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Bidirectional skeletal remodelling of SF₅-nitrobenzenes into azepine, bicyclic, and benzimidazole frameworks†

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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 SF₅-containing heterocycles from readily accessible SF₅-nitrobenzenes. Phosphorus-catalyzed iterative deoxygenation of SF₅-nitrobenzenes generates arylnitrene intermediates that undergo remarkably accelerated dearomative ring expansion, furnishing seven-membered SF₅-azepines within dramatically shortened reaction times compared to non-SF₅ analogues. These azepines function as versatile skeletal nodes, enabling divergent downstream transformations: photoinduced 4π-electrocyclization provides access to previously unexplored SF₅-azabicyclo[3.2.0]hepta-2,6-diene frameworks, while selective fluoroacylative activation promotes reverse skeletal reconstruction to restore aromaticity and deliver SF₅-substituted benzimidazoles. Collectively, this work demonstrates that strategic incorporation of the SF₅ 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 SF₅-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.

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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, CF₃-substituted heterocycles are particularly dominant, accounting for more than 40% of all fluorinated agrochemicals.^{1b} However, CF₃ 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, CF₃CO₂H).³ While CF₃ 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 CF₃ substituents has emerged as a critical challenge.

The pentafluorosulfanyl (SF₅) group represents a compelling solution.^{4,5} As a hypervalent sulfur–fluorine functionality, SF₅ combines strong electron-withdrawing character, high lipophilicity, and substantial steric bulk, and is therefore widely regarded as a “super-CF₃” substituent. Importantly, unlike CF₃, SF₅ does not rely on persistent C–F bonds and exhibits the potential for environmentally benign mineralization, positioning SF₅-containing molecules as classified as PFAS-free.^{3d} In molecular design, SF₅ functions as a bioisostere for CF₃, *tert*-butyl, and nitro groups, with comparable hydrophobicity and intrinsic volume (Fig. 1a). Despite these advantages, the structural diversity of SF₅-containing molecules—particularly SF₅-heterocycles—remains severely limited.^{5c}

This limitation arises from a fundamental synthetic bottleneck. Traditional SF₅ installation typically relies on radical reactions with alkenes or alkynes using SF₅Cl 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,

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Fig. 1 Background of this work. (a) Properties of SF₅ vs. CF₃, NO₂ and tBu-benzenes. (b) Previous work (c) This work.

specialized equipment, and stringent moisture control, rendering their application to the synthesis of SF₅-heterocycles highly limited.⁶ As a result, SF₅ chemistry has remained largely limited to simple alkyl, alkenyl, and alkynyl motifs. Only recently have new classes of SF₅ reagents or new protocols been developed,⁷ expanding the diversity of accessible substrates and reactivity profiles. Nevertheless, structurally complex heterocycles—particularly those incorporating SF₅ or SF₄ (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 SF₅ chemistry, where conventional ring-construction strategies are intrinsically constrained. Consistent with this concept, we recently reported the photo-induced synthesis of SF₅-azepine aryl ethers from SF₅-azido benzene with phenols *via* skeletal rearrangement, thereby establishing this approach as a viable entry to medium-sized SF₅-heterocycles (Fig. 1b).¹⁰ Notably, the strong electron-withdrawing nature of the SF₅ 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 SF₅-containing heterocycles, including SF₅-azepin-2-amines **3**, SF₅-azabicyclo[3.2.0]hepta-2,6-dienes **4**, and SF₅-benzimidazoles **5**. In particular, the SF₅-azabicyclo[3.2.0]hepta-2,6-diene derivatives represent the first examples of this rigid bicyclic scaffold bearing an SF₅ substituent (Fig. 1c). Importantly, the synthesis originates from readily available SF₅-nitrobenzenes **1**, rather than inherently energetic SF₅-azido benzenes, and proceeds through consecutive skeletal

rearrangements. These transformations establish a unified skeletal-editing manifold that interconverts aromatic, medium-sized, and bicyclic SF₅-containing architectures.

