Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2025, **16**, 16552

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

Received 20th July 2025
Accepted 11th August 2025

DOI: 10.1039/d5sc05409e

rsc.li/chemical-science

Difluoromethylene cyclobutyl sulfonium salts: versatile reagents for chemodivergent synthesis of difluoroalkylated cyclobutenes and cyclobutanes

Xiao-Tian Feng,†[ab] Qiao-Qiao Min,†[b] Song-Yu Zhang,[b] Hai-Yang Zhao[b] and Xingang Zhang *[ab]

Despite the significant applications of fluorinated cyclobutanes in industrial and diagnostic fields, efficient methods for synthesizing these valuable fluorinated structures remain limited. Here, we report a new difluoroalkylating reagent, 2-(difluoromethylene)cyclobutyl sulfonium salts (CB-DFASs). This reagent can be readily synthesized on a gram scale in three steps from readily available cyclobutanone enol silyl ether. CB-DFASs exhibit high reactivity and enable chemodivergent synthesis of structurally diverse difluoroalkylated cyclobutenes using a wide array of nucleophiles, including those based on carbon, oxygen, nitrogen, and sulfur, under mild conditions. The resulting products serve as versatile linchpins for diverse transformations, thereby enabling the synthesis of a variety of difluoroalkylated cyclobutanes. The synthetic utility of CB-DFASs has been demonstrated through the late-stage modification of complex pharmaceuticals and the rapid synthesis of analogues of bioactive molecules, highlighting their potential in drug discovery.

Introduction

The cyclobutane scaffold, distinguished by its unique three-dimensional conformation, stereochemical properties, and electrostatic characteristics,[1] has emerged as a significant structural motif in biological and medicinal chemistry. Its versatile nature has led to its widespread use as a bioisostere in diverse molecular frameworks, including ethane, pyrrolidine, piperidine, and aromatic rings.[2] This versatility is further highlighted by the fact that the FDA has approved more than 10 drugs incorporating a cyclobutane scaffold,[3] underscoring its significance in modern drug discovery efforts.

On the other hand, the site-selective introduction of fluorine atom(s) into organic molecules has emerged as a powerful strategy to fine-tune the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of bioactive molecules.[4] In fact, nearly half of the recent structural modifications in drug candidates involve the targeted incorporation of fluorine atoms.[5] In this context, fluorinated cyclobutanes have garnered significant attention due to their demonstrated utility in both industrial and diagnostic applications (Scheme 1a). For instance, cyclobutanes substituted with a CH_2F group serve as critical structural components in diagnostic agents such as fluciclovine (FACBC)[6] and its analogue FMACBC,[7] which are widely used in positron emission tomography (PET) imaging. Additionally, cyclobutanes functionalized with CF_2H, CF_2, and CF_3 groups have exhibited antiviral[8] and antitumor[9] activities, or acted as potent rat cannabinoid-1 receptor inhibitors.[10]

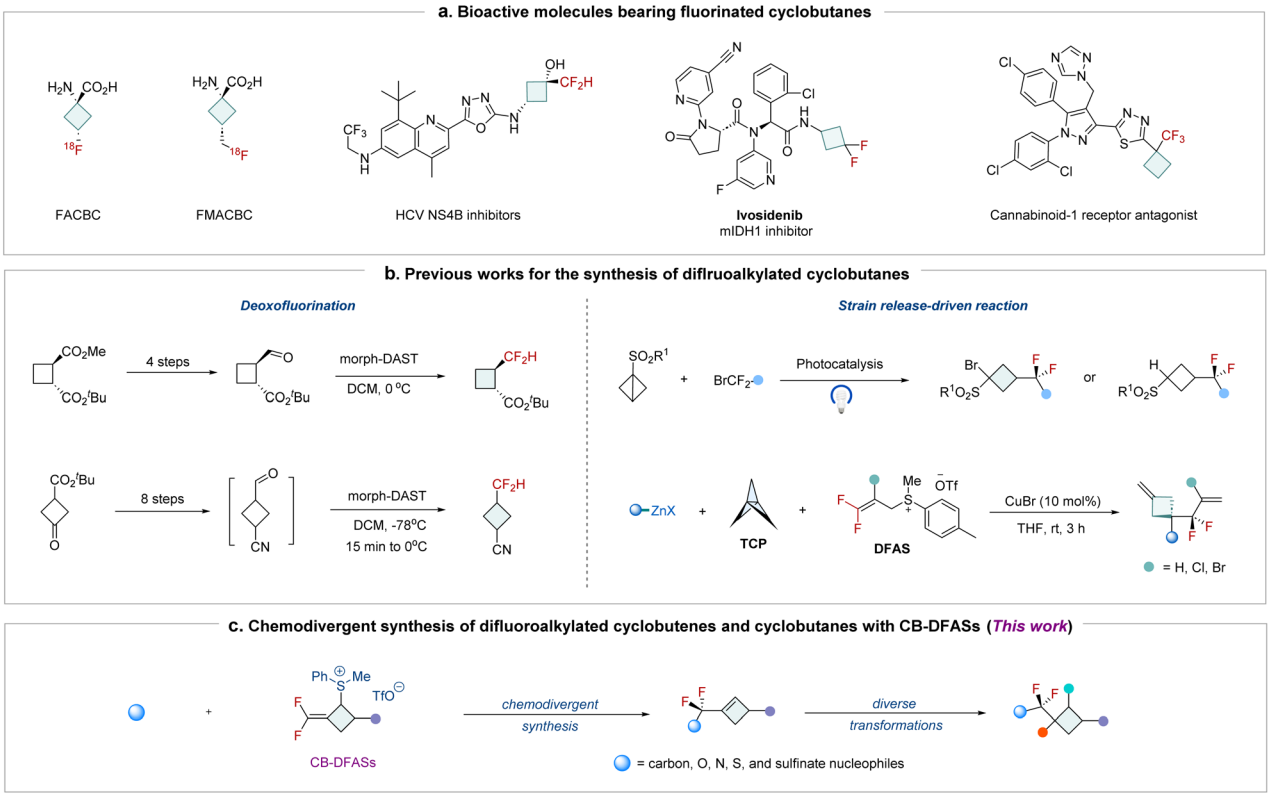
However, the current methods for synthesizing fluorinated cyclobutanes are limited, with most efforts predominantly focused on trifluoromethylation.[11,12a,b] For the synthesis of cyclobutanes containing a CF_2 moiety, existing methods largely rely on deoxyfluorination, which is hampered by narrow substrate scope and low efficiency[12c–e] (Scheme 1b). Although recent efforts using bicyclo[1.1.0]butane (BCB)[13] or bicyclo[1.1.1]pentane (TCP)[14] precursors through strain-release strategies have shown some success in accessing difluoroalkylated cyclobutanes (Scheme 1b), these approaches are still restricted by the use of specific substrates and exhibit only moderate functional group tolerance. Therefore, the development of new and general methods for the synthesis of difluoroalkylated cyclobutane frameworks remains highly desirable.

