Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d6sc01441k

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Bidirectional skeletal remodelling of SF_5-nitrobenzenes into azepine, bicyclic, and benzimidazole frameworks†

Muhamad Zulfaqar Bacho,[a] Shiwei Wu,[b] Takuya Muramatsu,[b] Chavakula Nagababu,[a] Daiki Harano,[b] Seishu Ochiai[b] and Norio Shibata *[ab]

Received 18th February 2026
Accepted 19th March 2026

DOI: 10.1039/d6sc01441k

rsc.li/chemical-science

The development of PFAS-free fluorinated scaffolds that preserve the desirable physicochemical attributes of perfluoroalkyl groups remains a central challenge in contemporary fluorine chemistry. Herein, we report a rapid and bidirectional skeletal-remodelling platform that enables controlled interconversion between aromatic, medium-sized, and bicyclic SF_5-containing heterocycles from readily accessible SF_5-nitrobenzenes. Phosphorus-catalyzed iterative deoxygenation of SF_5-nitrobenzenes generates arylnitrene intermediates that undergo remarkably accelerated dearomative ring expansion, furnishing seven-membered SF_5-azepines within dramatically shortened reaction times compared to non-SF_5 analogues. These azepines function as versatile skeletal nodes, enabling divergent downstream transformations: photoinduced 4π-electrocyclization provides access to previously unexplored SF_5-azabicyclo[3.2.0]hepta-2,6-diene frameworks, while selective fluoroacylative activation promotes reverse skeletal reconstruction to restore aromaticity and deliver SF_5-substituted benzimidazoles. Collectively, this work demonstrates that strategic incorporation of the SF_5 group not only expands accessible heterocyclic architectures but also fundamentally alters skeletal rearrangement kinetics, enabling rapid and controllable skeletal editing from a common, practical precursor. Given the OECD classification of SF_5-containing molecules as non-PFAS, this unified skeletal-remodelling approach substantially broadens the design space of fluorinated scaffolds for applications in pharmaceuticals, agrochemicals, and functional materials, advancing the principles of sustainable fluorine chemistry.

Introduction

Fluorinated heterocycles are indispensable motifs in agrochemicals, pharmaceuticals, and functional materials, as fluorine substitution profoundly enhances lipophilicity, metabolic stability, and target engagement.[1] In agrochemical design, CF_3-substituted heterocycles are particularly dominant, accounting for more than 40% of all fluorinated agrochemicals.[1b] However, CF_3 groups are classified as per- and polyfluoroalkyl substances (PFAS) under the OECD definition, and their extreme environmental persistence has become a serious global concern.[2] The exceptional stability of C–F bonds leads to long-term accumulation and the formation of highly mobile degradation products such as trifluoroacetic acid (TFA, CF_3CO_2H).[3] While CF_3 groups remain manageable in pharmaceuticals,[1a] their intentional environmental release *via* agrochemicals[1b,3] is increasingly unsustainable. Consequently, the development of PFAS-free fluorinated alternatives that retain the functional advantages of CF_3 substituents has emerged as a critical challenge.

The pentafluorosulfanyl (SF_5) group represents a compelling solution.[4,5] As a hypervalent sulfur–fluorine functionality, SF_5 combines strong electron-withdrawing character, high lipophilicity, and substantial steric bulk, and is therefore widely regarded as a "super-CF_3" substituent. Importantly, unlike CF_3, SF_5 does not rely on persistent C–F bonds and exhibits the potential for environmentally benign mineralization, positioning SF_5-containing molecules as classified as PFAS-free.[3d] In molecular design, SF_5 functions as a bioisostere for CF_3, *tert*-butyl, and nitro groups, with comparable hydrophobicity and intrinsic volume (Fig. 1a). Despite these advantages, the structural diversity of SF_5-containing molecules—particularly SF_5-heterocycles—remains severely limited.[5c]

This limitation arises from a fundamental synthetic bottleneck. Traditional SF_5 installation typically relies on radical reactions with alkenes or alkynes using SF_5Cl or related reagents, which significantly limits substrate scope.[5h] In contrast, oxidative chloro-fluorination of aryl sulfides and related protocols[4b] require harsh reaction conditions,

[a]Department of Nanopharmaceutical Sciences, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan. E-mail: nozshiba@nitech.ac.jp

[b]Department of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

† Dedicated to Professor David O'Hagan to mark his retirement from the University of St Andrews (UK) and his significant contributions to the field of organofluorine chemistry.

