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Fluorocyclization of Allyl Alcohols and Amines to Access 3-Functionalized Oxetanes and Azetidines

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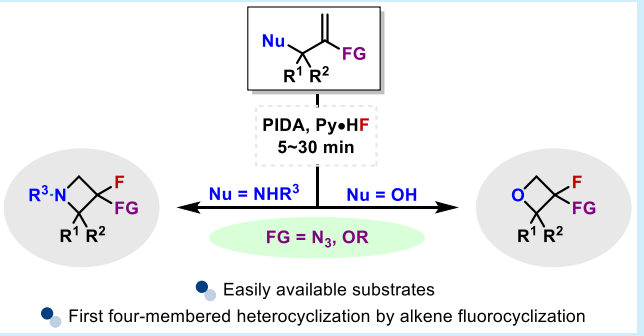
ABSTRACT: An efficient method to prepare 3-functionalized oxetanes and azetidines has been realized by fluorocyclization of readily available 2-azidoallyl/2-alkoxyallyl alcohols and amines. Notably, this is the first example applying the fluorocyclization strategy to construct four-membered heterocycles. The pendant electron-donating group ($-N_3$ or $-OR$) plays a crucial role in polarizing the C=C double bond and facilitating the cyclization process, as verified by DFT and experimental studies.



Strained small-ring heterocycles are of significance in drug candidates, bioactive natural products, and as useful intermediates in organic synthesis.[1] The utmost importance in current medicinal chemistry research is given to the saturated 3-substituted four-membered heterocycles, such as oxetanes and azetidines, which are ubiquitous core structures of many bioactive natural products and pharmaceuticals and have become an essential part of standard toolbox of the medicinal chemists (Figure S1).[2] Despite there being a number of methods for preparing saturated four-membered heterocycles,[2a,3] the development of cyclization approaches for forming saturated 3-functionalized four-membered heterocycles, especially medicinally relevant 3-fluoro and 3-azido derivatives, remains problematic mainly due to the poor kinetics of cyclization (the order is 5 > 3 > 6 > 7 > 4).[4] Consequently, the synthesis of these compounds largely relied on the functional group interconversion of 3-functionalized parent four-membered heterocycles,[2] which apparently are not cost-effective and could not be enough to meet demands in drug discovery. In contrast, cyclization from acyclic precursors remains a preferable strategy, providing the desired functional groups could be properly installed in the starting materials.

Intramolecular nucleophilic displacement cyclization represents a classical approach to access saturated four-membered ring frameworks (Figure 1A).[2a,5] The need for a starting material with both a nucleophilic center and a leaving group poses obvious constraints. Moreover, to make 3-functionalized four-membered rings, a trifunctional acyclic molecule is needed, and therefore, this method has been rarely exploited in the synthesis of such heterocycles.[2] We envision whether the required leaving group and functional group could be generated at once by difunctionalization of alkenes (Figure 1B).[6] In recent years, the fluorocyclization of alkenes has emerged as a useful method for the preparation of saturated fluorinated heterocycles from the addition of fluoride on alkenes, with a hypervalent iodine moiety acting as a leaving group formed in situ. This strategy has been successively explored by Gouverneur, Szabó, Nevado, Jacobsen, and others in the construction of five-, six-, seven-, and even three-membered heterocycles (Figure 1C).[7] Nevertheless, such a state-of-the-art strategy has not yet been implemented in the formation of four-membered rings, which could be ascribed to its aforementioned poor cyclization kinetics.[4] Recently, α-vinyl azides have emerged as a class of viable reaction partners in terms of iodine−fluorine chemistry as well as radical chemistry and exhibit distinctive reactivity.[7b,8] Herein, we report a four-membered cyclization of the easily available 2-azidoallyl alcohols and amines by using difluoroiodobenzene ($PhIF_2$) generated in situ from iodobenzene diacetate (PIDA) and HF.[9] This strategy represents the first example that applying fluorocyclization of alkenes in the formation of four-membered rings (Figure 1D).[7a] Notably, the azido and alkoxy group at α-position of allyl alcohol enable the initial electrophilic addition of hypervalent iodine reagents[10] and also retained in the final product as a useful handle.[11] The obtained oxetane and

