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Silver-Promoted (Radio)fluorination of Unsaturated Carbamates via a Radical Process

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Intramolecular fluorocyclization of unsaturated carbamates is described here using a hypervalent iodine reagent in the presence of silver catalyst. Both (hetero)aryl-substituted olefins and acrylamides can be utilized as effective substrates. Preliminary mechanistic investigations suggest the reaction proceeds via a cyclization/1,2-(hetero)aryl migration/fluorination cascade involving an unusual radical process. Furthermore, starting from no-carrier-added [^{18}F]TBAF, a simple one-pot, two-step cascade method was developed to generate ^{18}F-labeled heterocycles with high radiochemical purity.

The chemical, biological and physical properties of organic molecules can be significantly changed by introduction of fluorine atoms and thus organofluorine compounds are widely used in almost all aspects of chemical industry from pharmaceutical, medical, agrochemical, to material sectors.[1] Additionally, ^{18}F-labeled organic compounds enjoy broad use as positron emission tomography (PET) agents in diagnostic medicine and clinical pharmaceutical research.[2] Therefore, there is a significant need for the development of novel synthetic strategies providing easy access to complex fluorinated compounds.[3] In addition, due to the short half-life of ^{18}F, a late stage fluorination strategy would greatly simplify the synthesis of complex radiotracers from radiolabeling point of view.[4]

The intramolecular fluorocyclization of alkenes is an attractive transformation that constructs multiple bonds including a C–F bond in one step to form fluorinated cyclic structures,[5] which may serve as versatile building blocks for the construction of aliphatic fluorine-containing bioactive compounds.[1] Among the different methods that have been developed, fluorocyclization using electrophilic fluorinating reagents is one of most important approaches.[5,6] However, it is costly and often involves the use of fluorine gas to prepare the electrophilic fluorinating reagents, which restricted its applications in industry and laboratory especially in ^{18}F radiolabeling.[3,4] Additionally, electrophilic fluorination reactions generally suffer from low specific activity, which limits their applications in radiofluorination.[2] Recently, hypervalent iodine reagents have been used as very attractive fluorine sources in fluorocyclization reactions,[7] as they exhibit unique reactivity and can often be prepared from easily obtained, cheap fluorides. Although the reaction mechanism has not been elaborated in detail, an ionic pathway has been proposed to be involved in most of the reactions.[8] Alkyl olefins and styrene derivatives were utilized as efficient nucleophilic reagents in these reactions, but fluorocyclization of the substrates bearing electron-poor double bonds has not been reported.[7]

In this paper, we report a silver-promoted cyclization/1,2-(hetero)aryl migration/fluorination cascade using (hetero)aryl-substituted olefins and acrylamides as substrates and proceeding through a novel radical mechanism.[9] This methodology provides a straightforward approach to the preparation of various fluorinated or radiofluorinated oxazolidin-2-ones, oxazolidin-2,4-diones and 1,3-oxazinan-2-one under mild conditions.

Our initial test focused on using the air and moisture-stable fluoroiodine compound **1** as the fluorine source (Table 1).[10-12] Compound **1** has recently been exploited for the development of ionic fluorocyclization reactions of styrene and alkyl olefin derivatives.[11] Preparation of **1** involves fluoride and its chloro(OTs) analogue[10a,b] making it potentially applicable for no-carrier-added ^{18}F-radiofluorination. As shown in Table 1, starting from unsaturated carbamates (**2**), fluorinated oxazolidin-2-ones could be obtained, whose non-fluorinated analogues demonstrate very important bioactivities on treating bacterial infection.[13,14] For example, *N*-aryl-oxazolidin-2-ones are considered as a last resort treatment against gram-