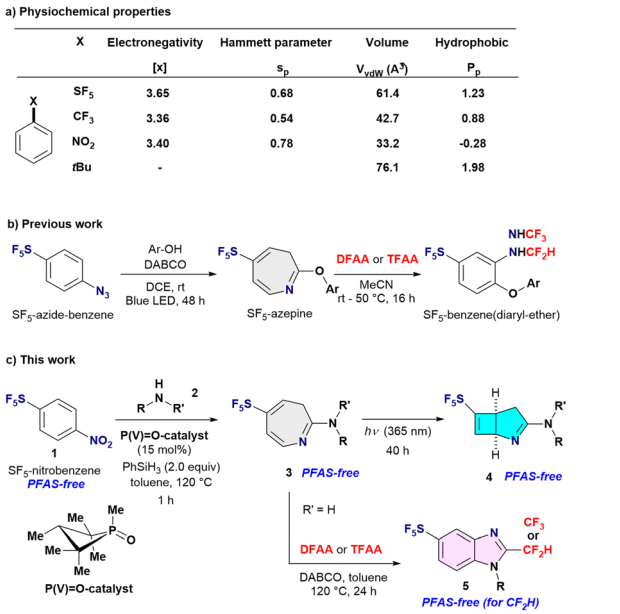


Fig. 1 Background of this work. (a) Properties of SF_5 *vs.* CF_3, NO_2 and *t*Bu-benzenes. (b) Previous work (c) This work.

specialized equipment, and stringent moisture control, rendering their application to the synthesis of SF_5-heterocycles highly limited.[6] As a result, SF_5 chemistry has remained largely limited to simple alkyl, alkenyl, and alkynyl motifs. Only recently have new classes of SF_5 reagents or new protocols been developed,[7] expanding the diversity of accessible substrates and reactivity profiles. Nevertheless, structurally complex heterocycles—particularly those incorporating SF_5 or SF_4 (ref. 8)—remain largely unexplored and synthetically inaccessible.

Concurrently, skeletal rearrangements have emerged as a powerful strategy for heterocycle synthesis, enabling rapid access to strained and unconventional architectures that are difficult to construct using classical cyclization methods.[9] We recognized that this framework-reorganization approach is uniquely suited to SF_5 chemistry, where conventional ring-construction strategies are intrinsically constrained. Consistent with this concept, we recently reported the photo-induced synthesis of SF_5-azepine aryl ethers from SF_5-azido benzene with phenols *via* skeletal rearrangement, thereby establishing this approach as a viable entry to medium-sized SF_5-heterocycles (Fig. 1b).[10] Notably, the strong electron-withdrawing nature of the SF_5 substituent was found to facilitate the key ring-expansion step from benzene to azepine frameworks. Encouraged by these findings, we herein extend this concept to sequential skeletal remodelling, enabling access to a range of previously inaccessible SF_5-containing heterocycles, including SF_5-azepin-2-amines **3**, SF_5-azabicyclo[3.2.0]hepta-2,6-dienes **4**, and SF_5-benzimidazoles **5**. In particular, the SF_5-azabicyclo [3.2.0]hepta-2,6-diene derivatives represent the first examples of this rigid bicyclic scaffold bearing an SF_5 substituent (Fig. 1c). Importantly, the synthesis originates from readily available SF_5-nitrobenzenes **1**, rather than inherently energetic SF_5-azido benzenes, and proceeds through consecutive skeletal rearrangements. These transformations establish a unified skeletal-editing manifold that interconverts aromatic, medium-sized, and bicyclic SF_5-containing architectures.