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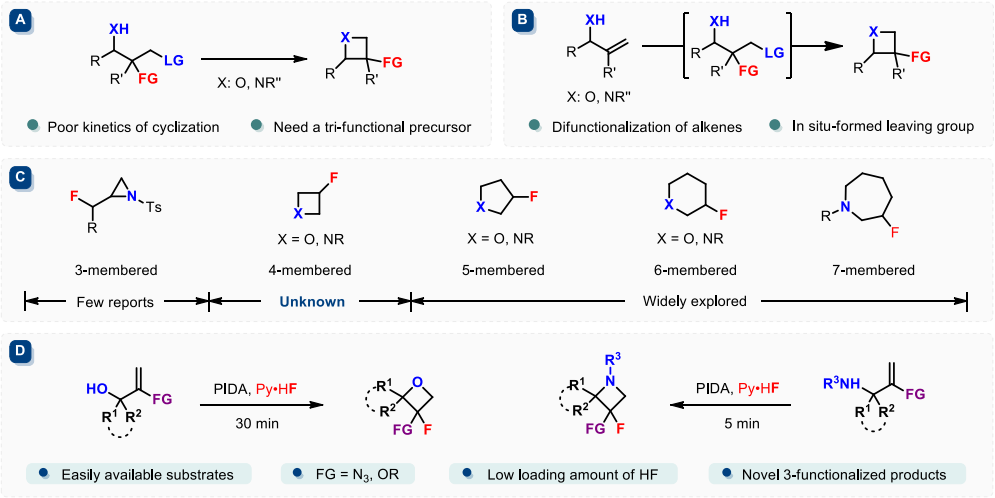

Figure 1. Synthetic strategies for 3-functionalized four-membered heterocycles. (A) Intramolecular cyclization strategy for 3-substituted four-membered heterocycles. LG: Leaving group; FG: functional group. (B) Our proposal: in situ incorporation of a leaving group followed cyclization. (C) Fluorocyclization: previous studies. (D) Fluorocyclization of 2-azidoallyl/2-alkoxyallyl alcohols and amines.

azetidine derivatives belong to a class of newly synthesized 3-fluoro-functionalized four-membered heterocycles that are inaccessible by other synthetic methods.[5d]

After careful screening of the reaction conditions (for details, see Table S1), the conditions (2-azidoallyl alcohols (1.0 equiv), Py·HF (1.5 equiv), PIDA (1.5 equiv), CH_2Cl_2 (0.1 M) at −45 °C) were chosen for the substrate scope and functional group tolerance studies. First, a variety of cyclic alcohols tethered with different functional groups undergo the desired fluorocyclization with good to excellent yield (**2**−**11**, 80−93% yields) (Figure 2A). Note that spiro[3.5]- or spiro[3.6]oxetane motifs represent the core structural units in the inhibitors of β-secretase and anticancer agents.[12] Also, the use of a tetrahydropyran derivative led to product **12** in a 84% yield. Furthermore, 7−15-membered macrocyclic compounds were efficiently converted into the corresponding oxetanes (**13**−**16**). Fluorenone derivatives also participated in this transformation and could convert to the consistent oxetanes in good yield (**17**, **18**; 82%, 78% yield, respectively). Strikingly, a wide variety of acyclic alcohols successfully converted into oxetane derivatives with almost identical efficiency to cyclic alcohols (**19**−**37**). Starting from the simplest acetone structure, the target product **19** could be obtained in 87% yield. Dialkyl alcohols were smoothly transferred into oxetanes with 83−96% yield (**20**−**22**). Diaryl groups furnished the 2,2-diaryloxetanes in good to high yield (**23**−**30**, 57−84% yield); note that these products have a similar quaternary carbon center in biodegradable insecticide EDO (Figure S1).[13] A modest drop in the yield was observed for the substrates with electron-withdrawing groups on the benzene ring (**25**−**27**, **29**, **30**). Further, ethisterone could be converted to the corresponding oxetane derivative **31** in 69% yield via a two-step operation. Monosubstituted and unsymmetrical aryl alcohol derivatives also proved to be effective substrates, although they afforded a diastereomeric mixture of products (**32**−**37**, 77−95% yield, dr = 1.1:1 to 4.9:1).

