Gem-difluorinative ring-expansion of alkenes

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Abstract

Incorporating fluorine into aliphatic rings induces significant alterations in molecular conformation, acidity/basicity, and lipophilicity. Current methods for synthesizing fluorinated aliphatic rings, however, involve manipulating functional groups within pre-existing ring systems. Here, we have developed a novel chemical reaction - *gem*-difluorinative ring-expansion of methylenecycloalkanes. The reaction involves iodine(III) species, and allows the preparation of *gem*-difluorinated macrocyclic, fused, spiro, bridged, and natural product-derived structures. The protocol's practicality is demonstrated through several decagram-scale syntheses.

Introduction

The unique properties of fluorine have facilitated its integration into various realms of academic and industrial research, spanning from pharmaceuticals and agrochemicals to advanced materials and polymers.[1-5] Notably, the incorporation of fluorine into lead drug candidates has been acknowledged as a potent strategy to enhance their pharmacokinetic and physicochemical attributes by fine-tuning potency, polarity, p*K*a-value, lipophilicity, and metabolic stability (Fig. 1A).[6-10] Beyond these properties, the introduction of a C–F bond into aliphatic systems often yields conformational alterations, driven by various stabilizing forces such as hyperconjugation, dipole-dipole, and charge-dipole interactions (Fig. 1B).[9,11,12] These effects also manifest in the intriguing geometry of the CF_2 group, a bioisostere of oxygen atom.[13] The substitution of two hydrogen atoms of a methylene with fluorine atoms significantly broadens the C-CF_2-C angle (Fig. 1C).[14] Concurrently, saturated rings are commonly employed in drug development due to their structural rigidity and diversity. This rigidity proves valuable in maintaining a specific three-dimensional shape, crucial for molecular recognition and binding to biological targets.[15-

[17] Recent studies have unveiled the potential of the C–F bond to serve as a conformational tool for synthesizing shape-controlled complex structures in a wide variety of aliphatic carbo- and heterocyclic systems.[7,11,18-20] Nevertheless, the synthesis of fluorinated cycles from readily available starting materials still poses significant challenges.

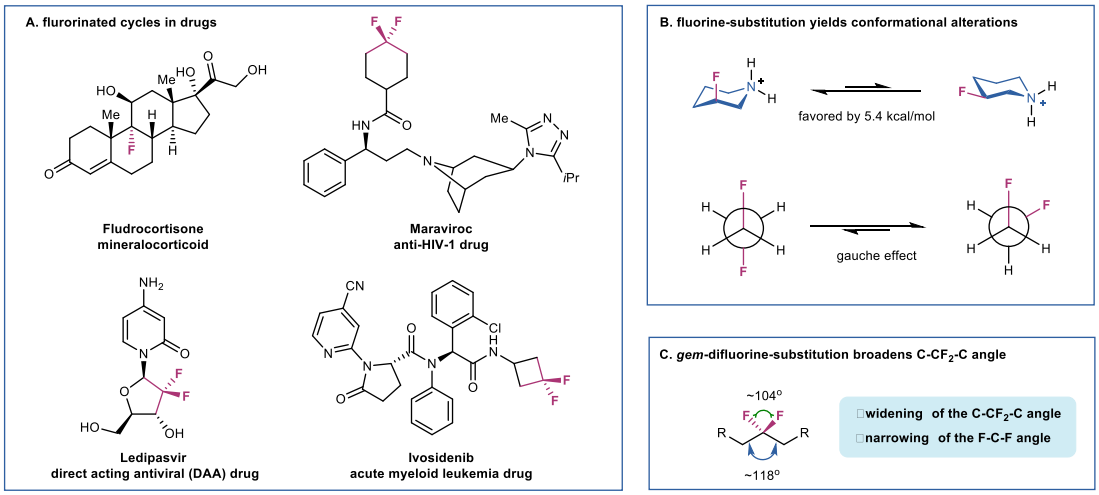

Fig.1| Unique properties of fluorine (A) Fluorinated cycles in drugs. **(B)** Fluorine-substitution yields conformational alterations. **(C)** *Gem*-difluorine-substitution broadens C-CF_2-C angle.