Results and discussion

Development of a rapid skeletal rearrangement to amino-SF_5-azepines

Seven-membered SF_5-heterocycles are essentially unexplored, despite the prevalence of azepine frameworks in biologically active molecules and marketed drugs.[11] Given our interest in 2-amino-SF_5-azepines, we first examined the skeletal remodelling of SF_5-azido benzene **6** using diethylamine **2a** as the nucleophile in the presence of DABCO, following our reported LED conditions (Fig. 2).[10] Under these conditions, the desired 2-diethylamino-SF_5-azepine **3a** was obtained in 45% yield after 48 h at room temperature, confirming the feasibility of azepine formation from SF_5-azido benzene, albeit with limited efficiency and prolonged reaction times. We next turned to an alternative nitrene-generation strategy based on phosphorus-catalyzed deoxygenation of SF_5-nitrobenzene, as developed by Radosevich and co-workers.[12] Under these conditions, phenylnitrene are generated thermally *via* **P(III)/P(V)=O** redox cycling from **P(V)=O-catalyst** with phenylsilane. Pleasingly, application of this protocol to SF_5-nitrobenzene **1a** proved markedly more effective, delivering the corresponding SF_5-azepine **3a** in 72% yield within only 1 h at 120 °C. Notably, in non-SF_5 systems, analogous nitrobenzene-to-azepine conversions under Radosevich conditions typically require approximately 12 h to reach completion.[12] To further probe the origin of this pronounced rate enhancement, we evaluated nitrobenzene **7** and fluoro-substituted nitrobenzene **8** under identical conditions. In

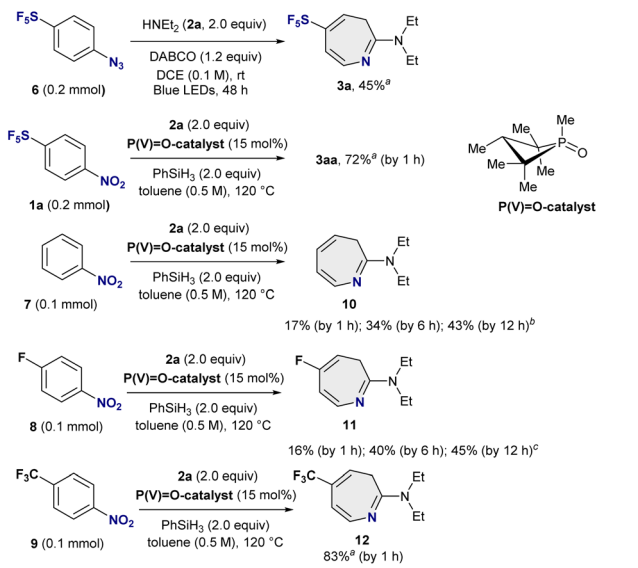
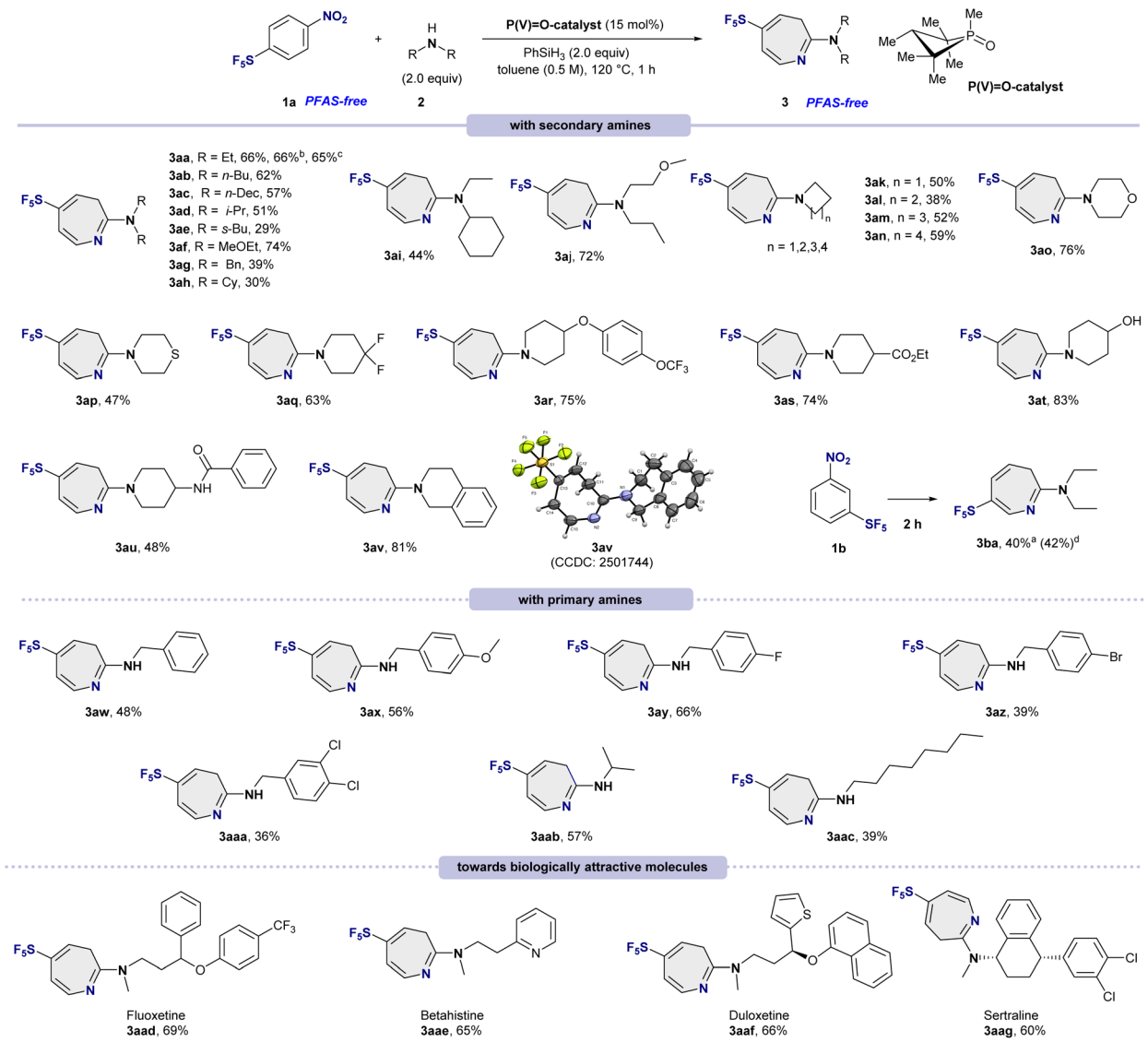


