

Cite this: *Chem. Sci.*, 2022, 13, 2686

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

Received 17th January 2022
Accepted 26th January 2022

DOI: 10.1039/d2sc00302c

rsc.li/chemical-science

A novel type of donor–acceptor cyclopropane with fluorine as the donor: (3 + 2)-cycloadditions with carbonyls†

Haidong Liu,^a Lifang Tian,^a Hui Wang,^a Zhi-Qiang Li,^a Chi Zhang,^a Fei Xue^b and Chao Feng^{a*}

gem-Difluorocyclopropane diester is disclosed as a new type of donor–acceptor cyclopropane, which smoothly participates in (3 + 2)-cycloadditions with various aldehydes and ketones. This work represents the first application of *gem*-difluorine substituents as an unconventional donor group for activating cyclopropane substrates in catalytic cycloaddition reactions. With this method, a wide variety of densely functionalized *gem*-difluorotetrahydrofuran skeletons, which are otherwise difficult to prepare, could be readily assembled in high yields under mild reaction conditions. Computational studies show that the cleavage of the C–C bond between the difluorine and diester moieties occurs upon a S_N2-type attack of the carbonyl oxygen.

Introduction

Donor–acceptor cyclopropanes (DACs) constitute an important class of building blocks in modern organic synthesis, which participate in diverse chemical transformations such as ring-opening functionalization, cycloaddition and skeleton rearrangement reactions.¹ The vicinal substituents with opposing electronic properties endow DACs with fascinating reactivities, which could be further activated *via* Lewis acid,² transition-metal³ and small-molecule catalysis.⁴ The continually enriched reaction patterns as well as their predictable behaviour enable DAC-involved reactions to find broad application in asymmetric transformation,⁵ natural product synthesis and drug development as well.⁶

While studying the correlation between the reactivity and structure, Werz and coworkers revealed that the properties of the donor group could exert more significant influence on the reaction efficiency, spanning more than four orders of magnitude.⁷ Generally, the donor group often involves carbon-,^{2,3b-g,4,8} nitrogen-^{2d,8f,g,9} and oxygen-based entities.^{8f-h,10} However, other heteroatom-based donor groups remain essentially unexplored. In this environment, the exploration of structurally novel DACs, especially those with unconventional heteroatom-based donor groups, is highly desirable for enriching DAC chemistry.

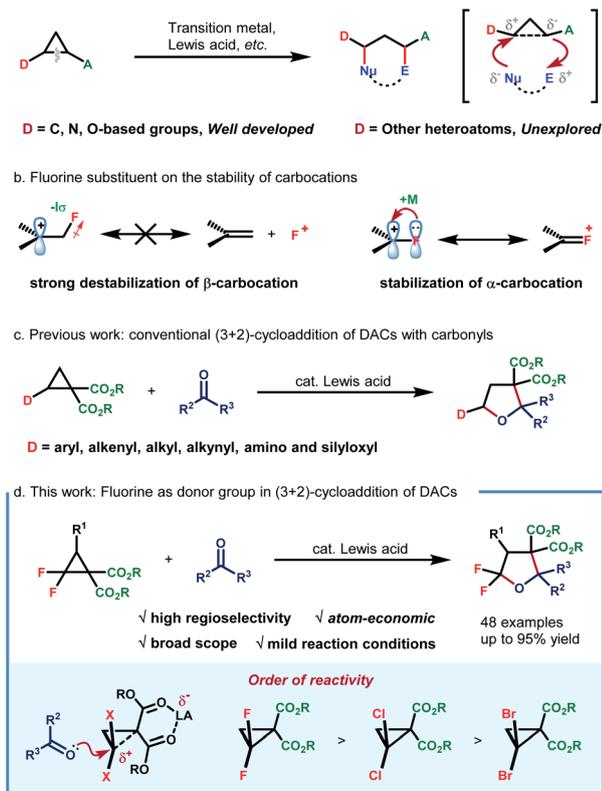
As the most electronegative element, fluorine has traditionally been treated as a type of potent σ -electron-withdrawing substituent. Because of its strong negative induction effect, the fluorine substituent always exhibits a strong destabilization effect on β -carbocations. Nevertheless, it is also revealed to display a decent resonance stabilization effect on α -carbocation, which is rationalized by p–p orbital interaction, thus resulting in positive charge delocalization by releasing an unshared electron pair of the fluorine substituent to the adjacent vacant p orbital of the cationic carbon center (termed the α -cation stabilizing effect of fluorine) (Scheme 1b).¹¹ In this regard, the fluorine atom could thus be regarded as a special type of electron-donating group due to the fact that π -electron donation outcompetes its intrinsic negative inductive effect. Although this special electronic effect was uncovered as early as 1974, its application in synthetic organic chemistry remains underdeveloped since then. By leveraging this unique electronic effect, a set of elegant protocols were successfully developed by Ichikawa and coworkers,¹² such as arylation of trifluoromethylated alkenes^{12a} and Friedel–Crafts type cyclization of difluoroalkenes.^{12b} Recently, our group has also developed a novel protocol for 1,3-fluoroallylation of aryl-substituted *gem*-difluorocyclopropane under photoredox catalysis.¹³ The fidelity of site-selective fluorine incorporation was rationalized by the cation stabilization capacity of the *gem*-difluorine substituent. Enlightened by these discoveries, we envisioned the possibility of extrapolating the α -cation stabilizing effect of fluorine by developing a new type of *gem*-difluorine-based DAC. If possible, a straightforward synthesis of CF₂-embedded hetero/carbocycles could be readily realized through cycloaddition reactions with unsaturated π -systems. With our continuous interest in fluorine chemistry^{13,14} and enlightened by the well-

