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Nucleophilic (Radio)Fluorination of α-Diazocarbonyl Compounds Enabled by Copper-Catalyzed H–F Insertion

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Supporting Information

ABSTRACT: The copper-catalyzed H–F insertion into α-diazocarbonyl compounds is described using potassium fluoride (KF) and hexafluoroisopropanol. Access to complex α-fluorocarbonyl derivatives is achieved under mild conditions, and the method is readily adapted to radiofluorination with [^{18}F]KF. This late-stage strategy provides an attractive route to ^{18}F-labeled biomolecules.

Methods for the construction of C–F bonds are of high synthetic value due to the broad applications of organofluorine compounds as pharmaceuticals, agrochemicals, and materials.[1] Additionally, strategies to incorporate fluorine-18 into organic molecules are important for the synthesis of radiotracers for positron emission tomography (PET), a minimally invasive molecular imaging technology used in diagnostic medicine and clinical pharmaceutical research.[2] The demand for increasingly complex radiotracers has stimulated the development of late-stage fluorination strategies.[3] Although PET applications are frequently cited as a rationale for the identification of these new fluorination techniques, the successful translation of contemporary fluorination approaches to practical and valuable radiofluorination protocols remains a critical challenge.[4] In addition to the inherent difficulties associated with forming C–F bonds,[5] several unique obstacles must be addressed to translate a fluorination reaction to the ^{18}F-radionuclide counterpart. Methods must use fluoride as a limiting reagent and take place rapidly, owing to the low available concentrations (nM to μM) of the short-lived ^{18}F-radioisotope (half-life = 110 min).[2] Additionally, the radiochemical protocol should proceed with high specific activity and be amenable to automation or use by nonspecialists.

To address these challenges, we sought to design a new catalytic method for the synthesis of α-fluorocarbonyl compounds that would enable late-stage fluorination and translate readily to radiosynthesis. Among medicinally relevant fluorinated molecules, the α-fluorocarbonyl motif is prevalent and serves as a versatile building block for the construction of numerous aliphatic fluorine-containing structures (Figure 1A).[5] Many highly selective catalytic methods have been identified for the synthesis of α-fluorocarbonyl derivatives using electrophilic fluorine sources.[3,6] However, these strategies are not well suited for radiofluorination in a clinical setting because electrophilic fluorination reagents generally suffer from low specific activity.[7] The α-[^{18}F]fluorocarbonyl scaffold is featured heavily in PET tracers, in part as a tag for labeling biomolecules such as peptides,

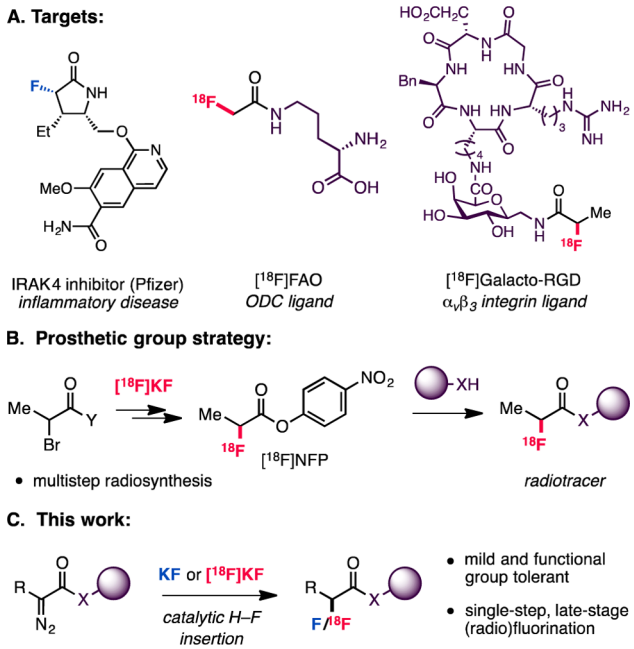

Figure 1. (A) α-Fluorocarbonyl-containing bioactive targets. (B) Multistep assembly of complex radiotracers using an α-fluoroacyl prosthetic group. (C) Catalytic (radio)fluorination of α-diazocarbonyl compounds.