Fig. 2 Skeletal rearrangement to amino-SF_5-azepines. [a]Yield was determined by ^{19}F-NMR spectroscopy (fluorobenzene as standard). [b]Yields were determined by ^{1}H-NMR spectroscopy (1,3,5-trimethylbenzene as standard). [c]Yields were determined by ^{19}F-NMR spectroscopy (benzotrifluoride as standard).

both cases, the corresponding azepin-2-amines (**10** and **11**) were obtained in only 16–17% yield after 1 h, with yields increasing gradually to 43–45% after 12 h. In sharp contrast, the SF_5-substituted nitrobenzene underwent rapid and efficient skeletal rearrangement, suggesting that the strongly electron-withdrawing SF_5 substituent significantly accelerates the ring-expansion process, likely by facilitating arylnitrene insertion and subsequent electrocyclic rearrangement.[10] Given this substantial rate enhancement and the improved safety and practicality of using SF_5-nitrobenzenes instead of SF_5-azido benzenes, we undertook a systematic investigation of the phosphorus-catalyzed conversion of SF_5-nitrobenzenes into SF_5-azepines. A similar acceleration in the ring-expansion was observed for trifluoromethyl-substituted nitrobenzene **9** under standard conditions, affording azepine-2-amine **12** in 83% yield within 1 h, compared to 12 h in the reported method.[12]

