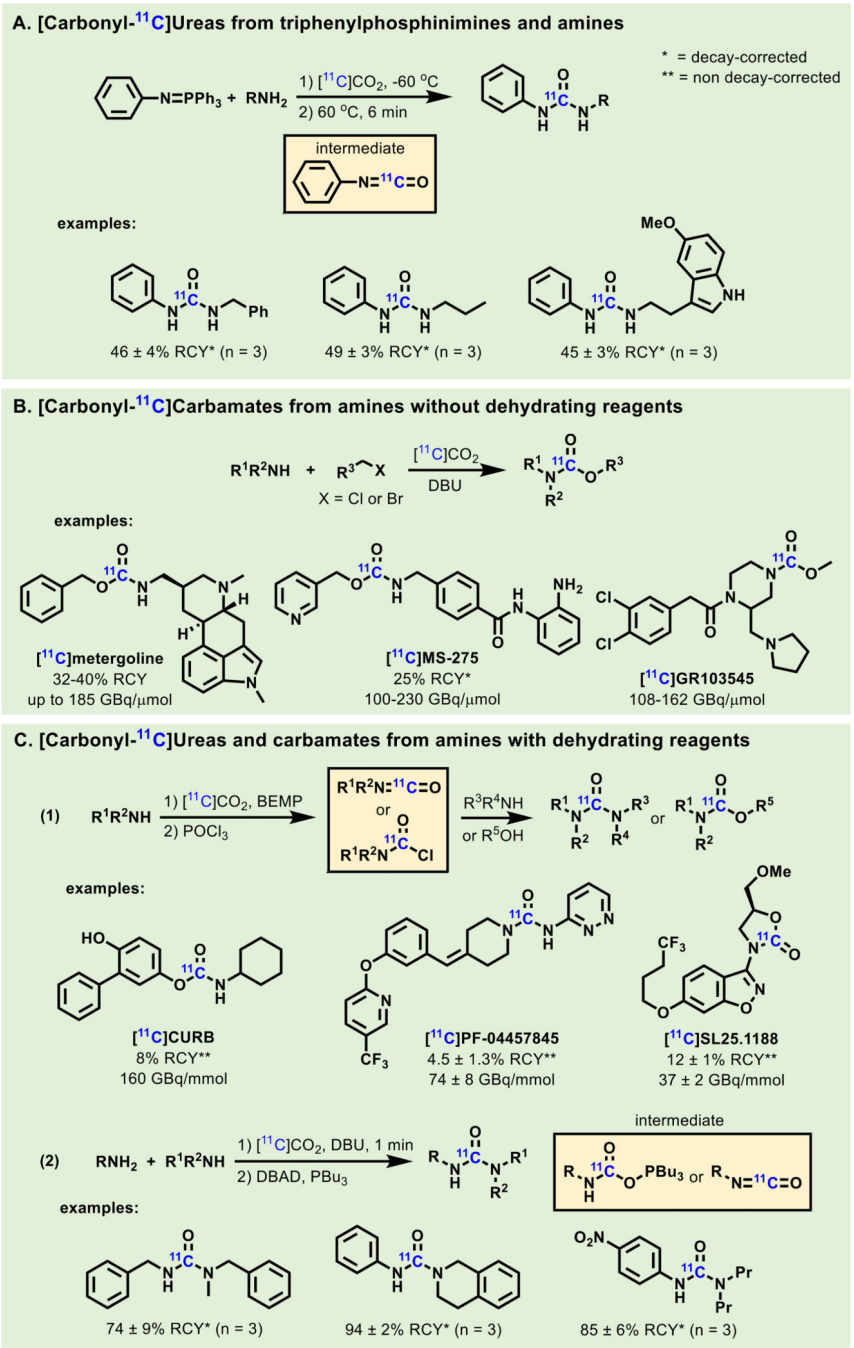

Scheme 4.

Synthesis of ^{11}C-labeled carbamates and ureas via [^{11}C]CO_2

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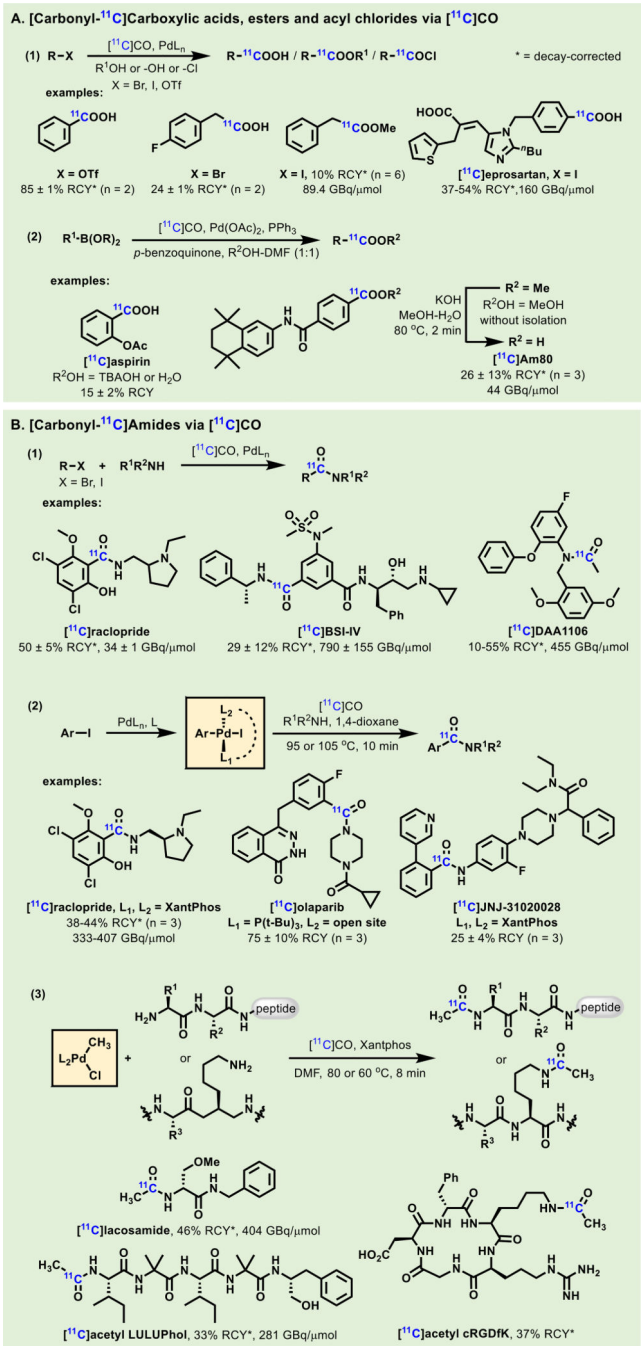

Scheme 5.

Pd-mediated formation of ^{11}C-labeled carboxylic acid and its derivatives via [^{11}C]CO

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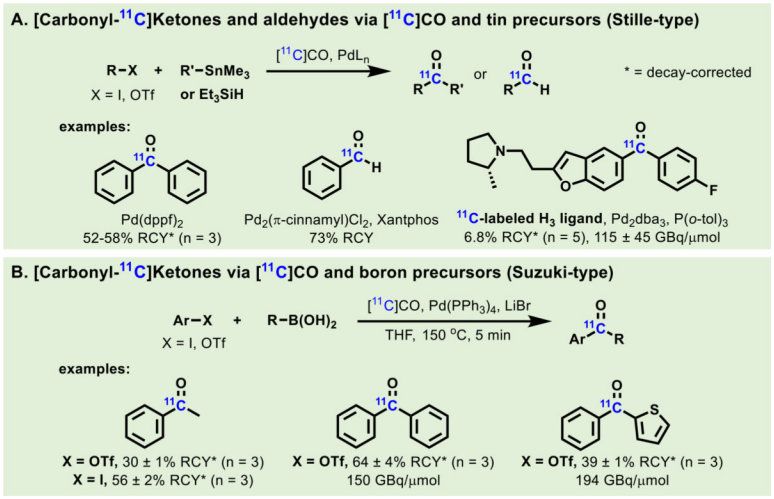
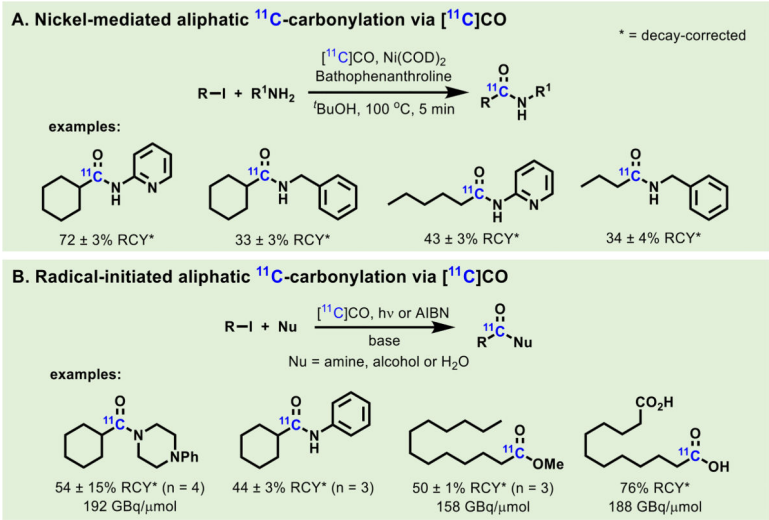


Scheme 6.

Pd-mediated formation of ^{11}C-ketones and aldehydes via [^{11}C]CO



Scheme 7.