To overcome these limitations, here, we report 2-(difluoromethylene)cyclobutyl sulfonium salts (CB-DFASs), a new type of difluoroalkylating reagent for the preparation of difluoroalkylated cyclobutenes and cyclobutanes (Scheme 1c). CB-DFASs enable high γ-regioselective functionalization, demonstrating remarkable substrate compatibility and the ability to react with a diverse array of nucleophiles, including those based on carbon, oxygen, nitrogen, and sulfur, under mild conditions.

[a]*School of Chemistry and Material Sciences, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, Hangzhou 310024, China. E-mail: xgzhang@mail.sioc.ac.cn*

[b]*State Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China*

† X.-T. Feng and Q.-Q. Min contributed equally to this work.

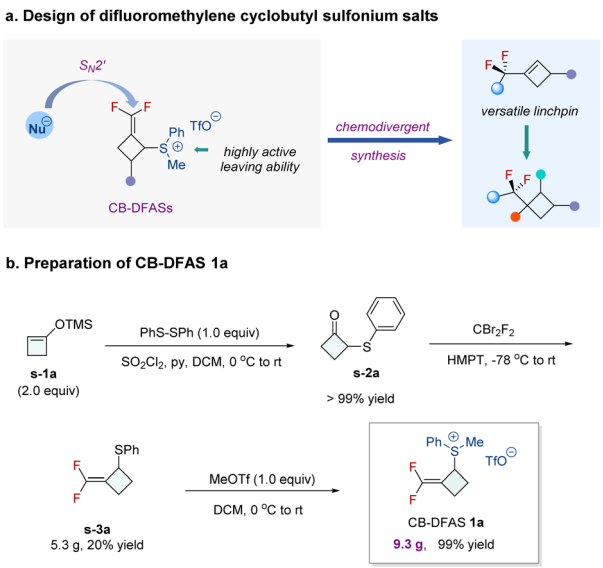


Scheme 1 Representative bioactive molecules bearing fluorinated cyclobutane moieties and strategies for the synthesis of difluoroalkylated cyclobutanes.

This approach provides a chemodivergent and highly efficient route to access difluoroalkylated cyclobutenes. The resulting fluorinated skeletons serve as versatile building blocks for constructing structurally diverse difluoroalkylated cyclobutanes, thereby holding great promise for modern drug discovery.

Results and discussion

Previously, we developed a new type of difluoroalkylating reagent, 3,3-difluoroallyl sulfonium salts (DFASs), which has proven highly effective in the synthesis of complex *gem*-difluoroallylated molecules.[15] However, the efficient synthesis of difluoroalkylated cyclobutenes and cyclobutanes remains challenging. Given the unique properties of the CF_2 group, such as its ability to enhance metabolic stability, increase the molecular dipole moment, and modulate the basicity of bioactive molecules,[16] we hypothesized that incorporating a sulfonium salt into a cyclobutane ring and utilizing an exocyclic double bond bearing a difluoromethylene group could provide a highly reactive reagent for the synthesis of difluoroalkylated cyclobutenes (Scheme 2a). This approach would be driven by the highly active leaving ability of the sulfonium salt *via* an S_N2' pathway, thereby enabling chemodivergent synthesis of difluoroalkylated cyclobutenes using a wide range of nucleophiles. Since cyclobutene is a versatile linchpin for diverse transformations, the successful synthesis of difluoromethylene cyclobutyl sulfonium salts (CB-DFASs) would also provide a valuable opportunity for diverse access to difluoroalkylated cyclobutanes. This advancement would thus add a new tool to the medicinal chemistry synthetic toolbox.

