Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2024, **15**, 12026

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 17th May 2024
Accepted 22nd June 2024

DOI: 10.1039/d4sc03230f

rsc.li/chemical-science

Chemo-, regio-, and stereoselective tetrafunctionalization of fluoroalkynes enables divergent synthesis of 5-7-membered azacycles†

Jia-Wei Chen,[a] Wen-Jun Ji,[a] Xue-Ying Huang,[a] Danhua Ge,[a] Zhi-Liang Shen,*[a] Kai Guo*[b] and Xue-Qiang Chu*[a]

Alkyne annulation has been widely used in organic synthesis for the construction of azacycles with unique structural and physicochemical properties. However, the analogous transformation of fluoroalkynes remains a challenge and has seen limited progress. Herein we report a 1,2,3,4-tetrafunctionalization of polyfluoroalkynes for the divergent construction of 5-7-membered (*E*)-1,2-difluorovinyl azacycles. The use of the fluorine atom as a detachable "activator" not only obviates the use of any transition metal catalysts and oxidizing reagents, but also ensures the [3–5 + 2]-annulation and defluorinative functionalization of fluoroalkynes with high chemo-, regio-, and stereoselectivities. This method exhibits a broad substrate scope, good functional group tolerance, and excellent scalability, providing a modular platform for accessing fluorinated skeletons of medicinal and biological interest. The late-stage modification of complex molecules, the multi-component 1,2-diamination of fluoroalkyne, and the synthesis of valuable organofluorides from the obtained products further highlight the real-world utility of this fluoroalkyne annulation technology.

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Introduction

Azacycles have aroused extensive research enthusiasm due to their prevalence among naturally occurring products, FDA-approved drugs, agrochemicals, and materials.[1] Fig. 1A exemplifies some biologically important N-heterocyclic structures such as pyrrole, imidazole, hydropyrazine, and diazepine derivatives. Nonetheless, there remains a lack of reliable synthetic methodologies for creating fragment libraries of 5-7-membered azacycles with enhanced molecular complexity and improved compatibility with functionalities.[2,3]

The selective and controllable functionalization of the C–F bond in polyfluorinated compounds has emerged as a complementary method to elegantly access complex, privileged molecules that are challenging to obtain from their nonfluorinated congeners.[4–12] In this context, the utilization of fluoroalkynes as coupling partners enriches alkyne chemistry where their multifaceted functions and distinct reactivity could allow nontraditional annulation (Fig. 1B).[13,14] Specifically, the presence of neighboring fluorine atoms polarizes the C–C triple bond, imposes steric congestion, and modulates the inherent reaction selectivity/reactivity of the π-system, resulting in chemo- and regioselective transformations.[15,16] The easily detachable fluorine atom also eliminates the need for expensive transition metal catalysts and external chemical oxidants, enabling redox-neutral and sustainable processes.[17,18] In addition, the availability and versatility of fluorine-functionalized motifs are crucial when taking into account biomedical areas, as they can confer physiochemical and pharmacodynamic advantages to the targeted products.[19] However, intermolecular defluorofunctionalization of fluoroalkynes is still scarce.[20–22]

Recently, defluorinative annulation of *gem*-difluoromethylene alkynes, pioneered by Loh/Feng,[23] Wang,[24] Rovis,[25] Yi/Zhou/Xu,[26,27] and others,[28–30] were found to easily allow rapid assembly of diverse heterocyclic skeletons with mono- or nonfluorinated unsaturated side chains (Fig. 1C). Indeed, many of the fluoroalkene products have attracted particular interest due to the combined features of fluorine and alkene.[31–33] The key to success lies in transition-metal-assisted regioselective fluoroalkyne insertion, which is followed by β-F elimination and downstream ring closure. Consequently, fluoroalkynes, taking advantage of the fluorine atom as a detachable "activator" and "handle", show promising abilities as modular C1 (ref. 23 and 24) or C2 (ref. 25–30) synthetic equivalents *via* tri- or tetrafunctionalization. Although novel and efficient, the advances come with caveats, namely, the use of costly metal catalysts (*e.g.*, Ru and Ir) and extra additives, the need for pre-

[a]*Technical Institute of Fluorochemistry, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China. E-mail: ias_zlshen@njtech.edu.cn; xueqiangchu@njtech.edu.cn*

[b]*College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, China. E-mail: guok@njtech.edu.cn*

† Electronic supplementary information (ESI) available: General information, experimental details, optimization of reaction conditions, mechanistic studies, characterization data for products, and NMR spectra of products. CCDC 2176621 (product **12**), 2293060 [product (E)-**66**] and 2330186 (product **69**). For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4sc03230f