^{11}C-Carbonylation of nonactivated aliphatic substrates via [^{11}C]CO

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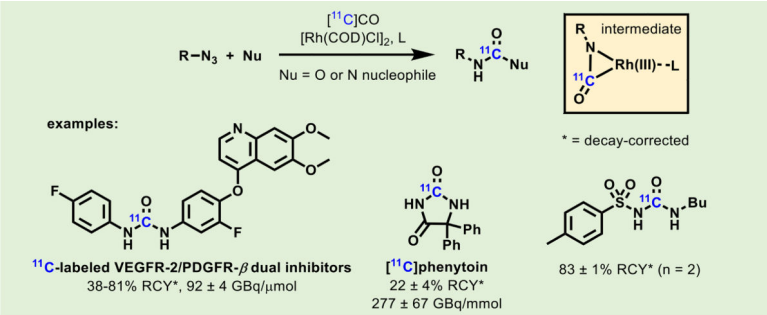
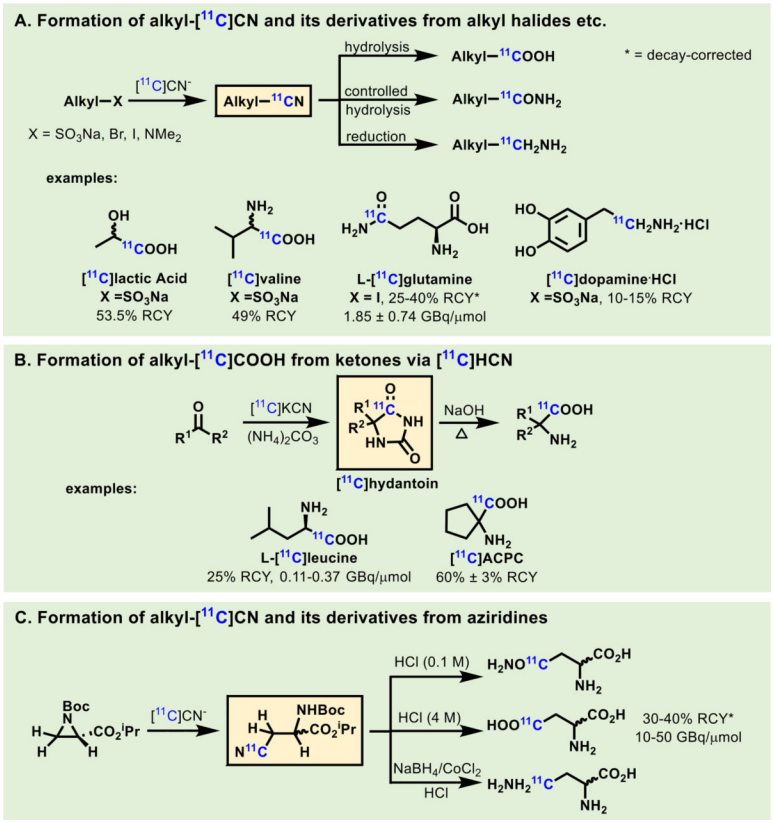


Scheme 8.

Formation of ^{11}C-carbonyl labeled ureas and carbamates via [^{11}C]CO



Scheme 9.

Formation of alkyl-^{11}CN and its derivatives

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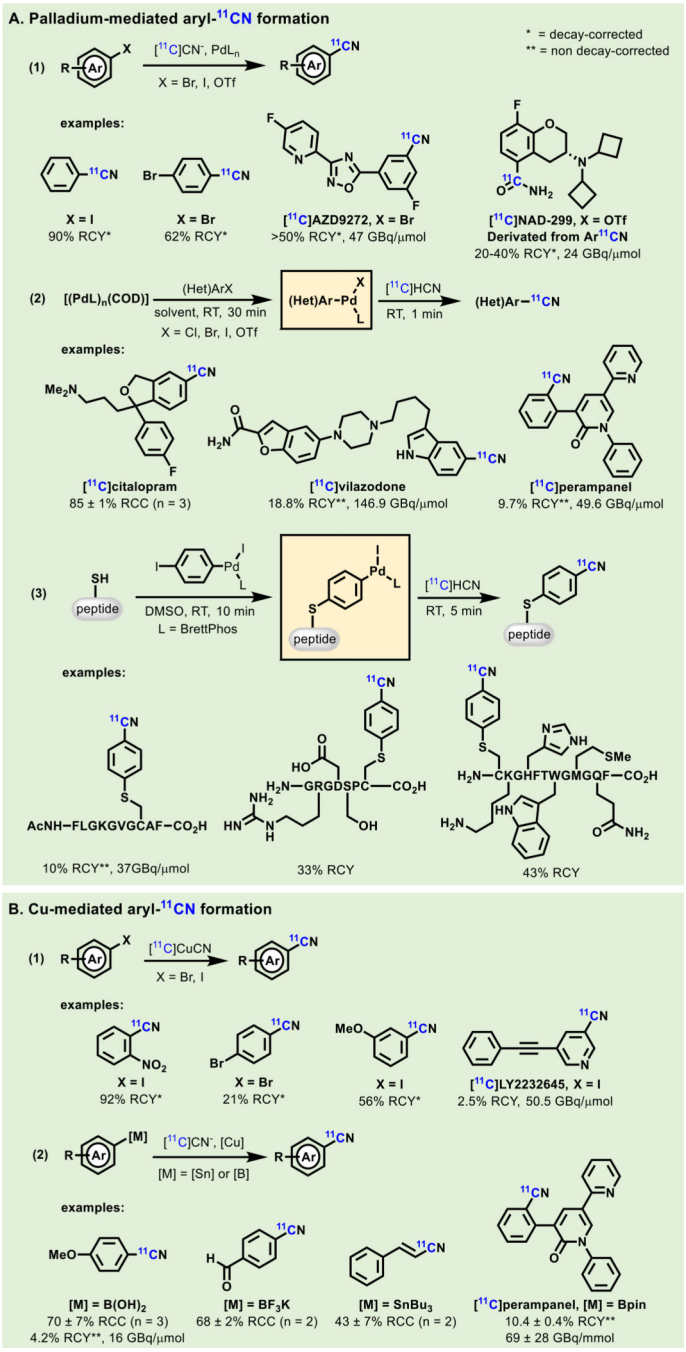
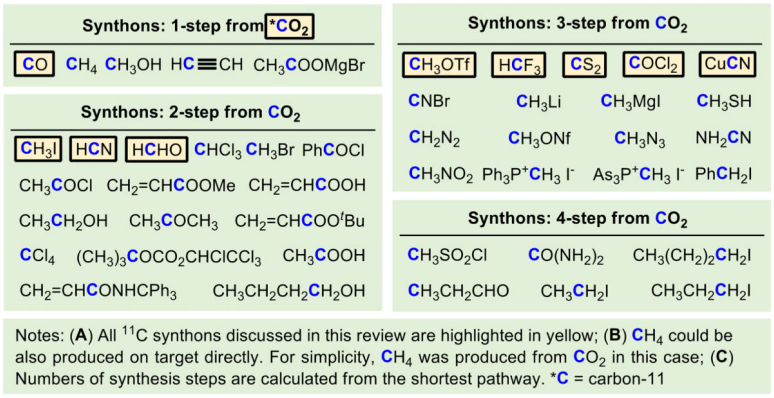


Scheme 10.
Formation of aromatic ^{11}CN and its derivatives



Scheme 11.

Selected ^{11}C Synthons prepared by 1–4 step reactions

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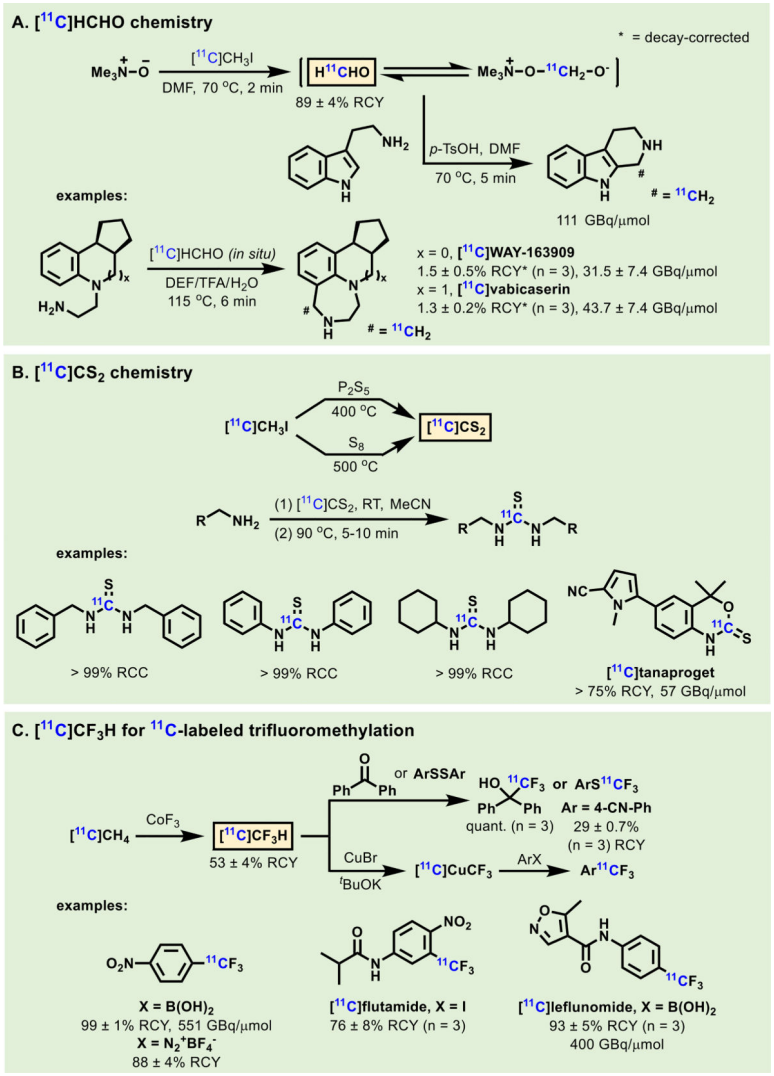