Substrate scope for skeletal rearrangement to amino-SF_5-azepines

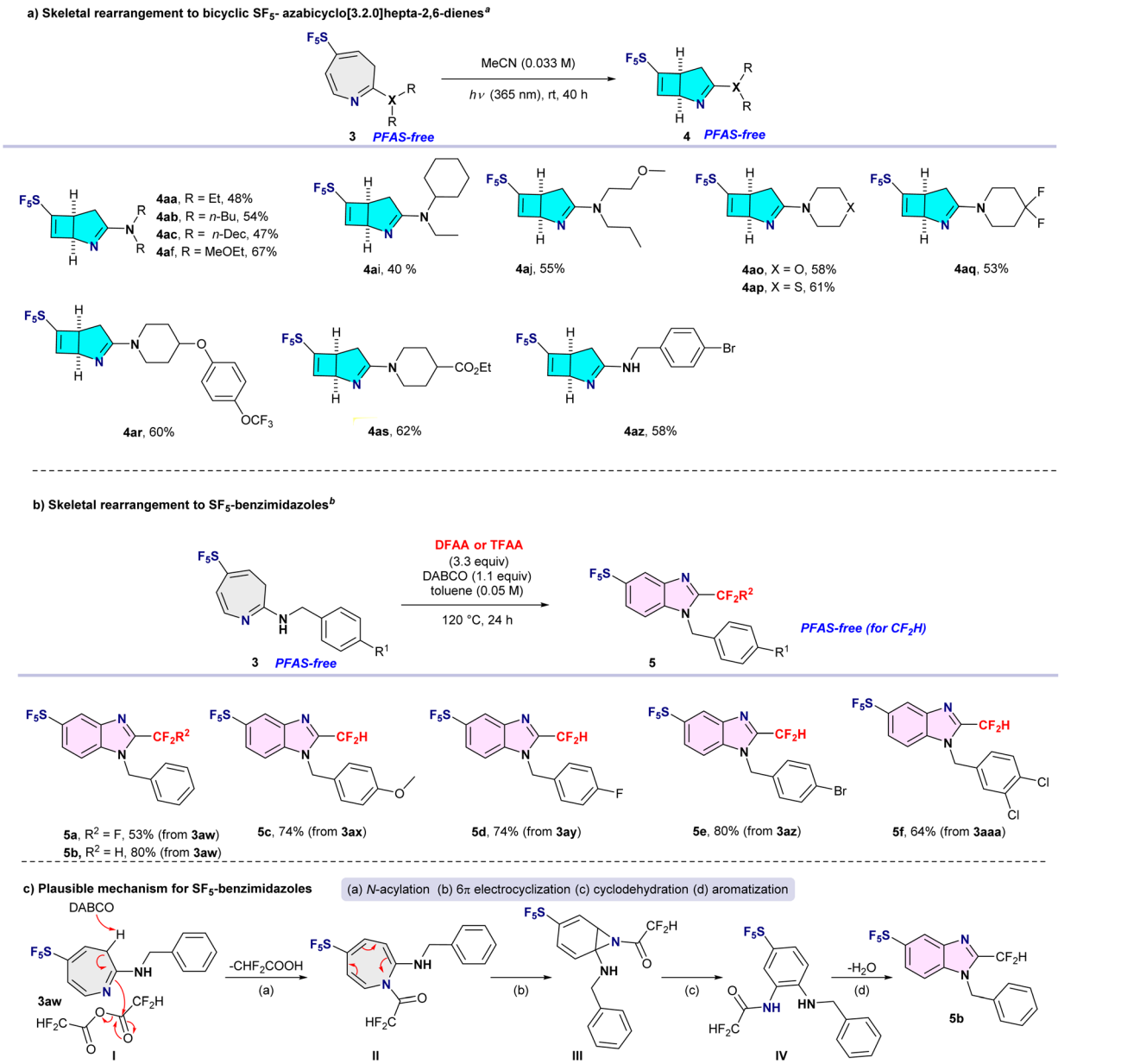
The generality of the phosphorus-catalyzed ring-expansion reaction was first evaluated with a broad range of acyclic secondary amines (Scheme 1, top). Straight-chain dialkylamines such as diethylamine (**2a**), dibutylamine (**2b**), and didecylamine (**2c**) were smoothly converted into the corresponding azepines **3aa–3ac** in 57–66% yields. Branched secondary amines were also compatible, although increased steric demand led to somewhat diminished efficiencies, affording products **3ad** and



Scheme 1 Substrate scope for skeletal rearrangement to amino-SF_5-azepines. [a]Unless otherwise noted, the reactions were carried out with **1a** (0.2 mmol, 1.0 equiv.), **2** (0.4 mmol, 2.0 equiv.), **P(V)═O-catalyst** (15 mol%), $PhSiH_3$ (0.4 mmol, 2.0 equiv.), in toluene (0.4 mL, 0.5 M) stirred at 120 °C for 1 hour. Isolated yields are given. [b]A mixture of **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.2 mmol, 2.0 equiv.), **P(V)═O-catalyst** (15 mol%), $PhSiH_3$ (0.2 mmol, 2.0 equiv.), in toluene (0.2 mL, 0.5 M) stirred at 120 °C for 1 hour. Isolated yields are given. [c]A mixture of **1a** (4.0 mmol, 1.0 equiv., 1.0 g), **2a** (8.0 mmol, 2.0 equiv.), **P(V)═O-catalyst** (15 mol%), $PhSiH_3$ (8.0 mmol, 2.0 equiv.), in toluene (8.0 mL, 0.5 M) stirred at 120 °C for 1 hour. Isolated yields are given. [d]Yield was determined by ^{19}F-NMR spectroscopy (fluorobenzene as standard).