© 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

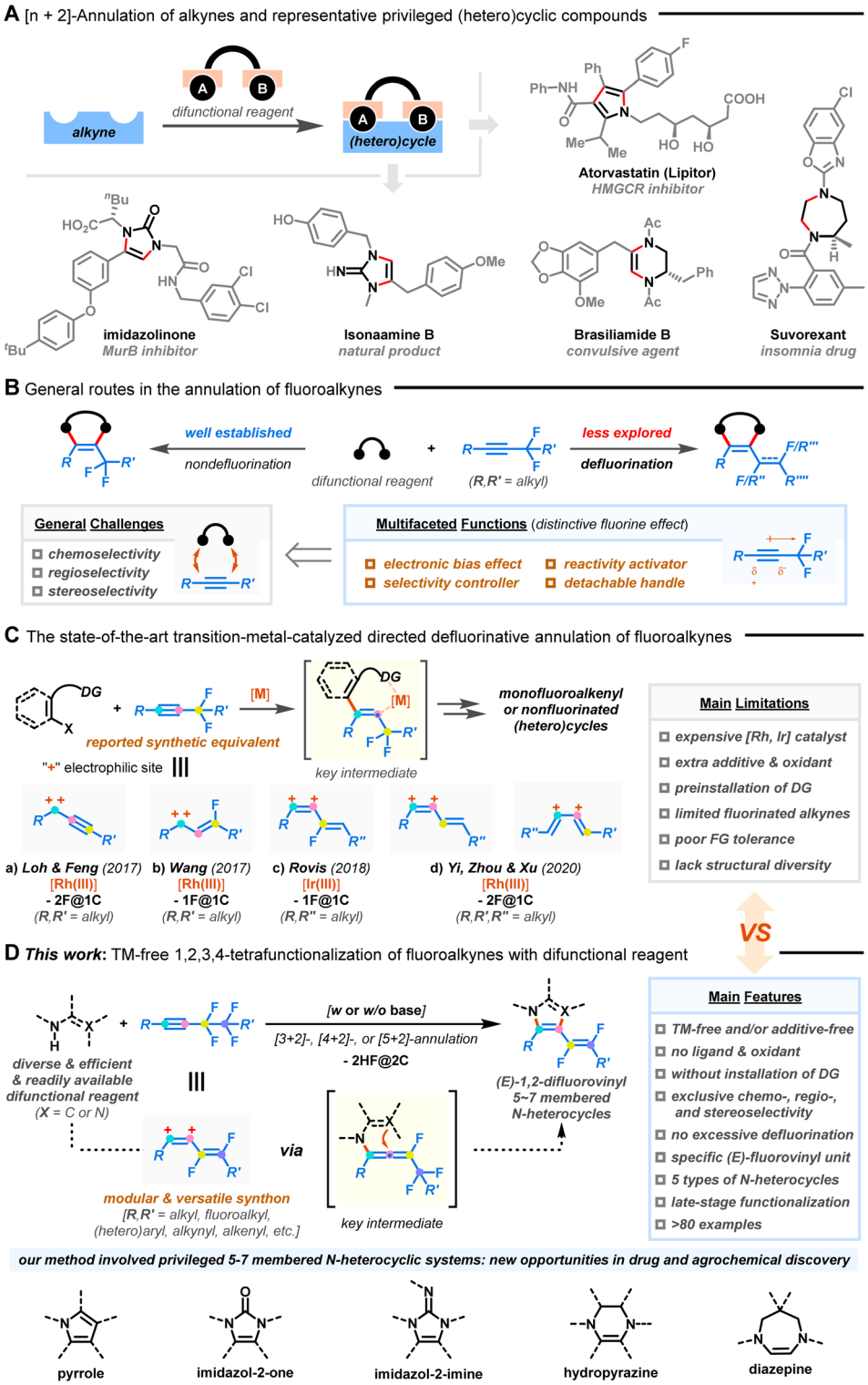

Fig. 1 Annulation of alkynes for the construction of (hetero)cyclic systems. (A) [*n* + 2]-annulation of alkynes and representative privileged (hetero)cyclic compounds. (B) General routes for the annulation of fluoroalkynes. (C) The state-of-the-art transition-metal-catalyzed directed defluorinative annulation of fluoroalkynes ("−2F@1C" means two C–F bond cleavages at a single carbon site; "−1F@1C" means one C–F bond cleavage at a single carbon site). (D) Divergent defluorinative [3–5 + 2]-annulation of fluoroalkynes with difunctional reagents (this work).

installed directing groups (DGs), limited substrate variation (R′, R″, and R‴ = alkyl groups, Fig. 1C-a–d), poor tolerance of functional groups, and harsh reaction conditions, all of which collectively hinder practical application of the methods.

Furthermore, these processes mainly focused on the manipulation of *gem*-difluoromethylene alkynes with a single fluorinated carbon atom (F@1C). A convenient procedure for the activation of two C–F bonds on two different fluorinated

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

carbon atoms (F@2C) remains relatively understudied but is highly desirable.[34,35] However, the occurrence of steric shielding by fluorine atoms on carbon centers, dipolar resonance structures, competitive multi-activations of C–F/C–C bonds, excessive defluorination, and undesired non-site-selective side reactions restricts the ready transformation of polyfluoroalkynes.

In this report, we describe a chemo-, regio-, and stereoselective [3–5 + 2]-annulation of less-studied polyfluoroalkynes through an alternative, mild, catalyst-free, oxidant-free, DG-free, and divergent sequence of 1,2-carboamination[36–39]/1,2-diamination[40–43] and defluorinative polyfunctionalization (Fig. 1D). Key allenyl intermediates could be generated in the absence of transition-metal catalysts and oxidants,[23–30] which allows for the downstream consecutive functionalization of two vicinal C(sp^3)–F bonds with ease. A wide range of (*E*)-1,2-difluorovinyl azacycles with five-, six-, and seven-membered rings, including pyrroles, imidazol-2-ones, imidazol-2-imines, hydropyrazines, and diazepines, were synthesized from readily available difunctional reagents and fluoroalkynes without resorting to substrate prefunctionalization. The strategy also distinguished itself with exceptional substrate scope, good functional group tolerance, and gram-scale ability. More impressively, the integration of a unique fluorovinyl motif with azacycles in one molecule could pave a substantial way for new drug and agrochemical discovery.[31–33]

Results and discussion

Evaluation of the reaction conditions

The investigation was commenced by testing the model reaction of perfluorobutyl alkyne **1a** and DBU (**2a**) under transition-metal-free conditions (see the ESI for more details, Table S1†). Pleasingly, 22% NMR yield of desired fluorovinyl bicyclic amidine **3**, with an *E*/*Z* ratio of 7.4/1, could be obtained in DMSO at room temperature for 6 h (entry 1). After systematic optimization of various reaction parameters, such as bases, solvents, reaction temperature, and reaction time, the highest isolated yield (80%) was obtained when performing the reaction in ^{i}PrOAc at 70 °C for 15 min (see entry 17, Table S1†). It is worth mentioning that the defluorination process was exclusively and highly chemo-, regio-, and stereoselective (*E*/*Z* > 30/1).

