A general $^{11}$C-labeling approach enabled by fluoride-mediated desilylation of organosilanes

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Carbon-11 ($^{11}$C) is one of the most ideal positron emitters for labeling bioactive molecules for molecular imaging studies. The lack of convenient and fast incorporation methods to introduce $^{11}$C into organic molecules often hampers the use of this radioisotope. Here, a fluoride-mediated desilylation (FMDS) $^{11}$C-labeling approach is reported. This method relies on thermodynamically favored Si-F bond formation to generate a carbanion, therefore enabling the highly efficient and speedy incorporation of $[^{11}\text{C}]\text{CO}_2$ and $[^{11}\text{C}]\text{CH}_3\text{I}$ into molecules with diversified structures. It provides facile and rapid access to $^{11}$C-labeled compounds with carbon-11 attached at various hybridized carbons as well as oxygen, sulfur and nitrogen atoms with broad functional group tolerance. The exemplified syntheses of several biologically and clinically important radiotracers illustrates the potentials of this methodology.
Positron emission tomography (PET) is a clinical and research imaging modality for the non-invasive investigation of biochemical and molecular events in living organisms using radioactive positron emitting tracers. In the past two decades, the application of PET to the study of various diseases (oncological, neurological and cardiovascular) has positioned this modality as one of the most powerful translational imaging tools available. Among several short-lived positron-emitting radionuclides used in PET imaging, carbon-11 (11C, $t_{1/2} = 20.4$ min, $E_{\beta^+} = 1.98$ MeV) stands out as unique. The ubiquitous presence of carbon in organic molecules makes 11C an attractive and important positron-emitting radionuclide for labeling a vast array of molecules of biological interest. Importantly, 11C-labeled molecules possess the same chemical and biological properties as the non-radioactive 12C-molecule of interest; thus making 11C extraordinarily useful for the exploration of molecules with well-characterized biological and pharmacological properties (i.e., metabolism, drug pharmacokinetics, receptor binding affinity, enzyme substrate affinity, etc.). In addition, the short half-life of 11C enables the possibility of performing multiple imaging studies in the same subject on a single day, which is especially beneficial for clinical researches. This unique utility of 11C demands that there be rapid and robust approaches available to incorporate 11C into various organic molecules in an efficient manner.

Carbon-11 labeled PET tracer syntheses generally start with the cyclotron production of [11C]CO$_2$ or [11C]CH$_4$, which are produced by the proton bombardment of N$_2$ gas (doped with O$_2$ or H$_2$) using the 14N(p,a)11C nuclear reaction. The most commonly produced radioactive intermediate [11C]CO$_2$ can be either used directly as a primary radiosynthon or be rapidly converted to more reactive secondary radiosynthons ([11C]CH$_3$I, [11C]CH$_2$OTf, [11C]HNC, [11C]HCHO, [11C]CO, [11C]COCI, etc.), enabling a variety of radiosynthetic strategies. After postreaction purification, typically using chromatographic and/or solid phase extraction (SPE) techniques, the desired 11C-labeled tracer is isolated and formulated for use in preclinical or clinical studies. The main challenge for a successful synthesis of 11C-labeled PET tracers is a rapid, robust, and practical radiolabeling method that yields a desired tracer dose of pharmaceutically acceptable quality, i.e. high radiochemical & chemical purity, and typically high specific activity ($A_s$) or molar activity ($A_m$). In addition, such a method should be easily adapted for automation to minimize radiation exposure to the operator, and the labeling precursors should be either commercially available or readily synthesized.$^{1-3}$

[11C]CO$_2$ has been directly used for PET tracer synthesis for decades. It is now routinely produced for the synthesis of carbon-11 labeled fatty acids such as [11C]acetic acid and [11C]palmitic acid via the Grignard reaction in many PET facilities worldwide. However, because of its inertness, radiolabeling reactions using [11C]CO$_2$ generally require the use of strong organometallic reagents, such as Grignard and organolithium reagents, which are sensitive to moisture and atmospheric 12CO$_2$ and less tolerant to the presence of various functional groups. These drawbacks impede the broader application of [11C]CO$_2$ for synthesizing highly functionalized molecules. To expand the utility of [11C]CO$_2$ for the synthesis of PET tracers with diverse structures, including multiple functional groups, researchers have recently reported on both the incorporation of [11C]CO$_2$ into molecules under milder conditions, and the introduction of 11C to specific positions that are not easily achieved using other secondary radiosynthons.$^{4-10}$ Despite such developments, the method of directly incorporating [11C]CO$_2$ for synthesis of 11C-labeled radiotracers remains sorely lacking in the field of PET chemistry. Hence, there is a heretofore unmet need to develop radiolabeling methodologies that can directly and promptly introduce [11C]CO$_2$ to molecules with diverse structure and/or containing multiple functional groups under mild reaction conditions.

