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An Efficient Synthesis of Fluorinated Azaheterocycles by Aminocyclization of Alkenes

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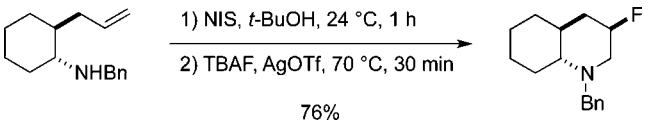
ABSTRACT



A general and efficient approach to important fluorinated azaheterocycles has been developed by incorporating nucleophilic fluorination into alkene difunctionalization. This intramolecular aminofluorination transformation of alkenes has been achieved via the aminocyclization of reactive unsaturated *N*-iodoamines, which can be generated in situ from either unsaturated *N*-chloramines or their amine precursors in a one-pot protocol.

Azaheterocycles, such as piperidines, have long been recognized as privileged pharmacophores for their remarkable biological activities and extensive use in synthetic pharmaceuticals.[1] Fluorinated azaheterocycles not only are isosteric to parent molecules but also can achieve improved bioavailability, lipophilicity, and metabolic stability.[2] Furthermore, the fluorine-18 radiolabeled azaheterocycles have innumerable applications in positron emission tomography (PET) and are valuable tools in drug discovery and biomedical research.[3] Therefore, developing effective and rapid fluorination methods to access fluorinated azaheterocycles is important and highly desired.

Although the synthesis of fluorinated azaheterocycles has received much attention,[2−4] fluorination methods to construct such azaheterocycles remained largely unexplored.[5,6] The incorporation of a fluorination step into alkene difunctionalization would represent a general and effective route as olefin functionalization has proved to be a powerful

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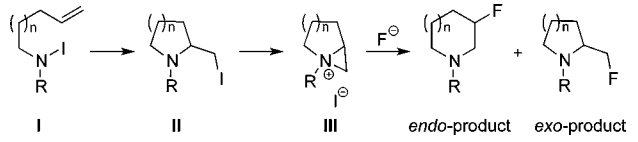
approach to access azaheterocycles.[7] Several alkene fluorination transformations have been recently achieved using an electrophilic fluoride.[8,9] Note that nucleophilic fluorinations would offer a higher specific radioactivity for ^{18}F-labeled radiomolecules than electrophilic fluorination.[3a] However, alkene difunctionalization incorporating nucleophilic fluorination has hardly been explored for preparing fluorinated azahetereocycles. The first example of using fluoride ions in alkene difunctionalization was reported by Liu's group on a Pd(II)-catalyzed oxidative aminofluorination, which was efficient but was restricted to terminal alkenes and required extended reaction time (24 h).[6] New strategies to effectively incorporate nucleophilic fluorination into alkene functionalization will not only offer a new method for the C−F bond formation but also greatly benefit the development of general and rapid routes to the important fluorinated azaheterocycles.[10]

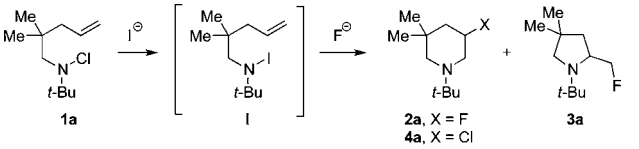
In this paper, we describe the development of a new approach to important fluorinated azaheterocycles by an intramolecular aminofluorination reaction of a diverse range of terminal and internal alkenes (Scheme 1). This transformation would involve an initial amino cyclization step of unsaturated *N*-iodoamines (**I**)[11] and a subsequent rearrangement of the pyrrolidine intermediate (**II**) to form the aziridinium intermediate (**III**) followed by a nucleophilic fluoride ring-opening in either *endo* or *exo* fashion.[12] This approach diminishes intrinsic toxicity concerns associated with transition metals, which is highly desired for practical use in biomedical and materials science. We have also established a one-pot protocol for a rapid fluorination step (< 30 min) that represents great potential for preparing ^{18}F-labeled azaheterocycles as novel PET imaging tools.