Substrate scope for polyfluoroalkynes

With the optimal conditions in hand, we explored the substrate scope of the intermolecular [3 + 2] annulation with respect to diversely functionalized fluoroalkynes (Fig. 2). First, a series of aryl and heteroaryl perfluorobutyl alkynes with varied substitution patterns could be smoothly converted into the corresponding azacycles in good yields with complete *E*-selectivity (Fig. 2A, **4–20**). Electron-donating (**4–9**), electron-withdrawing (**10–15**), functional groups (*e.g.*, ether, amino, halide, trifluoromethyl, ester, and nitrile; **8–15**), and heterocycles (*e.g.*, pyridine, thiophene, and pyrazole; **18–20**) were well tolerated in the metal-free system, thus providing great flexibility for further post-synthetic modification. Notably, methyl substituents at either the *meta*- (**5**) or *ortho*-position (**6**) of the phenyl ring did not hinder the reaction efficiency. Transformation of alkyl perfluorobutyl alkynes also successfully occurred (Fig. 2B). The substrates containing strained cyclohexyl (**21**), acyclic pentyl (**22**), phenyl (**23**), acetoxy (**24**), benzoxy (**25**), diphenylphosphoryloxy (**26**), benzyloxy (**27**), TBS-capped hydroxyl (**28**), hydroxyl (**29**), cyano (**30**), internal alkenyl (**31**), and terminal alkenyl (**32**), as well as the alkynyl group (**33**) were compatible and produced the *E*-isomeric products, which validated the mildness of the reaction conditions. Moreover, aryl fluoroalkynes possessing length-varied perfluoroalkyl chains (Fig. 2C; C2–C10; **34–38**) were found to react with DBU, resulting in the desired products in 11–94% yields. Among them, the low yield of product **34** is due to the instability of the embedded 1,2,2-trifluorovinyl pattern. When synthetically valuable units, such as iodine (**39**), sulfides (**40–42**), alkanes (**43** and **44**), arene (**45**), heterocycles (**46** and **47**), and alkenes (**48–50**), were introduced on the side of the fluoroalkyl group, no significant loss in yield is witnessed, although there is a decrease in *E*/*Z*-selectivity in some cases (**43–50**). In particular, these difluorovinyl azacycles are otherwise unattainable through traditional or Ru/Ir-catalyzed methods,[23–30,36] exemplifying the versatility and practicality of the present protocol.

Substrate scope for difunctional reagents

Subsequently, the use of diverse difunctional reagents as competent reaction partners was studied (Fig. 3A). Besides bicyclic derivatives (33–83% yields; **51**, **63**, **64**), pyrrole products with versatile groups were obtained in moderate to good yields with excellent stereoselectivities by using acetamidines derived from commercially available butan-1-amine (**52**), steric cyclopropanamine (**53**), (hetero)aryl ethanamines (**54** and **55**), benzylamine (**56**), 3-morpholinopropan-1-amine (**57**), 2-methoxyethan-1-amine (**58**), 2-(methylthio)ethan-1-amine (**59**), amino acid esters (**60** and **61**), and prop-2-yn-1-amine (**62**). Especially, pyrrole is the core structure of many approved pharmaceuticals. (Hetero)arene, amine, ether, sulfide, ester, and alkyne functionalities did not interfere with intermolecular defluorination. 1,2,3-Triphenylguanidine and 1,3-diarylurea could also be annulated to afford products **65–67** in 63–77% yields, which would otherwise be difficult to synthesize. One apparent advantage of our methodology is that it can be applied to efficient synthesis of 6-7-membered (*E*)-1,2-difluorovinyl hydropyrazine (**68**) and diazepines (**69–70**) through the reaction of 1,2-disulfonamide **2s** and 1,3-disulfonamides **2t–u** with fluoroalkyne **1a**, which significantly enhances product diversity and accessibility. The corresponding structures of products **12**, (*E*)-**66**, and **69** were characterized by X-ray crystallographic analysis (see ESI†).

Substrate scope for complex molecules

The broad substrate scope tolerance of this defluorinative technology encouraged us to apply it to late-stage elaboration of more complex compounds (Fig. 3B). To our delight, a large variety of biologically and pharmaceutically relevant molecules, such as fluoxetine (**71**), L-menthol (**72**), glucose (**73**), metiapine (**74**, **83**), ibuprofen (**75**), isoxepac (**76**), oxaprozin (**77**), tryptamine (**79**),