Results and discussion

Development of a rapid skeletal rearrangement to amino-SF₅-azepines

Seven-membered SF₅-heterocycles are essentially unexplored, despite the prevalence of azepine frameworks in biologically active molecules and marketed drugs.¹¹ Given our interest in 2-amino-SF₅-azepines, we first examined the skeletal remodelling of SF₅-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-SF₅-azepine **3a** was obtained in 45% yield after 48 h at room temperature, confirming the feasibility of azepine formation from SF₅-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 SF₅-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 SF₅-nitrobenzene **1a** proved markedly more effective, delivering the corresponding SF₅-azepine **3a** in 72% yield within only 1 h at 120 °C. Notably, in non-SF₅ 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-SF₅-azepines. ^aYield was determined by ¹⁹F-NMR spectroscopy (fluorobenzene as standard). ^bYields were determined by ¹H-NMR spectroscopy (1,3,5-trimethylbenzene as standard). ^cYields were determined by ¹⁹F-NMR spectroscopy (benzotrifluoride as standard).

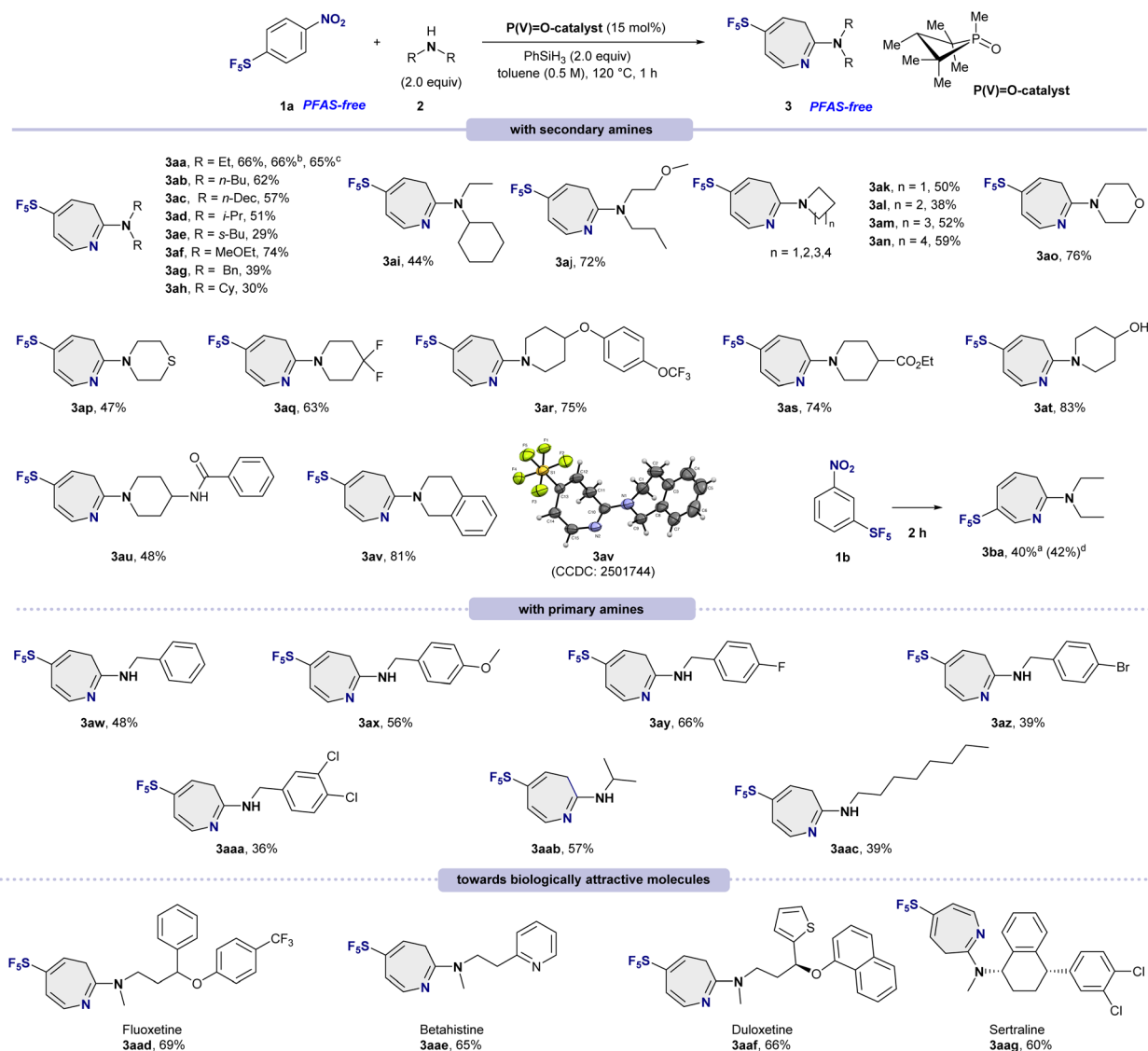


both cases, the corresponding azepin-2-amines (**10** and **11**) were obtained in only 16–17% yield after 1 h, with yields increasing gradually to 43–45% after 12 h. In sharp contrast, the SF₅-substituted nitrobenzene underwent rapid and efficient skeletal rearrangement, suggesting that the strongly electron-withdrawing SF₅ substituent significantly accelerates the ring-expansion process, likely by facilitating aryl nitrene insertion and subsequent electrocyclic rearrangement.