Ring expansion reactions provide a fascinating avenue for constructing saturated rings. While ring expansion reactions involving the introduction of heteroatoms (such as Baeyer-Villiger oxidation[21] and Beckmann rearrangement[22] involving nitrogen) are widely employed, ring homologation reactions remain relatively underappreciated. Classic protocols such as Demjanov,[23] Tiffeneau Demjanov,[24] Wagner Meerwein,[25-28] pinacol rearrangement,[29-31] and the reaction of ketones with diazomethane[32] are usually associated with intricate preparation of rearrangement precursors and/or the use of unstable and hazardous reagents.

We consider readily available methylenecycloalkanes as valuable precursors for ring-homologation. As early as more than 50 years ago, methylenecycloalkanes have been utilized in thallium(III)-oxidized rearrangement reactions (Fig. 2A).[33] The initial Markovnikov hydroxythallation is followed by an intramolecular 1,2-alkyl shift to provide a general pathway to ring-enlarged cycloalkanones. The toxicity of thallium(III), however, greatly limits its widespread applications. This protocol was later elegantly upgraded to greener catalytic versions,[34-36] as exemplified by Zhu's Pd^{II}/Pd^{IV} catalytic conversion of 1,1-disubstituted alkenes to ketones (Fig. 2A).[34] The iodine(III)-mediated fluorination of alkenes have proven efficient methods for the synthesis of organofluorides and have met with tremendous success in recent years.[37-48] We thus envisioned an alternative strategy for ring expansion (Fig. 2B). Specifically, the fluoroiodination of exocyclic alkene would deliver intermediate **I**. The high leaving aptitude of I(III) in intermediate **I** would trigger a 1,2-alkyl shift to provide a α-fluorine stabilized cation, which upon a fluoride trap, forms a ring-homologated difluorinated cycle. Surprisingly, although the 1,2-aryl migrative ring expansion reactions of phenyl-fused methylenecycloalkanes have been very well established,[18,49-51] their 1,2-alkyl shift version is thus far unknown. Challenges could be foreseen (Fig. 2C). For instance, the steric bulky of 1,1-disubstituted alkene may resist an

iodine(III) coordination, the side hydrofluorination may outcompete to form ring size retained tertiary alkylfluoride (path a). Alternatively, the lower aptitude of 1,2-alkyl migration may result in a competing intermolecular fluoride displacement, again, results in an unproductive ring size retained 1,2-difluorination product (path b).

In this report, we have developed a novel chemical reaction - *gem*-difluorinative ring-expansion of alkenes. We detail how fine-tuning the electronic properties of I(III) species (Fig. 2D) allows us to mitigate undesired ring size-retained hydrofluoronation and 1,2-difluorination products, enabling the productive synthesis of ring-enlarged difluorinated rings. The method efficiently constructs a diverse array of rings, including macro-, fused-, spiro-, bridged- and natural product-derived structures. The reaction is rapid and practical, as demonstrated by decagram synthesis of adamantane derivative within 30 minutes (Fig. 2E).