^aTechnical Institute of Fluorochemistry (TIF), Institute of Advanced Synthesis (IAS), School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, P. R. China. E-mail: iamcfeng@njtech.edu.cn

^bInstitute of Material Physics & Chemistry, College of Science, Nanjing Forestry University, Nanjing 210037, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d2sc00302c





Scheme 1 Ring-opening functionalization of donor-acceptor cyclopropanes.

developed cycloaddition of D-A cyclopropanes with carbonyls (Scheme 1c),¹⁵ we herein report our recent progress in the AlCl_3 -catalyzed (3 + 2)-cycloaddition of *gem*-difluorocyclopropane diester with aldehydes/ketones (Scheme 1d). By making use of this method, a large variety structurally diverse multi-substituted *gem*-difluorotetrahydrofurans, which could not be readily prepared by traditional methods, are efficiently constructed in high yields with good diastereoselectivities.

Results and discussion

At the outset, the starting DAC *gem*-difluorocyclopropane diester **1a** was readily prepared following Chen's method using $\text{FSO}_2\text{CF}_2\text{CO}_2\text{TMS}$ as the difluorocarbene precursor with dibenzyl 2-methylenemalonate in 74% yield.¹⁶ Subsequently, the reaction of **1a** with different unsaturated systems was examined.¹⁷ We found that the cycloadduct was only observed when an aldehyde or ketone was used as the dipolarophile for (3 + 2)-cycloadditions, while using 20 mol% AlCl_3 as the Lewis acid and DCM as the solvent at room temperature. The desired product **3aa** was detected in 65% yield (Table 1, entry 1). Other Lewis acids such as $\text{Zn}(\text{OTf})_2$ and $\text{Yb}(\text{OTf})_3$ all gave inferior results, whereas $\text{In}(\text{OTf})_3$ led to the formation of **3aa** in comparable yield (entry 2–6). In view of the poor mass balance of substrate **1a**, we surmised that product **3aa** might degrade, to some extent, under the current reaction conditions. Consistent with our hypothesis, lowering the reaction temperature led to

Table 1 Reaction condition optimization^a

Entry	Lewis acid	Conversion of 1a (%)	Yield (%)
1	AlCl_3	97	65
2	$\text{Zn}(\text{OTf})_2$	12	11
3	$\text{Yb}(\text{OTf})_3$	47	34
4	MgI_2	65	0
5	$\text{In}(\text{OTf})_3$	100	62
6	$\text{Sn}(\text{OTf})_2$	100	0
7 ^b	AlCl_3	98	77
8 ^c	AlCl_3	99	82
9 ^{c,d,e}	AlCl_3	100	95(92)
10 ^{c,d}	—	0	0

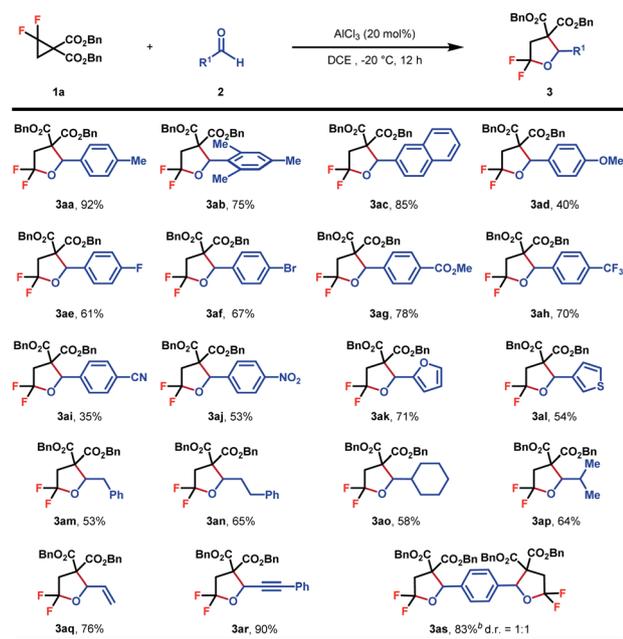
^a Reaction performed with **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), Lewis acid (20 mol%), DCM (0.1 M), and 12 h. Yield was determined by ^{19}F NMR analysis using 1-iodo-4-(trifluoromethyl)benzene as the internal standard. ^b Reaction performed at 0 °C. ^c Reaction performed at -20 °C. ^d Reaction performed with DCE as solvent. ^e Isolated yield was given in parentheses.