3ae in 29–51% yields. An electron-rich ether-substituted amine (**2f**) was well tolerated, delivering **3af** in 74% yield. Aromatic and alicyclic secondary amines, including dibenzylamine (**2g**), dicyclohexylamine (**2h**), and unsymmetrical amines (**2i–2j**), furnished azepines **3ag–3aj** in 30–72% yields. The influence of cyclic amine ring size was next evaluated. Four-, five-, six-, and seven-membered cyclic amines (**2k–2n**) participated successfully, affording azepines **3ak–3an** in moderate yields (38–59%). Notably, heteroatom-containing cyclic amines also proved to be competent nucleophiles: morpholine (**2o**), thiomorpholine (**2p**), and difluorinated piperidine (**2q**) delivered products **3ao–3aq** in good to excellent yields (47–76%). In addition, a complex aryloxy-substituted piperidine (**2r**) underwent smooth coupling to afford **3ar** in 75% yield, highlighting the functional-group tolerance of the process.

To further assess the generality of the ketenimine intermediate derived from **1a**, we investigated nucleophiles bearing diverse functional groups. Esters (**2s**), alcohols (**2t**), amides (**2u**), and bicyclic amines (**2v**) were all successfully incorporated, furnishing products **3as–3av** in 48–83% yields. The structure of **3av** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 2501744). Notably, this transformation is applicable not only to *p*-substituted SF_5-nitrobenzene **1a** but



Scheme 2 Skeletal editing of azepines: transformations to bicyclic SF_5-azabicyclo[3.2.0]hepta-2,6-dienes and SF_5-benzimidazoles [a]Reaction conditions: **3** (0.1 mmol, 1.0 equiv.) in MeCN (3.0 mL, 0.033M) irradiated under (365 nm) at rt for 40 hours. Isolated yields are given. [b]Reaction conditions: **3** (0.1 mmol, 1.0 equiv.), DABCO (0.11 mmol, 1.1 equiv.), TFAA or DFAA (0.33 mmol, 3.3 equiv.) in toluene (2.0 mL, 0.05 M) at 120 °C for 24 hours. Isolated yields are given.

also to *m*-substituted analogue **1b**, which afforded the regioselective product **3ba** in 40% isolated yield.

Encouraged by the breadth of secondary amine compatibility, we extended the methodology to primary amines (Scheme 1, middle). Benzylamines bearing either electron-donating or electron-withdrawing substituents at the *para* position (**2w–2aa**) underwent efficient ring expansion to give products **3aw–3aaa** in 36–66% yields. Primary aliphatic amines (**2ab** and **2ac**) were likewise competent substrates, affording azepines **3aab** and **3aac** in 39–57% yields.

Finally, the synthetic utility of this transformation was demonstrated through late-stage functionalization of biologically relevant amines (Scheme 1, bottom). Complex drug-derived amines, including fluoxetine (**2ad**), betahistine (**2ae**), duloxetine (**2af**), and sertraline (**2ag**), were successfully converted into the corresponding SF_5-azepine derivatives **3aad–3aag** in good yields (60–69%). These results underscore the robustness of the method and its potential for late-stage diversification in medicinal and agrochemical discovery.

Anilines were not suitable as amine nucleophiles; instead of azepines **3**, N–N bond coupling products were formed, consistent with previous reports.[13]

Second skeletal rearrangement to bicyclic SF_5- azabicyclo [3.2.0]hepta-2,6-dienes