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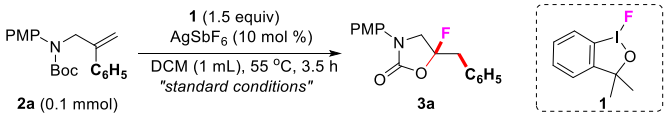
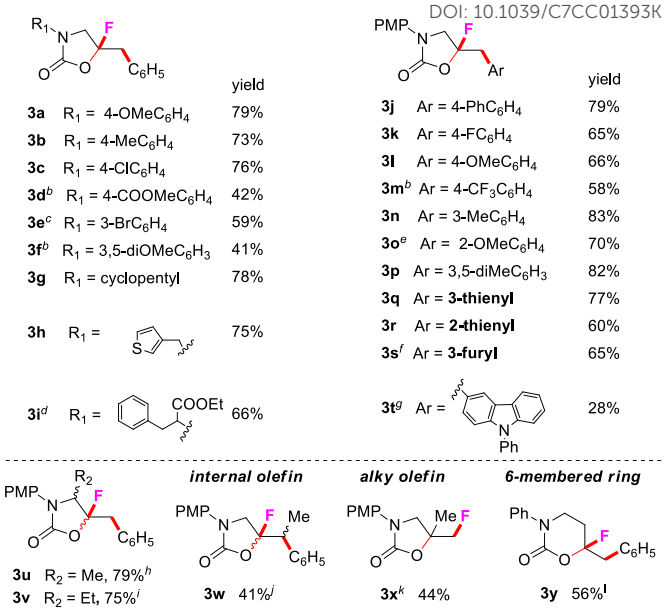
Table 1. Selected Results of Conditions Optimization



entry	variation from the standard conditions	Yield [%][a]
1	none	90 (79[b])
2	12 h instead of 3.5 h	89 (74)
3	$AgBF_4$ instead of $AgSbF_6$	84
4	AgOTf instead of $AgSbF_6$	42
5	AgF_2 instead of $AgSbF_6$	trace
6	[Cu] or [Fe] instead of $AgSbF_6$	<30
7	10 μL H_2O was added	<10
8	AgOTf instead of AgSbF6[c]	-
9	4Å MS was added	-
10	without $AgSbF_6$	-
11	1.0 equiv of $AgSbF_6$	18

[a] ^{1}H NMR yield with dibromomethane as internal standard, PMP = 4-OMeC$_6$H$_4$. [b] Isolated yield. [c] With additional KF (0.5 equiv).

Table 2. Substrate Scope of (Hetero)Aryl-Substituted Olefins[a]

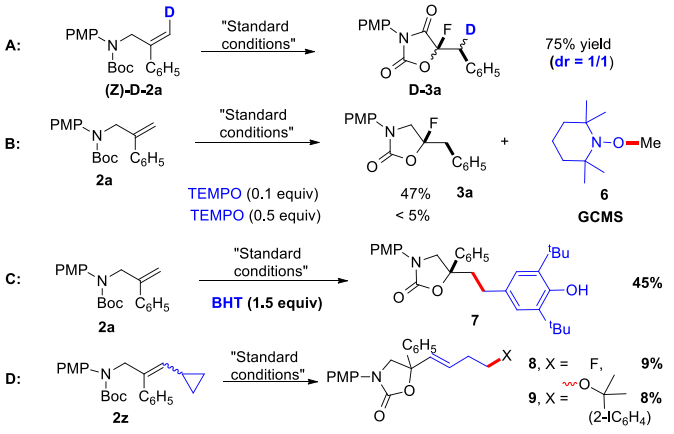


[a] The conditions: **2a** (0.2 mmol), **1** (0.3 mmol), $AgSbF_6$ (0.02 mmol) and DCM (2 mL), 55 °C, 3.5 h, isolated yield, dr was determined from ^{19}F NMR spectrum. [b] 3 equiv **1** for 12 h. [c] 5 h. [d] 12 h, dr = 1.3/1. [e] R_1 = C_6H_5. [f] 3 equiv **1** at 35 °C for 5 h. [g] 3 equiv **1** at 0 °C for 24 h. [h] dr = 2.3/1. [i] dr = 1.5/1. [j] 18 h, dr = 1.4/1. [k] 12 h. [l] 7 h.