a significant enhancement in reaction yields (entry 7–8). Further promotion in reaction efficiency was observed when DCE was used as the solvent, resulting in the isolation of **3aa** in 92% yield (entry 9). Finally, control experiments showed that the Lewis acid is of critical importance for product formation (entry 10).

With the optimized conditions in hand, the generality of this (3 + 2)-cycloaddition was investigated with respect to different aldehydes by reacting with **1a** (Table 2). Various substituted aromatic aldehydes were evaluated firstly. A range of functional groups with diverse electronic properties, either electron-rich (**3aa–3ad**) or deficient (**3ae–3aj**), were well tolerated under the standard reaction conditions to afford the corresponding products in moderate to good yields. The steric hindrance seemed to have no obvious effect on the reaction efficiency, and in the case of mesitylaldehyde **2b**, product **3ab** was obtained in 75% yield. The relatively low yield of cyano-substituted aldehydes might be caused by its Lewis basic nature, which may, to some extent, result in the attenuation of the reactivity of the catalyst (**3ai**). To our delight, heteroaromatic aldehydes performed equally well, which gave rise to biheterocyclic products in good yields (**3ak–3al**). In addition to aromatic aldehydes, aliphatic aldehydes, either as primary (**3am–3an**) or secondary (**3ao–3ap**) ones, were also viable substrates, which delivered the desired products in 53–65% yields. Pleasingly, the substrate scope could be further extended to acrolein and phenylpropargyl aldehydes to obtain *gem*-difluorotetrahydrofuran with extra alkene (**3aq**) or alkyne (**3ar**) structural motifs, which provided versatile handles for further synthetic elaboration. Finally, the reaction of *p*-phthalaldehyde with 2.5 equiv. of **1a** also proceeded smoothly to give **3as** in 83% yield as a mixture of two diastereoisomers.

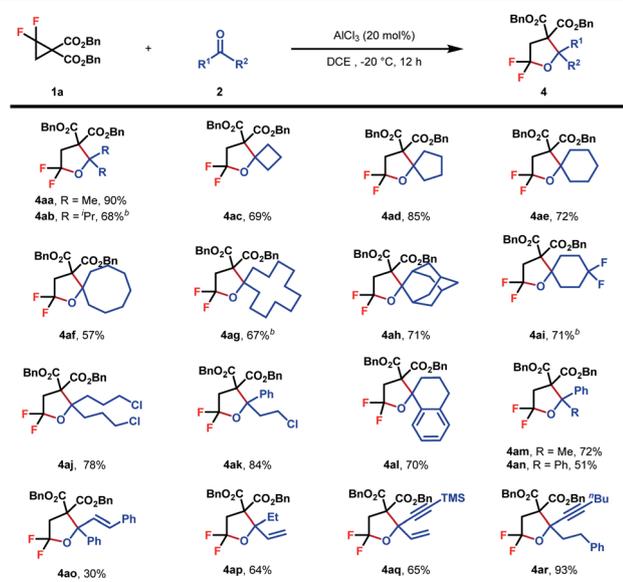
Encouraged by these outcomes, we turned to evaluate the scope of ketones as cycloaddition partners (Table 3). The



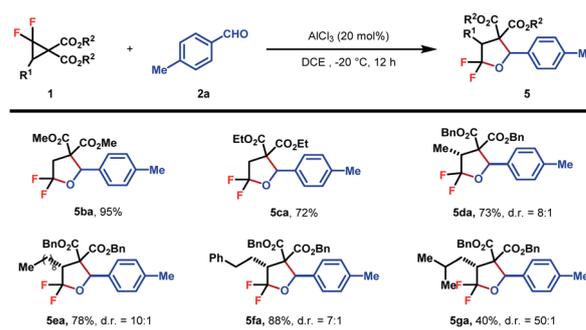
Table 2 Substrate scope of aldehydes^a

^a Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), AlCl₃ (20 mol%), DCE (0.1 M), -20 °C, and 12 h. Diastereomeric ratios were determined by ¹H NMR analysis of the crude reaction mixture. Isolated yield. ^b **1a** (0.5 mmol, 2.5 equiv.) and terephthalaldehyde (0.2 mmol, 1.0 equiv.).