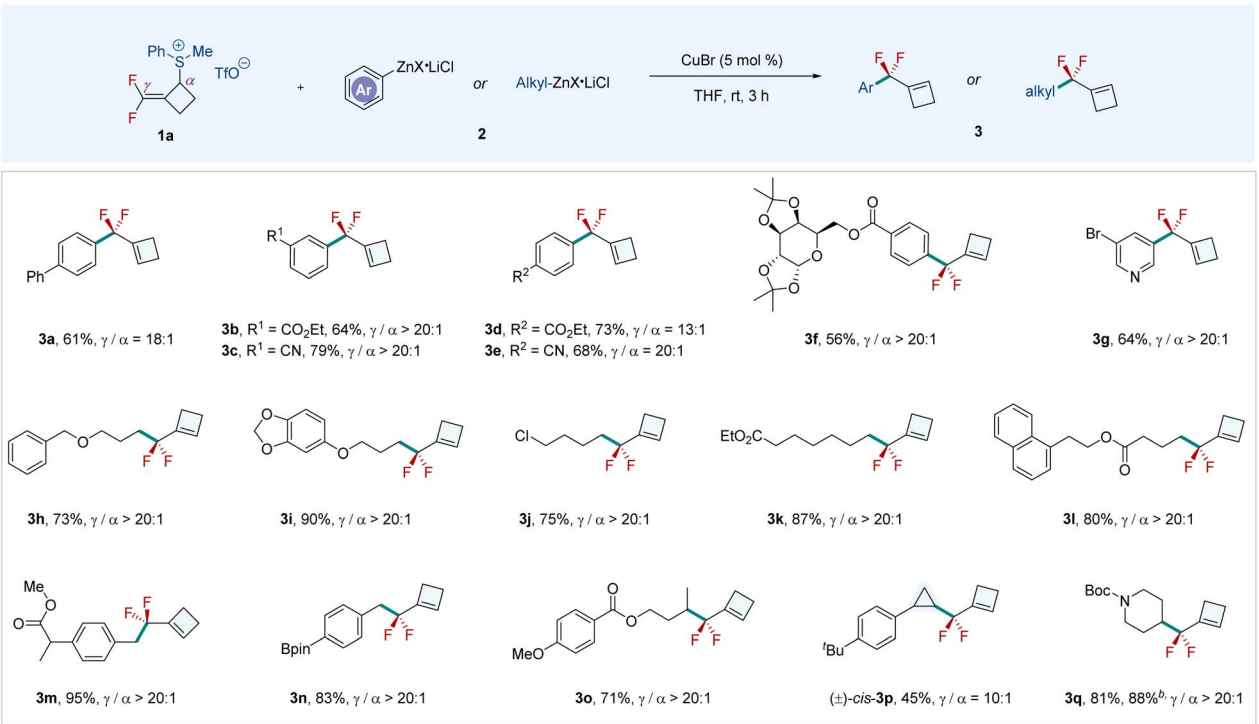


Scheme 2 Design and synthesis of difluoromethylene cyclobuyl sulfonium salt **1**.

