

Communication

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

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Supporting Information Placeholder

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 [¹⁸F]KF. This late-stage strategy provides an attractive route to ¹⁸F-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 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 ¹⁸F-radiionuclide counterpart. Methods must use fluoride as a limiting reagent and take place rapidly, owing to the low available concentrations (nM to μ M) of the short-lived ¹⁸F-radiosotope (half-life = 110 min).² Additionally, the radiochemical protocol should proceed with high specific activity and be amenable to automation or use by non-specialists.

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 radio-synthesis. Among medically 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 -[¹⁸F]fluorocarbonyl scaffold is featured heavily in PET tracers, in part as a tag for labeling biomolecules such as peptides, which are desirable as PET probes due to their binding specificity.⁸ Typically, C–¹⁸F bonds are formed by nucleophilic substitution with [¹⁸F]KF in the presence of phase transfer reagent Kryptofix 2.2.2. (K₂₂₂). 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 -[¹⁸F]fluorocarbonyl targets.⁹ Instead, an indirect method is pursued wherein fluorine-18 is first introduced into a reactive precursor, such as activated ester [¹⁸F]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 [¹⁸F]KF.

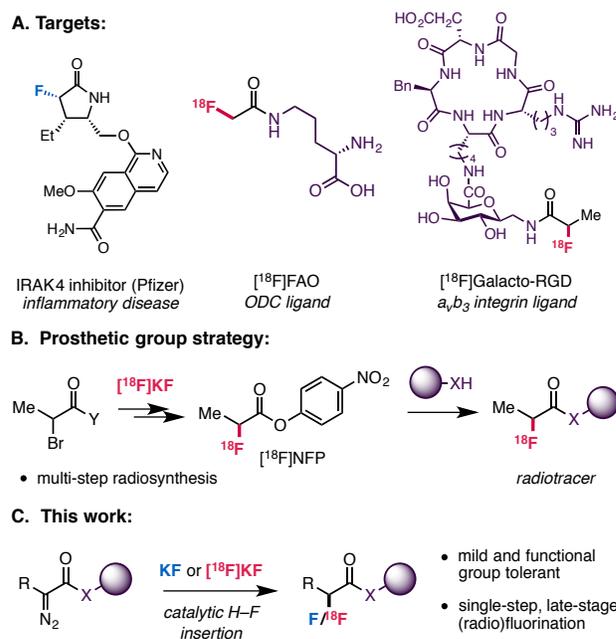


Figure 1. (A) α -Fluorocarbonyl-containing bioactive targets. (B) Multistep assembly of complex radiotracers using an α -fluoroacyl prosthetic group. (C) Catalytic (radio)fluorination of α -diazocarbonyl compounds.

Identification of catalytic schemes for α -fluorocarbonyl synthesis that use 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.

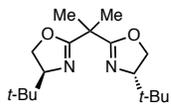
Here we report the development of a copper-catalyzed fluorination of α -diazocarbonyl compounds with KF (Figure 1C). This reaction facilitates the direct installation of fluorine-19 and fluorine-18 into advanced substrates under mild and functional group-tolerant conditions. We chose to investigate α -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 Et₃N•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 [¹⁸F]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).

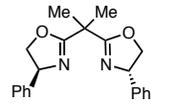
Interestingly, HFIP is necessary for productive chemistry (entry 4). Deuterium-labeling experiments indicate the OH proton of HFIP is incorporated into the product; however other proton sources with similar pK_as are inadequate substitutes (entries 5 and 6), suggesting an additional role for HFIP. Although 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 is significantly improved by increasing the equivalents of HFIP (entries 7 and 8). We hypothesize that HFIP solvates the otherwise insoluble KF and that 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 and may prove useful for enhancing the reactivity of other fluorination reactions using KF.²¹ 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 proved Cu(I) is most effective, as Rh₂(OAc)₂ delivered **2a** in modest yield (entry 11).²² Although the optimal conditions with [Cu(MeCN)₄]PF₆ and bis(oxazoline) **L1** afford **2a** in low ee, modest asymmetric induction is achieved using [Cu(OTf)₂]•PhMe (31% ee, entry 12), demonstrating for the first time that enantioselective halogen–hydrogen insertion is feasible using transition metal catalysis.

Table 1. Reaction optimization.