reaction worked well with symmetrical aliphatic ketones (**4aa–4aj**), even those steric congested ones (**4ab** and **4ah**). In some cases (**4ab**, **4ag**, and **4ai**), when AlCl₃ was used as the Lewis acid

Table 3 Substrate scope of ketones^a

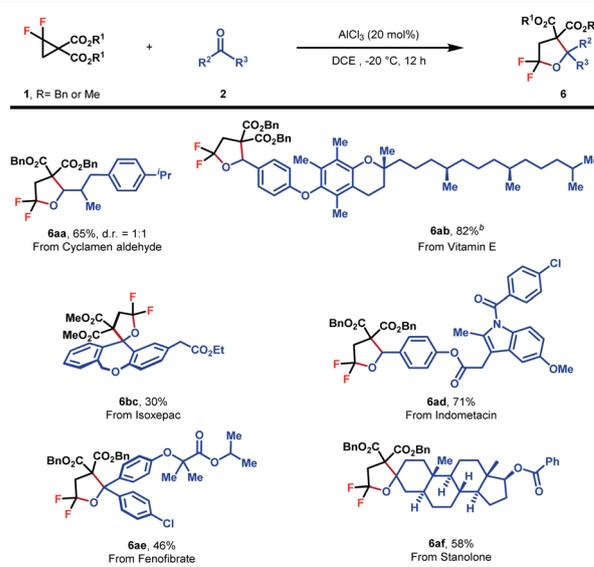
^a Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), AlCl₃ (20 mol%), DCE (0.1 M), -20 °C, and 12 h. Diastereomeric ratios were determined by ¹H NMR analysis of the crude reaction mixture. Isolated yield. ^b In(OTf)₃ (20 mol%) instead of AlCl₃ (20 mol%).

Table 4 Substrate scope of DACs^a

^a Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), AlCl₃ (20 mol%), DCE (0.1 M), -20 °C, and 12 h. Diastereomeric ratios were determined by ¹H NMR analysis of the crude reaction mixture. Isolated yield.

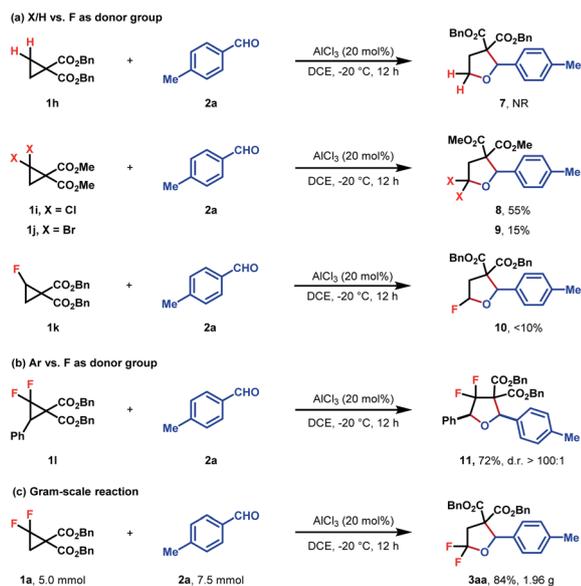
catalyst, byproduct dibenzyl 2-(2-chloro-2,2-difluoroethyl) malonate could be detected, the formation of which was interpreted by a competitive nucleophilic attack of chloride ions originating from AlCl₃. This issue, however, could be circumvented by replacing AlCl₃ with In(OTf)₃ to guarantee satisfactory yields. Simple unsymmetrical aliphatic and aromatic ketones also performed well to yield the corresponding products (**4ak–4ar**). A series of functional groups, including halogen (**4ak**), terminal and internal alkenes (**4ap**, **4aq**, and **4ao**) and internal alkynes (**4aq** and **4ar**), proved to be compatible with the reaction conditions, showing the good compatibility of this reaction.

The substrate scope of DACs was then explored (Table 4). The switching of the benzylic ester to methyl ester did not affect the

Table 5 Late-stage functionalization^a

^a Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), AlCl₃ (20 mol%), DCE (0.1 M), -20 °C, and 12 h. Diastereomeric ratios were determined by ¹H NMR analysis of the crude reaction mixture. Isolated yield. ^b In(OTf)₃ (20 mol%) instead of AlCl₃ (20 mol%).