¹⁰ Given this substantial rate enhancement and the improved safety and practicality of using SF₅-nitrobenzenes instead of SF₅-azido benzenes, we undertook a systematic investigation of the phosphorus-catalyzed conversion of SF₅-nitrobenzenes into SF₅-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-SF₅-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-SF₅-azepines. ^aUnless 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%), PhSiH₃ (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. ^bA mixture of **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.2 mmol, 2.0 equiv.), P(V)=O-catalyst (15 mol%), PhSiH₃ (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. ^cA 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%), PhSiH₃ (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. ^dYield was determined by ¹⁹F-NMR spectroscopy (fluorobenzene as standard).

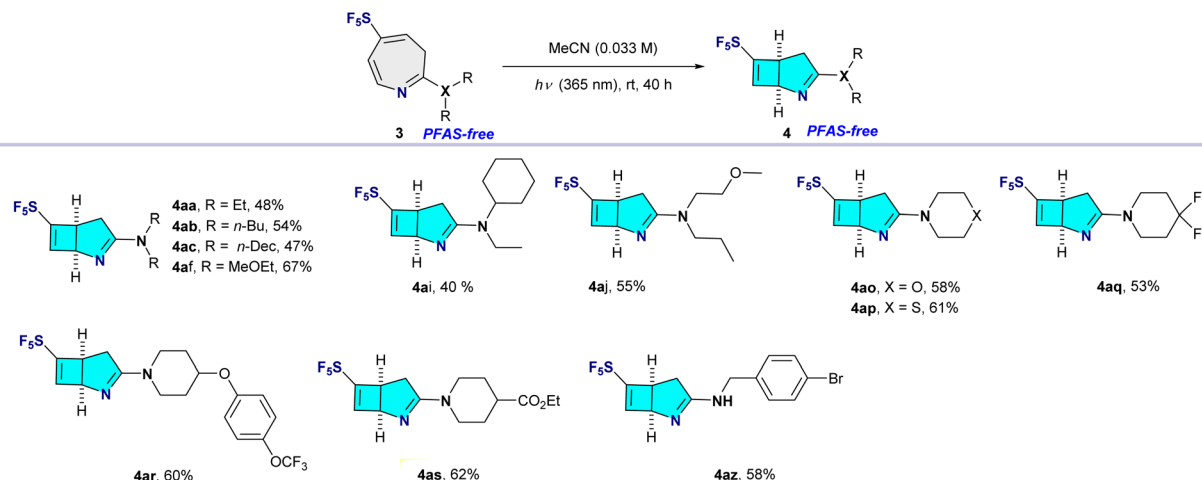


3ae in 29–51% yields. An electron-rich ether-substituted amine (**2f**) was well tolerated, delivering **3af** in 74% yield. Aromatic and alicyclic secondary amines, including dibenzylamine (**2g**), dicyclohexylamine (**2h**), and unsymmetrical amines (**2i–2j**), furnished azepines **3ag–3aj** in 30–72% 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