© 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

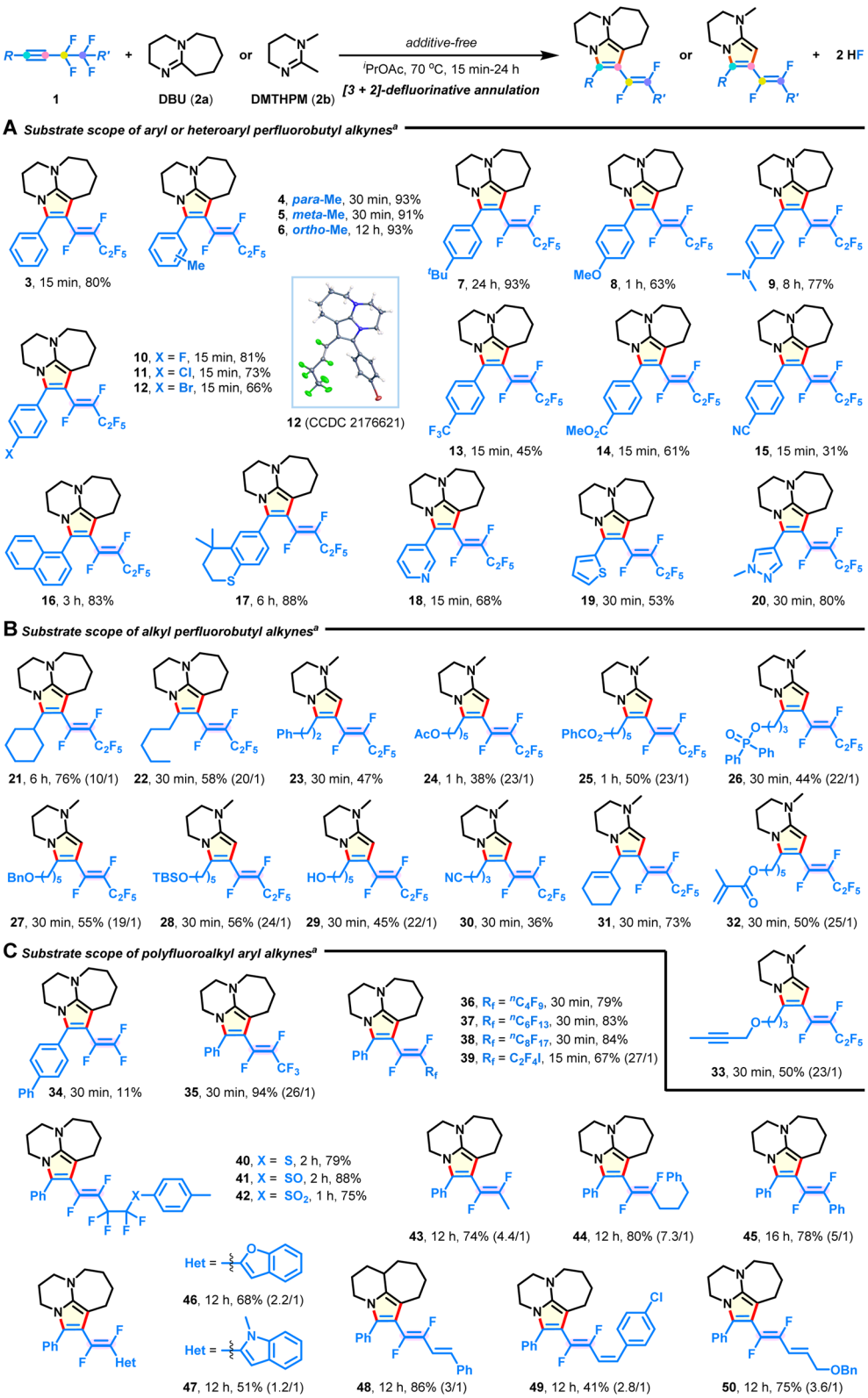

Fig. 2 Substrate scope of fluoroalkynes. (A) Substrate scope of aryl or heteroaryl perfluorobutyl alkynes. (B) Substrate scope of alkyl perfluorobutyl alkynes. (C) Substrate scope of polyfluoroalkyl aryl alkynes. [a]Reaction conditions: fluoroalkyne **1** (0.3 mmol), DBU (1.05 mmol, **2a**) or DMTHPM (1.05 mmol, **2b**) in ^{i}PrOAc (2 mL) at 70 °C under N_2 for 15 min-24 h; *E*/*Z* selectivities were >30 : 1 except in some cases where the ratios are given in parentheses.

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

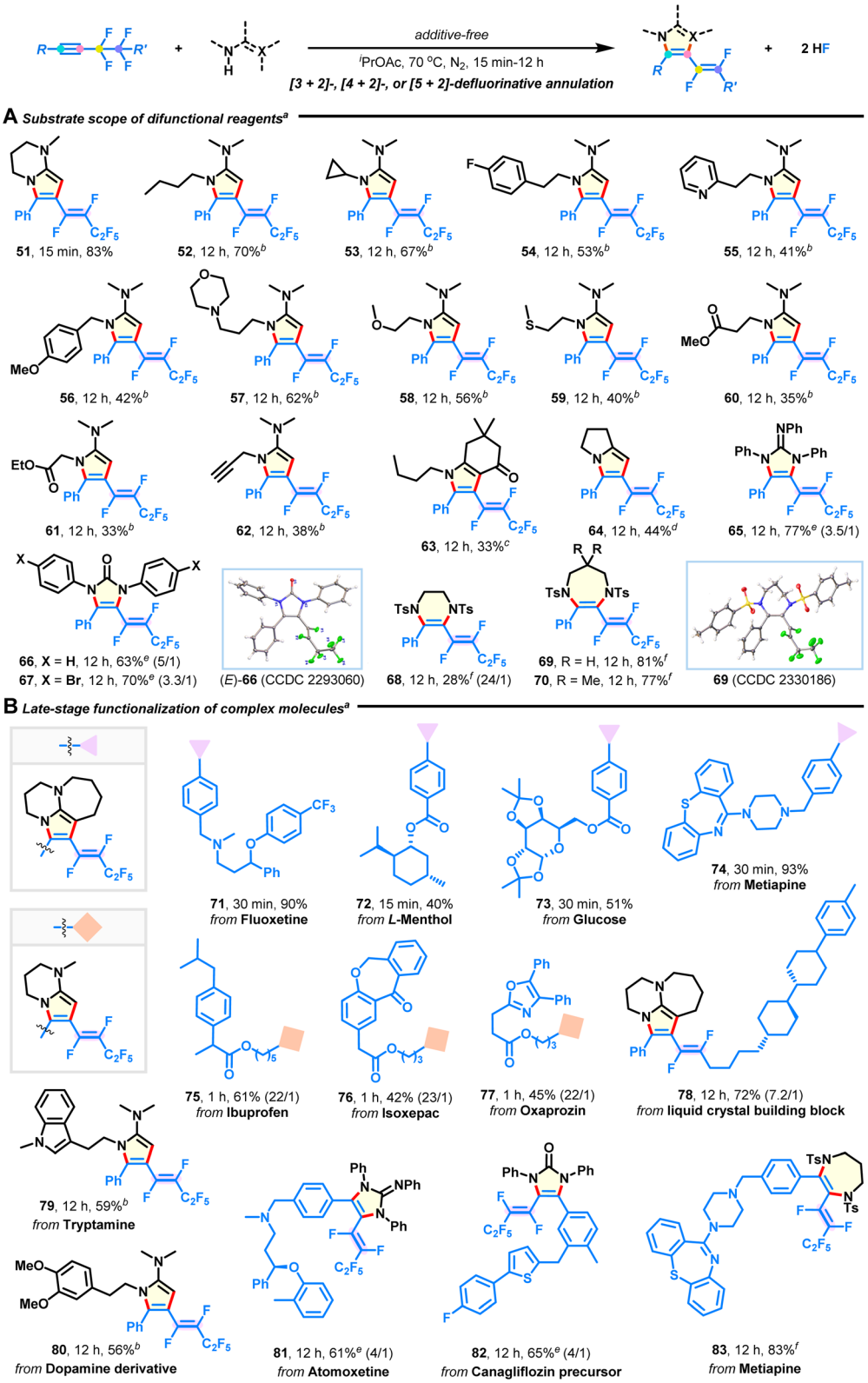

Fig. 3 Substrate scope of difunctional reagents and late-stage functionalization of complex molecules. (A) Substrate scope of difunctional reagents. (B) Late-stage modification of complex molecules. [a]Reaction conditions: fluoroalkyne (0.3 mmol) and difunctional reagent (1.05 mmol) in ⁱPrOAc (2 mL) at 70 °C under N_2 for 15 min to 12 h; *E*/*Z* selectivities were >30 : 1 except in some cases where the ratios are given in parentheses. [b]Under neat conditions at 90 °C. [c]Cs_2CO_3 (1.05 mmol) was used. [d]1-Methylimidazole (0.75 mmol) was used. [e]Cs_2CO_3 (0.75 mmol) was used in DMSO at 90 °C. [f]Cs_2CO_3 (0.9 mmol) was used in DMF at 110 °C.