Scheme 1. Proposed Aminofluorination of *N*-Iodoamine Alkenes



Considering the high reactivity and instability of the *N*-iodoamine intermediate **I**, we initiated our studies by generating *N*-iodoamine catalytically in situ from the treatment of the more stable but less reactive *N*-chloramine[13] precursors with an iodide source (Table 1).[14] To this end, NaI was found to be effective for the conversion of *N*-chloramine **1a** to 3-chloropiperidine **4a** in the absence of fluoride sources. We next examined the NaI-catalyzed aminofluorination of **1a** in the presence of AgF using various solvents (e.g., $CHCl_3$, THF, MeCN, and *t*-BuOH).[14] Encouragingly, the aminofluorinated product **2a** was obtained in 50% yield in *t*-BuOH (entry 2), which proved to be the best solvent for this reaction and is also known to enhance the efficiency of nucleophilic fluorination.[15] Among all fluoride sources tested, AgF was the most efficient fluorination reagent. This suggests the role of silver salt in facilitating the rearrangement/aziridinium ring-opening step. Control experiments showed that the iodide catalyst was essential for this transformation (entry 3) while NaI was more effective than Bu_4NI[11a] as the iodide source (entry 4). We later noticed that the conditions with 10 mol % NaI (entry 2) occasionally provided much lower

Table 1. Iodide-Catalyzed Aminofluorination of Unsaturated *N*-Chloramine **1a**[a]



					yield[b] (%)	
entry	I^- source (equiv)	solvent	temp (°C)	time (h)	**2a**	**4a**
1[c]	NaI (0.1)	$CHCl_3$	50	1	–	97
2	NaI (0.1)	*t*-BuOH	50	4	50	43
3	None	*t*-BuOH	50	4	–	–
4	Bu_4NI (0.1)	*t*-BuOH	50	5	12	12
5	NaI (0.5)	*t*-BuOH	50	4	81	–
6[d]	NaI (0.1)	*t*-BuOH	50	5[e]	64	–
7[d]	NaI (0.1)	*t*-BuOH	70	0.75[e]	75	–

[a] Reaction conditions: **1a** (1.0 equiv, 0.1 mmol, 0.2 M), AgF (3.0 equiv). [b] Determined by ^{1}H NMR spectroscopy with DMF as a quantitative internal standard. Neither 3-iodopiperidine nor *exo*-product **3a** was detected by NMR. [c] Reaction in the absence of AgF. [d] Stepwise addition: upon complete conversion of **1a** to **4a** promoted by NaI (< 1 h), AgF was added. [e] Reaction time after the addition of AgF.[14]

(8) Examples for intramolecular alkene electrophilic fluorination: (a) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (b) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376. (c) Xu, T.; Mu, X.; Peng, H. H.; Liu, G. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 8176.

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(10) During the preparation of this manuscript, two intramolecular aminofluorination reactions of alkenes were reported. (a) Using PhI(OPiv)$_2$/hydrogen fluoride−pyridine: Wang, Q.; Zhong, W. H.; Wei, X.; Ning, M. H.; Meng, X. B.; Li, Z. J. *Org. Biomol. Chem.* **2012**, *10*, 8566. (b) Using difluoroiodonium salts: Kong, W.; Feige, P.; de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2469.

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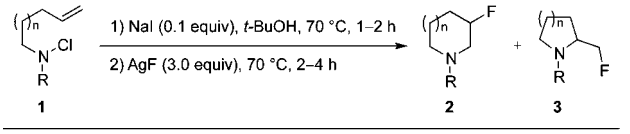
yields. However, the use of 50 mol % of NaI consistently gave a higher yield (entry 5). A comparable yield of **2a** was also obtained consistently with 10 mol % of NaI when a stepwise reaction was performed, where AgF was added upon consumption of the *N*-chloramine **1a** (entry 6). This indicated the presence of AgF may hinder cyclization by coordination with the iodide catalyst. Using this stepwise protocol, we observed a faster conversion of the cyclized intermediates into ring-opened products at elevated temperatures. The fluorination reaction at 70 °C (45 min) provided **2a** in 75% yield (entry 7).