Herein, we report our recent development of a fluoride-mediated desilylation (FMDs) 11C-labeling approach derived from a fluoride desilylation promoted nucleophilic reaction.$^{11}$ Carbon-11 labeled carboxylic acids containing various functional groups with 11C attached at different hybridized carbons (sp, sp$^2$, and sp$^3$) are synthesized by in situ generation of various nucleophiles via fluoride agents and organosilanes, followed by a quick 11C-carboxylation reaction. Moreover, this method is also readily extended to label organic molecules with [11C]CH$_3$I as the radiolabeling synthon.

**Results**

**Synthesis of [11C]acetoacetic acid via FMDs 11C-carboxylation.**

To support the PET imaging study of the metabolic process of ketone bodies in brain tumors, we recently developed a production method for [11C]acetoacetic acid ([11C]3) following a literature method$^{12,13}$, in which isopropenyl acetate, 1, was first reacted with methyl lithium to form lithium enolate. 2. Next, the enolate, 2, was used for reacting with [11C]CO$_2$ to form the desired product [11C]3 (Fig. 1a). One of the difficulties encountered in the production process was that the chemical impurities were occasionally detected in the final product and proved difficult to remove using standard purification methods. To assure robust production of a high quality [11C]3 tracer, we sought to develop a different approach to [11C]CO$_2$ incorporation under milder conditions, such conditions would avoid the use of a harsh organometallic reagent, which not only generated the desired enolate but also caused some side reaction(s). After an extensive literature search, we found that a fluoride ion desilylation enolate generation method reported by Noyori in 1983 could be amenable for this purpose.$^{14}$

The exploration of a FMDs 11C-carboxylation strategy for synthesis of [11C]3 began by using (isopropenyl)trimethylsilane, 4, as the organosilane reagent and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) as the fluoride ion source.$^{14,15}$ Binary solvent systems (tetrahydrofuran (THF) and dichloromethane (DCM)) were employed for the reaction due to the low solubility of TASF in THF.$^{16}$ The initial experiment provided us [11C]3 with a 5% radiochemical yield (RCY, based on HPLC analysis of the crude product). The formation of [11C]3 via FMDs 11C-carboxylation approach could be understood from the mechanistic scheme in Fig. 1b. The driving force of the enolate anion formation under such mild conditions comes from the strength of the silicon-fluorine bond (139 kcal/mol), which makes enolate generation via fluoride-mediated desilylation as a thermodynamically favored process.$^{14}$ After several preliminary experiments, the RCY (based on HPLC analysis of the crude product) of [11C]3 quickly improved to over 50%. However, purification with either ion-exchange or semi-prep HPLC methods failed to provide a product with acceptable chemical purity. This was due to the large amount of TASF reagent and water incompatible solvent DCM used for reactions. At this stage, cesium fluoride (CsF) was tested as a replacement for TASF to overcome these problems.$^{17,18}$ The modification of experimental conditions (such as using THF and dimethylformamide (DMF) (3/1, V/V) binary solvents, trapping [11C]CO$_2$ at low temperature, pre-drying the CsF reagent using azotropic evaporation, adjusting the quantity of the ion exchange resin as well as introducing an Al–N cartridge at the end of the purification process for removal of extra fluoride ion) dramatically improved the overall reaction yield and the chemical purity of the final product. An optimized synthetic protocol (Fig. 1c) was developed that was suitable for production under cGMP compliant...
Exploration of synthesis of ¹¹C-carboxylates and derivatives.

The success in developing an updated method for synthesizing [¹¹C]3 triggered our interest in exploring carbon nucleophiles, generated in situ via FMDS approach, for ¹¹C-carboxylation. Although FMDS method had been used to generate a variety of nucleophiles in many organic reactions (such as alkylation, alkylation, alkylation, arylation, vinylation, and cyanoation), and had been broadly used to synthesize complex molecules, there are only a handful of reports of directly using organosilanes for carboxylation reaction without involving any transition metal catalysts. While organometallic reagent catalyzed carboxylation has already drawn extensive attention to radiochemistry research, to the best of our knowledge, we have not found any reports of the use of the FMDS methodology for direct ¹¹C-carboxylation. It is comprehensible that the high cost and necessity of stoichiometric amounts of organosilane reagents made this method less attractive in synthetic organic chemistry research when compared to other organometallic reagent catalyzed carboxylation methodologies. For ¹¹C-labeled radiotracer production, however, the primary costs comes from cyclotron bombardment for generation of [¹¹C]CO₂, highly complex equipment-dependent automated synthesis, and elaborate quality control processes. The quantities of chemicals required for ¹¹C-labeling reactions are at the micromole and milliliter level, hence the cost of reagents is a minor consideration. Based upon these prerequisites, adopting a FMDS strategy for ¹¹C-carboxylation provides many potential advantages, such as: (1) The simplicity of the whole reaction system, since only four reagents (organosilane, fluoride source, solvent, [¹¹C]CO₂) are involved in the labeling reactions and there is no organometallic catalyst, ligand(s), base, etc. needed; (2) Less precaution is needed for preparation compared with organometallic reagent based ¹¹C-carboxylation methods since most organosilanes and fluoride source (such as CsF) are not sensitive to atmospheric ¹²CO₂. This difference implies another advantage, i.e. the ¹¹C-labeled PET tracers with high molar activity could be obtained under less stringent conditions; (3) The mildness of the FMDS ¹¹C-labeling strategy could help us to synthesize ¹¹C-carboxylic acids and their derivatives attached to compounds with diversified functional groups thereby dramatically broadening the scope of ¹¹C-labeling via direct use of [¹¹C]CO₂ as a radiosynthon.