© 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

dopamine (**80**), atomoxetine (**81**), and canagliflozin (**82**) were successfully employed to merge with azacyclic frameworks, delivering some intriguing adducts in 40–93% yields with equally excellent stereoselectivities (except products **81** and **82**). Furthermore, the liquid crystal (LC) building block (**78**) was amenable to this reaction, which will provide chemists an attractive alternative for manufacturing new fluorinated LC materials.[44]

Multi-component 1,2-diamination

To increase the applicability of our technique for accessing 1,2-difluorovinyl scaffolds, we examined the multi-component 1,2-diamination of fluoroalkyne **1a**. As shown in Fig. 4A, the desired 1,3-diene-1,2-diamine **85** was synthesized in 80% yield with an *E*/*Z* ratio of 3.4/1 when TsNHMe (**84**) was employed as the amination reagent. Furthermore, cyclic dihydroimidazole (**86**) showed decreased reactivity, but with high *Z*-selectivity

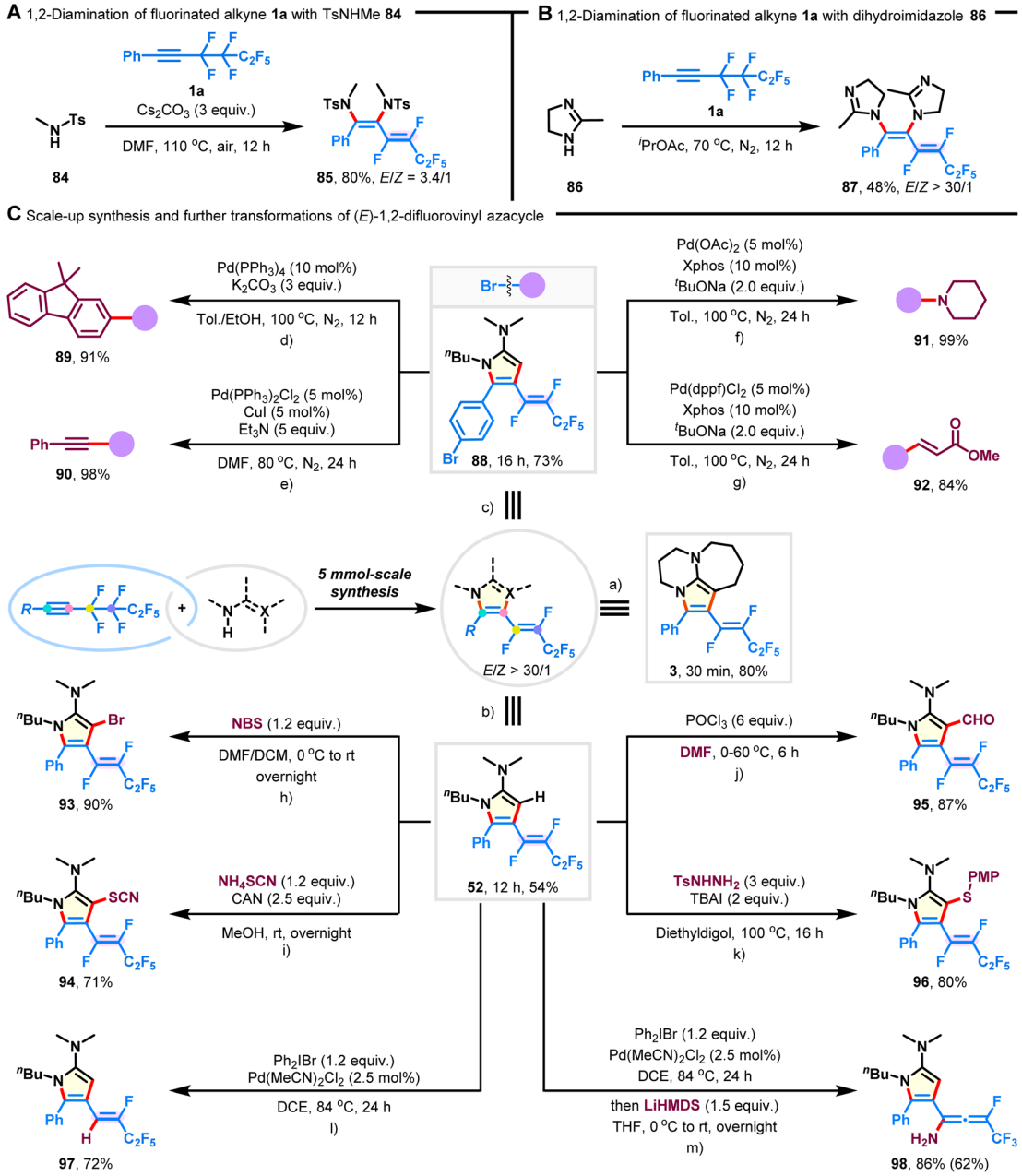

Fig. 4 Three-component 1,2-diamination, scale-up synthesis, and further transformation of products. (A) Three-component 1,2-diamination of fluoroalkyne **1a** with TsNHMe (**84**). (B) Three-component 1,2-diamination of fluoroalkyne **1a** with dihydroimidazole (**86**). (C) 5 mmol-scale synthesis and further transformations of (*E*)-1,2-difluorovinyl azacycles. (a) Fluoroalkyne **1a** (5 mmol) and DBU (**2a**) (17.5 mmol) in ^{i}PrOAc (30 mL) at 70 °C under N_2 for 30 min. (b) Fluoroalkyne **1a** (5 mmol) and acetimidamide **2c** (17.5 mmol) under neat conditions for 12 h. (c) Fluoroalkyne **1j** (5 mmol) and acetimidamide **2c** (17.5 mmol) under neat conditions for 16 h. (d) Product **88** (0.3 mmol) and (9,9-dimethyl-9*H*-fluoren-2-yl)boronic acid (0.6 mmol) were used. (e) Product **88** (0.3 mmol) and phenylacetylene (0.9 mmol) were used. (f) Product **88** (0.3 mmol) and piperidine (0.6 mmol) were used. (g) Product **88** (0.3 mmol) and methyl acrylate (0.9 mmol) were used. (h–l) Product **52** (0.3 mmol) was used. (m) Product **97** (0.3 mmol) was used in the second step; yield in parentheses was over two steps.