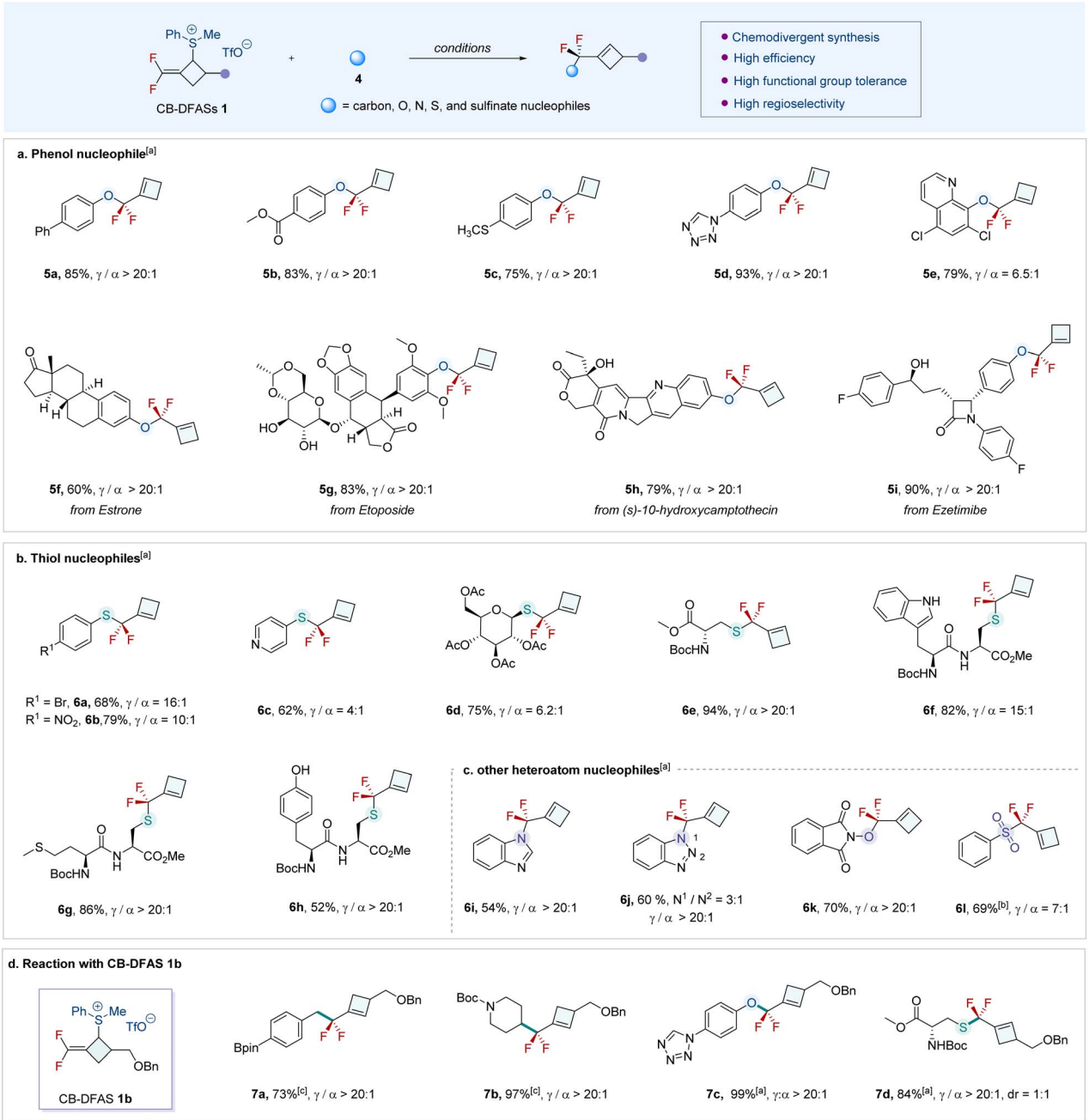
The synthesis of CB-DFAS **1a** commenced with the formation of a phenyl thioether, achieved through the reaction of cyclobutanone enol silyl ether **s-1a** with *in situ* generated PhSCl from the reaction between PhS-SPh and SO_2Cl_2 (ref. 17) (Scheme 2b). This transformation proceeded smoothly under mild conditions, yielding the desired product **s-1a** in nearly quantitative yield. Subsequently, the Wittig reaction of **s-2a** with CBr_2F_2 in the presence of HMPT furnished **s-3a**. Although this step exhibited low efficiency, the reaction can be scaled up to a 5 gram scale to meet the requirements of the subsequent step. Finally, methylation of **s-2a** with methyl triflate produced CB-DFAS **1a** as a stable oil, with a quantitative yield obtained on a 9 gram scale. The resulting reagent is moisture-insensitive and can be stored as a solution in CH_2Cl_2, facilitating its application in subsequent synthetic processes.

With CB-DFAS **1a** in hand, we explored the scope of the copper-catalyzed cross-coupling reaction of **1a** with various organozinc reagents (Scheme 3). The difluoroalkylating reagent **1a** exhibited high reactivity and excellent γ-regioselectivity with a broad range of organozinc reagents, including aryl and alkylzinc species, using CuBr (5 mol%) as the catalyst.[15] Arylzinc reagents containing ester or nitrile groups did not compromise the reaction efficiency (**3b–3e**), and even the carbohydrate-derived arylzinc reagent afforded the corresponding aryldifluoroalkylated cyclobutene **3f** smoothly. Notably, the bromopyridinylzinc reagent was also compatible, with the heteroaryl bromide moiety remaining intact (**3g**). This advancement highlights the high reactivity of **1a** and its potential for highly chemoselective synthesis of difluoroalkylated cyclobutenes. Alkylzinc reagents were equally effective coupling partners, yielding higher product yields. The reaction demonstrated high functional group tolerance. Synthetically versatile groups, such as alkyl chloride (**3j**), carboxylic acid esters (**3k**, **3l**, **3m**, and **3o**), boronate (**3n**), and Boc-protected amine (**3q**), were all compatible with the copper-catalyzed process, providing ample opportunities for downstream transformations. Notably, secondary alkylzinc reagents were successfully employed (**3o–3q**), yielding products of significant interest in medicinal chemistry, such as those bearing cyclopropane and cyclobutene rings linked by a CF_2 group (**3p**), which otherwise is difficult to access *via* conventional methods. Moreover, the reaction can be readily scaled up. For instance, the synthesis of compound **3q** was successfully conducted on a 6 mmol scale using only 0.2 mol% CuBr, resulting in even higher yields, underscoring the synthetic utility of this protocol.