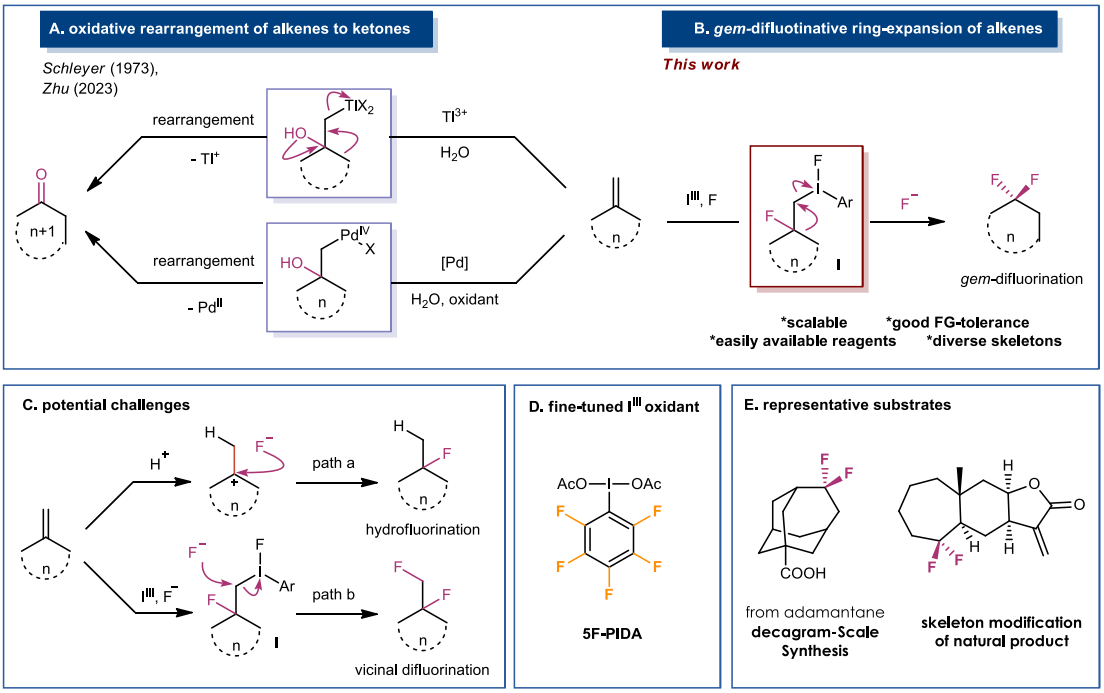

Fig.2| Ring-expansion of alkenes (A) Previous art: oxidative rearrangement of alkenes to ketones. **(B)** This work: *gem*-difluorinative ring-expansion of alkenes. **(C)** Potential challenges. **(D)** Fine-tuned I^{III} oxidant. **(E)** Representative products.

Results and Discussion

In the beginning, we selected (4-methylenecyclohexyl)benzene **S1** (0.2 mmol) as our model substrate. We first tried the catalytic systems independently developed by Gilmour[52] and Jacobsen.[53] With 1-iodo-4-methylbenzene (20 mol %) as catalyst and Selectfluor as oxidant (Gilmour's conditions, 10 min), the reaction mostly led to the background hydrofluorination of alkene, with no ring-enlarged product being found (left, Fig. 3A). The addition of amine to neutralize the acidity proved also unsuccessful. With *m*CPBA as oxidant (Jacobsen's conditions), the reaction gave the hydroxyfluorination product, which is believed to be derived from an undesired epoxidation/fluoride ring-opening process (right, Fig. 3A). These results suggest the protonation or epoxidation

reaction of 1,1-disubstituted exocyclic double bond is kinetically faster than the generation of active I(III) catalyst or its coordination with alkene. To minimize these side reactions and considering the easy availability of arylhyperiodine reagents, we turned our attention to the stoichiometric reaction. Utilizing commercial available PIDA (phenyliodine(III) diacetate) **I-1** as oxidant in dichloromethane (DCM) at room temperature for 10 minutes, we were pleased to observe the successful formation of the difluorinated ring-expansion product **1**, but in a low yield of 33% (Fig. 3B). The classic ring-size retrained 1,2-difluorinated products were isolated as the major side product (Fig. 2C). Further tuning of the electronic property of arylhyperiodine reagents revealed that the ones with electron-donating group generally favored the vicinal difluorinated product whereas the electron-poor ones preferentially delivered the geminal difluorinated product. The different **1**/**1c** ratios versus σ constants of different substituent were plotted according to the Hammett equation (Fig. 3C). The positive ρ (1.68) value suggested that negative charge is being developed on the arylhyperiodine group in the product-determining step. Guided by this trend, we finally identified 5F-PIDA as the optimal one which gave moderate yield but mitigated the formation of **1c**. Further optimization by varying the amine:HF ratio proved fruitful, and under the optimal conditions of using 5F-PIDA as the oxidant, amine:HF (1:5.5) as fluorine source, we obtained the desired product in a 90% ^{19}F NMR yield (81% isolated yield) (Fig. 3D).