Scheme 2 Control experiments and gram-scale reaction.

reaction efficiency and **5ba** was obtained in a similar yield, higher than that of the ethyl ester analogue (**5ca**). A set of *gem*-difluorocyclopropane diesters with an additional alkyl substituent at C3 were synthesized and found to react well with **2a** to afford the desired products in fair to good yields and high to excellent diastereoselectivities (**5da–5ga**). Increasing the steric hindrance of the alkyl substituent was beneficial to the stereoselectivity, albeit at the expense of yield (**5ga**). The *trans*-configuration of **5da** was determined by NOESY of the major isomer and others were assigned in analogy. Note that in these cases, the bond between the *gem*-difluorine and diester group was cleaved selectively, indicating a more favored nucleophilic attack at the *gem*-difluorocarbon atom.

To further show the synthetic applicability, this method was applied to the late-stage functionalization of some natural products and pharmaceutically relevant molecules (Table 5).

Cyclamen aldehydes and aldehydes derived from vitamin E and indometacin all proceeded well with **1a**, providing **6aa**, **6ab** and **6ad** in good to high yields. Furthermore, ketone reaction partners originating from fenofibrate, stanalone and isoxepac also underwent the (3 + 2)-cycloaddition uneventfully, affording hex-substituted tetrahydrofurans in moderate yields (**6bc**, **6ae** and **6af**). Taken together, the method developed herein could enable modular construction for the rapid installation of *gem*-difluoro-heterocycle into molecular structures of interest.

To better investigate the role of fluorine atoms in this reaction, a series of control experiments were then executed. The reaction of simple cyclopropane diester **1h** with **2a** under standard conditions resulted in the full recovery of **1h** (Scheme 2a). Furthermore, *gem*-dichloro and *gem*-dibromocyclopropane diesters **1i** and **1j** were also prepared and subjected to the standard reaction conditions, which, however, delivered the desired products **8** and **9** in 55% and 15% yields, respectively (Scheme 2a). These two experiments revealed that the order of reactivity of cyclopropane entities in cycloadditions follows F > Cl > Br > H. The higher reactivity of F-based cyclopropane could be rationalized by the fact that the 2p-orbitals of fluorine are roughly the same size as that of the carbon atom, which leads to more effective resonance stabilization of positive charge developing at the α -carbon atom. When monofluorocyclopropane **1k** was employed, the desired product **10** was detected in less than 10% yield, indicating the relatively weak π -electron donating ability of the mono-fluorine atom in activating the substrate for ring-opening functionalization. However, when *gem*-difluorocyclopropane diesters with an aryl group at C3 were subjected to the standard conditions, the oxygen of carbonyl exclusively attacked the C3 position and 3,3-difluoro substituted tetrahydrofuran **11** was obtained as the sole product, indicating that as compared with the *gem*-difluorine substituent, the aryl group is more apt to stabilize the adjacent positive charge (Scheme 2b). A gram-scale reaction using the model substrate was also performed, which produced the desired product **3aa** without an obvious reduction in yield (Scheme 2c).

To gain more insight into the mechanism, density functional theory (DFT) calculation of this (3 + 2)-cycloaddition reaction was

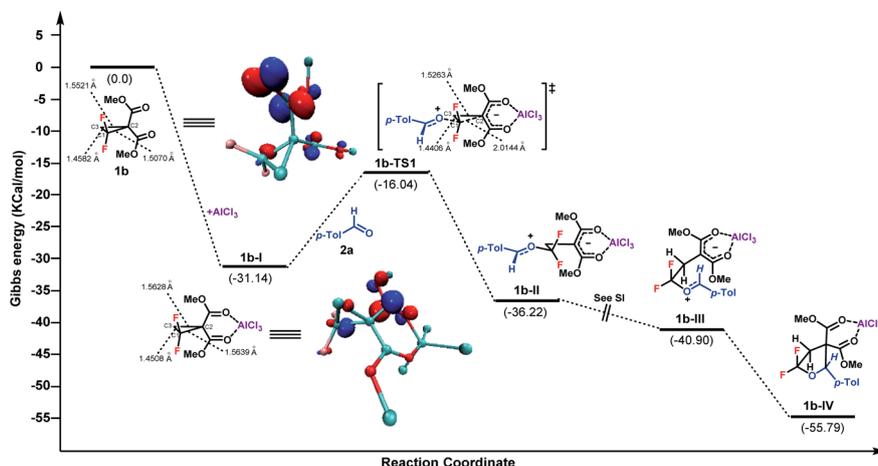


Fig. 1 DFT calculation for the (3 + 2)-cycloaddition of *gem*-difluorocyclopropane and aldehyde. LUMO of **1b** and **1b-I** with an isovalue of 0.1 atomic units.