© 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

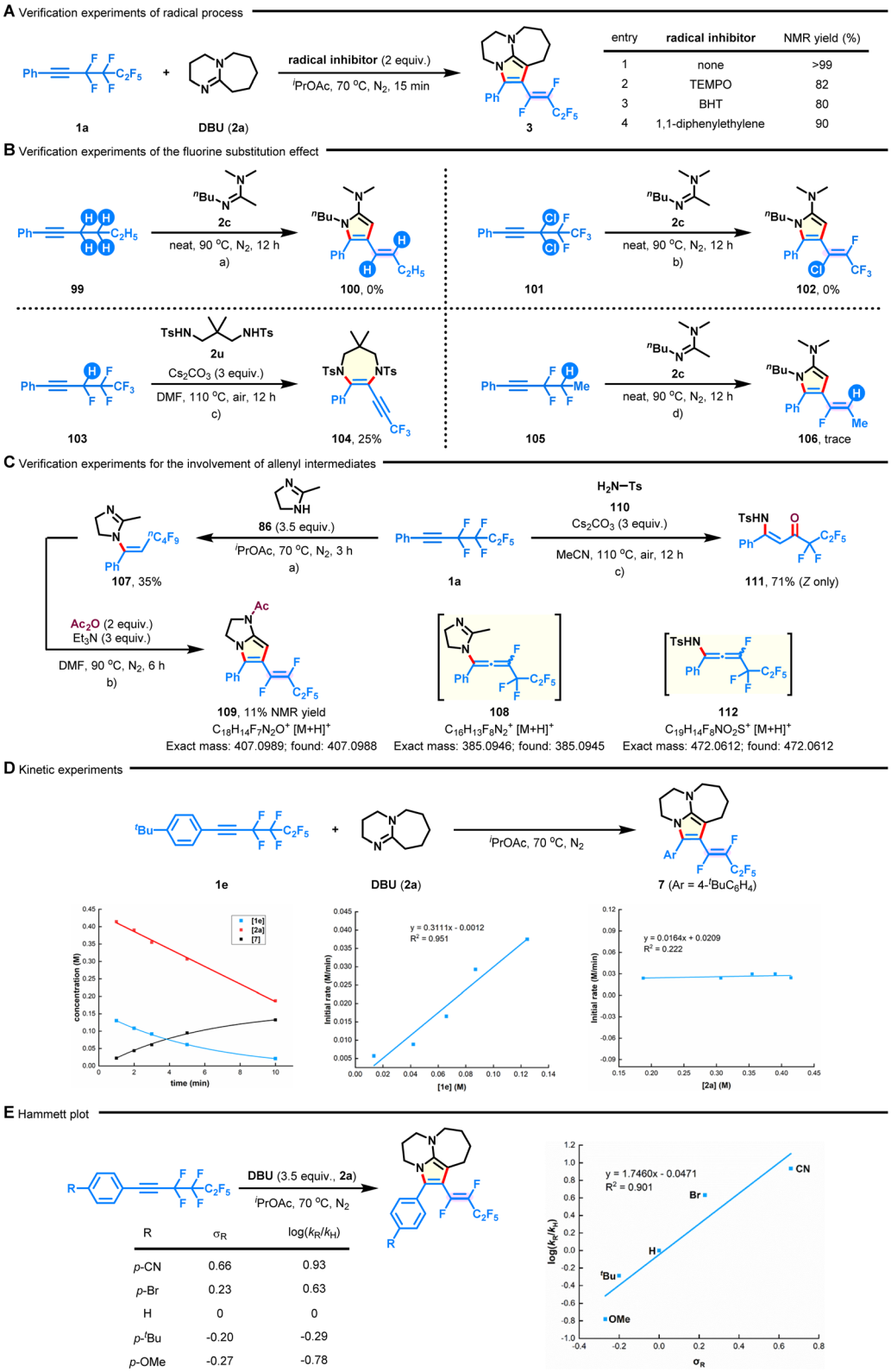

Fig. 5 Control experiments. (A) Verification experiments of the radical process. (B) Verification experiments of the fluorine substitution effect. (C) Verification experiments for the involvement of allenyl intermediates. (D) Kinetic experiments. (E) Hammett plot of substituted polyfluoroalkynes.

preserved (Fig. 4B; 48% yield, E/Z > 30/1; **87**). It is important to note that competitive hydroaminated products were not observed.[45]

Scale-up synthesis

The scalability of this procedure was demonstrated by the preparation of azacycles **3**, **52**, and **88** on a 5 mmol scale, which

© 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

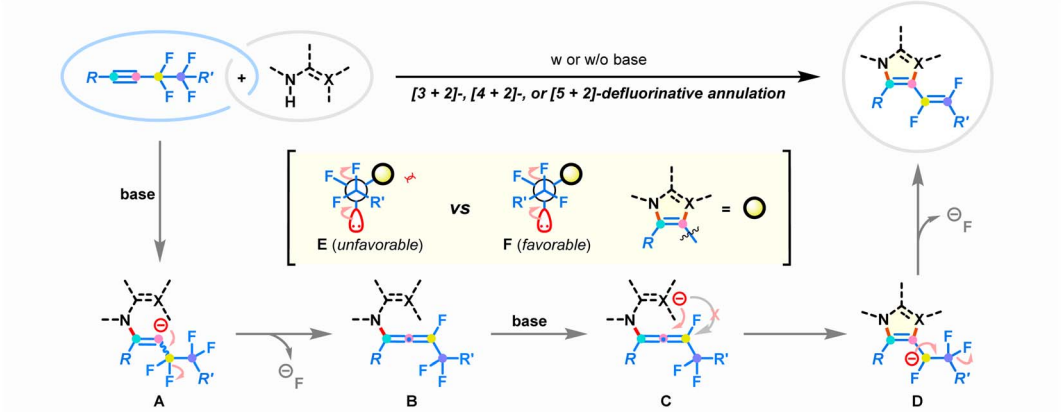

Fig. 6 Proposed reaction mechanism.

were isolated without any significant loss in reaction selectivity or yield (Fig. 4C-a–c; 54–80% yield, E/Z > 30/1).

Synthetic applications

Given that the obtained azacycles are decorated with various functionalities, it becomes feasible to introduce more diverse structural features through post-functionalization. The bromide substituent on product **88** could be facilely transformed into valuable motifs, such as fused arene (Fig. 4C-d; 91% yield; **89**), alkyne (Fig. 4C-e; 98% yield; **90**), amine (Fig. 4C-f; 99% yield; **91**), and acrylate (Fig. 4C-g; 84% yield; **92**). Particularly, the structure and the configuration of the fluorovinyl group remained intact during these Pd-catalyzed cross-coupling reactions. Besides, product **52** underwent bromination, thiocyanation, formylation, and thioetherification, generating the corresponding pyrrole compounds **93–96** in good yields without the erosion of stereopurity (Fig. 4C-h and k). In addition, one of the C(sp^2)–F bonds on the product **52** could be selectively removed in the presence of $Pd(MeCN)_2Cl_2$ and Ph_2IBr (Fig. 4C-l; 72% yield, **97**), and the ready transformation to fluorinated allenyl amine was achieved upon treatment with LiHMDS (Fig. 4C-m; 86% yield, **98**).