We first explored ¹¹C-carboxylation using alkynytrimethylsilylanes, and CsF for sp-hybridized carbanion generation. After preliminary tests, it was found that a combination of THF and dimethyl sulfoxide (DMSO) worked better for these ¹¹C-carboxylation reactions, which stoichiometric reagent ([¹¹C]CO₂ and [¹²C]CO₂ together) at nano- or subnano-moles level, than DMSO alone (Fig. 2). The selected reaction conditions not only trapped [¹¹C]CO₂ efficiently (usually >90% [¹¹C]CO₂ radioactivity was retained in the reaction mixture), but also transferred it into 3-substituted propiolic-[¹-¹¹C]acid upon heating the reaction mixture at 40 °C for 5 min with excellent radiochemical yield (RCY, [¹¹C]7a-b, e-f, ranging from 72.4 to 98.5%); all radiochemical yields displayed for the rest of work were determined by multiplying the radiochemical purity as determined by HPLC times isolated radioactivity divided by the starting [¹¹C]CO₂ (decay corrected), unless stated otherwise despite the difference in functional groups (either electron withdrawing or donating) and their positions in the phenyl ring (ortho, para, or meta). The replacement of DMSO with DMF was
less impactful for the $^{11}$C-carboxylation (3-(4-bromophenyl) propiolic-$[1-^{11}$C]acid, $[11$C]7c, yield = 66.5 ± 11.8%). In addition, the $^{11}$C-carboxylation conditions were also adaptable with naphthalenyl (6g), 3-thienyl (6h), methyl, and ethyl esters (6i and 6k), and chloropropyl groups (6j) attached ethynyltrimethylsilanes and all reagents provided the corresponding 3-substituted propiolic-$[1-^{11}$C]acids, $[11$C]7g-k, with excellent yields as well. Decreasing the amount and concentration of precursor (6k, 0.05 mmol and 0.167 M vs 6i, 0.25 mmol and 0.33 M) only slightly decreased the incorporation of $[11$C]CO$_2$ into the desired 3-substituted propiolic-$[1-^{11}$C]acid (yields of $[11$C]7l and $[11$C]7k, 95.8 ± 4.0% vs 87.7 ± 7.5% (5).

To further demonstrate the versatility of this $^{11}$C-carboxylation method, we explored the amenability of a quick conversion of $^{11}$C-carboxylic acids into their ester and amide derivatives (Fig. 2). The desired product, 3-pyridyl attached methyl $[1-^{11}$C]propiolate, $[11$C]9, was formed with a $28.0 ± 2.6%$ yield without any optimization of reaction conditions by the $^{11}$C-carboxylation reaction of alkynyltrimethylsilanes, 7l, followed with the methyl esterification by adding methyl iodide (0.75 mmol) to the same reaction vial and heating at 40 °C for 5 min. The transformation of $^{11}$C-carboxylic acid into carboxamide was also exemplified by smoothly converting $[11$C]carboxylic acid, $[11$C]7f, to its benzylamide derivative, $[11$C]9. As an intermediate, $[11$C]7f was first purified using solid phase extraction (SPE) technique with a C18 plus cartridge. The radioactivity was then eluted from the cartridge using THF into a second reaction vial, and reacted with a N-hydroxysuccinimide (HOSu) and dicyclohexylcarbodiimide (DCC) at 60 °C for 5 min. The desired benzylamide derivative, $[11$C]9, was formed by adding benzylamine (1.0 mmol) and heating the reaction mixture at 60 °C for 5 min with an overall yield of 20.6%.