Scheme 12.
Miscellaneous ^{11}C-synthons and reagents

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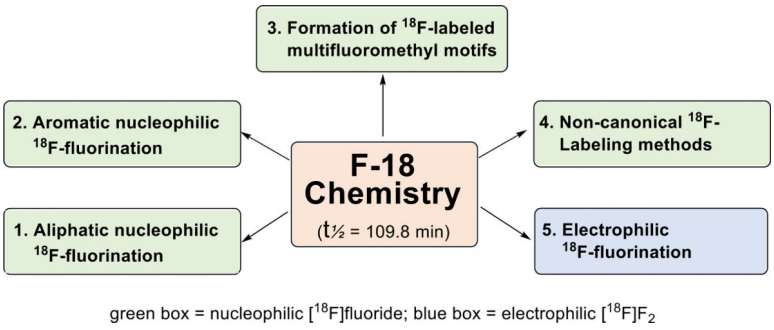
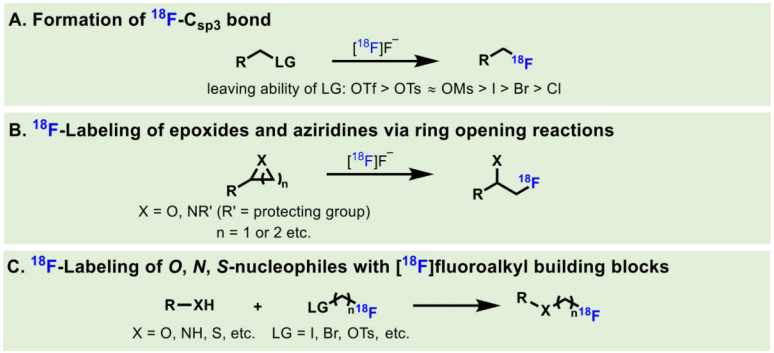


Scheme 13.
Overview of ^{18}F chemistry.



Scheme 14.

Common strategies for synthesis of ^{18}F-alkyl groups

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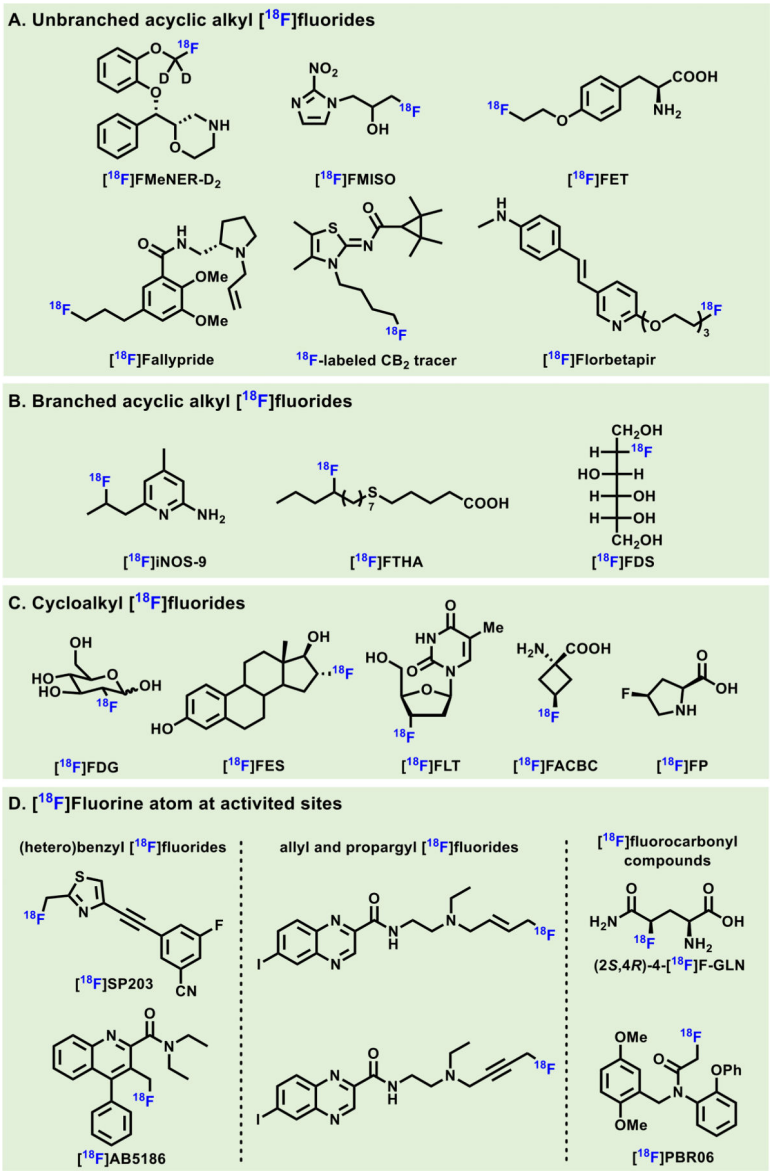

Scheme 15.

Representative chemotypes of aliphatic [^{18}F]fluorides

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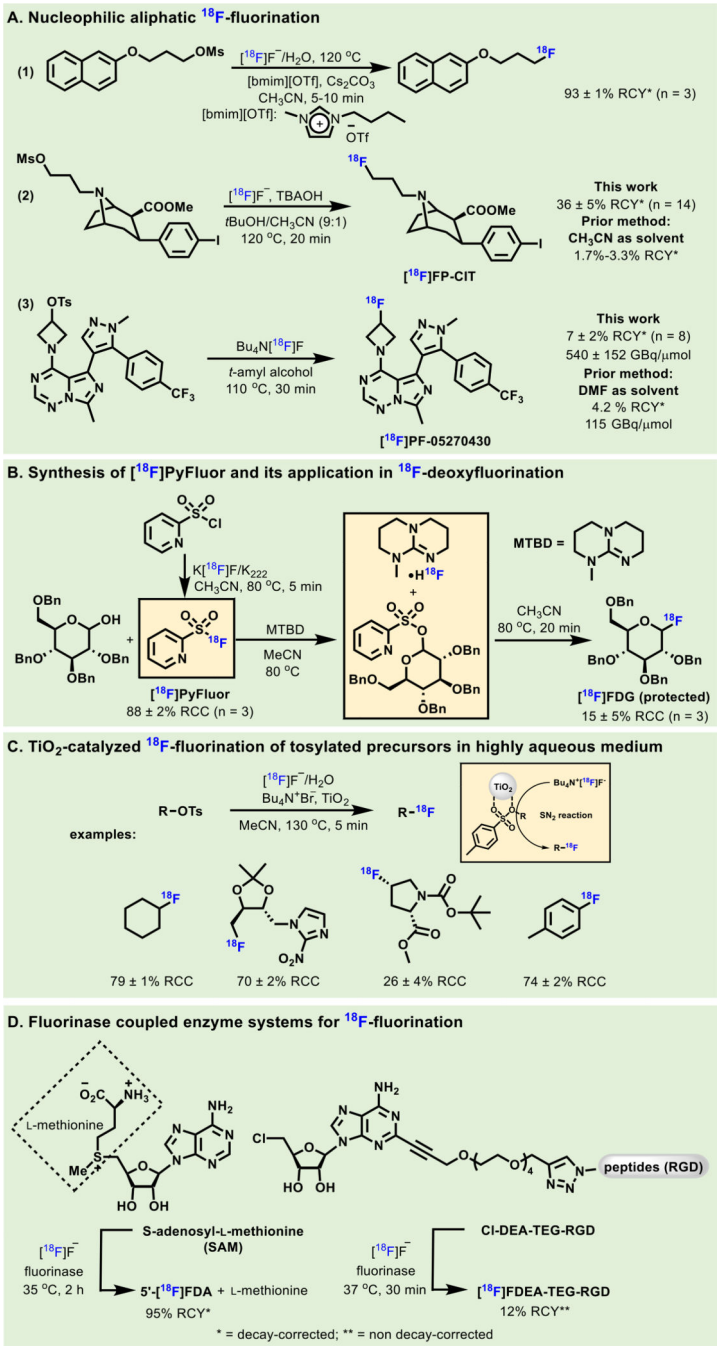

Scheme 16.
Unconventional aliphatic ^{18}F-fluorination reactions

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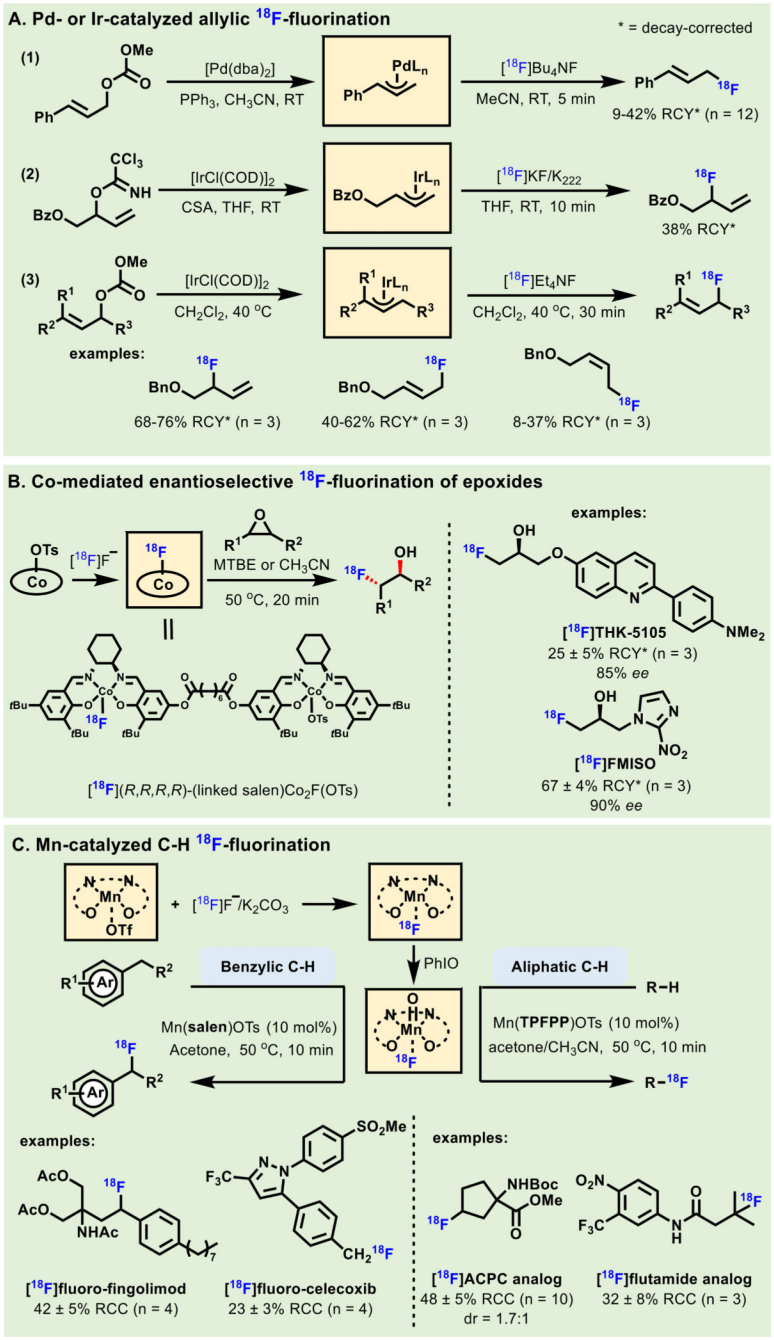

Scheme 17.