Mechanistic investigations

To gain a preliminary understanding of the reaction mechanism, several control experiments were conducted, and the results are shown in Fig. 5. First, the [n + 2]-defluorinative annulation process was not impeded in the presence of TEMPO (tetramethylpiperidine-1-oxyl), BHT (2,6-di-*tert*-butyl-4-methylphenol), or 1,1-diphenylethylene, revealing that a radical pathway could be excluded at this stage (Fig. 5A). Subsequently, the role of the fluoroalkyl group in this transformation was studied. No desired annulated products were detected in the cases of nonfluorinated hex-1-yn-1-ylbenzene (**99**) and *gem*-dichlorine congener **101** under neat conditions (Fig. 5B-a and b). Although the reaction between 1,3-disulfonamide **2u** and (3,4,4,5,5,5-hexafluoropent-1-yn-1-yl)benzene (**103**) successfully delivered 3,3,3-trifluoroprop-1-yn-1-yl azacycle **104** in 25% yield, only a trace amount of product **106** was observed when analogous (3,3,4-trifluoropent-1-yn-1-yl)benzene (**105**) was used (Fig. 5B-c and d). Together with the experiments described above, these observations demonstrate the indispensability of the perfluoroethane-1,2-diyl group on substrates. It deserves to be mentioned that the formation of product **104** could be attributed to a base-promoted dehydrofluoration of *in situ* formed α-fluoroalkene.[46] Furthermore, by shortening the reaction time of fluoroalkyne **1a** with dihydroimidazole (**86**) to 3 h (Fig. 4B), the hydroaminated product **107** was observed, which could be further converted into bicyclic product **109** in the presence of Ac_2O and Et_3N (Fig. 5C-a and b). This result means that the initial reaction might proceed through intermolecular hydroamination,[45] followed by intramolecular defluorinative annulation, ultimately accomplishing the concessive C–F bond functionalization. Interestingly, when **1a** was reacted with $TsNH_2$ (**110**), it led to the generation of (*Z*)-*N*-Ts-enaminone **111** in 71% yield (Fig. 5C-c). The results, combined with the occurrence of possible intermediates **108** and **112** (detected by HRMS analysis, see the ESI† for more details), correlate with the intermediacy of key fluoroallenes in the system.[47,48] On the other hand, the plots of kinetic experiments suggested a first-order kinetic dependence on **1e** but a zero-order kinetic dependence on **2a** (Fig. 5D). The electronic effect of the polyfluoroalkynes (such as 4-OMe, 4-^{t}Bu, 4-Br, and 4-CN) on the reaction rate was verified by Hammett studies (Fig. 5E).[49] The positive slope ($\rho = 1.746$) in the Hammett plot might suggest that electron-deficient aryl intermediates would be more favourable during the defluorocyclization process.

Proposed reaction mechanism

Based on the control experiments and the aforementioned reports,[23–30,36,43,45–48] a plausible mechanism for the developed defluorinative annulation is proposed in Fig. 6. Initially, the deprotonation of the amino group in the difunctional reagent enables the nucleophilic attack on fluoroalkynes. The electronic bias of the π-system by the polarization of the adjacent perfluoroethane-1,2-diyl substituent is considered to be the crucial factor that ensures regioselective addition.[45] The resulting reactive alkenyl anion **A** undergoes immediately β-F-elimination to deliver key fluoroallene species **B**.[46,47] At this

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

stage, the strong electron-withdrawing properties of the perfluoroalkyl group and fluorine atom lead to the ensuing intramolecular cyclization to selectively take place at the proximal double bond of allene species **B**, affording new 5-7-membered azacycles **D**. Finally, the following defluorinative E1cb elimination at the fluoroalkyl chain results in the stereoselective generation of (*E*)-1,2-difluorovinyl products. Notably, the steric repulsion between the R′ group and the azacycle core in conformational mode **F** favors the exclusive production of *E*-type products. On the other hand, the successive heterolytic cleavage of two vicinal C–F bonds removes electrons from the reaction composite, enabling the annulation to occur in a redox-neutral manner.[36–43]

Conclusions

In summary, we have developed a modular strategy for the [3–5 + 2]-annulation and 1,2,3,4-tetrafunctionalization of readily accessible polyfluoroalkynes with di-nucleophiles. This method provides practical and scalable access to a wide range of 5-7-membered azacycles with a specific (*E*)-1,2-difluorovinyl unit. Other notable features of the present strategy include a broad substrate scope, good functional group tolerance, and excellent chemo-/regio-/stereoselectivity. The late-stage modification of complex structures, the multi-component 1,2-diamination of fluoroalkyne, and the synthesis of valuable organofluorides from the obtained products further highlight the real-world utility of this defluorinative annulation technology. The controllable and selective cleavage of two C(sp^3)–F bonds at the fluoroalkyl chain contributes to the catalyst-free and oxidant-free heterocycle construction. As such, we believe this intriguing approach would open new avenues and inspire further developments in organic synthetic chemistry and pharmaceutical research.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

X. Q. C. conceived the project. J. W. C., W. J. J., X. Y. H., D. H. G., Z. L. S., and X. Q. C. conducted all experimental work and analyzed the data. The manuscript was written by Z. L. S., K. G., and X. Q. C. with contributions and proofreading from all authors. Z. L .S., K. G., and X. Q. C. directed the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (22001121) and Nanjing Tech University.