conducted with the Gaussian 09 program at the B3-LYP level of theory with the 6-31G(d, p) basis set in MeCN implicitly.¹⁸ The Gibbs free energy profile for the cycloaddition process is shown in Fig. 1. In the presence of AlCl₃, the intermediate **1b-I** was produced first upon coordination, with a Gibbs free energy downhill of 31.14 kcal mol⁻¹. Then, a S_N2 nucleophilic attack of aldehyde **2a** to C1 of **1b-I** occurred to generate the intermediate **1b-II**. The activation barrier of this procedure was 15.1 kcal mol⁻¹. Followed by a barrierless C1–C3 bond rotation, ensuing intramolecular cyclization afforded the final product, upon disassociation of AlCl₃. According to the Gibbs free energy profiles, the S_N2 ring-opening C–C bond cleavage was found to be the rate-determining step. Overall, the calculated reaction pathway is in good accordance with the model proposed by Johnson *et al.* of the Lewis acid catalyzed (3 + 2)-cycloaddition of D–A cyclopropanes with aldehydes.^{2b} Furthermore, the electron distributions of **1b**, **1b-I** and **1b-TS1**, in terms of Mulliken charge, were obtained respectively.¹⁷ Compared to **1b**, the positive charges on the C1 of **1b-I** increased from 0.610 to 0.649 after AlCl₃ coordination. As expected, more positive charge on C1 was observed for the transition state **TS1**. In contrast, the C2 and C3 of **1b** and **1b-I** always showed negative charge. The length of the C–C bond between C1 and C2 was also found to be elongated from 1.5070 Å to 1.5639 Å after Lewis acid coordination. In addition, according to the theory of frontier molecular orbitals, the atom with a higher contribution to the LUMO is more susceptible to nucleophilic attack. The LUMOs of **1b** and **1b-I** were therefore calculated, which indicated the largest coefficients at C1 for both entities.¹⁷ Taken together, these results indicate that the attack of nucleophile **2a** at the C1 of **1b** is controlled by both the electrostatic effect and orbital interaction.

Conclusions

In summary, by taking advantage of the π -electron donation properties of fluorine, a new class of DCAs is developed, which could participate in Lewis-acid catalyzed (3 + 2)-cycloadditions with aldehydes/ketones, thus enabling a straightforward construction of densely substituted *gem*-difluorotetrahydrofurans. This work represents the first example of using *gem*-difluorine as the donor group in DAC involved reactions, which also opens up a new reaction mode of *gem*-difluorocyclopropanes. The critical role of fluorine is probed by control experiments as well as DFT calculations. Further applications of the α -cation stabilizing effect of fluorine are underway in our laboratory.

Data availability

Data for this work, including experimental procedures, characterization data for all new compounds, and DFT computational details are provided in the ESI.†

Author contributions

C. F. conceived and directed the project. H. L., H. W. and Z.-Q. L. performed the experiment and collected the data. L. T.

performed all DFT calculations. H. L., C. Z. and C. F. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the “Thousand Talents Plan” Youth Program, the “Jiangsu Specially-Appointed Professor Plan”, and the National Natural Science Foundation of China (21871138).

Notes and references

- Reviews of D–A cyclopropanes: (a) P. Singh, R. K. Varshnaya, R. Dey and P. Banerjee, *Adv. Synth. Catal.*, 2020, **362**, 1447–1484; (b) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504–5523; (c) D. B. Werz and A. T. Biju, *Angew. Chem., Int. Ed.*, 2020, **59**, 3385–3398; (d) A. U. Augustin and D. B. Werz, *Acc. Chem. Res.*, 2021, **54**, 1528–1541; (e) M. A. Cavitt, L. H. Phun and S. France, *Chem. Soc. Rev.*, 2014, **43**, 804–818; (f) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano and J. Waser, *Chem. Commun.*, 2014, **50**, 10912–10928; (g) B. L. Pagenkopf and N. Vemula, *Eur. J. Org. Chem.*, 2017, **2017**, 2561–2567.
- For selected examples, see: (a) I. S. Young and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2003, **42**, 3023–3026; (b) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 8642–8650; (c) S. Xing, W. Pan, C. Liu, J. Ren and Z. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 3215–3218; (d) A. U. Augustin, M. Senses, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2017, **56**, 14293–14296; (e) D.-C. Wang, M.-S. Xie, H.-M. Guo, G.-R. Qu, M.-C. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2016, **55**, 14111–14115; (f) A. T. Parsons, A. G. Smith, A. J. Neel and J. S. Johnson, *J. Am. Chem. Soc.*, 2010, **132**, 9688–9692.
- For the review, see: (a) J. Wang, S. A. Blaszczyk, X. Li and W. Tang, *Chem. Rev.*, 2021, **121**, 110–139; (b) B. M. Trost and P. J. Morris, *Angew. Chem., Int. Ed.*, 2011, **50**, 6167–6170; (c) A. P. Dieskau, M. S. Holzwarth and B. Plietker, *J. Am. Chem. Soc.*, 2012, **134**, 5048–5051; (d) Y. Miyake, S. Endo, T. Moriyama, K. Sakata and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2013, **52**, 1758–1762; (e) Q. Cheng, J.-H. Xie, Y.-C. Weng and S.-L. You, *Angew. Chem., Int. Ed.*, 2019, **58**, 5739–5743; (f) J. Moran, A. G. Smith, R. M. Carris, J. S. Johnson and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 18618–18621; (g) R. Tombe, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2013, **15**, 1791–1793; (h) F. de Nanteuil, E. Serrano, D. Perrotta and J. Waser, *J. Am. Chem. Soc.*, 2014, **136**, 6239–6242.
- (a) J. Blom, A. Vidal-Albalat, J. Jørgensen, C. L. Barløse, K. S. Jessen, M. V. Iversen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2017, **56**, 11831–11835; (b) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2015, **137**, 1685–1691; (c) E. Sanchez-Diez, D. L. Vesga, E. Reyes, U. Uria,