which are desirable as PET probes due to their binding specificity.[8] Typically, C–^{18}F bonds are formed by nucleophilic substitution with [^{18}F]KF in the presence of phase transfer reagent Kryptofix 2.2.2 (K_{222}). While this approach takes advantage of nucleophilic fluoride as a readily available, high specific activity source of fluorine-18, the harsh conditions necessary for substitution (high temperatures and basicity) are not suitable for the direct radiofluorination of most α-[^{18}F]-fluorocarbonyl targets.[9] Instead, an indirect method is pursued wherein fluorine-18 is first introduced into a reactive precursor, such as activated ester [^{18}F]NFP, and then into the compound of interest (Figure 1B).[2b] This prosthetic group strategy necessitates multiple radiochemical steps, highlighting the limitations of classic nucleophilic substitution with [^{18}F]KF. Identification of catalytic schemes for α-fluorocarbonyl synthesis that use

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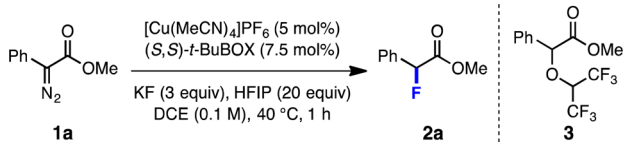
nucleophilic fluoride, tolerate biologically relevant functionality, and are amenable to radiofluorination would enable the radiosynthesis of previously challenging or inaccessible PET tracers in a single step. Furthermore, such methods could prove complementary in scope to known electrophilic fluorination reactions.

Here we report the development of a copper-catalyzed fluorination of α-diazocarbonyl compounds with KF (Figure 1C). This reaction facilitates the direct installation of fluorine-19 and fluorine-18 into advanced substrates under mild and functional-group-tolerant conditions. We chose to investigate α-diazocarbonyl compounds as precursors to α-fluorocarbonyl derivatives since the diazo functionality is known to react rapidly with transition metals to form electrophilic metal carbenoids that can insert into carbon−hydrogen, carbon−heteroatom, and heteroatom−hydrogen bonds under mild conditions.[10] Although this approach has become a powerful tool to forge new C−X (X = C, Si, N, O, S) bonds regio- and stereoselectively,[11] the catalytic insertion into halogen−hydrogen bonds has not been reported. The Davies group has recently described a silver-catalyzed fluorination of vinyl diazoacetates with $Et_3N{\cdot}3HF$, but this transformation yields γ-fluoro-α,β-unsaturated carbonyl compounds rather than fluorinating at the carbenoid position.[12] Direct fluorination of α-diazocarbonyl substrates may be accomplished with highly reactive and acidic HF-containing reagents.[13−16] Only simple, unfunctionalized substrates are tolerated, however, and translation to PET applications is challenging.[17]

As an alternative to using stoichiometric HF or HF-containing reagents, we envisioned accessing the reactive equivalent from the combination of a mild fluoride reagent and proton source. Initial experiments were conducted using diazoacetate **1a** as a model substrate with a copper(I) catalyst and a commercially available bis(oxazoline) ligand **L1** (Table 1). Previously, our laboratory reported the enantioselective hydrofluorination of epoxides and aziridines using benzoyl fluoride (PhCOF) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a latent HF source.[18] For the HF insertion chemistry, this combination yielded the desired α-fluoroester **2a** (entry 2); however, since [^{18}F]PhCOF is not readily accessible, we evaluated other reagents that offer more convenient sources of fluorine-18. Promisingly, the combination of KF and HFIP provided the desired product in 68% yield (entry 1).