With the effective conditions for aminofluorination identified, we examined the generality and efficiency of this transformation with a range of substrates containing different substitution on the nitrogen atom, olefin moiety, and alkyl backbone (Table 2). For **1a**–**1c** substrates bearing various alkyl groups on nitrogen, all formed 3-fluoropiperidine products with excellent yields and high *endo* selectivity (entries 1–3). Substrates **1d** and **1e**, containing a ring at the β-position, both effectively provided the spiro products with *endo* selectivity (entries 4 and 5). The reaction of substrate **1f**, which lacks substitution at the β-position, also afforded the aminofluorination products but without regioselectivity (entry 6). These results suggest that substitution at the β-position favors the *endo* nucleophilic ring opening.[16] The hexenyl compound **1g** was also a viable substrate that gave the aminofluorination products with modest selectivity favoring the 7-membered *endo*-ring-opened product **2g** (entry 7). Next we examined the effects of substitution on the alkene and the backbone. For disubstituted olefins **1h**–**1j**, their reactions all successfully afforded the desired products with modest regioselectivity and excellent diastereoselectivity (entries 8–10). The *Z* alkene exclusively gave the *cis*-aminofluorinated cyclic amine, and the *E* alkene gave only the *trans* product. For the effects of backbone substitution, monosubstitution at the β-position resulted in good regio- and diastereoselectivity and favored the formation of the *endo* ring-opened product **2k** with *cis* stereoselectivity (entry 11).[16] For monosubstitution at the α- and γ-positions, little or modest regioselectivity was observed while the 3-fluoropiperidine products showed higher diastereoselectivity than did the 2-(fluoromethyl)pyrrolidine products (entries 12 and 13). The conditions were also efficient for the cyclic substrate **1n**, providing fluorinated bridged heterocyclic product **2n** in good yield and stereoselectivity (entry 14).

We next looked into developing a one-pot protocol for chlorination and aminofluorination of unsaturated amines, as elimination of the *N*-chloramine isolation step would be attractive.[17] It was hypothesized that when the *N*-chlorosuccinimide (NCS) oxidizes the amine to the *N*-chloramine, the succinimide byproduct would be a spectator in the subsequent reactions. To test this, unsaturated amines were first treated with NCS followed by treatment with NaI in *t*-BuOH while AgF was added upon

Table 2. Synthesis of Fluorinated Azaheterocycles by Aminofluorination of Unsaturated *N*-Chloramines



1 **2** **3**

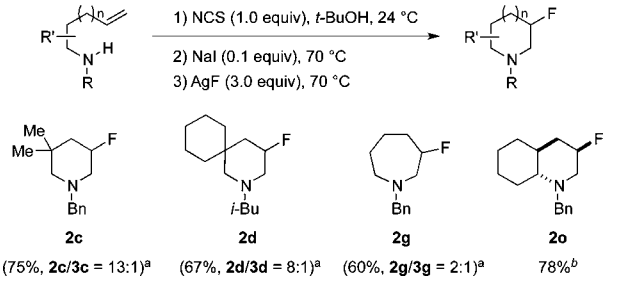
entry	*N*-chloramine	**2** and **3**	yield[a]	**2**/**3** (dr)[b]
1	**1a** R = *t*-Bu	**2a**	82%[c]	>15:1
2	**1b** R = Bu	**2b**	86%[c]	>15:1
3	**1c** R = Bn	**2c**	88%	13:1
4	**1d**	**2d**	88%	8:1
5	**1e**	**2e**, **3e**	78%	2.5:1
6	**1f**	**2f**, **3f**	75%	1:1
7	**1g**	**2g**, **3g**	49%	2:1
8	**1h**	**2h**	78%[c]	>20:1
9	**1i**	**2i**	72%	2.7:1 (**2i**: *cis* only)
10	**1j**	**2j**	70%	4.5:1 (**2j**: *trans* only)
11	**1k**	**2k**	85%	4.6:1 (**2k**: 8:1)
12	**1l**	**2l**, **3l**	72%	0.9:1 (**2l**: 5.5:1) (**3l**: 3.3:1)
13	**1m**	**2m**, **3m**	57%	0.7:1 (**2m** only) (**3m**: 1.1:1)
14	**1n**	**2n**	63%	only **2n** (**2n**: 3.5:1)

[a] Isolated yields for both products **2** and **3**. [b] Regioselectivity (ratio of **2**/**3**) and diastereoselectivity (dr) were determined by ^{1}H NMR spectroscopy and/or GC–MS analysis of the reaction mixture. Major diastereomer is shown. [c] Yields determined by ^{1}H NMR spectroscopy with DMF as a quantitative internal standard.