Upon successful addition of the $^{11}$C-carboxylate moiety at sp-hybridized alkynyl carbons, we immediately turned our focus to different organosilane substrates, specifically trimethylsilyl (TMS) groups attached at the sp$^2$-hybridized carbon, for synthesizing $^{11}$C-carboxylic acids using FMDS $^{11}$C-carboxylation approach (Fig. 3). Unlike the synthesis of various $^{11}$C-propriolic acids, in which the reaction parameters required minor variation, the reaction temperature for the synthesis of different aryl/heteroaryl $^{11}$C-carboxylic acids, $[11$C]11, had to be modified significantly. Acetophenone ester trimethylsilyl ether, 10a, similar to silyl enol ether 4, displayed high reactivity and the β-carbonyl $[11$C]carboxylic acid, $[11$C]11a, was obtained with a $71.3 ± 15.1%$ yield under similar reaction conditions as propiolic-$[1-^{11}$C]acids, with only a change of solvent to DMF. The di- and tri-halide substituted trimethylsilylbenzene, 10b and 10c, displayed high propensity to convert to the corresponding $[11$C]benzoic acids, $[11$C]11b and $[11$C]11c with excellent conversion yields. The substrate reactivity dropped significantly when the halide groups were moved from ortho- to meta-positions and when one fluoride was changed to bromine ($[11$C]11c vs $[11$C]11d, 60 °C, 5 min, 84.6 ± 4.3% vs 170 °C, 8 min, 18.8 ± 1.8%).$24 The removal of one bromide group from meta- position further decreased the reactivity of the substrate and the reaction temperature had to be increased to 180 °C to maintain comparable reaction yields ($[11$C] 11e, 19.4 ± 7.1%). The change of the bromide group from meta- to para- position further reduced reaction yields and only 11.1 ± 1.8% of the desired 4-bromo-$[1-^{11}$C]benzoic acid, $[11$C]11f, was obtained under the same reaction conditions.
When trimethylsilylbenzene, 10g, was tested, only 1.4% of desired [11C]benzoic acid, [11C]11g, was observed at extreme conditions (200 °C, 8 min) and no product was detected at lower reaction temperature (150 and 160 °C). The other indolent substrate, (1-naphthyl)trimethylsilane, 10h, showed slightly better reactivity under the same conditions and [11C]11h was obtained with a 5 ± 2.6% yield at lower reactant concentration (0.167 M vs 0.33 M). A similar trend in reactivity was found when pyridyltrimethylsilanes were tested as substrates for 11C-carboxylation (Fig. 3). With the more electron-withdrawing group, fluoro, attached at the ortho-position, the substrate 10i clearly showed higher reactivity (80 °C, 8 min, 20.3 ± 6.0% [11C]11i) than substrate 10h, which has a less electron negative chloride atom substituted at meta-position of the TMS group (160 °C, 8 min, 22.8 ± 2.0% [11C]11j)). Without the chlorine substitution, 2-trimethylsilylpyridine, 10k, clearly showed weaker reactivity and the product [11C]11k was obtained in lower yields under the same reaction conditions as [11C]11j (160 °C, 8 min, 13.2 ± 2.3%). The other two heteroaryl trimethylsilanes also presented dramatically different reactivity: 2-trimethylsilylbenzo[b]thioazole, 10l, displayed a high propensity to form [11C]11l (r.t., 2 min, 74.9 ± 6.2%). While 2-[(tert-butylimidazol-1-yl)dimethylsilane 10m, exhibited low reactivity with only a 6.5% of the desired [11C]11m even when the reaction mixture was heated to 200 °C for 8 min (only 1.3% [11C]11m was detected with reaction mixture was heated to 160 °C for 8 min).