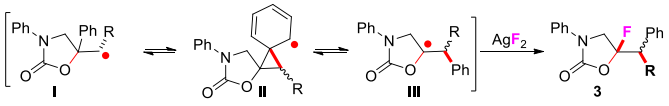
positive bacterial pathogens which are resistant to other antibiotics, including methicillins and vancomycins. After screening different conditions (Table S1 in the Supporting Information (SI)), the styrene-derived carbamate (**2a**) was found to partake in cyclization in combination with $AgSbF_6$ as the catalyst (entry 1, Table 1), providing fluorinated *N*-aryl-oxazolidin-2-one (**3a**) in 79% isolated yield. Other metal catalysts, such as $AgBF_4$, AgOTf and AgF_2 provided reduced yields (entries 3-6) and small amount of water reduced the reactivity dramatically (entry 7). When additional fluoride anion was added, compound **3a** was not observed in present of AgOTf (entry 8). No desired product **3a** was formed in absence of Ag catalysts (entries 9-10), even in the presence of molecular sieves.[11] The yield was reduced when one equivalent of $AgSbF_6$ was used, due to the elimination reaction of product **3a** in the presence of $AgSbF_6$ (entry 11 and Scheme S1 in SI).

Using the optimal conditions, the scope of substrates was investigated (Table 2). We first examined the reagents with different substituted phenyl groups on the nitrogen (**3a-f**), both electron-donating and -withdrawing phenyl substituents were well tolerated, leading to moderate to good yields of *N*-aryl-oxazolidin-2-ones. Functional groups on phenyl group, such as halogens (**3c, e**), ester (**3d**) and methoxyl groups (**3a, f**) were compatible with these reaction conditions. Additionally, alkyl substituted agents (**3g-i**) performed well in this process giving 66-78% yields. The nature of the aromatic migrating group (**3j-t**) was also investigated. Phenyl groups substituted with both electron-donating and -withdrawing groups were found to migrate efficiently (**3j-p**). Although 9H-carbazole was found to be a poor migration group (**3t**), other heteroaryl groups, such as thienyl and furyl groups (**3q-s**), were used for the first time as efficient migrating groups in fluorocyclization induced by hypervalent iodine reagents.[11] The substituted group R_2 did not affect the efficiency of the reaction (**3u-v**). The internal olefin (*Z*)-**2w** could also be used as a substrate, providing the desired product (**3w**) in moderate yield. With an alkyl olefin as the substrate, fluorinated oxazolidin-2-one (**3x**) was formed without migration. In addition to the 5-membered ring formation, the 6-membered cyclic product (**3y**), a key structure found in novel antiretroviral and antibacterial drugs,[15] could also be generated smoothly by this method.

In order to reveal some details of the catalytic mechanism, the side products in the reaction of **1** and **2a** were isolated and identified. In addition to the product 2-(2-iodophenyl)propan-2-ol (**4,** 85% yield), 1-(2-iodophenyl)ethanone (**5**, 8% NMR yield) was observed (Scheme S2 in SI). In addition, the deuterated compound (*Z*)-**D-2a** was subjected to the reaction conditions (Scheme 1A), and the resulting compound **D-3a** was observed with a diastereomeric ratio of 1:1 and no H-D scrambling. Along with the low diastereoselectivity achieved in the reactions of substrates **2u-2w** (Scheme 3), these results are interesting and contrast with the known hypervalent iodine(III)-mediated ionic fluorinations in which good to high diastereoselectivity can be generally obtained,[5,11] suggesting



Scheme 1. Radical Experiments



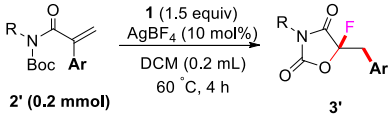
Scheme 2. Proposed Radical Mechanisms of Aryl Transfer Step

that this reaction may proceed through an unknown mechanism.