To further demonstrate the general applicability of this protocol for the chemodivergent synthesis of difluoroalkylated cyclobutenes, we explored the reactivity of CB-DFAS **1** with a broad range of heteroatom nucleophiles, including oxygen-, sulfur-, and nitrogen-based nucleophiles (Scheme 4). Given that phenols are commonly found in numerous biologically active molecules and natural products and that the introduction of a difluoroalkylated cyclobutene moiety could potentially lead to the discovery of new bioactive compounds, we initiated our studies with the reaction of **1** with a series of phenols (Scheme 4a). Inspired by our previous results,[18] we found that using



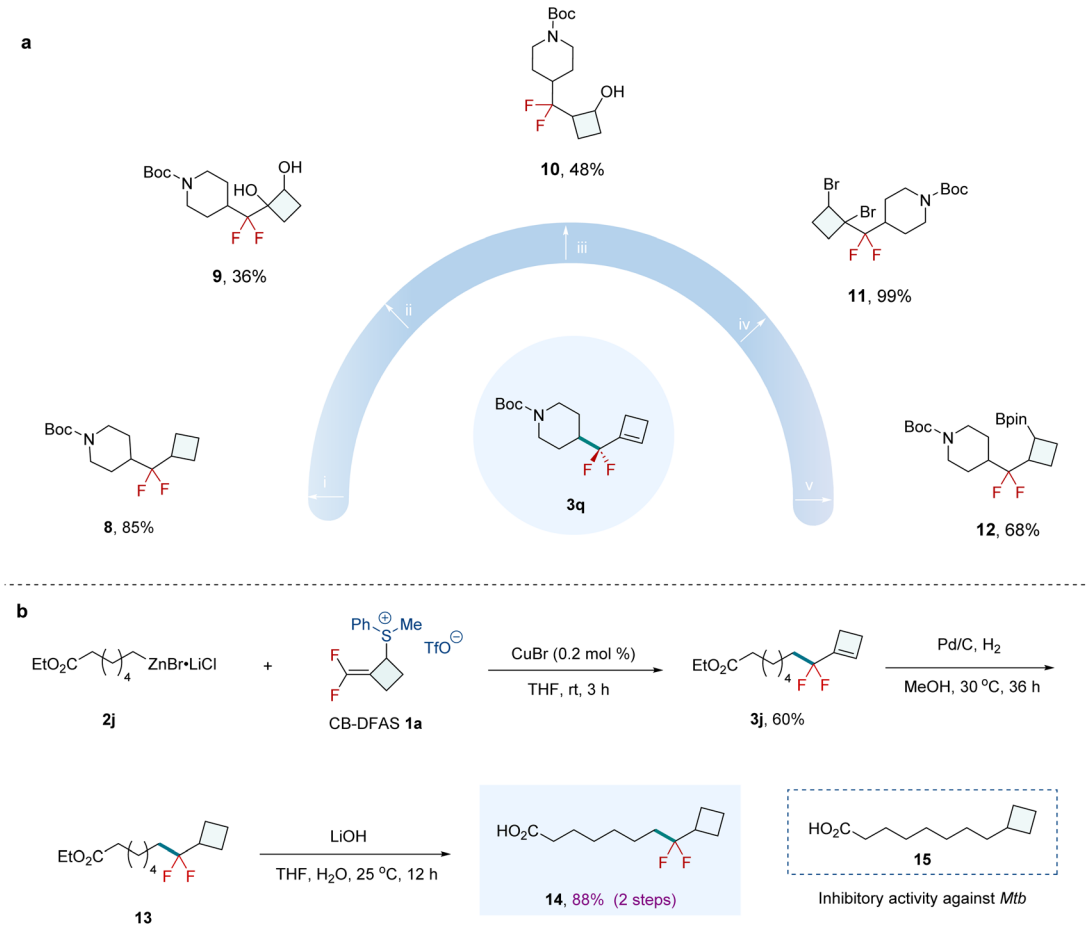
Scheme 3 Copper-catalyzed cross-coupling of organozinc reagents with CB-DFAS **1a**. [a] Reaction conditions (unless otherwise specified): **1a** (1.05 equiv.), **2** (0.2–0.3 mmol, 1.0 equiv.), THF (2.0 mL), 3 h. All reported yields are isolated yields. [b] The reaction was conducted on a 6 mmol scale using 0.2 mol% CuBr.



Scheme 4 Reaction of nucleophiles with CB-DFASs 1. [a] Conditions A: **1a** (1.2 equiv.), heteroatom nucleophile **4** (0.2–0.3 mmol 1.0 equiv.), K_2CO_3 (2.0 equiv.), acetone (2.0 mL), rt, 3 h; [b] condition B: **1a** (0.2 mmol, 1.0 equiv.), sodium benzenesulfinate (1.2 equiv.), K_2CO_3 (0.4 mmol, 2.0 equiv.), DMSO (2.0 mL); [c] conditions C: **1b** (1.05 equiv.), **2** (0.2 mmol 1.0 equiv.), CuBr (5 mol%), THF (2.0 mL), rt, 3 h. All reported yields are isolated yields.

K_2CO_3 (2.0 equiv.) as the base and acetone as the solvent afforded the desired product **5a** in 85% isolated yield with excellent γ-regioselectivity (γ/α > 20 : 1) at room temperature. The electronic nature of the substituent on the phenol did not significantly affect the reaction efficiency and regioselectivity (**5a**-**5c**). However, sterically hindered substrates, such as 5,7-dichloroquinolin-8-ol, led to diminished regioselectivity (**5e**). The high reaction efficiency and regioselectivity were further exemplified by the successful late-stage modification of complex molecules. For instance, estrone (**5f**), the anticancer agents etoposide (**5g**) and 10-hydroxycamptothecin (**5h**), and the cholesterol absorption inhibitor ezetimibe (**5i**) were all successfully modified without interference from the presence of free hydroxyl groups or their complex structures.