Following the exploratory synthesis of various aryl and heteroaryl 11C-carboxylic acids, we further extended our investigation to employ FMDS strategy for 11C-carboxylation using organosilanes with the TMS group attached at the sp2-hybridized carbon (Fig. 4). Three benzylsilanes showed similar reactivity with or without bromine substituted in the aromatic ring (12a and 12b vs 12c) and these reactions (120–140 °C, 5–8 min) gave the desired [11C]phenylacetic acids ([11C]13a–c) with good yields (54–72%)28. Remarkably, two other benzyltrimethylsilane type substrates, (9-trimethylsilyl)fluoroacetic acid, [11C]13d, and bis(1H-inden-1-yl)dimethylsilane 12e, gave corresponding 11C-carboxylic acids, [11C]13d–e, with excellent yields even at ambient temperature. A large variation in RCY was seen for methyltrimethylsilanes bearing a variety of substitutions (12f–k, Fig. 4). Trifluoromethyl trimethylsilane 12f displayed extremely high reactivity and 11C-carboxylation had to be performed using extreme conditions, i.e., the collection of [11C]CO2 was processed at −78 °C using THF as the solvent. After [11C]CO2 trapping, the reaction vessel was maintained at room temperature (r.t.) for 2 min to afford over 90% conversion of [11C]CO2 to the desired [11C]trifluoroacetic acid, [11C]13f. The extended reaction time (from 2 to 5 min) at r.t. was detrimental to the reaction with a reduced yield of 19%. When dichloromethyltrimethylsilane, 12g, was tested, both the collection of [11C]CO2 and the reaction were maintained at r.t. and the reaction solvent was switched to a dual solvent system (THF/DMF, 2/1, v/v) to afford [11C]dichloroacetic acid, [11C]13g, with a yield of 39.2 ± 10.7%. The substrate Ethyl 3-(trimethylsilyl)acetate, 12h, needed to be maintained at 40 °C for 5 min to provide monoethyl [1-11C]malonate, [11C]13h, with an excellent yield (95.5 ± 0.7%). Interestingly, phenylsulfonyl and phenylthio substituted methyl trimethylsilanes, 12i and 12j, showed quite different reactivity toward 11C-carboxylation. The former gave desired product, [11C]13i, with a 86.6 ± 21.4% yield at 60 °C for 5 min. The latter, however, displayed moderate reactivity and provided desired phenylthio substituted [1-11C]acetic acid, [11C]13j, with only a 18.8 ± 2.7% yield even when heated at 100 °C for 5 min. It was found that the allyltrimethylsilane derivative, 12k, was less reactive, as the reaction mixture had to be heated to 160 °C for 8 min to produce the corresponding 11C-carboxylic acid, [11C]13k, with a 19.3 ± 1.8% yield.

Fig. 3 FMDS [11C]-carboxylation with sp2-hybridized carbon attached trimethylsilanes. *Solvent DMF (0.25 mL) + THF (0.5 mL), precursor is sp2-hybridized carbon attached silyl enol ether; **Precursors are highly moisture sensitive; ***There was no detected product at 150 and 160 °C; ****Precursor 10 mg (0.05 mmol) in DMF (0.3 mL) (**).
The different reactivity of sp-, sp²-, and sp³-carbon attached organosilanes used in FMDS ¹¹C-carboxylation reactions can be explained by the pK_a value of the conjugate acid of the fluoride-desilylation generated anionic nucleophile. The carbanions generated by FMDS process can be assigned to three groups based upon the pK_a values of their conjugate acids: Group 1 (pK_a ~20–35) usually form stabilized anions and display high reactivity. Trimethylsilanes (4, 6, 10a-c, 10l, 12d-i) all belong to this category. Group 2 (pK_a ~35–45) includes carbanions attaching one weakly anion stabilizing group such as allyl, benzyl, and heterocyclic benzyl analogs, and phenylthiomethyl. Aryl groups bearing one or more electron-withdrawing substituents formed carbanions also can be included in Group 2. Trimethylsilane substrates (10d-f, 10i-k, 12a-c, and 12j-k) could be categorized in this group. Last, group 3 contains very weakly stabilized anions (pK_a values of their conjugate acids is usually >45). The examples in our study, such as 10g-h and 10m, can be assigned to this category and usually gave minimal (<10% RCY or non-detectable) desired ¹¹C-carboxylic acids.

**Extension of FMDS ¹¹C-labeling approach for ¹¹C-methylation.**

Bolstered by the success of using FMDS ¹¹C-carboxylation strategy to synthesize various ¹¹C-carboxylic acids and their derivatives, we next attempted the translation of this radiolabeling approach for ¹¹C-methylation. Since methyl iodide (CH₃I) and methyl triflate (CH₃OTf) are much better electrophiles compared with the chemically inert CO₂, we assumed that FMDS ¹¹C-carboxylation approach should be easily adaptable for ¹¹C-methylation and the following results supported our speculation. We started exploration of ¹¹C-methylation using FMDS approach, again, from the protocol reported by Noyori in 1983. After screening various experimental conditions (Table 1), it was found that the combination of [¹¹C]CH₃I/CsF/DMF (Table 1, entry 4) was the optimal choice compared with the more reactive [¹¹C] CH₃OTf (Table 1, entry 3) or the more labile fluoride source TASF (Table 1, entry 1 and 2). The silyl enol ether, 4, converted to the desired ⁴⁻¹¹C butanone, [¹¹C]14, with a 43.7 ± 16.4% yield while maintaining the reaction at r.t. for 2 min after the collection of [¹¹C]CH₃I to the reaction vial (Table 1, entry 4).