Aldehydes and ketones are basic organic synthetic feedstock. We therefore envisage that developing a one-pot multistep method to prepare 3-functionalized oxetanes directly from aldehydes and ketones should be feasible and more synthetically practical. Observing efficient performance in each step, we eventually achieved this and efficiently obtained 3-functionalized oxetanes from ketones via a cascade alkynylation hydroazidation and fluorocyclization sequence (Figure 2B). Both cyclic and acyclic ketones were equally converted into corresponding 3-functionalized oxetanes. This conversion integrates the universality of carbonyl compounds with the 3-functionalized oxetanes, which greatly improves the possibility of its abundant applications in the field of medicinal chemistry. In addition to the modification of ethisterone, the late-stage diversification of citronellal **38** was also realized in 66% yield through the sequential three-step operation.

Next, we speculated that such a fluorocyclization strategy could also be extended to the synthesis of azetidine scaffolds. While monitoring the fluorocyclization reaction, progress was sluggish at −45 °C; thus, we performed the reaction at 25 °C. To our delight, a variety of *N*-protected (sulfonyl or acyl) 2-azidoallyl amines was successfully applied in the fluorocyclization (Figure 2C). Except for the 4-NO_2 group (**43**), the electronic nature and position of substituents on the benzene ring nearly did not influence on the efficiency of azetidine formation (**39**−**50**). The azetidine structure was unambiguously confirmed by single-crystal X-ray diffraction analysis of **41** (CCDC No. 1943313). The aryl sulfonyl group could be replaced with an alkyl sulfonyl group without affecting the reaction outcome (**52**, **53**). Such an efficient construction of alkylsulfonyl-protected azetidine represents a possible technique for the synthesis of Olumiant (marketed drug for the treatment of rheumatoid arthritis).[14] Furthermore, the acyl-protected α-amino vinyl azides also delivered desired products in good to high yield (**54**−**64**, 59−88% yields). Note that the acyl-protected azetidine structural unit occurs in several pharmaceuticals, for instance, Cobimetinib, a high-profile drug for the treatment of melanoma.[15] Finally, the reaction of the amine attached to the secondary or tertiary carbon proceeded as well and afforded the cyclized products in high yield (**65**−**67**, 82−93% yields).

Considering the azido group with many possibilities for further modification and the potency of a fluorine atom to modulate chemical and biological properties of molecules,[16] we expect such derivatives would constitute a new chemical space for exploration in the drug discovery. To demonstrate the

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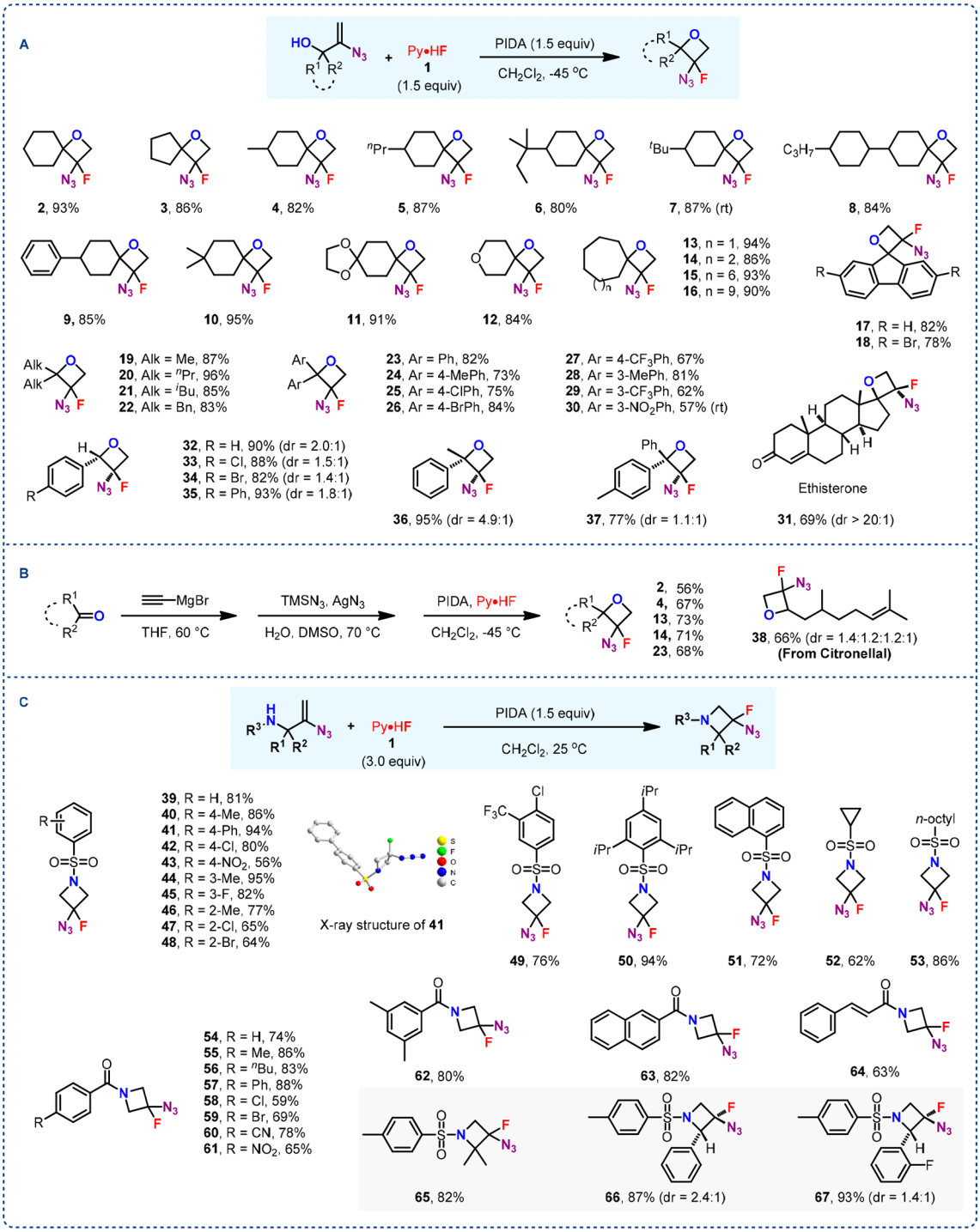