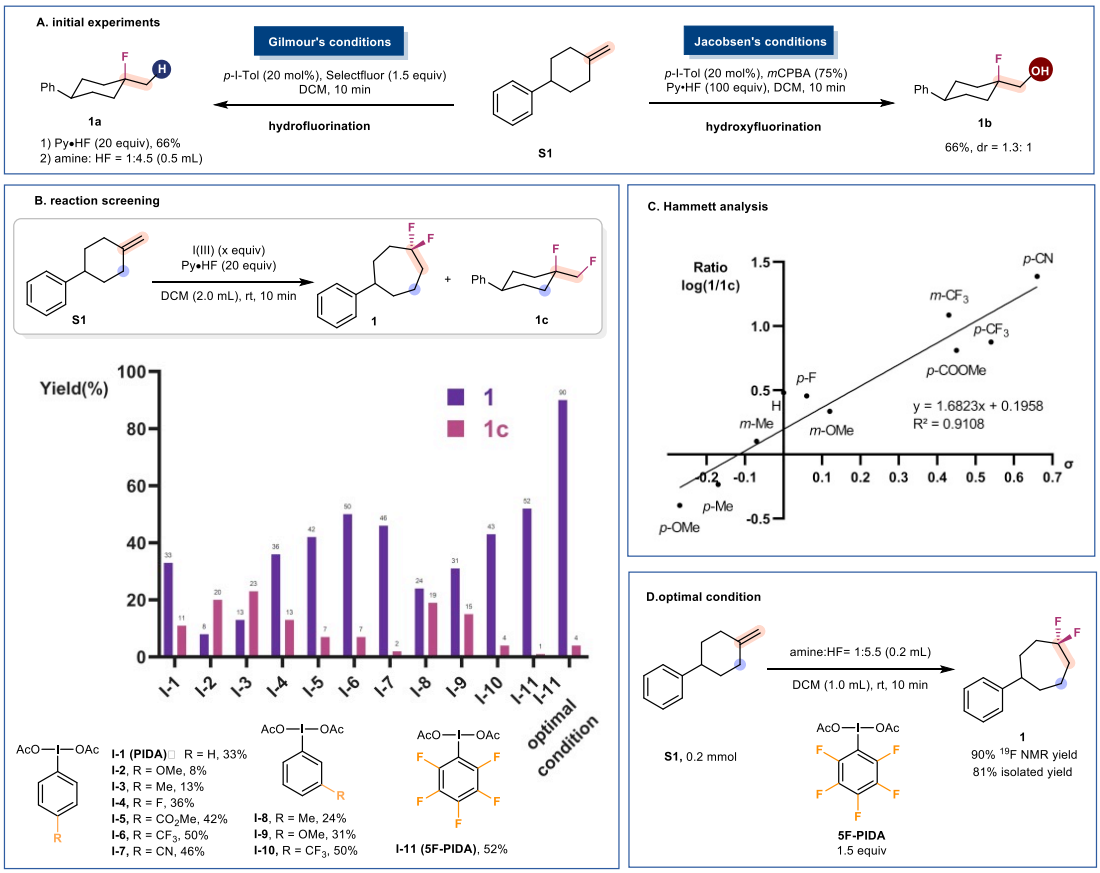

Fig.3| Optimization of the reaction conditions. [a]Reaction condition: **S1** (0.2 mmol), "F" source, I(III) reagent (1.5 equiv), solvent (1-2 mL), room temperature, 10 min. [b]$PhCF_3$ as internal standard. [c]isolated yield. [d]ethyl bromodifluoroacetate as internal standard. Amine: HF = 1: 4.5 (0.4 mL) is mixture of 0.27 mL

NEt_3·HF and 0.13 mL Py·HF; Amine: HF = 1: 5.0 (0.4 mL) is mixture of 0.23 mL NEt3·HF and 0.17 mL Py·HF; Amine: HF = 1: 5.5 (0.4 mL) is mixture of 0.20 mL NEt_3·HF and 0.20 mL Py·HF ; Amine: HF = 1: 7.0 (0.4 mL) is mixture of 0.11 mL NEt_3·HF and 0.29 mL Py·HF.