To study the mechanism further, several radical experimentals were performed. When the radical trapping reagent 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction, it resulted in a decrease in the yield of **3a** and the formation of the radical trapping product, 1-methoxy-2,2,6,6-tetramethylpiperidine (**6**) which was identified by GCMS (Scheme 1B), suggesting that a methyl radical may be generated during the catalytic process. Upon addition of 2,6-di-tert-butyl-4-methylphenol (BHT), the radical trapping product (**7**) was isolated in 45% yield (Scheme 1C). When compound **2z** was prepared and subjected to the reaction conditions, the ring opening products **8** and **9** were identified as reaction products (Scheme 1D). These two results strongly indicate that a methylene radical **I** (Scheme 2) in the 5-position of oxazolidin-2-one may be formed in this catalytic process. The radical rearrangement of **I** may take place, overcoming a low barrier,[16] and forming the radical intermediate (**III**) *via* a three-membered ring cyclic structure (**II**). Then the fluorine atom transfers from Ag(II)−F to the methylene radical (**III**) to form the desired product (**3**).[9,17] An alternative explanation, involving Ag(II) oxidizes the alkyl radical (**III**) to a carbocation which is subsequently captured by a fluoride anion, cannot be excluded.

Benefitting from the novel radical mechanisms, this reaction may be tolerated by other olefins in place of activated styrene derivatives. Finally, we found that phenyl substituted acrylamide was compatible with this catalytic system affording the desired product under modified reaction conditions (Table S2 in SI). A brief investigation of acrylamides (**2'**) was conducted, producing the results shown in Scheme 3. Similar to styrene derivatives, phenyl rings with electron-withdrawing or -donating groups and heteroaryl rings are good migration groups, all providing the desired oxazolidine-2,4-diones (**3'**) in acceptable yields. This is particularly interesting because fluorocyclization mediated by hypervalent iodine reagents using acrylamides as nucleophilic reagents has not been reported previously.[7]

Although different fluorination techniques have been developed, the successful translation of these approaches to practical radiofluorination syntheses remains a challenge.[3,4] The unique obstacles for radiofluorination include the fact that only trace amounts of [^{18}F]fluoride are available for synthetic



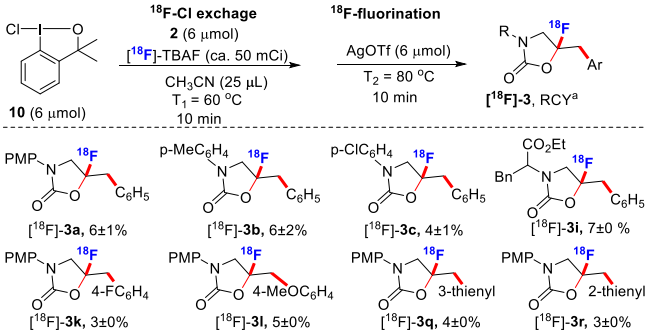
R	Ar	yield
C_6H_5	C_6H_5	**3'a**, 48%
4-ClC_6H_4	C_6H_5	**3'b,** 54%
4-ClC_6H_4	3,5-DiMeC_6H_3	**3'c,** 43%
4-ClC_6H_4	4-FC_6H_4	**3'd**, 49%
4-ClC_6H_4	4-MeOC_6H_4	**3'e**, 56%
4-ClC_6H_4	3-thienyl	**3'f**, 43%

Scheme 3. Substrate Scope of Acrylamides **2'**

reactions; the reaction must take place rapidly due to the 110 min half-life time of the ^{18}F-radioisotope, and the concern associated with radiation exposure.[4c,d] Encouraged by our promising fluorination results,[18] we explored radiolabeling of alkene precursors (**2a-c**) by means of a one-pot synthesis to minimize the radiosynthetic reaction time (See Scheme S3 in SI). Unfortunately, the [^{18}F]-fluorine-containing heterocyclic products could not be successfully produced by this protocol. This could be the result of AgCl formation due to the reaction between chloroiodane (**10**) and AgOTf which impedes the radio-fluorination process.