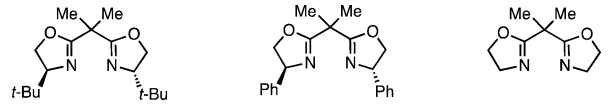
Interestingly, HFIP is necessary for productive chemistry (entry 4). Deuterium-labeling experiments indicate the OH proton of HFIP is incorporated into the product; however, other proton sources with similar pK_as are inadequate substitutes (entries 5 and 6), suggesting an additional role for HFIP. Although HFIP is considered a poor nucleophile,[19] competitive O−H insertion (**3**) is observed as the major side product, along with dimerization of the diazo substrate.[20] Counterintuitively, the yield and selectivity of the reaction are significantly improved by increasing the equivalents of HFIP (entries 7 and 8). We hypothesize HFIP solvates the otherwise insoluble KF and increasing HFIP concentration alters the solvent coordination environment of fluoride, leading to a more reactive species. This finding appears related to the influence of *t*-BuOH on reactions with TBAF[21] and may prove useful for enhancing the reactivity of other fluorination reactions using KF. The reaction is less efficient with other commercial bis(oxazoline) ligands such as **L2** and achiral ligand **L3** (entries 9 and 10). Evaluation of other transition metal catalysts indicated that Cu(I) is most effective, as $Rh_2(OAc)_4$ delivered **2a** in modest yield (entry 11).[22] Although

Table 1. Reaction Optimization



entry	conditions	Yield **2a**[a] (%)	Yield **3**[a] (%)
1	standard conditions	68[b]	2
2	PhCOF (2 equiv), HFIP (4 equiv), DBN (20 mol%) instead of KF/HFIP	64[c]	1
3	no Cu or ligand	1	4
4	no HFIP	0	n/a
5	TFE instead of HFIP	22	n/a
6	phenol instead of HFIP	7	n/a
7	HFIP (3 equiv)	39	35
8	HFIP (10 equiv)	64	5
9	ligand **L2** instead of **L1**	35[d]	15
10	ligand **L3** instead of **L1**	57	10
11	$Rh_2(OAc)_4$ instead of Cu/ligand	53	4
12	$[Cu(OTf)]_2$•PhMe instead of $[Cu(MeCN)_4]PF_6$	62[e]	2

[a]Determined by ^{19}F NMR, 0.1 mmol scale using fluorobenzene as an external standard. [b]9% ee, determined by chiral HPLC. [c]15% yield in the absence of Cu and ligand. [d]23% ee. [e]31% ee.



L1 (*S,S*)-*t*-BuBOX **L2** **L3**

the optimal conditions with $[Cu(MeCN)_4]PF_6$ and bis(oxazoline) **L1** afford **2a** in low ee, modest asymmetric induction is achieved using $[Cu(OTf)]_2{\cdot}$PhMe (31% ee, entry 12), demonstrating for the first time that enantioselective halogen−hydrogen insertion is feasible using transition metal catalysis.

With the optimized conditions in hand, we next explored the scope of this transformation and found that a variety of aryldiazoacetate substrates perform well (Table 2). Substitution around the aromatic ring is well tolerated (**2b−d**), including at the *ortho* position, which suppresses substrate dimerization. High yields of the desired products containing σ- and π-electron-withdrawing substituents (**2e−k**) are obtained, albeit with slightly longer reaction times or higher temperatures (**2g−i**). Electron-rich α-diazocarbonyl substrates are less effective under the reaction conditions; nevertheless, fluorinated products **2l**, **2m**, and **2o** are furnished in 30%, 46%, and 72% yields, respectively. Notably, many valuable functional groups are tolerated in the reaction, including azides (**2k**), silyl-protected alcohols (**2n**), and Lewis basic functionality (**2o**, **2p**). These results are significant as many of these common functional groups are not compatible with current electrophilic α-fluorination methods. Furthermore, this straightforward protocol is readily scalable, as **2i** was isolated in 89% yield in a multigram-scale reaction set up on the benchtop.[22]

The reaction is also generalizable to other α-diazocarbonyl precursors, including terminal diazoacetates (**2q**), diazoketones (**2r**), and diazoacetamides (**2s−2y**). Acceptor/acceptor α-diazoester compounds, however, are unreactive,[16b] and α-alkyl-α-diazoacetates predominately undergo elimination to afford α,β-unsaturated esters with only trace amounts of the desired fluorinated products.[22] To probe the scope of the reaction further,