Encouraged by the success with the modification of complex phenols, we extended our investigation to thiol substrates (Scheme 4b). Compared to phenols, thiophenols exhibited diminished regioselectivity (γ/α ratios ranging from 10 : 1 to



Scheme 5 Transformations of the **3q** and synthesis of complex analogues. (i) Pd/C (5 mol%), H_2, THF, 30 °C, 8 h. (ii) $K_2OsO_2(OH)_4$ (5 mol%), NMO (2.0 equiv.), acetone, H_2O, rt, 20 h (iii) (1) BH_3 THF (1.5 equiv.), THF, 0 °C, 2 h; (2) NaOH (14.0 equiv., 2 N), H_2O_2 (16.0 equiv., 30% wt in water), rt, 2 h. (iv) CCl_4 (0.3 mL), Br_2 (1.5 equiv.), 0 °C, 2 h; (v) $Ir_2Cl_2(COD)_2$ (2.5 mol%), DPPE (5 mol%), DCM, HBpin (1.5 equiv.), −20 °C to rt, 20 h.

16 : 1) (**6a**, **6b**). When pyridine-4-thiol was examined, lower regioselectivity was observed (**6c**), likely due to its relatively weaker nucleophilicity, which favours attack at the α-position of the substrate. However, aliphatic thiols generally demonstrated high efficiency and regioselectivity (**6e–6h**). Although 1-thioglycoside resulted in moderate selectivity (**6d**), likely due to steric effects, excellent regioselectivity was observed when using protected cysteine (**6e**) and cysteine-containing dipeptides (**6f–6h**). Remarkably, when the dipeptide contained an unprotected side chain, including nucleophilic residues such as tryptophan (**6f**), methionine (**6g**), and even tyrosine (**6h**), no competitive side products from the reaction of these nucleophilic moieties with the substrate were observed. This advancement highlights the high chemoselectivity of the substrate with the thiol group. Given the versatility of cyclobutene as a synthetic moiety, its installation onto bioactive peptides may offer new opportunities for bioconjugation and peptide engineering.

Under the same reaction conditions, nitrogen-based nucleophiles, such as benzimidazole (**6i**) and benzotriazole (**6j**), were also applied to the reaction without diminishing the γ-regioselectivity (Scheme 4c). However, for benzotriazole, two regioisomers bearing the difluoroalkyl group at the N^1 and N^2 positions (N^1 N^2 = 3 : 1) were observed (**6j**).[19] Notably, *N*-hydroxyphthalimide was also a suitable substrate (**6k**), providing an opportunity to study this previously unknown fluoroalkylated compound. Finally, by replacing the solvent from acetone to DMSO, sodium benzenesulfinate was also amenable to the reaction, yielding difluoroalkylsulfonyl benzene **6l** in good yield and with high γ-selectivity.

To test the reactivity of other CB-DFASs, we prepared CB-DFAS **1b** using a similar procedure to that of CB-DFAS **1a**. Compound **1b** also exhibited high activity and selectivity across a range of nucleophiles. As shown in Scheme 4d, the reaction of **1b** with organozinc reagents (**7a** and **7b**), phenol (**7c**), and protected cysteine (**7d**) all provided the corresponding difluoroalkylated cyclobutenes with high efficiency and excellent γ-regioselectivity. These results demonstrate the high versatility of these new sulfonium salts as a useful tool for organic synthesis and medicinal chemistry.

The synthetic utility of this approach is further demonstrated by the diverse transformations of the resulting cyclobutenes into difluoroalkylated cyclobutanes. As depicted in Scheme 5a, hydrogenation of cyclobutene **3q** efficiently yielded difluoroalkylated cyclobutane **8**. Dihydroxylation of **3q**

proceeded smoothly, affording diol **9** in synthetically useful yield. Hydroboration-oxidation of **3q** furnished cyclobutanol **10** in moderate yield. Bromination of **3q** with Br_2 provided the dibrominated compound **11** in nearly quantitative yield, offering an efficient and convenient method for introducing halogen functionality. Notably, iridium-catalyzed borylation enabled the introduction of a boronic ester group into the cyclobutane structure,[20] yielding compound **12** efficiently. Given that these difluoroalkylated cyclobutanes possess versatile synthetic handles, they provide good opportunities for further derivatizations to access a wide range of difluoroalkylated cyclobutanes. The promising functional compatibility and synthetic efficiency of the current protocol also encouraged us to evaluate its applications in the rapid modification of biologically active molecules and natural products. As shown in Scheme 5b, the analogue of a compound with inhibitory activity against Mtb[21] can be rapidly synthesized in just three steps, with the current approach serving as the key step. This highlights the potential applications of CB-DFASs in modern drug discovery and development.