Notes and references

1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
2 C.-V. T. Vo, M. U. Luescher and J. W. Bode, *Nat. Chem.*, 2014, **6**, 310–314.
3 Z. Ma, W. Xu, Y.-D. Wu and J. S. Zhou, *J. Am. Chem. Soc.*, 2023, **145**, 16464–16473.
4 Y.-J. Yu, F.-L. Zhang, T.-Y. Peng, C.-L. Wang, J. Cheng, C. Chen, K. N. Houk and Y.-F. Wang, *Science*, 2021, **371**, 1232–1240.
5 C. Zhu, M.-M. Sun, K. Chen, H. Liu and C. Feng, *Angew. Chem., Int. Ed.*, 2021, **60**, 20237–20242.
6 L. Li, X. Zhang, Y. Ning, X. Zhang, B. Liu, Z. Zhang, P. Sivaguru, G. Zanoni, S. Li, E. A. Anderson and X. Bi, *Nat. Commun.*, 2022, **13**, 4280.
7 M. Hu, Y. Liang, L. Ru, S. Ye, L. Zhang, X. Huang, M. Bao, L. Kong and B. Peng, *Angew. Chem., Int. Ed.*, 2023, **62**, e202306914.
8 J. Huang, Q. Gao, T. Zhong, S. Chen, W. Lin, J. Han and J. Xie, *Nat. Commun.*, 2023, **14**, 8292.
9 Y. Zhang, J. Wang, Y. Guo, S. Liu and X. Shen, *Angew. Chem., Int. Ed.*, 2024, **63**, e202315269.
10 H. Qian, Z. P. Cheng, Y. Luo, L. Lv, S. Chen and Z. Li, *J. Am. Chem. Soc.*, 2024, **146**, 24–32.
11 M. Chen, Y. Cui, X. Chen, R. Shang and X. Zhang, *Nat. Commun.*, 2024, **15**, 419.
12 S. Bonfante, C. Lorber, J. M. Lynam, A. Simonneau and J. M. Slattery, *J. Am. Chem. Soc.*, 2024, **146**, 2005–2014.
13 M. C. Pacheco, S. Purser and V. Gouverneur, *Chem. Rev.*, 2008, **108**, 1943–1981.
14 S. Arimitsu, *Chem. Rec.*, 2023, **23**, e202300021.
15 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
16 J.-D. Hamel and J.-F. Paquin, *Chem. Commun.*, 2018, **54**, 10224–10239.
17 L. V. Hooker and J. S. Bandar, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308880.
18 D. Ge and X.-Q. Chu, *Org. Chem. Front.*, 2022, **9**, 2013–2055.
19 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
20 S. Arimitsu and G. B. Hammond, *J. Org. Chem.*, 2007, **72**, 8559–8561.
21 R. Surmont, G. Verniest and N. De Kimpe, *Org. Lett.*, 2009, **11**, 2920–2923.
22 A. Nasr El Dine, D. Gree, T. Roisnel, E. Caytan, A. Hachem and R. Gree, *Eur. J. Org Chem.*, 2016, **2016**, 556–561.
23 C.-Q. Wang, L. Ye, C. Feng and T.-P. Loh, *J. Am. Chem. Soc.*, 2017, **139**, 1762–1765.
24 T. Li, C. Zhou, X. Yan and J. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 4048–4052.
25 F. Romanov-Michailidis, B. D. Ravetz, D. W. Paley and T. Rovis, *J. Am. Chem. Soc.*, 2018, **140**, 5370–5374.
26 H. Gao, S. Lin, S. Zhang, W. Chen, X. Liu, G. Yang, R. A. Lerner, H. Xu, Z. Zhou and W. Yi, *Angew. Chem., Int. Ed.*, 2021, **60**, 1959–1966.

© 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 24 2024. Downloaded on 2025/8/11 2:57:56.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

27 H. Gao, M. Sun, H. Zhang, M. Bian, M. Wu, G. Zhu, Z. Zhou and W. Yi, *Org. Lett.*, 2019, **21**, 5229–5233.
28 F. Zhao, J. Qiao, Y. Lu, X. Zhang, L. Dai, X. Gong, H. Mao, S. Lu, X. Wu and S. Liu, *Org. Lett.*, 2021, **23**, 5766–5771.
29 Y. Luo, H.-Y. Zhou, Y.-C. Gang and L. Dong, *Org. Lett.*, 2022, **24**, 6940–6944.
30 Y. Yang, N. Li, J. Zhao, Y. Jiang, X. Zhang and X. Fan, *Adv. Synth. Catal.*, 2021, **363**, 3600–3606.
31 S. Couve-Bonnaire, D. Cahard and X. Pannecoucke, *Org. Biomol. Chem.*, 2007, **5**, 1151–1157.
32 S. Morand, P. Jubault, J.-P. Bouillon and S. Couve-Bonnaire, *Chem.–Eur. J.*, 2021, **27**, 17273–17292.
33 M.-Z. Lu, J. Goh, M. Maraswami, Z. Jia, J.-S. Tian and T.-P. Loh, *Chem. Rev.*, 2022, **122**, 17479–17646.
34 R. Doi, M. Yasuda, N. Kajita, K. Koh and S. Ogoshi, *J. Am. Chem. Soc.*, 2023, **145**, 11449–11456.
35 C. Douvris and O. V. Ozerov, *Science*, 2008, **321**, 1188–1190.
36 D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474–16475.
37 Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 4572–4576.
38 S. Rakshit, F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9585–9587.
39 H. Xiong, N. Ramkumar, M.-F. Chiou, W. Jian, Y. Li, J.-H. Su, X. Zhang and H. Bao, *Nat. Commun.*, 2019, **10**, 122.
40 Y. Zhu, R. G. Cornwall, H. Du, B. Zhao and Y. Shi, *Acc. Chem. Res.*, 2014, **47**, 3665–3678.
41 Y. Fukudome, H. Naito, T. Hata and H. Urabe, *J. Am. Chem. Soc.*, 2008, **130**, 1820–1821.
42 B. Yao, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2012, **51**, 5170–5174.
43 J. Pan, X. Li, F. Lin, J. Liu and N. Jiao, *Chem*, 2018, **4**, 1427–1442.
44 M. Kuroboshi, K. Kanie and T. Hiyama, *Adv. Synth. Catal.*, 2001, **343**, 235–250.
45 M. Patel, R. K. Saunthwal and A. K. Verma, *Acc. Chem. Res.*, 2017, **50**, 240–254.
46 P. Tian, C. Feng and T.-P. Loh, *Nat. Commun.*, 2015, **6**, 7472.
47 T. J. O'Connor, B. K. Mai, J. Nafie, P. Liu and F. D. Toste, *J. Am. Chem. Soc.*, 2021, **143**, 13759–13768.
48 J. S. Ng and T. Hayashi, *Angew. Chem., Int. Ed.*, 2021, **60**, 20771–20775.
49 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.