With the optimized reaction conditions in hand, we embarked on investigating the scope and limitations of this gem-difluorinated ring-expansion reaction. As depicted in Figure 4, we first explored the 6→7 ring expansion reaction. Methylene cyclohexanes bearing various substituent groups such as aryl (**1**), primary alkyl (**2**), secondary alkyl (**3-5**), and tertiary alkyl (**6, 7**) efficiently underwent the reaction to afford the corresponding gem-difluorinated seven-membered ring products in moderate to good yields. Functional groups including ester (**8, 9**), benzyloxy (**10**), cyano (**11**), carboxylic acid (**12**), and ketone (**14**) were well tolerated. The Cbz (benzyloxycarbonyl)-protected methylene piperidine bearing an exocyclic double bond was compatible as well (**13**). In the cases of unsymmetric substrates, the exclusive migration of the less-substituted carbon was observed with phenyl substitution (**15**). Interestingly, this regioselectivity was reversed for mono-alkyl substituted substrate (**16**). The di-alkyl substituted substrate showed lower selectivity (**17**).

To further define the scope, the 5→6 and 4→5 ring expansion reactions were also attempted. Five-membered *cis*-bicyclo [3.3.0] rings were found to undergo the desired ring expansion to afford the bicyclo [3.4.0] gem-difluorinated skeletons (**18**, **19**), which are otherwise difficult to construct using traditional methods. Furthermore, the aza-bicyclo [3.4.0] product was easily obtained in high yield (**20**). Likewise, a series of substituted methylene cyclobutanes were successfully transformed into the corresponding five-membered difluorinated products (**21-26**). The low yields for some cases are due to the low boiling points of the products. The macrocycles with 12- and 15-membered rings afforded the corresponding difluorinated alkanes as expected (**27**, **28**).

The spiro- and bridged cycles are of great importance in drug discovery but are synthetically challenging. We are pleased to find that the *N*-Cbz protected aza-spiro rings could efficiently undergo reaction to provide the *gem*-difluorinated spiro-rings (**29-31**). Furthermore, by using our methods, a diverse array of methylene-substituted adamantane were converted to their fluorinated analogues. The survival of free tertial alcohol highlighted the mildness of this protocol (**33**). Functional groups such as carbonyl (**37**), hydroxy (**33**), carboxylic acid (**34**), ester (**35**), and chloro (**36**) provided valuable synthetic handles for follow-up decorations. Depending on the loading of oxidant, the mono- or di-ring expansion reaction could be selectively accomplished (**39**, **40**). Of note, **29** and **34** could be prepared in decagram-scale.

The skeleton modification of bioactive natural products is key for lead identification. Traditional methods generally rely on de novo synthesis due to the lack of method for direct ring editing and the concerns of chemo-selectivity. To further challenge the robustness of our protocol, several natural products, complex bioactive compounds or their derivatives are employed. **S41**, derived from L-menthone, and **S42**, derived from Corodane, were successfully modified to their fluorinated analogue **41** and **42**, respectively. Isoalantolactone, bearing two exocyclic double bonds, could be selectively

fluorinated on the electron-rich bond with good regioselectivity (**43**). β-Eudesmol, with a free tertial alcohol on the side chain, was a viable substrate as well (**44**). Finally, under the standard conditions, we found that the acyclic 1,1-disubstituted alkene also underwent the desired reaction through the anticipated 1,2-alkyl migration, showcasing the generality of the protocol (**45**).