Figure 2. Synthesis of oxetanes and azetidines.

practicality of the method, a gram-scale synthesis was performed for oxetane **2** and azetidine **40**, respectively, and they were obtained in a little decreased high yield compared with the small-scale reaction (**2**, 1.5 g, 81%; **40**, 2.1 g, 77%) (Figure 3). We further exploited these compounds as the synthetic intermediates, regarding the ring-opening reaction of four-membered heterocycles and the versatile nature of the azido group in organic synthesis. For instance, products **2** and **40** were readily converted to the amines **68** and **72**, respectively, by reduction with $LiAlH_4$,[17] along with the removal of fluorine; the azido group in **2** and **40** was easily converted to 1,2,3-triazole through base-mediated 1,3-dipolar cycloaddition with alkynes (**69**,[18] **70**,[19] **73**[18]); moreover, treatment of **40** by submission of tetra-*n*-butylammonium bromide (TBAB) led to the corresponding ring-opening product of azetidine **74** in 88% yield.[20]

We designed and performed some control experiments to gain mechanistic insights (for details, see Figure S2). First, we prepared $PhIF_2$ separately and applied it in the reaction with substrate **1** under similar conditions, which resulted in the target product in 92% yield, thus suggesting that the intermediate $PhIF_2$ was involved in the reaction (Figure 4a).

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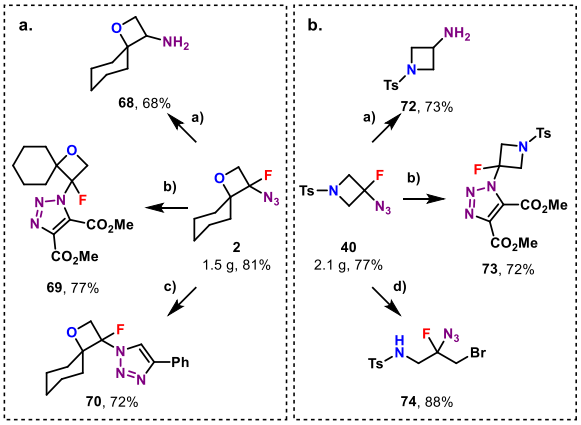

Figure 3. Gram-scale synthesis and applications. Reaction conditions: (a) **2**/**40** (0.5 mmol) and $LiAlH_4$ (1.2 equiv) in THF (10.0 mL) at 25 °C for 3 h. (b) **2**/**40** (0.5 mmol) and DMAD (1.2 equiv) in H_2O (8.0 mL) at 70 °C for 8 h. (c) **2** (0.5 mmol), phenylacetylene (1.2 equiv), CuI (10 mol %), and TEA (20 mol %) in THF (2.0 mL) at 25 °C for 3 h. (d) **40** (0.5 mmol), TBAB (1.0 equiv), and $BF_3{\cdot}OEt_2$ (1.0 equiv) in DCM (2.0 mL) at 25 °C for 20 min.