With gram-scale quantities of azepine **3aa** available, we next investigated the photochemical 4π-electrocyclization developed by Leonori[14] for the synthesis of bicyclic SF_5-attached azabicyclo [3.2.0]hepta-2,6-dienes (Scheme 2a, top). Under simple irradiation of azepines **3** at 365 nm in acetonitrile at room temperature cleanly delivered the corresponding bicyclic products, SF_5-attached azabicyclo[3.2.0]hepta-2,6-dienes **4** in moderate to good yields. SF_5-azepines **3** bearing electron-donating alkyl substituents, including ethyl (**3aa**), *n*-butyl (**3ab**), *n*-decyl (**3ac**), and 2-methoxyethyl (**3af**) groups, were well tolerated, affording bicyclic derivatives **4aa**, **4ab**, **4ac**, and **4af** in yields of up to 67%. Azepines containing unsymmetrical secondary amines (**3ai** and **3aj**) also underwent smooth skeletal rearrangement to furnish bicyclic products **4ai** and **4aj** in 40–55% yields. Notably, this photochemical transformation proved compatible with cyclic amine-substituted azepines: substrates **3ao–3as** were efficiently converted into the corresponding bicyclic compounds **4ao–4as** in consistently good yields (53–62%). Furthermore, SF_5-azepines bearing primary amine substituents, exemplified by 4-bromobenzylamine-derived azepine **3az**, participated smoothly to afford bicyclic product **4az** in 58% yield. The relative stereochemistry of the bicyclic products **4** was established by detailed 2D NMR analysis of compound **4az** (see SI) and was found to be fully consistent with previously reported azabicyclo[3.2.0] frameworks.[14]

Third skeletal rearrangement to SF_5-benzimidazoles

To further probe the structural plasticity of the SF_5-azepine framework and to demonstrate bidirectional skeletal editing from a common intermediate, we investigated the re-aromatization of SF_5-azepines to SF_5-benzimidazoles. Following a protocol related to that reported by Radosevich and co-workers,[12] a primary amine-substituted azepine (**3aw**, derived from benzylamine) was treated with trifluoroacetic anhydride (TFAA) in the presence of DABCO in toluene at 120 °C for 24 h. Under these conditions, re-aromatization of the azepine core was accompanied by intramolecular cyclodehydration, affording the corresponding SF_5-benzimidazole **5a** in 53% yield (Scheme 2b, middle). This cyclodehydration is plausibly driven by electrophilic activation of the azepine nitrogen by the acyl anhydride, followed by intramolecular nucleophilic attack of the pendant amine and subsequent loss of water to restore aromaticity (Scheme 2c, bottom)

Because the CF_3 group is classified as a PFAS motif, we next examined the transformation using difluoroacetic anhydride (DFAA) under otherwise identical conditions. As anticipated, the reaction proceeded efficiently to deliver the CF_2H-substituted SF_5-benzimidazole **5b** in 80% yield. Notably, this skeletal reconstruction pathway proved tolerant of diverse substituents on the aromatic ring, including OMe, F, Br, and Cl, furnishing a series of CF_2H-substituted SF_5-benzimidazoles (**5c–5f**) in good to excellent yields.

Conclusions

This study demonstrates that skeletal rearrangement of SF_5-nitrobenzenes provides a general and efficient strategy for constructing diverse SF_5-heterocycles, including SF_5-azepines, SF_5-azabicyclo[3.2.0] frameworks, and SF_5-benzimidazoles. Importantly, these motifs represent PFAS-free alternatives to CF_3-based scaffolds, offering structurally rich and functionally attractive building blocks for pharmaceuticals, agrochemicals, and materials science. In light of the OECD classification of SF_5-containing molecules as non-PFAS, this work contributes to the advancement of sustainable fluorine chemistry by demonstrating that strategic skeletal remodelling can unlock both reactivity and chemical space unique to SF_5 substitution.

Author contributions

MZB optimized the reaction conditions, surveyed the substrate scope, analyzed the data and discussed the results with NS. SW, TM, and CN prepared starting materials and attempted reactions. DH helped to prepare the starting materials. SO took the X-ray crystallography of **3av**. MZB wrote the initial draft and NS wrote the manuscript. NS supervised the study. All authors contributed to the manuscript and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2501744 contains the supplementary crystallographic data for this paper.[15]

The data that support the findings of this study are available within the article and the supplementary information (SI). Supplementary information: materials and methods, experimental procedures, characterization data, and NMR spectra. See DOI: https://doi.org/10.1039/d6sc01441k.

Acknowledgements

This study was supported by the CREST program of the Japan Science and Technology Agency, entitled "Precise Material Science for Degradation and Stability" (grant number: JPMJCR21L1), by Dr Seiji Motojima (CMC Research Institute, Japan), and Kenji Koike (Tosoh Corporation).

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