With the initial CsF/DMF/[¹¹C]CH₃I conditions defined, we next evaluated the scope of FMDS ¹¹C-methylation using a variety of organosilane reagents (Fig. 5). All phenoxyssilane substrates that were tested gave good to excellent ¹¹C-methylation yields under mild reaction conditions despite the variation of electron-donating (15d-e), neutral (15a) or withdrawing (15b, 15b′, 15c, 15f-g) groups attached at the phenyl ring. The change of tert-butyldimethylsilyl (TBDMS) to trisopropylsilyl (TIPS) (15b vs 15b′) had minimal impact upon the labeling yields (81.9 ± 1.2% [¹¹C]16b vs 85.7 ± 8.4% [¹¹C]16b). Even the precursor, 15b, with a phenyl ring that possessed three functional groups afforded excellent reaction yields (81.8 ± 2.7% [¹¹C]16b). The naphthyl group containing compound tert-butyldimethylsilylethynylsilane, 15i, was labile under the reaction conditions. The reactions formed large amount of radioactive by-products even with reactions at r.t. for 5 min and only gave a moderate yield (42.9 ± 13.8% [¹¹C]16i). The trimethylphenylsilylethynylsilane, 15j, on the contrary, provided excellent yields (91.3 ± 6.2% [¹¹C]16j) under the same reaction conditions. Benzoxyltrimethylsilane, 15k, displayed moderate reactivity and the radiolabeling yield only reached 32.7 ± 5.5% ([¹¹C]16k) when the reaction mixture was heated at 100 °C for 5 min. Both N- trimethylsilyl substituted substrates gave excellent labeling yields (92.4 ± 2.0% [¹¹C]16l and 93.4 ± 3.1% [¹¹C]16m) despite quite different reaction conditions (80 °C vs r.t.). The substrate 15n (which is the same as 10m) displayed excellent reactivity and labeling reactions were performed at r.t. for 5 min to afford 2-(methyl-¹¹C)benzo[d]thiazole [¹¹C]16o with a 50.1 ± 8.8% yield. Using the semi-prep HPLC for purification, [³⁻¹¹C]ibuprofen, [¹¹C]16o, was obtained with a 26.6 ± 0.6% yield (based upon the product separated from semi-prep HPLC) from a triethylsilylethynylsilane (TES) group attached compound 15o after ¹¹C-methylation at 40 °C for 5 min and saponification by 4 M NaOH. Similar to the synthesis process of [⁴⁻¹¹C]butanone [¹¹C]14, Acetophenone enol trimethylsilyl ether, 15p (same as 10a), was employed as the precursor and TASF as the fluoride reagent, the desired product [³⁻¹¹C]propiophenone, [¹¹C]16p, was synthesized with a 68.2 ± 8.9% yield (based upon the product separated from semi-prep HPLC).

The significance of our FMDS ¹¹C-labeling method was not only demonstrated by the successful synthesis of thirty...
seven different $^{11}$C-carboxylic acids, but also exemplified by the in situ quick and smooth conversion of the $^{11}$C-carboxylic acids to their methyl ester and benzylamide derivatives. Additionally, we have readily extended this method to the $^{11}$C-methylation process. The robustness of FMDS $^{11}$C-methylation approach was illustrated by fast and facile synthesis of seventeen different $^{11}$C-methylated compounds with diversified structures by selectively attaching [$^{11}$C]CH$_3^+$ group to the specific position (oxygen, sulfur, nitrogen and carbon atoms) of these molecules.

**Exploratory synthesis of three radiotracers.** As a final demonstration of the strength of FMDS $^{11}$C-labeling method and its feasibility for practical radiotracer production, in addition to the aforementioned cGMP-compliant production of [$^{11}$C]AcAc ([11C]3), we further explored the practical synthesis of three $^{11}$C-labeled organic molecules, ([11C]raclopride [11C]18, [11C]succinic acid [11C]19, and [11C]dichloroacetic acid [11C]13g), which are of biological and clinical interest but synthetically challenging molecules. To facilitate the regular production and the

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**Table 1 FMDS $^{11}$C-methylation reaction conditions screening.**

| Entry | Fluoride source | [$^{11}$C]Methylation agent and solvent(s) | RCY (%) |
|-------|-----------------|------------------------------------------|---------|
| 1     | TASF            | [$^{11}$C]CH$_3$OTf, THF/DCM (0.5 mL/0.25 mL) | 12.7%   |
| 2     | TASF            | [$^{11}$C]CH$_3$I, THF/DCM (0.5 mL/0.25 mL) | 40.7%   |
| 3     | CsF             | [$^{11}$C]CH$_3$OTf, DMF (0.75 mL) | 26.6%   |
| 4     | CsF             | [$^{11}$C]CH$_3$I, DMF (0.75 mL) | **43.7 ± 16.4%**, *n* = 3 |