Transition metal-mediated aliphatic ^{18}F-fluorination

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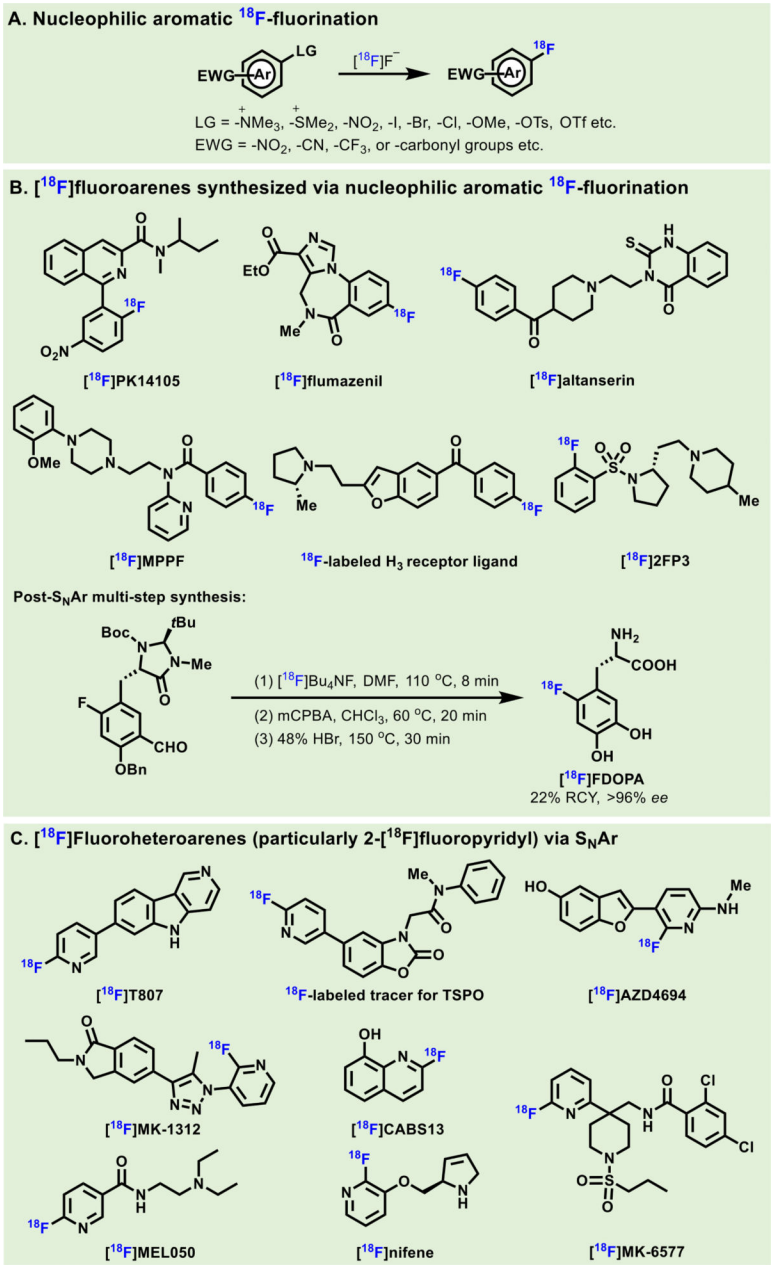

Scheme 18.

Aromatic nucleophilic substitution (S_NAr) with [^{18}F]fluoride ion

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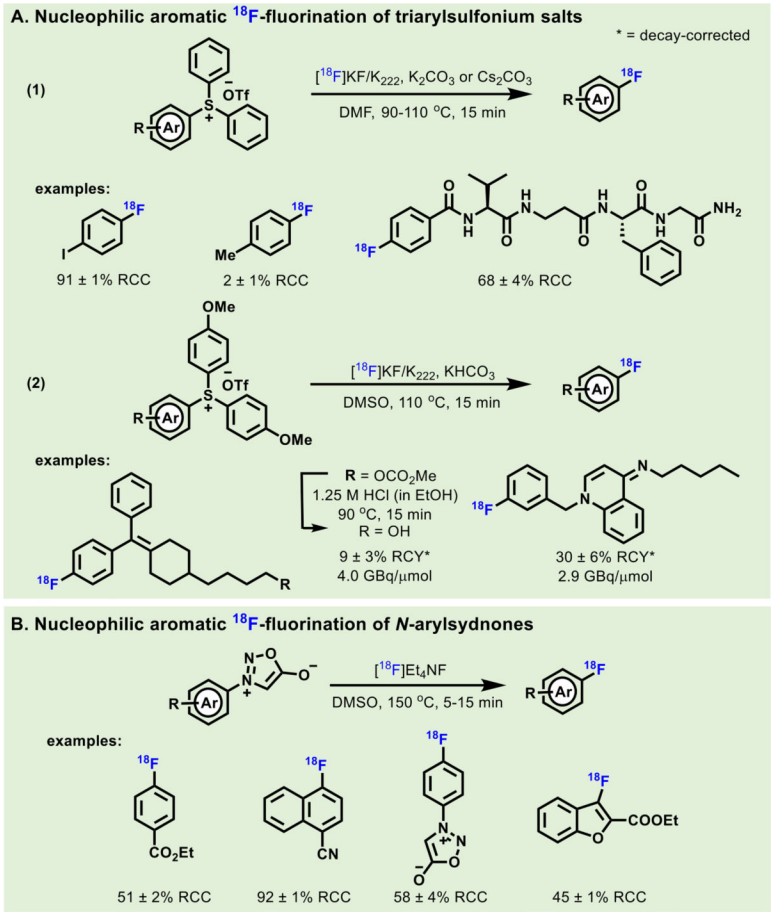
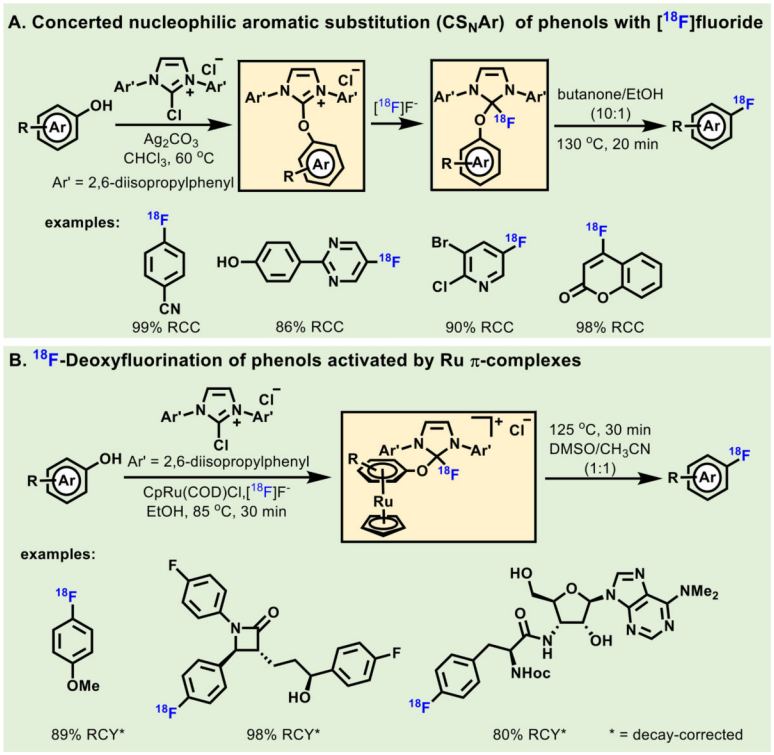


Scheme 19.

Unconventional aromatic nucleophilic substitution (S_NAr) with [^{18}F]fluoride



Scheme 20.