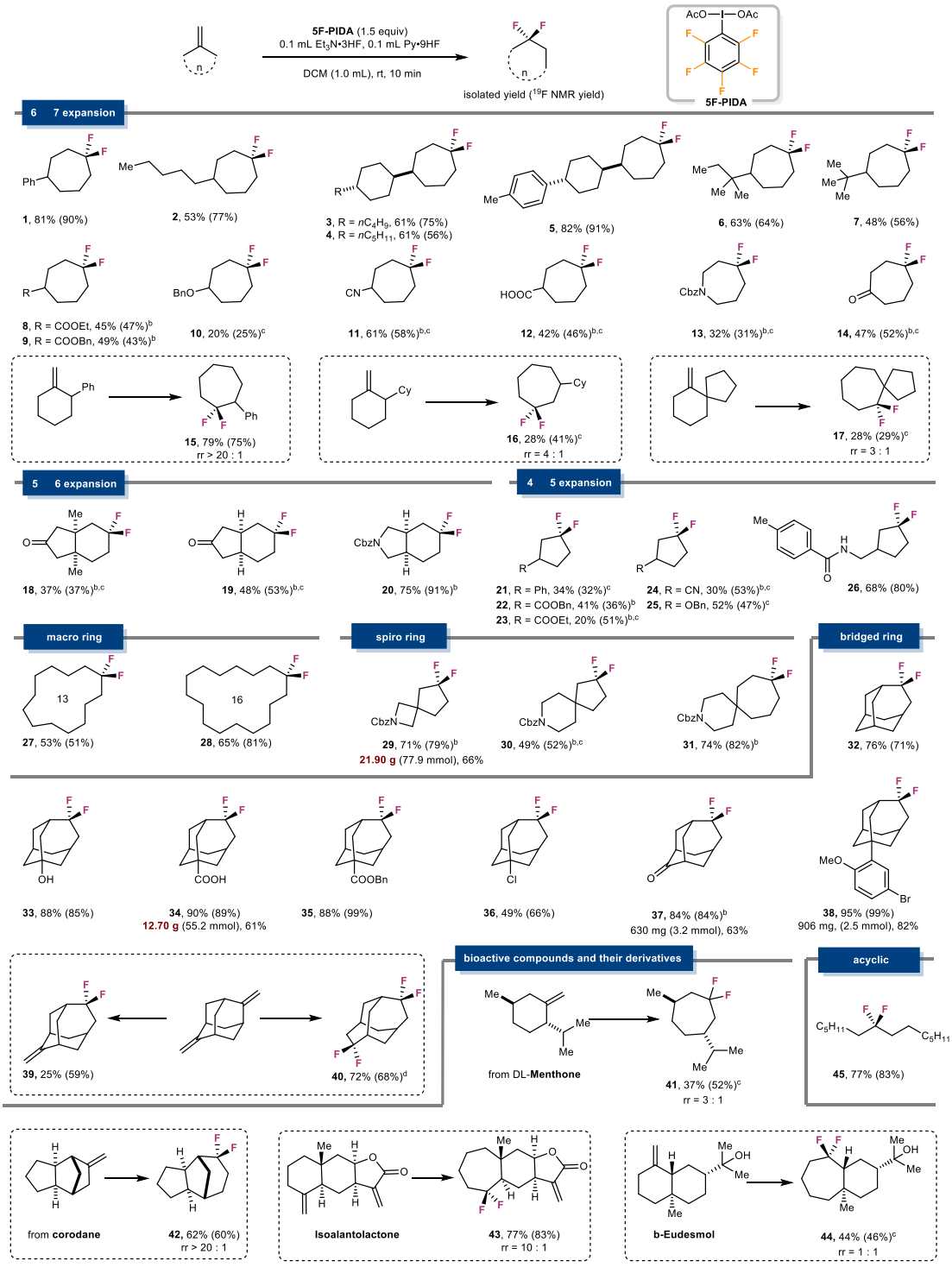

Fig. 4| Substrate scope [a]Reaction condition: S1 (0.2 mmol), Amine: HF = 1: 5.5 (0.2 mL) is mixture of 0.1 mL NEt_3·HF and 0.1 mL Py·HF, 5F-PIDA (1.5 equiv), DCM (1 mL), room temperature, 10 min. [b]40 equiv Py·HF (0.224 mL). [c]0.5 mmol scale. [d]Amine: HF = 1: 5.5 (0.4 mL), 5F-PIDA (3.0 equiv).

Synthetic applications.

Considering the prevalence of CF_2 moiety and the tremendous success of adamantanyl (Ad) group in drug development, we proposed our synthesized CF_2-Ad group as a promising bioisostere of Ad. Therefore, the synthesis of Ad-containing drug analogues using the building block obtained above (**34**, **37**, **38** in Figure 4) were conducted. The carboxylic acid in **34** was firstly converted to the correspond hydroxamic acid (**46**, Fig. 5). Following a Lossen rearrangement, CF_2-Ad amine (**47**, analogue of Amantadine, antiviral drug) was obtained in good yield. **47** could be further decorated to **48** (analogue of Tromantadine, antiviral drug) via an acylation-substitution sequence. On the other hand, an interrupted Lossen rearrangement of **46** in the presence of external amine furnished **49** (analogue of AR-9281, epoxide hydrolase inhibitor). In another vein, **34** was transformed to cyanide **50**, which upon Grigand addition and reduction, furnished **51** (analogue of Rimatadine, antiviral drug). Starting from **37**, a reductive amination of the ketone moiety gave **52** (analogue of SQ-109, antibiotic for treatment of TB). A Suzuki-Miyaura coupling of **38**, followed by successive deprotection led to the construction of **55** (analogue of Adatotene, anti-tumor agent). And finally, deprotection of the Cbz group in **29** with hydrogenation provided a valuable building block **56**.