*Fig. 5 FMDS $^{11}$C-methylation.* a Tert-Butyldimethylsilyl (TBDMS) group attached compounds as labeling precursors; b Triisopropylsilyl (TIPS) group attached compound as labeling precursor; c Triethylsilyl (TES) group attached ethyl ester as labeling precursor; [11C]CH$_3$I was collected at r.t., 3 min, then 40 °C, 2 min; Next saponification: 4 M NaOH, 120 °C, 5 min; products were purified by semi-prep HPLC. d TASF was used as fluoride source, THF (0.5 mL)/DCM (0.25 mL) was used as solvent, [11C]CH$_3$I was collected at −40 °C, 3 min, reaction mixture was left at r.t., 2 min, products were purified by semi-prep HPLC; starting radioactivity of [11C]CH$_3$I: 7.3 ± 2.67 GBq; total synthesis time: 37.7 ± 1.2 min; radiochemical purity (RCP) > 99% and A$_{nm}$: 29.7 ± 10.9 GBq/µmol (end of bombardment, EOB).
purification process of these tracers, a lower amount of organo-silane substrate (5 mg) was used for the synthesis of these radiotracers. Raclopride is a dopamine D2/D3 receptor antagonist and its carbon-11 labeled isotopologue, [11C]raclopride ([11C]18), is commonly produced as a PET tracer in many PET radiochemistry facilities (Fig. 6a) for evaluating the density or occupancy of the D2-dopamine receptor. Although the [11C]ethyl iodide based N-ethylation method had been reported before for synthesizing this tracer at its early development stage37, the phenox y group 11C-methylation method using [11C]CH3I/11C]CH3OTf as the radiosynthon has become the regular synthesis method for routine production of this clinically important tracer38,39, although the 11C-carbonylation method was also intensively investigated40. In this research, FMDS 11C-methylation approach was successfully implemented to synthesize this tracer. Using dual TBDMS attached precursor 17, the 11C-labeling and in situ deprotection of TBDMS group produced [11C]raclopride, [11C]18, with 27.8 ± 2.2% yield after purification through the solid phase extraction (SPE) method, which is lower than reference reported methods37-40. Further optimizations in the future, such as changing TBDMS group to more labile TMS or TES groups and therefore decreasing 11C-methylation reaction temperature, should help us to improve the production yield.

Succinic acid is an endogenous dicarboxylic acid which had been identified as an oncometabolite41. Carbon-11 labeled succinic acid may have the potential to map the metabolic process of cancer cells and help cancer diagnosis, staging and re-staging41,42. Carbon-11 labeled dicarboxylic acids were synthesized by nucleophilic 11C-cyanation and followed by basic hydrolysis43. However, this method requires an additional process of cancer cells and help cancer diagnosis, staging and re-staging. In this study, the 4-ethoxy-4-oxobut-2-ynoic-[1-11C]acid, [11C]19, was first synthesized by FMDS 11C-carboxylation method (described in Fig. 2). After two quick and efficient SPE purifications to remove unreacted [11C]CO2, CsF and solvent, etc., the 11C-intermediate, [11C]7k, was eluted to the second reaction vial and mixed with Al-Ni alloy in basic solution for alkyne reduction (50 °C, 5 min)44. The desired [11C]succinic acid, [11C]19, was obtained with a 50.1 ± 12.3% yield (Fig. 6b) following acidification and filtration through a celite plug.

Dichloroacetic acid (DCAA) is a small halogenated acetic acid analog, it can affect cancer cell metabolism and antagonize its growth by inhibiting mitochondrial pyruvate dehydrogenase kinases. DCAA has been investigated clinically for the treatment of various cancers (including brain, colon, breast, colorectal, and skin cancers). Its therapeutic applications and intriguing pharmacological properties have attracted a lot of attention from medical researchers45,46. The combination of PET imaging technique and 11C-labeled DCAA, potentially, could facilitate researchers' understanding of in vivo metabolic processes and pharmacokinetics of this low-price, low toxicity and promising cancer drug candidate. Employing FMDS 11C-carboxylation protocol for synthesis of [11C]13g (Fig. 4) followed by a quick SPE workup and semi-prep HPLC purification process, with only 5 min cyclotron beam time (producing 11.8 ± 4.2 GBq starting [11C]CO2 radioactivity), we obtained 1.1 GBq of the desired [11C] DCAA, [11C]13g, (RCY, 31.8 ± 3.1%) with over 99% radio-chemical purity in a 35.7 ± 3.2 min synthetic process (Fig. 6c). The product had \( A_{\text{m}} = 71.7 ± 18.1 \) GBq/µmol (EOB), which should be satisfactory for oncological imaging studies in humans.