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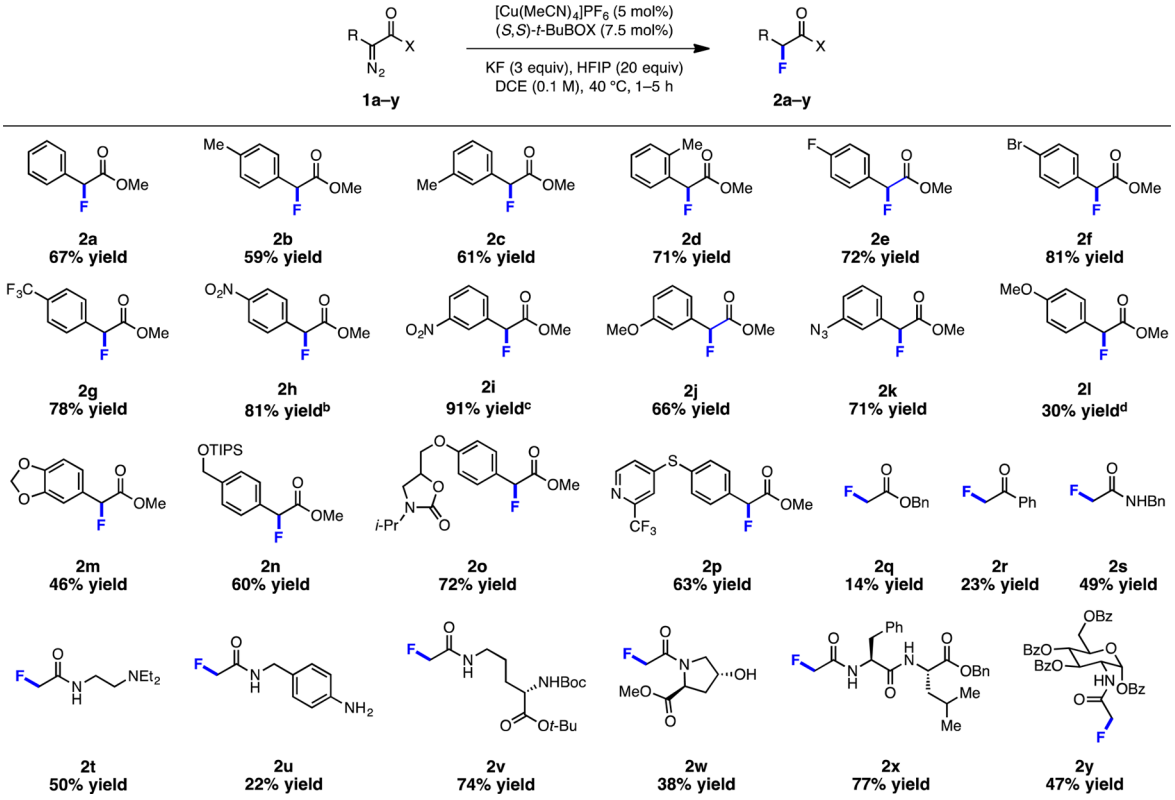
Table 2. Scope of Fluorination[a]



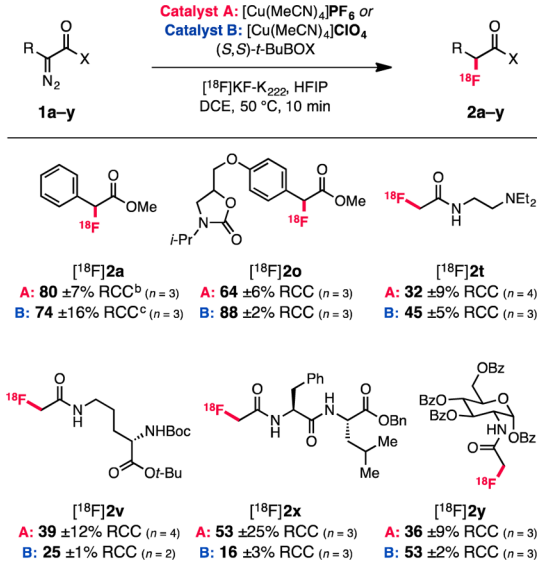
[a]Yields are the average of two runs, 0.18−0.5 mmol scale. [b]Reaction run at 50 °C for 24 h. [c]Reaction run at 45 °C. [d]Reaction run at rt.