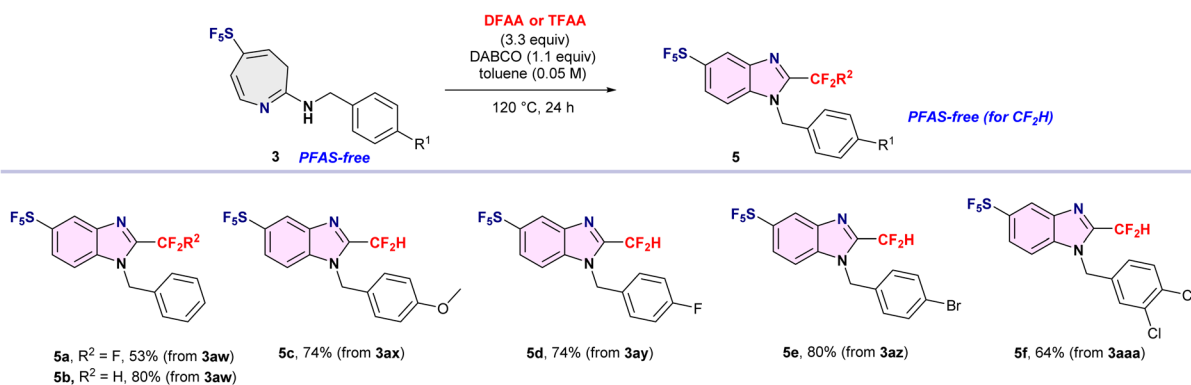
aryloxy-substituted piperidine (**2r**) underwent smooth coupling to afford **3ar** in 75% yield, highlighting the functional-group tolerance of the process.

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 SF₅-nitrobenzene **1a** but

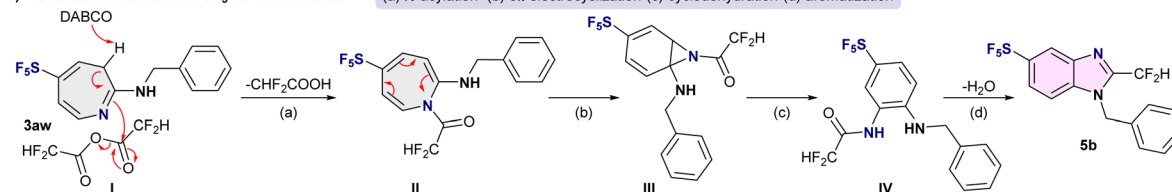
a) Skeletal rearrangement to bicyclic SF₅-azabicyclo[3.2.0]hepta-2,6-dienes^a



b) Skeletal rearrangement to SF₅-benzimidazoles^b



c) Plausible mechanism for SF₅-benzimidazoles



Scheme 2 Skeletal editing of azepines: transformations to bicyclic SF₅-azabicyclo[3.2.0]hepta-2,6-dienes and SF₅-benzimidazoles^aReaction 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. ^bReaction 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 SF₅-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 SF₅-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 Leonori¹⁴ for the synthesis of bicyclic SF₅-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, SF₅-attached azabicyclo[3.2.0]hepta-2,6-dienes **4** in moderate to good yields. SF₅-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, SF₅-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 SF₅-benzimidazoles

To further probe the structural plasticity of the SF₅-azepine framework and to demonstrate bidirectional skeletal editing from a common intermediate, we investigated the re-aromatization of SF₅-azepines to SF₅-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 SF₅-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 CF₃ 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 CF₂H-substituted SF₅-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 CF₂H-substituted SF₅-benzimidazoles (**5c–5f**) in good to excellent yields.

Conclusions

This study demonstrates that skeletal rearrangement of SF₅-nitrobenzenes provides a general and efficient strategy for constructing diverse SF₅-heterocycles, including SF₅-azepines, SF₅-azabicyclo[3.2.0] frameworks, and SF₅-benzimidazoles. Importantly, these motifs represent PFAS-free alternatives to CF₃-based scaffolds, offering structurally rich and functionally attractive building blocks for pharmaceuticals, agrochemicals, and materials science. In light of the OECD classification of SF₅-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 SF₅ 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>.

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