(16) Origins of the observed *endo* selectivity for those substitutions on alkene and backbone are under investigation.

(17) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598.

Scheme 2. One-Pot Protocol for Chlorination and NaI-Catalyzed Aminofluorination of Unsaturated Amines



[a] Yields (combined for products **2** and **3**) and regioselectivity determined by ^{1}H NMR spectroscopy with DMF as a quantitative internal standard. [b] Isolated yield.

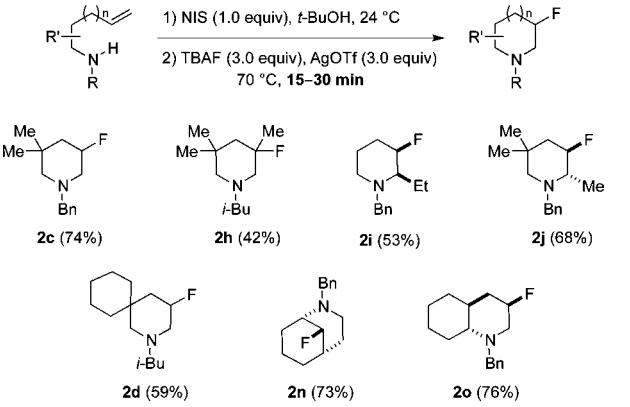
consumption of the *N*-chloramine (Scheme 2). With this one-pot procedure, aminofluorination products **2c**, **2d**, **2g**, and **2o** were all formed effectively. These results demonstrated that the aminofluorination of alkenes can be achieved from either *N*-chloramines or their amine precursors.

To explore this transformation for its applications in synthesizing ^{18}F-labeled azaheterocycles (~110 min half-life), we examined if the nucleophilic fluorination could be accelerated by the stoichiometric formation of reactive 3-iodopiperidine intermediates through a one-pot *N*-iodosuccinimide (NIS) iodination[18] and aminofluorination protocol. We also examined the combined treatment of TBAF or KF with different silver salts for alternative fluorination conditions, since either [^{18}F]TBAF or [^{18}F]KF is readily available (commercially),[3] while [^{18}F]AgF is not. We were encouraged to observe that the fluorination step using a 1:1 ratio of TBAF and AgOTf led to the rapid formation of aminofluorinated products (15−30 min). This protocol was effective across a variety of acyclic and cyclic substrates (Scheme 3). These results suggest this method holds great potential in preparing ^{18}F-labeled azaheterocycles to develop novel PET imaging tools.

In summary, we have developed an efficient alkene aminofluorination approach to synthesize fluorinated piperidines and other azaheterocycles of great importance

(18) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027.

Scheme 3. Rapid Aminofluorination via Stoichiometric Formations of Unsaturated *N*-Iodoamines[a]



[a] Results listed as the major product in isolated yield.

to the pharmaceutical and chemical industries. The aminofluorination reactions of a broad scope of alkene substrates have been achieved via the reactive *N*-iodoamine intermediates formed in situ, either catalytically from *N*-chloramines and NaI or stoichiometrically from amine and NIS. In particular, the latter protocol allows for a more rapid fluorination step, suggesting its great promise in synthesizing ^{18}F-labeled azaheterocycles for PET imaging. Furthermore, this approach can serve as a general strategy to incorporate a variety of nucleophiles to access diversely functionalized azaheterocycles in a modular fashion.

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Supporting Information Available. Experimental procedures, additional screening data, and characterization data for new compounds including ^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.