we investigated the fluorination of α-diazo substrates derived from biologically relevant structures. Importantly, this approach provides access to fluorinated amino acid derivatives (**2v**, **2w**), peptides (**2x**), and glycosides (**2y**) bearing unprotected, protic amines (**2u**) and alcohols (**2w**). The exceptional functional group tolerance of these examples highlights the mildness of the reaction conditions and the potential for late-stage fluorination

We then sought to demonstrate the utility of this transformation by identifying a practical radiochemical protocol. By designing our reaction with KF, we envisioned this method would be readily adaptable to the direct, late-stage radiofluorination of α-diazocarbonyl compounds simply by applying $[^{18}F]$KF and K_{222} to our standard reaction conditions. Typically, radiochemical protocols differ substantially from their synthetic counterparts, and most syntheses employing $[^{18}F]$KF require high temperatures (>100 °C) for reactivity. Therefore, we were pleased to find substrate **1a** underwent radiofluorination in excellent radiochemical conversion (80% RCC) using the combination of $[^{18}F]$KF-K_{222} and HFIP at 50 °C (Table 3). Control experiments without copper or HFIP delivered no significant radiochemical conversion,[22] and the reaction conditions are remarkably similar to the ^{19}F-protocol.

Under these standard conditions, however, $[^{18}F]$**2a** was obtained in poor specific activity (24 mCi/μmol), suggesting at least one reagent other than KF contains labile fluoride. Consistent with previous reports,[23] we found that HFIP is not a significant fluoride source; yet, in the absence of KF, the hexafluorophosphate anion of the copper catalyst generates small amounts of product.[22] Replacing hexafluorophosphate with a perchlorate anion restores specific activity to 1300 mCi/μmol, a value consistent with other no-carrier-added radiofluorinations (Catalyst B in Table 3). Thus, for applications requiring high specific activity, $[Cu(MeCN)_4]ClO_4$ should be used in place of $[Cu(MeCN)_4]PF_6$.

Table 3. Radiofluorination Using $[^{18}F]$KF[a]



[a]RCC determined by radio-TLC and corrected for insoluble activity; identity of product confirmed by radio-HPLC. [b]Specific activity: 24 mCi/μmol EOB. [c]Specific activity: 1300 mCi/μmol EOB.

Based on these results and with insights gained from the ^{19}F-catalytic system, we interrogated the generality of the α-radiofluorination. Complex α-diazocarbonyl substrates were subjected to the procedure with $[^{18}F]$KF-K_{222}, and trends in the functional group tolerance of the ^{19}F-conditions were recapitu-

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lated in the radiofluorination (Table 3). Diazo esters and amides are competent in the reaction, and Lewis basic ([^{18}F]**2o**, [^{18}F]**2t**) as well as protic functionality on peptides ([^{18}F]**2x**) and glycosides ([^{18}F]**2y**) is compatible. Moreover, known radiotracer N^5-[^{18}F]FAO ([^{18}F]**2v**)[24] is readily accessible using this practical approach, as is the homologue of PET probe [^{18}F]FPDA ([^{18}F]**2t**).[25] Notably, the one-step copper-catalyzed radiofluorination is significantly higher yielding than the synthetic sequences previously reported in the literature: whereas [^{18}F]FPDA required installation of a prosthetic group over four radiochemical steps with 3% overall RCY,[25] [^{18}F]**2t** can be generated in 45% RCC in a single step. Likewise, N^5-[^{18}F]FAO, which was previously prepared by S_N2 displacement of bromide with 8% RCY,[24] can be labeled under our conditions in 39% RCC. This method establishes a strategic alternative for the radiofluorination of complex biomolecules via their diazoacetylated precursors.[26]

This work introduces a new method for catalytic C−F/^{18}F bond formation enabled by copper catalysis and the use of KF-HFIP as a reactive fluoride source. The approach generates useful α-fluorocarbonyl derivatives under mild reaction conditions and is compatible with a variety of valuable functional groups. Furthermore, by considering translation to fluorine-18 in our design and employing commonly used [^{18}F]KF-K_{222}, we are able to effect the one-step radiofluorination of biomolecules under operationally convenient conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06770.

Experimental procedures, additional reaction optimization, and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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