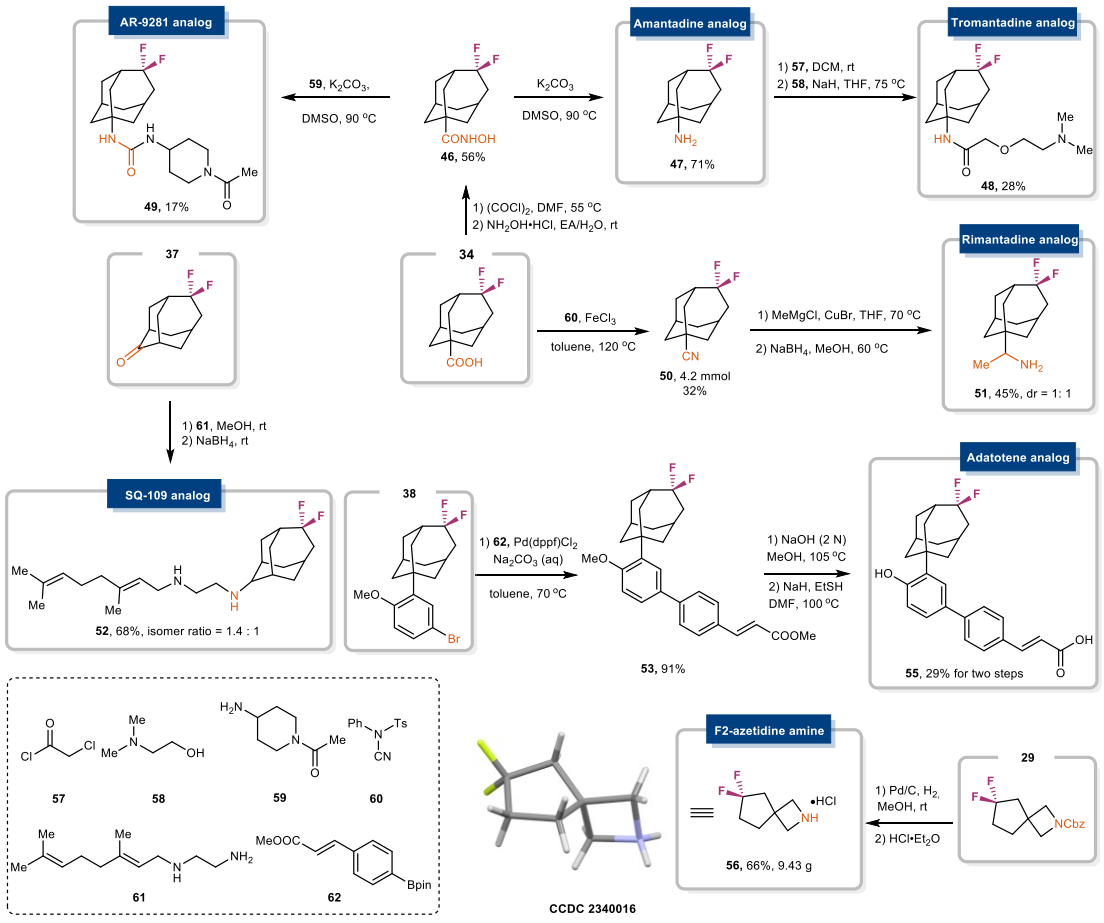

Fig. 5| Synthetic applications.