- L. Carrillo and J. L. Vicario, *Org. Lett.*, 2016, **18**, 1270–1273; (d) J. Wallbaum, L. K. B. Garve, P. G. Jones and D. B. Werz, *Chem.–Eur. J.*, 2016, **22**, 18756–18759.
- 5 (a) V. Pirenne, B. Muriel and J. Waser, *Chem. Rev.*, 2021, **121**, 227–263; (b) Y. Xia, X. Liu and X. Feng, *Angew. Chem., Int. Ed.*, 2021, **60**, 9192–9204.
- 6 For reviews, see: (a) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051–3060; (b) B. M. Trost, W.-J. Bai, C. Hohn, Y. Bai and J. J. Cregg, *J. Am. Chem. Soc.*, 2018, **140**, 6710–6717; (c) R. Frei, D. Staedler, A. Raja, R. Franke, F. Sasse, S. Gerber-Lemaire and J. Waser, *Angew. Chem., Int. Ed.*, 2013, **52**, 13373–13376; (d) F. De Simone, J. Gertsch and J. Waser, *Angew. Chem., Int. Ed.*, 2010, **49**, 5767–5770; (e) P. Liu, Y. Cui, K. Chen, X. Zhou, W. Pan, J. Ren and Z. Wang, *Org. Lett.*, 2018, **20**, 2517–2521; (f) B. Sun, J. Ren, S. Xing and Z. Wang, *Adv. Synth. Catal.*, 2018, **360**, 1529–1537.
- 7 (a) A. Kreft, A. Lücht, J. Grunenberg, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2019, **58**, 1955–1959; (b) A. Kreft, P. G. Jones and D. B. Werz, *Org. Lett.*, 2018, **20**, 2059–2062.
- 8 For selected examples, see: (a) S. Haubenreisser, P. Hensenne, S. Schröder and M. Niggemann, *Org. Lett.*, 2013, **15**, 2262–2265; (b) A. G. Smith, M. C. Slade and J. S. Johnson, *Org. Lett.*, 2011, **13**, 1996–1999; (c) W. Zhu, J. Fang, Y. Liu, J. Ren and Z. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 2032–2037; (d) A. U. Augustin, M. Busse, P. G. Jones and D. B. Werz, *Org. Lett.*, 2018, **20**, 820–823; (e) M. P. Sibi, Z. Ma and C. P. Jasperse, *J. Am. Chem. Soc.*, 2005, **127**, 5764–5765; (f) J. Preindl, S. Chakrabarty and J. Waser, *Chem. Sci.*, 2017, **8**, 7112–7118; (g) L. K. B. Garve, P. Barkawitz, P. G. Jones and D. B. Werz, *Org. Lett.*, 2014, **16**, 5804–5807; (h) S. Xing, Y. Li, Z. Li, C. Liu, J. Ren and Z. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 12605–12609.
- 9 For selected examples, see: (a) F. Benfatti, F. de Nanteuil and J. Waser, *Org. Lett.*, 2012, **14**, 386–389; (b) F. Benfatti, F. de Nanteuil and J. Waser, *Chem.–Eur. J.*, 2012, **18**, 4844–4849; (c) F. de Nanteuil and J. Waser, *Angew. Chem., Int. Ed.*, 2011, **50**, 12075–12079; (d) S. Racine, F. de Nanteuil, E. Serrano and J. Waser, *Angew. Chem., Int. Ed.*, 2014, **53**, 8484–8487; (e) D. Perrotta, M.-M. Wang and J. Waser, *Angew. Chem., Int. Ed.*, 2018, **57**, 5120–5123; (f) B. Muriel, A. Gagnebin and J. Waser, *Chem. Sci.*, 2019, **10**, 10716–10722; (g) M.-C. Zhang, D.-C. Wang, M.-S. Xie, G.-R. Qu, H.-M. Guo and S.-L. You, *Chem.*, 2019, **5**, 156–167.
- 10 For selected examples, see: (a) H.-U. Reissig, H. Holzinger and G. Glomsda, *Tetrahedron*, 1989, **45**, 3139–3150; (b) H.-U. Reissig, *Tetrahedron Lett.*, 1981, **22**, 2981–2984.