Conclusions

In conclusion, we have successfully developed a new type of highly active yet bench-stable difluoroalkylating reagent, 2-(difluoromethylene)cyclobutyl sulfonium salts (CB-DFASs). This reagent exhibits exceptional reactivity in both copper-catalyzed coupling reactions and transition-metal-free difluoroalkylation reactions with a wide range of nucleophiles. Its key features include (1) synthetic versatility: CB-DFASs enable the efficient and rapid construction of CF_2–C and CF_2–X (X = O, S, N) bonds under mild conditions using organozinc reagents and heteroatom nucleophiles. Both difluoroalkylated cyclobutenes and cyclobutanes can be readily synthesized using CB-DFASs. (2) High functional group tolerance: the current protocol demonstrates excellent compatibility with a wide array of functional groups, including those present in complex drug molecules, amino acids, and dipeptide systems. (3) High regioselectivity and chemoselectivity: CB-DFASs exhibit high regioselectivity and chemoselectivity, providing a straightforward route for the selective introduction of difluoroalkylated cyclobutenes and cyclobutanes into complex molecules. These transformations are often difficult to achieve using conventional methods. Given these advantages, we anticipate that this new type of difluoroalkylating reagent, CB-DFASs, will find applications in the synthesis of complex fluoroalkylated cyclobutenes and cyclobutanes, which are of significant interest in life and materials sciences.

Author contributions

X. Z. conceived and designed the experiments. X. Z. directed the project. X.-T. F. and Q.-Q. M. performed the experiments. S.-Y. Z. prepared some starting materials. X.-T. F., H.-Y. Z., and Q.-Q. M. analyzed the data in the SI. X. Z. wrote the paper. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

All experimental data, procedures for data analysis, and pertinent data sets are provided in the SI. See DOI: **https://doi.org/10.1039/d5sc05409e**.

Acknowledgements

Financial support for this work was provided by the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB0590000), the National Natural Science Foundation of China (22193072 and 22301307), and the Shanghai Pujiang Program (23PJ1415900).

Notes and references

1 For selected reviews, see:(*a*) M. R. Bauer, P. Di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. Ian Storer and B. C. Whitehurst, *RSC Med. Chem.*, 2021, **12**, 448–471; (*b*) C. Hui, Y. Liu, M. Jiang and P. Wu, *Trends Chem.*, 2022, **4**, 677–681; (*c*) D. J. Hamilton, M. Beemsterboer, C. M. Carter, J. Elsayed, R. E. M. Huiberts, H. F. Klein, P. O'Brien, I. J. P. de Esch and M. Wijtmans, *ChemMedChem*, 2022, **17**, e202200113; (*d*) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and D. Blanco-Ania, *ChemMedChem*, 2022, **17**, e202200020.

2 (*a*) U. R. Anumala, J. Waaler, Y. Nkizinkiko, A. Ignatev, K. Lazarow, P. Lindemann, P. A. Olsen, S. Murthy, E. Obaji, A. G. Majouga, S. Leonov, J. P. von Kries, L. Lehtio, S. Krauss and M. Nazare, *J. Med. Chem.*, 2017, **60**, 10013–10025; (*b*) K. G. Liu, J. I. Kim, K. Olszewski, A. M. Barsotti, K. Morris, C. Lamarque, X. Yu, J. Gaffney, X. J. Feng, J. P. Patel and M. V. Poyurovsky, *J. Med. Chem.*, 2020, **63**, 5201–5211.

3 *"Drug bank online" can be found under*, 2022, **https://go.drugbank.com/structures/search/small_molecule_drugs/structure#results**, accessed 31st January 2022.

4 (*a*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (*b*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369; (*c*) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi and V. A. Soloshonok, *Chem.–Eur. J.*, 2019, **25**, 11797–11819; (*d*) N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880.

5 (*a*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (*b*) D. E. Yerien, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, **14**, 8398–8427; (*c*) S. Meyer, J. Häfliger and R. Gilmour, *Chem. Sci.*, 2021, **12**, 10686–10695; (*d*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359.

6 W. Yu, L. Williams, V. M. Camp, E. Malveaux, J. J. Olson and M. M. Goodman, *Bioorg. Med. Chem.*, 2009, **17**, 1982–1990.

7 (*a*) L. Martarello, J. McConathy, V. M. Camp, E. J. Malveaux, N. E. Simpson, C. P. Simpson, J. J. Olson, G. D. Bowers and M. M. Goodman, *J. Med. Chem.*, 2002, **45**, 2250–2259; (*b*) A. W. Wong, M. J. Adam, S. G. Withers and J. Label, *Compd. Radiopharm.*, 2001, **44**, 385–394.

8 B. Phillips, R. Cai, W. Delaney, Z. Du, M. Ji, H. Jin, J. Lee, J. Li, A. Niedziela-Majka, M. Mish, H. J. Pyun, J. Saugier, N. Tirunagari, J. Wang, H. Yang, Q. Wu, C. Sheng and C. Zonte, *J. Med. Chem.*, 2014, **57**, 2161–2166.