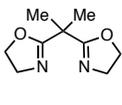
entry	conditions	Yield 2a ^a (%)	Yield 3 ^a (%)
1	standard conditions	68 ^b	2
2	PhCOF (2 equiv), HFIP (4 equiv), DBN (20 mol%) instead of KF/HFIP	64 ^c	1
3	no Cu or ligand	1	4
4	no HFIP	0	n/a
5	TFE instead of HFIP	22	n/a
6	phenol instead of HFIP	7	n/a
7	HFIP (3 equiv)	39	35
8	HFIP (10 equiv)	64	5
9	ligand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



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



L2

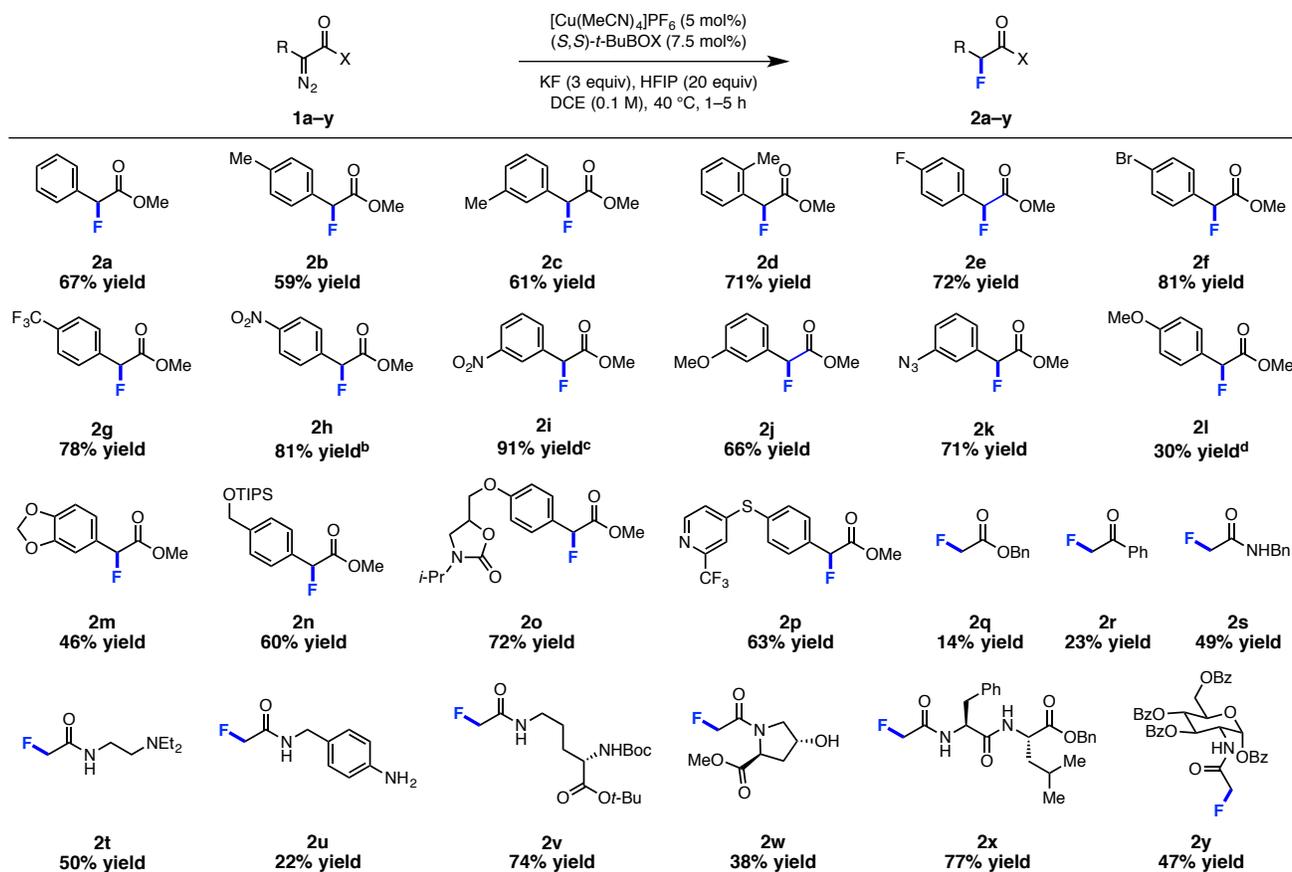


L3

^aDetermined by ¹⁹F NMR, 0.1 mmol scale using fluorobenzene as an external standard. ^b9% ee, determined by chiral HPLC. ^c15% yield in the absence of Cu and ligand. ^d23% ee. ^e31% ee.

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 multi-gram-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 predominantly 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, we investigated the fluorination of α -diazo substrates derived

Table 2. Scope of fluorination.^a

^aYields are the average of two runs, 0.18-0.5 mmol scale. ^bReaction run at 50 °C for 24 h. ^cReaction run at 45 °C. ^dReaction run at rt.