- 11 (a) C. Ni and J. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441–5454; (b) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (c) R. E. Banks and J. C. Tatlow, *J. Fluorine Chem.*, 1986, **33**, 227–346; (d) *Organofluorine Chemistry*, ed. B. E. Smart and J. C. Tatlow, Plenum Press, New York, 1994, pp. 57–88; (e) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006; (f) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214–231; (g) K. Fuchibe, Y. Mayumi, N. Zhao, S. Watanabe, M. Yokota and J. Ichikawa, *Angew. Chem., Int. Ed.*, 2013, **52**, 7825–7828.
- 12 (a) K. Fuchibe, H. Hatta, K. Oh, R. Oki and J. Ichikawa, *Angew. Chem., Int. Ed.*, 2017, **56**, 5890–5893; (b) K. Fuchibe, H. Jyono, M. Fujiwara, T. Kudo, M. Yokota and J. Ichikawa, *Chem.–Eur. J.*, 2011, **17**, 12175–12185.
- 13 H. Liu, Y. Li, D.-X. Wang, M.-M. Sun and C. Feng, *Org. Lett.*, 2020, **22**, 8681–8686.
- 14 (a) H. Liu, L. Ge, D.-X. Wang, N. Chen and C. Feng, *Angew. Chem., Int. Ed.*, 2019, **58**, 3918–3922; (b) H.-J. Tang, L.-Z. Lin, C. Feng and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2017, **56**, 9872–9876; (c) H.-J. Tang, X. Zhang, Y.-F. Zhang and C. Feng, *Angew. Chem., Int. Ed.*, 2020, **59**, 5242–5247; (d) C.-Q. Wang, Y. Zhang and C. Feng, *Angew. Chem., Int. Ed.*, 2017, **56**, 14918–14922; (e) C. Zhu, M.-M. Sun, K. Chen, H. Liu and C. Feng, *Angew. Chem., Int. Ed.*, 2021, **60**, 20237–20242; (f) L. Tang, Z.-Y. Liu, W. She and C. Feng, *Chem. Sci.*, 2019, **10**, 8701–8705; (g) P. Tian, C.-Q. Wang, S.-H. Cai, S. Song, L. Ye, C. Feng and T.-P. Loh, *J. Am. Chem. Soc.*, 2016, **138**, 15869–15872; (h) C. Zhu, Z.-Y. Liu, L. Tang, H. Zhang, Y.-F. Zhang, P. J. Walsh and C. Feng, *Nat. Commun.*, 2020, **11**, 4860; (i) C.-Q. Wang, Y. Li and C. Feng, *Cell Rep. Phys. Sci.*, 2021, **2**, 100461.
- 15 (a) P. D. Pohlhaus and J. S. Johnson, *J. Am. Chem. Soc.*, 2005, **127**, 16014–16015; (b) A. T. Parsons and J. S. Johnson, *J. Am. Chem. Soc.*, 2009, **131**, 3122–3123; (c) P. Yang, Y. Shen, M. Feng, G. Yang and Z. Chai, *Eur. J. Org. Chem.*, 2018, **2018**, 4103–4112; (d) P. D. Pohlhaus and J. S. Johnson, *J. Org. Chem.*, 2005, **70**, 1057–1059; (e) G. Yang, Y. Shen, K. Li, Y. Sun and Y. Hua, *J. Org. Chem.*, 2011, **76**, 229–233; (f) G. Yang, Y. Sun, Y. Shen, Z. Chai, S. Zhou, J. Chu and J. Chai, *J. Org. Chem.*, 2013, **78**, 5393–5400.
- 16 F. Tian, V. Kruger, O. Bautista, J.-X. Duan, A.-R. Li, W. R. Dolbier and Q.-Y. Chen, *Org. Lett.*, 2000, **2**, 563–564.
- 17 See the ESI† for details.
- 18 (a) M. J. Frischi, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision D.01*; (b) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652; (c) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **37**, 785–789; (d) R. Peverati and D. G. Truhlar, *J. Phys. Chem. Lett.*, 2011, **2**, 2810–2817.