We next checked the influence of fluorine incorporation on the conformation of F2-azetidine ring (Fig. 6A). In accordance with literature observation, a significant broadening of the C-CF_2-C angle (108.1 °) was observed, compared to the adjacent C-CH_2-C angles (105.1 ° and 103.7 °). In addition, the lengths of the C-C attached to the CF_2 moiety were shortened, making the skeleton less symmetric. In addition, the lengths of the C-C attached to the CF_2 moiety were shortened, making the skeleton less symmetric. The influence of fluorine incorporation on acidity/basicity and lipophilicity were also measured (Fig. 6B). As expected, the fluorine incorporation reduced the basicity of amine, and increase the acidity of the carboxylic acid, but to a less extent due to the long distance between the fluorine atoms and basic/acidic groups. Previous observation shows that the difluoromethyl substituents can marginally decrease the Log P values. This is indeed the case as the CF_2-Ad amine is slightly less lipophilic than the amantadine.

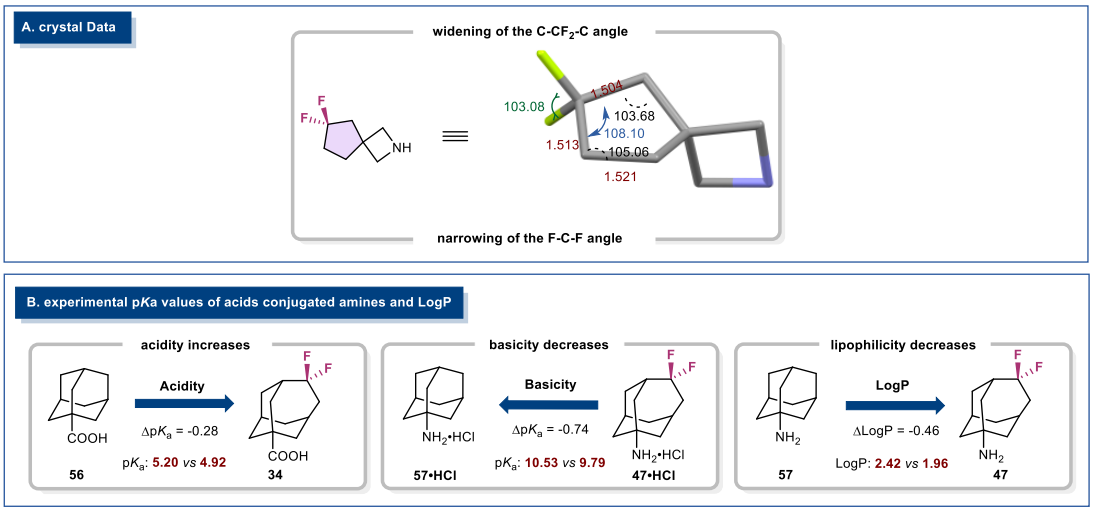

Fig. 6| Physicochemical and conformational analysis.

Conclusions

Fluorinated aliphatic ring systems hold significant importance in the realm of functional molecules, yet their synthesis from readily available precursors presents ongoing challenges. In this report, we have developed a novel chemical reaction - *gem*-difluorinative ring-expansion of alkenes. The reaction involves I(III)-reagent, and facilitates the creation of a diverse range of difluorinated aliphatic rings. These include macrocyclic, fused, spiro, bridged, and natural product-derived structures. Notably, this transformation diverges from conventional I(III)/F^- conditions, necessitating the precise tuning of the electronic properties of the I(III) species, notably employing the highly electron-deficient 5F-PIDA. The robustness of this protocol is demonstrated through several decagram-scale syntheses and the efficient structural modification of a variety of adamantane-containing drugs and natural products. Moreover, we systematically assess the physicochemical and conformational alterations conferred by the *gem*-difluoromethyl group.

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Author Contributions

Q.L., P.K.M. and H.W. conceived the project. Y.L. designed and performed the experimental work. V.S. and I.L. adjusted and performed the decagram scale-up experimental work. X.-B.L., J.-H.X., J.-Y.W., J.-L.F., S.L., Y.L. contributed to the analysis and interpretation of data. P.K.M. and H.W. wrote the manuscript. All authors contributed to or approved the final version of the paper.

Keywords: *gem*-difluorination; ring-expansion; alkene; drug modification; natural product

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Graphical Abstract.

New chemical reaction, - *gem*-difluorinative ring-expansion of alkenes, - has been developed.