^{18}F-Deoxyfluorination of phenols via concerted S_NAr

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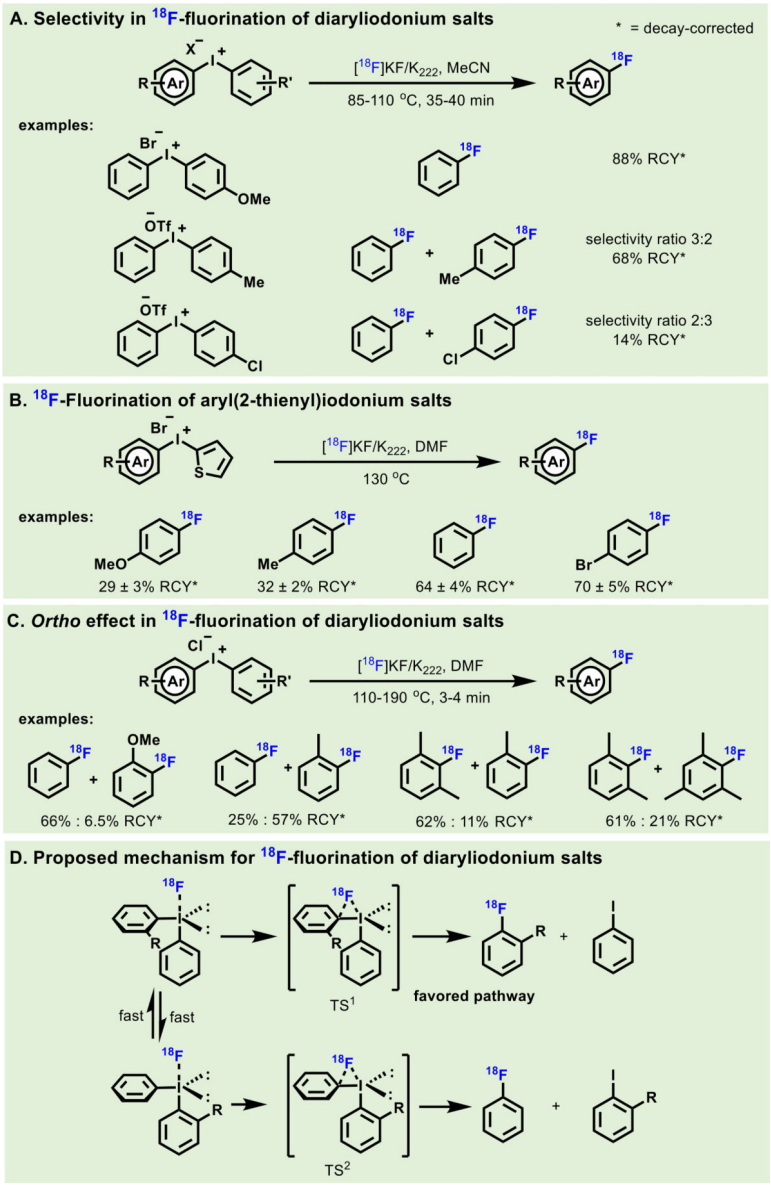

Scheme 21.
^{18}F-Fluorination of diaryliodonium salts

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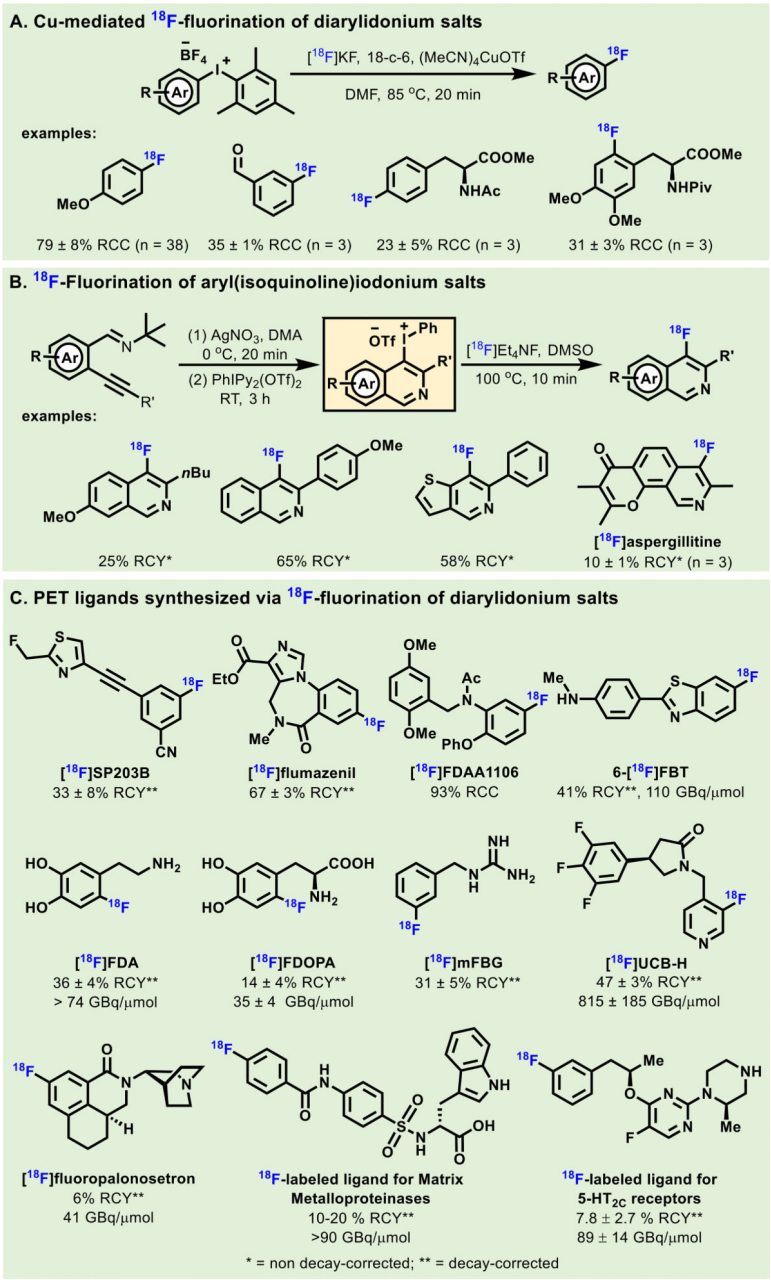

Scheme 22.

Recent application in the ^{18}F-fluorination of diaryliodonium salts

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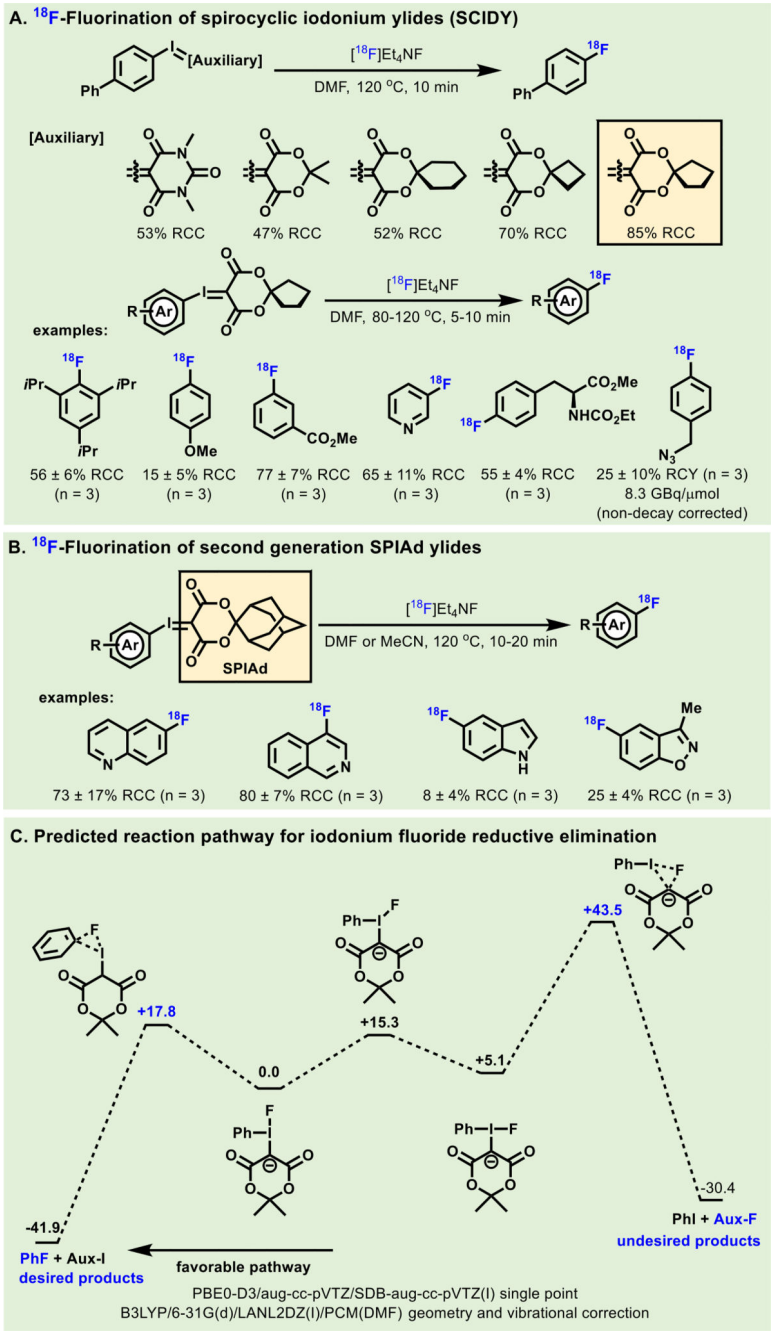

Scheme 23.

^{18}F-Fluorination of aryliodonium ylides

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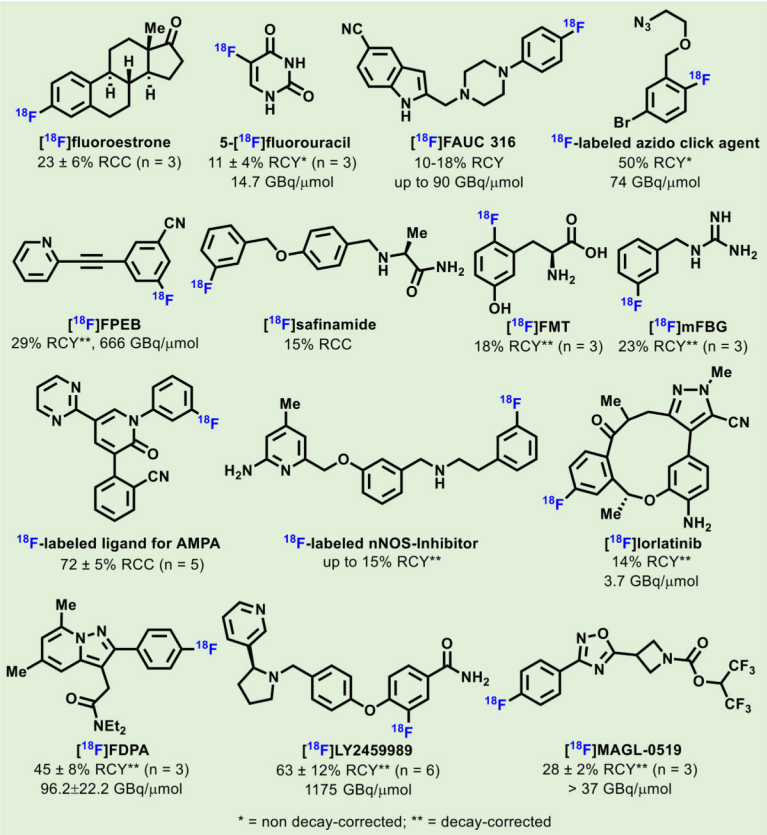

Scheme 24.