9 J. Popovici-Muller, R. M. Lemieux, E. Artin, J. O. Saunders, F. G. Salituro, J. Travins, G. Cianchetta, Z. Cai, D. Zhou, D. Cui, P. Chen, K. Straley, E. Tobin, F. Wang, M. D. David, V. Penard-Lacronique, C. Quivoron, V. Saada, S. De Botton, S. Gross, L. Dang, H. Yang, L. Utley, Y. Chen, H. Kim, S. Jin, Z. Gu, G. Yao, Z. Luo, X. Lv, C. Fang, L. Yan, A. Olaharski, L. Silverman, S. Biller, S.-S. M. Su and K. Yen, *ACS Med. Chem. Lett.*, 2018, **9**, 300–305.

10 J. Lee, H. J. Seo, S. H. Lee, J. Kim, M. E. Jung, S.-H. Lee, K.-S. Song, J. Lee, S. Y. Kang, M. J. Kim, M.-S. Kim, E.-J. Son, M. Lee and H.-K. Han, *Bioorg. Med. Chem.*, 2010, **18**, 6377–6388.

11 For selected examples, see:(*a*) J. A. Kautzky, T. Wang, R. W. Evans and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2018, **140**, 6522–6526; (*b*) C. Dong, X. F. Bai, J. Y. Lv, Y. M. Cui, J. Cao, Z. J. Zheng and L. W. Xu, *Molecules*, 2017, **22**, 769; (*c*) D. S. Radchenko, O. M. Michurin, A. V. Chernykh, O. Lukin and P. K. Mykhailiuk, *Tetrahedron Lett.*, 2013, **54**, 1897–1898; (*d*) A. A. Homon, O. V. Hryshchuk, S. Trofymchuk, O. Michurin, Y. Kuchkovska, D. S. Radchenko and O. O. Grygorenko, *Eur. J. Org Chem.*, 2018, 5596–5604; (*e*) D. J. P. Kornfilt and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2019, **141**, 6853–6858; (*f*) X. Creary, *Beilstein J. Org. Chem.*, 2019, **15**, 1769–1780; (*g*) P. J. Sarver, V. Bacauanu, E. C. Sherer, D. M. Schultz and D. W. C. MacMillan, *Nat. Chem.*, 2020, **12**, 459–467.

12 For selected examples, see:(*a*) W. R. Dolbier, T. A. Gray, J. J. Keaffaber, L. Celewicz and H. Koroniak, *J. Am. Chem. Soc.*, 1990, **112**, 363–367; (*b*) M. Bugera, S. Trofymchuk, K. Tarasenko, O. Zaporozhets, Y. Pustovit and P. K. Mykhailiuk, *J. Org. Chem.*, 2019, **84**, 16105–16115; (*c*) W. R. Hasek, W. C. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, 1960, **82**, 543–551; (*d*) O. P. Demchuk, B. V. Bobovskyi, B. V. Vashchenko, O. V. Hryshchuk, A. Skreminskyi, A. V. Chernykh, V. S. Moskvina, O. V. Hordiyenko, D. M. Volochnyuk and O. O. Grygorenko, *Eur. J. Org Chem.*, 2023, **26**, e202300292; (*e*) O. P. Demchuk, O. V. Hryshchuk, B. V. Vashchenko, S. A. Trofymchuk, K. P. Melnykov, A. Skreminskiy, D. M. Volochnyuk and O. O. Grygorenko, *Eur. J. Org Chem.*, 2021, **1**, 87–95.

13 Y. Duan, Y. Xu, Y. Li, L. Mao, J. Feng, R. Zhang, W. Tang, T. Lu, Y. Chen and J. Feng, *Green Chem.*, 2024, **26**, 5512–5518.

14 X.-T. Feng, Q.-Q. Min, X. Zeng, H.-Y. Zhao and X. Zhang, *ACS Catal.*, 2024, **14**, 5879–5887.

15 X.-T. Feng, J.-X. Ren, X. Gao, Q.-Q. Min and X. Zhang, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210103.

16 (*a*) R. Mondal, M. Agbaria and Z. Nairoukh, *Chem.–Eur. J.*, 2021, **27**, 7193–7213; (*b*) S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk and O. O. Grygorenko, *Chem.–Eur. J.*, 2022, **28**, e202200331.

17 M. A. Saley, E. M. Hamed and A. Houmam, *ChemElectroChem*, 2024, **11**, e202300786.

18 M. Zhou, J.-X. Ren, X.-T. Feng, H.-Y. Zhao, X.-P. Fu, Q.-Q. Min and X. Zhang, *Chem. Sci.*, 2024, **15**, 2937–2945.

19 F. Ye, Y. Ge, A. Spannenberg, H. Neumann, L.-W. Xu and M. Beller, *Nat. Commun.*, 2021, **12**, 3257.

20 M. C. Van Zandt, G. E. Jagdmann, D. L. Whitehouse, M. Ji, J. Savoy, O. Potapova, A. Cousido-Siah, A. Mitschler, E. I. Howard, A. M. Pyle and A. D. Podjarny, *J. Med. Chem.*, 2019, **62**, 8164–8177.

21 W. Sittiwong, D. K. Zinniel, R. J. Fenton, D. D. Marshall, C. B. Story, B. Kim, J.-Y. Lee, R. Powers, R. G. Barletta and P. H. Dussault, *ChemMedChem*, 2014, **9**, 1838–1849.