**Discussion**

The development of a robust FMDS 11C-labeling strategy, although still in its early stages, opens up the potential for the synthesis of 11C-labeled organic carboxylic acids and their derivatives directly using [11C]CO2. The simplicity, high degree of reproducibility, and broad scope of the transformation of this approach, as showcased by the 11C-labeling of various biologically interesting organic molecules, makes it a promising approach in radiotracer chemistry. In addition, the expansion of FMDS 11C-labeling method using [11C]CH3I as a radiosynthon is a beneficial supplement to current [11C]CH3I/[11C]CH3OTf based radiochemistry. The further extension and application of FMDS 11C-labeling method to solve several long-standing problems in 11C-radiotracer chemistry will be reported in due course.
Methods

General procedures of \( ^{11}C\)CO\(_2\) production. \( ^{11}C\)CO\(_2\) was generated by bombarding \( N_2 \) gas (360 psi 99.9999% pure \( N_2 \) doped with 0.5% \( O_2 \) via the \( ^{14}N(p,a)\) \( ^{11}C \) nuclear reaction using a EBCO TR-19/9 cyclotron. General bombardment conditions: 2–40 min beam time with 25 \( \mu \)C current (3.7–44.4 GBq: 100–120 mCi). After the bombardment, target gas containing radioactivity was released and delivered to a home-made automated \( ^{11}C\)CO\(_2\) purification box for controlled trap and-release of the radioactive gas. Where the \( ^{11}C\)CO\(_2\) production was first trapped by water cooled MS (MS) furnace at room temperature (200 mg molecular sieve 13X, 100/120 mesh, Supelco). Next, the furnace is heated to 190 °C and \( ^{11}C\)CO\(_2\) was released and delivered to the reaction vial using helium flow (10 mL/min). Once the radioactivity collected in the reaction vial plateaued, the delivery was stopped and \( ^{11}C\)CO\(_2\) production and collection was done. It took 3–4 min from end of bombardment (EOB) to end of the collection of \( ^{11}C\)CO\(_2\) in the reaction vial.

General procedures of FMDS \( ^{11}C\)-carboxylation reaction. Once the \( ^{11}C\)CO\(_2\) was ready, the \( ^{11}C\)CO\(_2\) delivery line with a 4-inch needle was inserted into a reaction vial containing the anhydrous fluoride reagent and solvent reaction mixture. The vial was equipped with outlet line (an ascarite trap was attached at the outlet line) and the reaction mixture was checked again as starting radioactivity. After the bombardment, target gas containing radioactivity was released and delivered to a home-made automated \( ^{11}C\)CO\(_2\) purification box for controlled trap and-release of the radioactive gas. Where the \( ^{11}C\)CO\(_2\) production was first trapped by water cooled MS (MS) furnace at room temperature (200 mg molecular sieve 13X, 100/120 mesh, Supelco). Next, the furnace is heated to 190 °C and \( ^{11}C\)CO\(_2\) was released and delivered to the reaction vial using helium flow (10 mL/min). Once the radioactivity collected in the reaction vial plateaued, the delivery was stopped and \( ^{11}C\)CO\(_2\) production and collection was done. It took 3–4 min from end of bombardment (EOB) to end of the collection of \( ^{11}C\)CO\(_2\) in the reaction vial.

FMDS11C-methylation reaction since unreacted \( ^{11}C\)CH\(_3\)I or by-product \( ^{11}C\)CH\(_3\)OH dissolved well in the reaction mixture. However, it was found that the value of \( A_0 \) was slightly less than the value of \( A_0 \) after decay correction in some experiments. It is most likely because of the small leakage of \( ^{11}C\)CH\(_3\)I or by-product \( ^{11}C\)CH\(_3\)OH from reaction vial. A small portion of reaction mixture (0.1 mL) was removed and diluted with an acidic solution (CH\(_3\)CN/1% formic acid, 90/10) in a septum sealed glass vial the radioactivity of this sample was counted and recorded. Next, an analytical sample, which was a mixture of an aliquot of sample solution (usually 10 \( \mu \)L) and a product standard solution (usually 10 \( \mu \)L, 1mg/mL solution), was analyzed by analytical HPLC. The percentage of radio-peak in radiochromatogram coincident with the product reference UV peak was regarded as radiochemical purity (RCP) and also as radiochemical yield (RCY, decay corrected) if \( A_\text{prod} = A_0 \) or RCY = RCP × (\( A_\text{prod} / A_0 \)) at the case of \( A_\text{prod} < A_0 \). If the reaction mixture was submitted for the purification process (solid phase extraction, semi-prep HPLC, anion/cation resins exchange method, or the combination of two of these methods), the total amount of radioactivity of purified product was regarded as \( A_\text{prod} \). The radiochemical yield (RCY, decay corrected) was calculated as \( A_\text{prod} / A_0 \) × 100%. Total synthesis times were calculated from EOB to the end of radioactive product collection after the purification.

Molar activity \( (A_0) \). \( A_0 \) values, decay corrected back to EOB and recorded in GBq/\( m\)ol, were determined from the carbon-11 activity in the HPLC product peak and the mass of compound.

Data availability

Complete experimental procedures and compound characterization data are available in the Supplementary Information, or from the corresponding author upon request.

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