Representative examples for ^{18}F-fluorination of aryliodonium ylides

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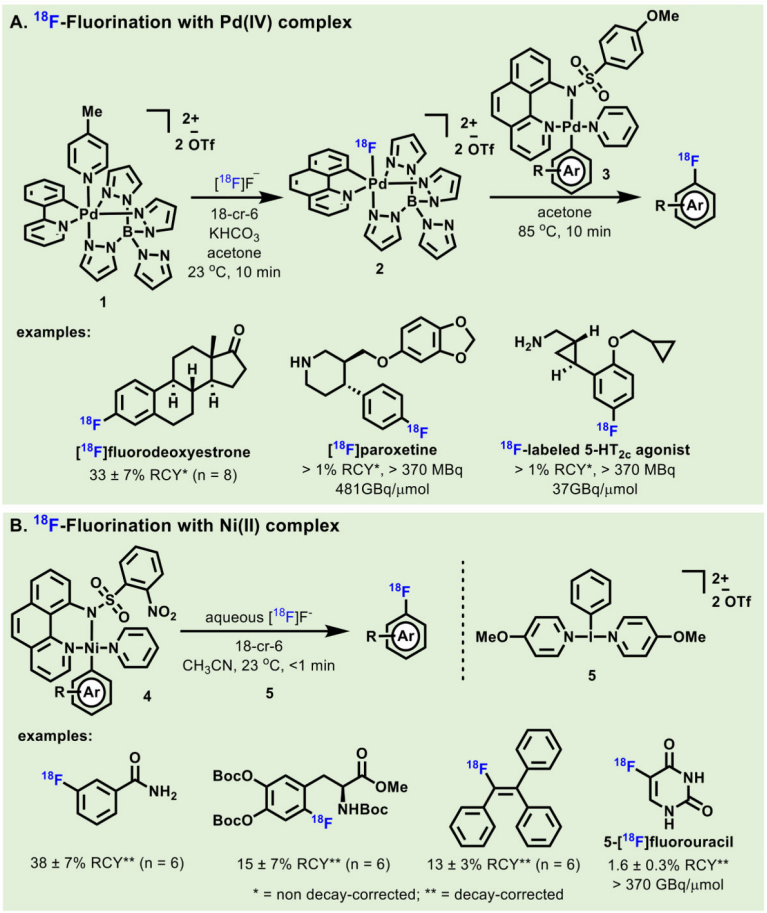

Scheme 25.

Pd- or Ni-mediated aromatic fluorination with [^{18}F1fluoride

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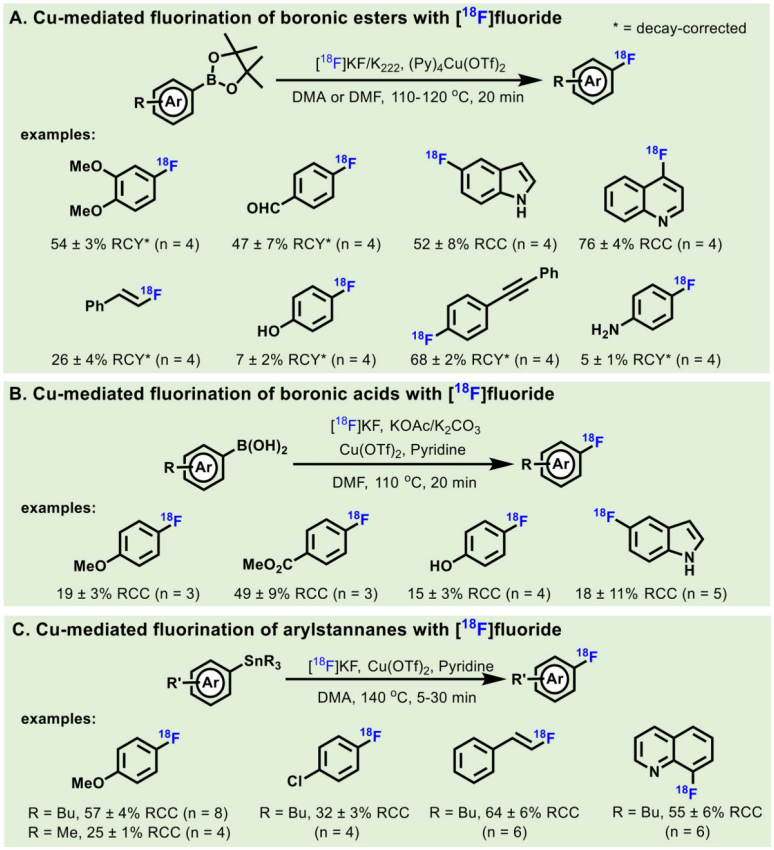

Scheme 26.
Cu-mediated aromatic fluorination with [^{18}F]fluoride

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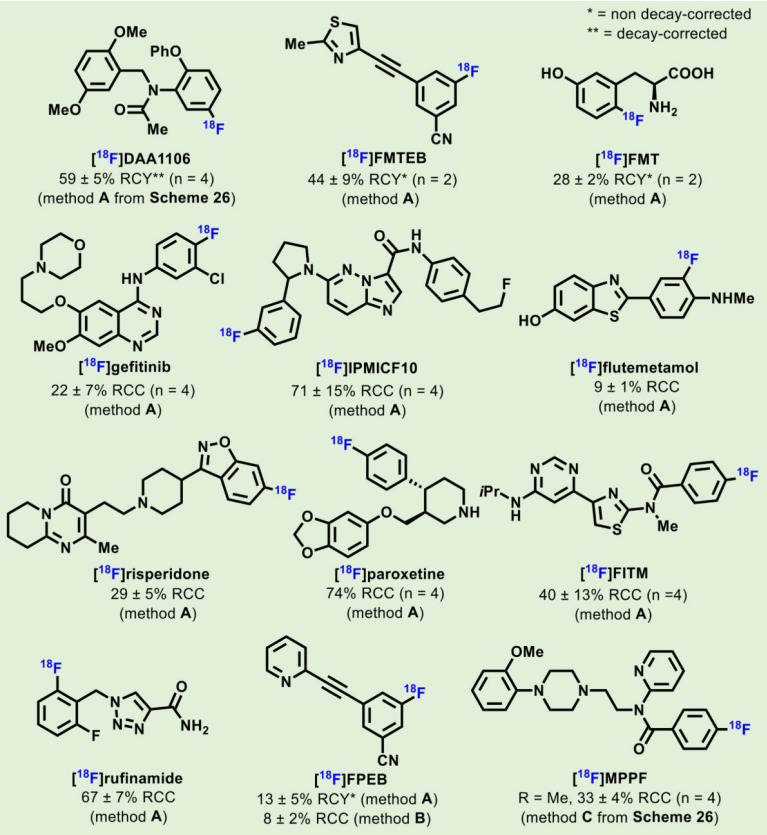
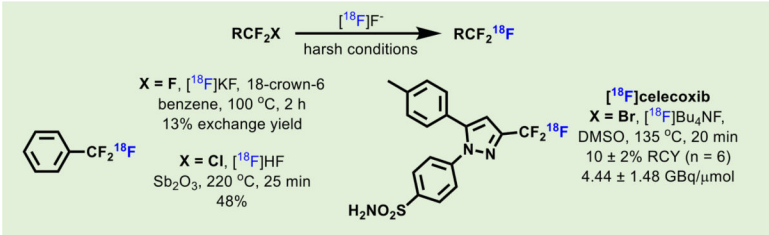


Scheme 27.