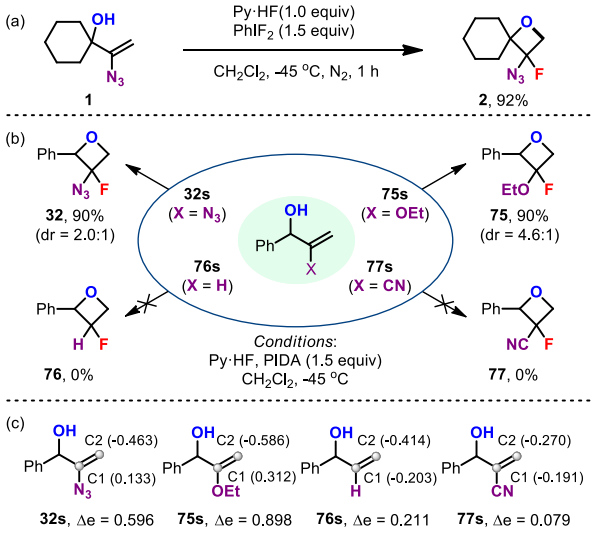

Figure 4. Control experiments.

While the 2-azidoallyl alcohol **32s** and 2-ethoxyallyl alcohol **75s** gave the expected oxetane **32** and **75** in 90% yields under the standard conditions, no reaction was observed for allyl alcohol **76s** and 2-cyanoallyl alcohol **77s**, which were all recovered after the reaction (Figure 4b). Natural population analysis (NPA) charge analysis was also performed and displayed the different degrees of polarization of the C=C double bond on **32s**, **75s**, **76s**, and **77s** (Figure 4c; for details, see Figures S4–S7). Therefore, the role of the azido group as well as the ethoxy group is ascribed to its strong polarization effect that facilitates the initial electrophilic attack of the C=C double bond by the hypervalent iodine moiety.

To gain more mechanistic insights into the four-membered fluorocyclization of alkenes, DFT calculations were performed (for details, see Figure S2). Indeed, after the formation of iodonium ion intermediate **II**, the fluorination of **32s** via a six-membered ring transition state (**TS-I**) is 12.1 kcal/mol more favorable over the fluorination of **76s** (**TS-IA**), thus ruling out the fluorocyclization feasibility of allyl alcohol **76s**, which is in line with aforementioned experimental results (Figure 4b). During the formation of iodonium ion, it is worth noting that two molecules of HF as the Brønsted acid are found to most favor the activation of the hypervalent iodine reagent, which is consistent with the reported calculation results by Houk and Xue.[21] For 2-azidoallyl alcohol **32s**, the fluorination step is facile and highly exergonic, as the formed fluorinated intermediate **IV** is −26.6 kcal/mol in free energy. Following the step of fluorination, the cyclization subsequently occurs via intramolecular nucleophilic attack of the hydroxyl group to the C−I bond of fluorinated intermediate **IV** via transition state **TS-II**, thereby leading to final fluorocyclization product **32**. Note that in **TS-II** both the nucleophilic hydroxyl group and the fluorine group on iodine center are activated by HF molecule, as similar to the report by Liu et al.[22] In the reaction pathway of **32s**, the fluorination step is the rate-determining step (**TS-I**, 3.8 kcal/mol), and these calculation results are in accordance with the observed experimental results.

In conclusion, we have for the first time realized the formation of four-membered heterocycles through the alkene fluorocyclization strategy, starting from the readily available 2-azidoallyl/2-alkoxyallyl alcohols/amines. Combined experimental and computational studies revealed that the strong electron-donating group plays a critical role to polarize the C=C double bond and facilitate the kinetically unfavorable intramolecular cyclization. Given the relevance of C-3 functionalized oxetanes and azetidines in medicinal research and the rich chemistry of the azido group in organic synthesis as well as the modulating effect of molecular properties by fluorine, the work described here would benefit the drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01062.

Experimental details, characterization data, NMR spectra, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1943313 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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