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

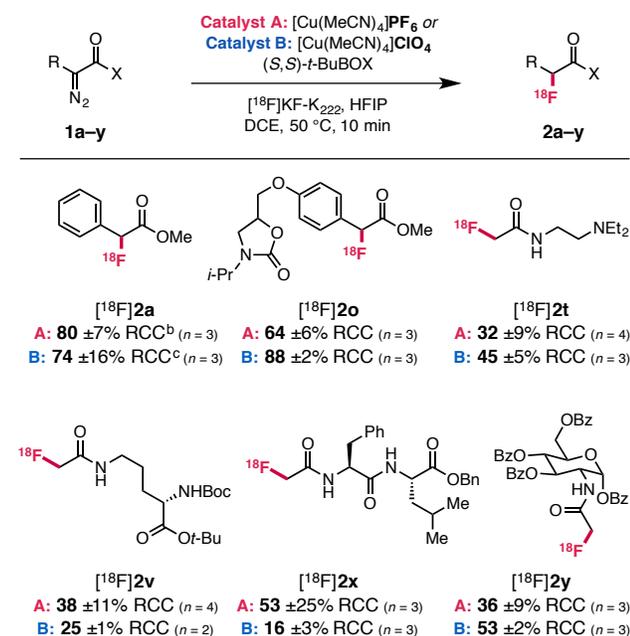
We then sought to demonstrate the utility of this transformation by identifying a practical radiochemical protocol. By designing our reaction with KF, we envisioned this method would be readily adaptable to the direct, late-stage radiofluorination of α -diazocarbonyl compounds simply by applying [¹⁸F]KF and K₂₂₂ to our standard reaction conditions. Typically, radiochemical protocols differ substantially from their synthetic counterparts, and most syntheses employing [¹⁸F]KF require high temperatures (>100 °C) for reactivity. Therefore, we were pleased to find that substrate **1a** underwent radiofluorination in excellent radiochemical conversion (80% RCC) using the combination of [¹⁸F]KF-K₂₂₂ and HFIP at 50 °C (Table 3). Control experiments without copper or HFIP delivered no significant radiochemical conversion, and the reaction conditions are remarkably similar to the ¹⁹F-protocol.

Under these standard conditions, however, [¹⁸F]**2a** was obtained in poor specific activity (24 mCi/ μ mol) suggesting that 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/ μ mol, a value consistent with other no-carrier-added radiofluorinations (Catalyst B in Ta-

ble 3). Thus for applications requiring high specific activity, [Cu(MeCN)₄]ClO₄ should be used in place of [Cu(MeCN)₄]PF₆.

Based on these results and with insights gained from the ¹⁹F-catalytic system, we interrogated the generality of the α -radiofluorination. Complex α -diazocarbonyl substrates were subjected to the procedure with [¹⁸F]KF-K₂₂₂, and trends in the functional group tolerance of the ¹⁹F-conditions were recapitulated in the radiofluorination (Table 3). Diazo esters and amides are competent in the reaction, and Lewis basic ([¹⁸F]**2o**, [¹⁸F]**2t**) as well as protic functionality on peptides ([¹⁸F]**2x**) and glycosides ([¹⁸F]**2y**) is compatible. Moreover, known radiotracer *N*⁵-[¹⁸F]FAO ([¹⁸F]**2v**)²⁴ is readily accessible using this practical approach, as is the homologue of PET probe [¹⁸F]FPDA ([¹⁸F]**2t**).²⁵ Notably, the one-step copper-catalyzed radiofluorination is significantly higher yielding than the synthetic sequences previously reported in the literature: whereas [¹⁸F]FPDA required installation of a prosthetic group over four radiochemical steps with 3% overall RCY, [¹⁸F]**2t** can be generated in 45% RCC in a single step. Likewise, *N*⁵-[¹⁸F]FAO, which was previously prepared by S_N2 displacement of bromide with 8% RCY, can be labeled under our conditions in 38% 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/¹⁸F 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

Table 3. Radiofluorination using [¹⁸F]KF.^a

^aRCC determined by radio-TLC and corrected for insoluble activity; identity of product confirmed by radio-HPLC. ^bSpecific activity: 24 mCi/μmol EOB. ^cSpecific activity: 1300 mCi/μmol EOB.

and employing commonly used [¹⁸F]KF-K₂₂₂, we are able to effect the one-step radiofluorination of biomolecules under operationally convenient conditions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional reaction optimization, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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25 examples with KF
up to 91% yield

6 examples with [¹⁸F]KF
up to 88 ±2% RCC