Representative examples for Cu-mediated aromatic ^{18}F- fluorination



Scheme 28.
Traditional halogen-^{18}F exchange reactions

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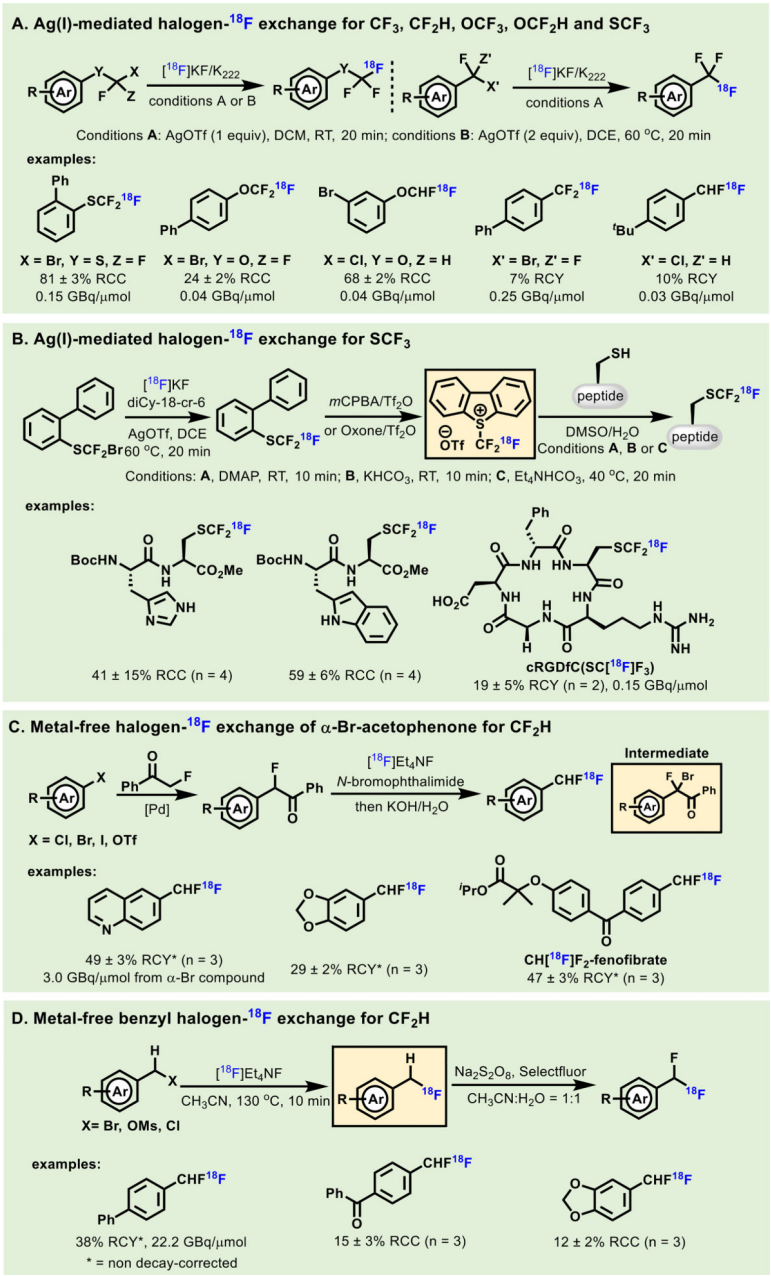

Scheme 29.

Facilitated halogen-^{18}F exchange for [^{18}F]CF_3/[^{18}F]CF_2H formation

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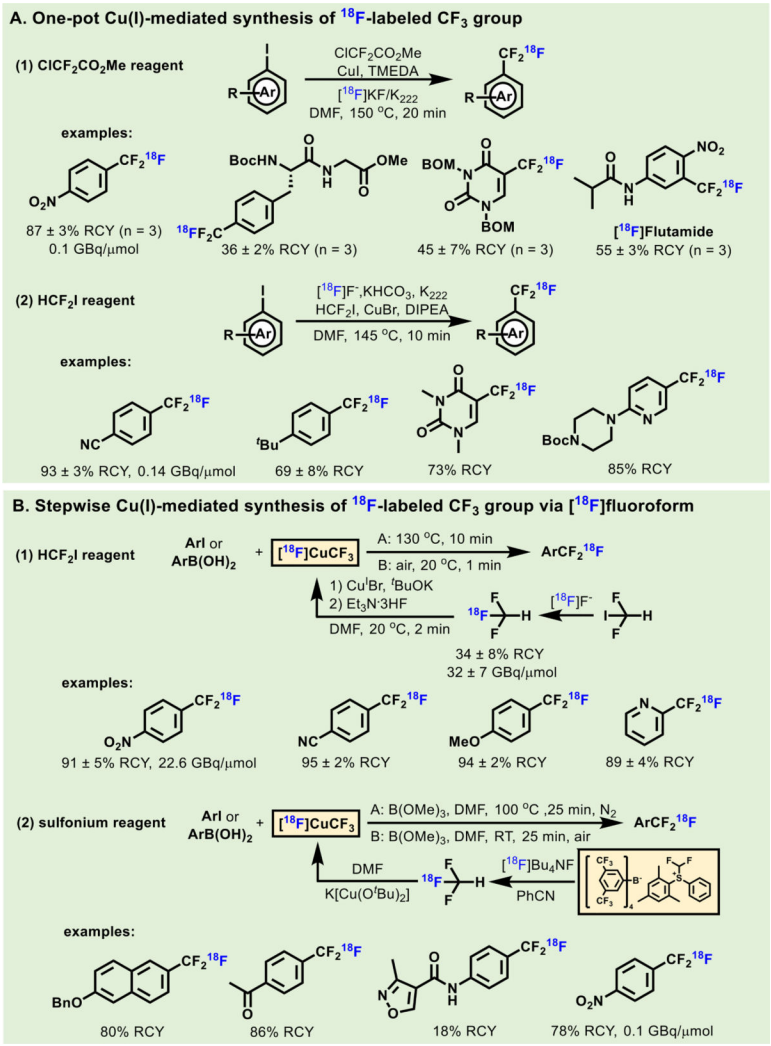
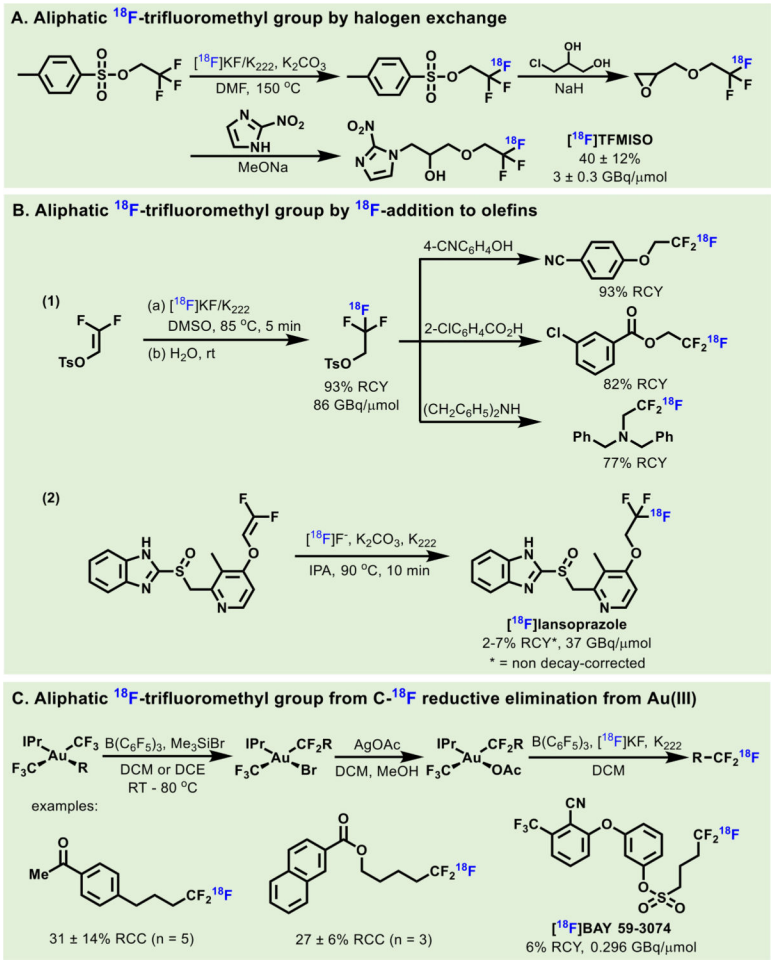


Scheme 30.

Cu(I)-mediated ^{18}F-labeled CF_3 formation via [^{18}F]fluoride and difluorocarbene



Scheme 31.
Formation of ^{18}F-labeled alkyl-CF_3 compounds

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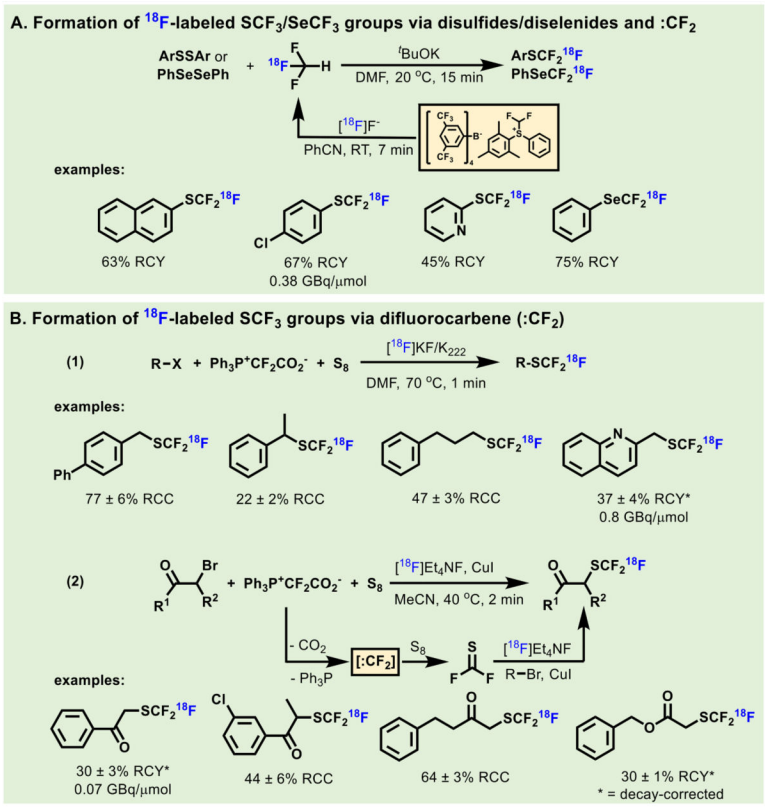

Scheme 32.