To solve this problem, we decided to attempt two-step one-pot labeling of the alkene precursor (**2a-c**) and the synthetic parameters were varied in a search for a suitable condition for radiofluorination (Table S3). As the radiosynthetic method consists of two radiochemical steps, ^{18}F-Cl exchange and ^{18}F-fluorination, we first varied the reaction temperatures in both steps. We found that the ^{18}F-fluorination temperature has an effect on the radiochemical yield (RCY), while the ^{18}F-Cl exchange temperature has a minimal impact (entries 1-3). The ^{18}F-Cl exchange temperature and ^{18}F-fluorination temperature were therefore set at 60 °C and 80 °C respectively. The next parameters that have a significant effect are the concentration of the reactants, the solvent, and the silver salt. In the case of the concentration and the solvent, the radioactive heterocyclic compound [^{18}F]-**3a** could be prepared successfully only at a high concentration (0.24 μM) of **2a** in acetonitrile solution. We failed to observe any radio signals of the product when either a low concentration or the DMSO/DMF solvent systems were used in the radiofluorination reaction (entries 5-7). In addition, we observed that the Ag salt is required in this reaction and the type of silver salt has an impact on the RCY of the reaction (entries 9, 11, 12, and 15). $AgSbF_6$ yielded the highest RCY. However, the radiofluorination failed when the amount of $AgSbF_6$ was diminished to 0.5 or 0.05 equivalents (entries 13-14). With using AgOTf instead of $AgSbF_6$ as catalyst to avoid adding additional ^{19}F fluoride, the specific activity of [^{18}F]-**3a** was determined to be 34.2±2.1 GBq/μmol (entry 2). Using the conditions, we prepared various ^{18}F-oxazolidin-2-ones with high radiochemical purity and the radiochemical yields (RCY) are shown in Scheme 4.

To confirm that our synthetic ^{18}F-oxazolidin-2-ones are stable, we evaluated the stability of [^{18}F]-**3a** *in vitro* and *in vivo*



Scheme 4. Radiosynthesis of [^{18}F]-**3** (n=3). [a]Decay corrected RCY is calculated by dividing the activity of isolated product with the total amount of ^{18}F-activity used in each reaction (decay corrected).

and found that [^{18}F]-**3a** is extremely stable in aqueous solution displaying negligible decomposition up to 3 h after incubation in phosphate buffer solution at pH 7.5 (Figure S1, SI). In term of *in vivo* stability, we observed no bone uptake signals due to tracer defluorination in the small animal PET/CT images of nude mice obtained at 1 h after the injection of [^{18}F]-**3a** (Figure S2, SI). The observed C−F bond stability supports its application in biomedical research *in vivo*.[19]

In summary, we have developed an efficient synthesis of fluorinated oxazolidin-2-ones, oxazolidine-2,4-diones and 1,3-oxazinan-2-ones via an intramolecular fluorocyclization strategy. The transformation exhibits broad substrate scope with tolerance of diverse functional groups, and provides versatile building blocks for the construction of related bioactive molecules. Preliminary mechanistic studies suggest that the unique reactivity and selectivity profile of this synthetic reaction can be attributed to the involvement of an unusual radical-mediated pathway. Additionally, the modified one-pot, two-step process using no-carrier-added ^{18}F-nucleophilic agents can be used to construct multiple bonds and generate ^{18}F-labeled heterocycles rapidly, and this enables the synthesis of previously inaccessible PET radiotracers for use in biomedical research. Further mechanistic research and applications in PET is in progress in our group.

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