^{18}F-Labeled SCF_3/$SeCF_3$ formation with [^{18}F]fluoride and :CF_2

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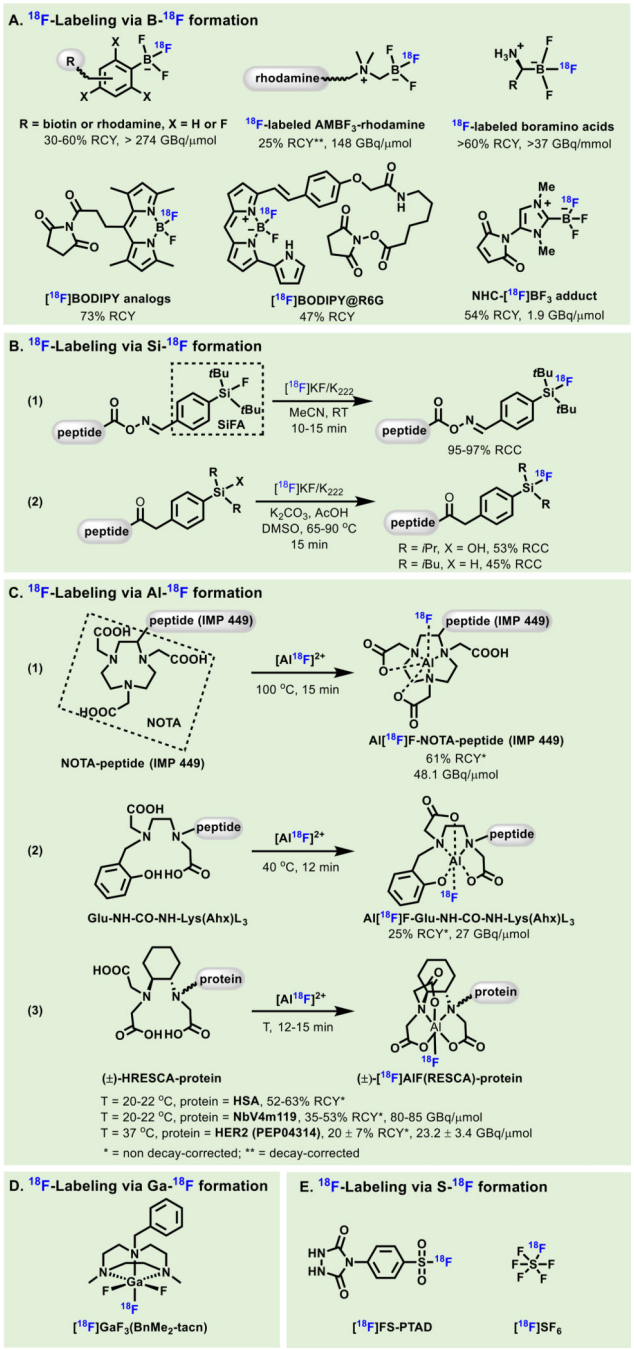
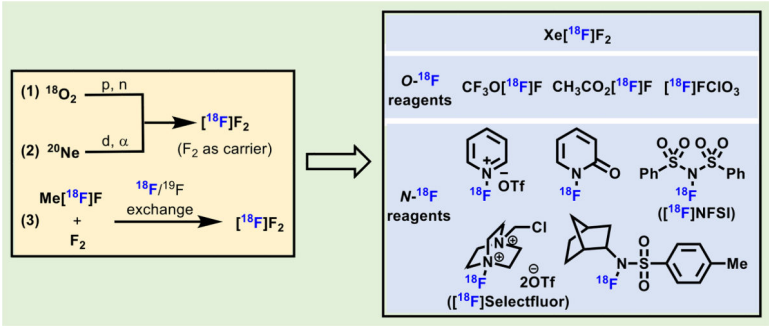


Scheme 33.
Non-canonical ^{18}F-labeling methods



Scheme 34.
Preparation of electrophilic ^{18}F-fluorinating reagents

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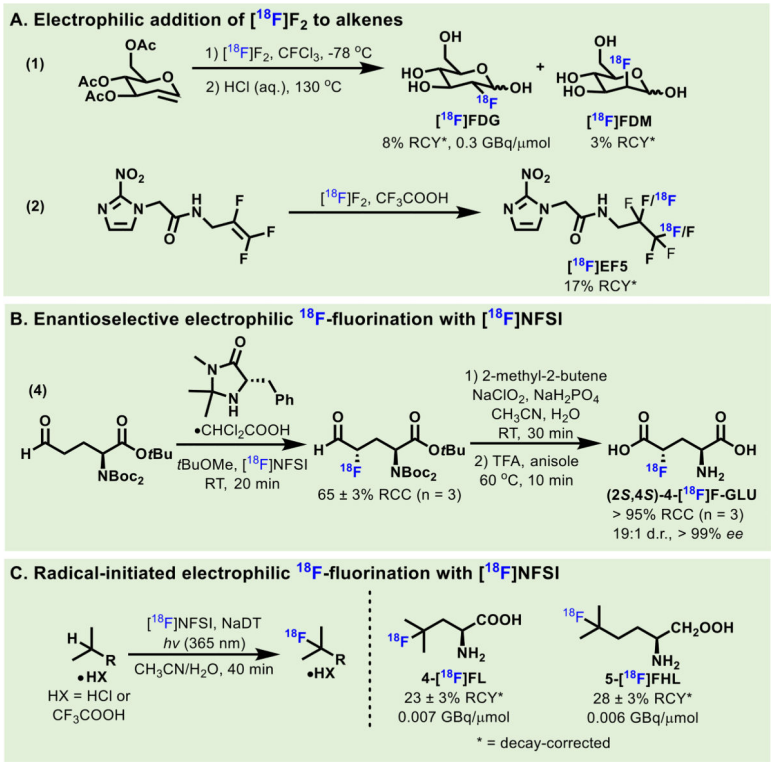
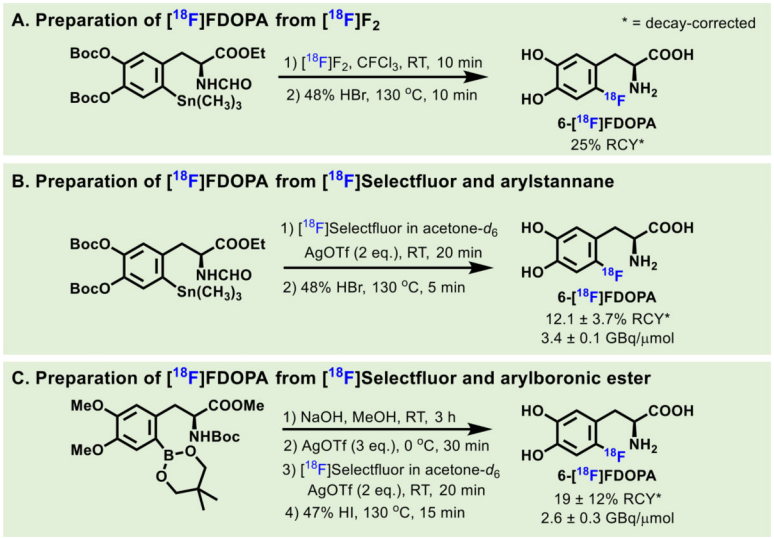


Scheme 35.
Electrophilic ^{18}F-fluorination for ^{18}F-alkyl formation



Scheme 36.
Electrophilic ^{18}F-fluorination for arenes

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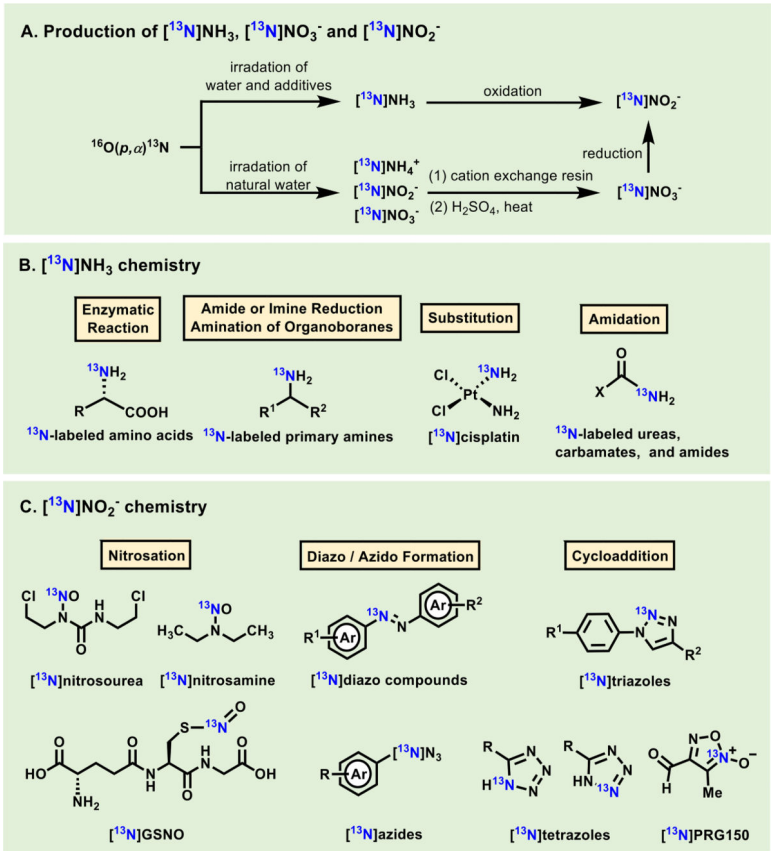
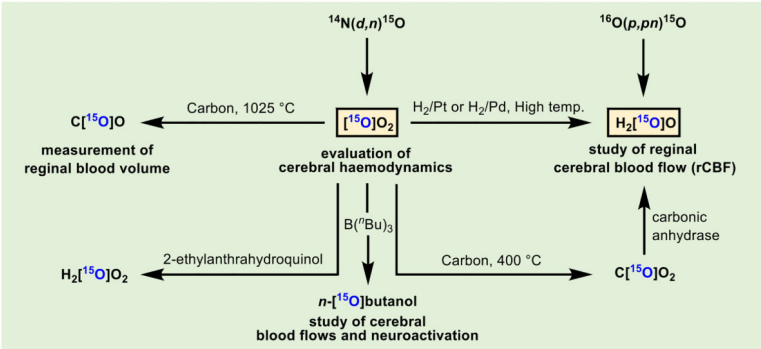


Scheme 37.
^{13}N chemistry



Scheme 38.
^{15}O chemistry

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