OL Organic Letters

pubs.acs.org/OrgLett Letter

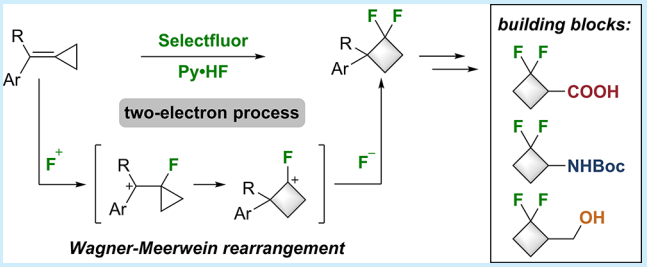
gem-Difluorination of Methylenecyclopropanes (MCPs) Featuring a Wagner–Meerwein Rearrangement: Synthesis of 2-Arylsubstituted *gem*-Difluorocyclobutanes

Peng-Peng Lin, Long-Ling Huang, Si-Xin Feng, Shuang Yang, Honggen Wang, Zhi-Shu Huang, and Qingjiang Li*

Cite This: *Org. Lett.* 2021, 23, 3088–3093 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The geminal difluorocyclobutane core is a valuable structural element in medicinal chemistry. Strategies for *gem*-difluorocyclobutanes, especially the 2-substituted cases, are limiting and often suffer from harsh reaction conditions. Reported herein is a migratory *gem*-difluorination of aryl-substituted methylenecycloproanes (MCPs) for the synthesis of 2-arylsubstituted *gem*-difluorocyclobutanes. Commercially available Selectfluor (F-TEDA-BF_4) and Py·HF were used as the fluorine sources. The protocol proceeds via a Wagner–Meerwein rearrangement with mild reaction conditions, good functional group tolerance, and moderate to good yields. The product could be readily transformed to *gem*-difluorocyclobutane-containing carboxylic acid, amine, and alcohol, all of which are useful building blocks for biologically active molecule synthesis.



Cyclobutanes, as the second most strained carbocycles, are intriguing structural motifs frequently found in naturally occurring products and biologically active molecules.[1] Due to their high structural rigidity and defined substituent spatial conformation, cyclobutanes are usually defined as privileged structural elements for structure-based drug discovery in medicinal chemistry.[2] In addition, they also serve as versatile building blocks in synthetic transformations such as ring-expansion or ring-cleavage reactions by releasing their inherent strain energies (*ca.* 26.7 kcal mol^{-1}).[3] On the other hand, organofluorine compounds are increasingly utilized in pharmaceutical, agrochemical, and materials sciences.[4] The incorporation of fluorine or fluorinated moieties into organic molecules often improves the biological properties of parent compounds, including lipophilicity, metabolic stability, bioavailability, and binding affinity.[5] Therefore, the above combined fluorinated cyclobutane structure might possess broad biological profiles and find more potential applications in medicinal chemistry (Figure 1).[6]

Although a great deal of methods have been developed to access diversely substituted fluorocyclobutanes,[7] to date, only a handful of methods exist for the synthesis of 2-substituted *gem*-difluorocyclobutanes.[8,9,11] Among these, thermal [2 + 2] cycloaddition could typically be applied to the synthesis of 2-substituted *gem*-difluorocyclobutanes by the reaction of alkenes with *gem*-difluoroallene derivatives (Scheme 1a).[8] The need for high temperature, the difficulty of handling gaseous *gem*-difluoroallene, and the intrinsic chemoselectivity for the two orthogonal double bonds on allenes limit its widespread

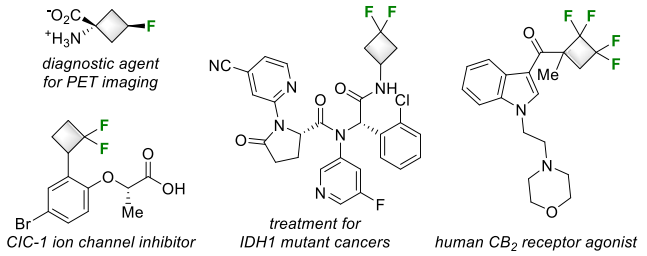


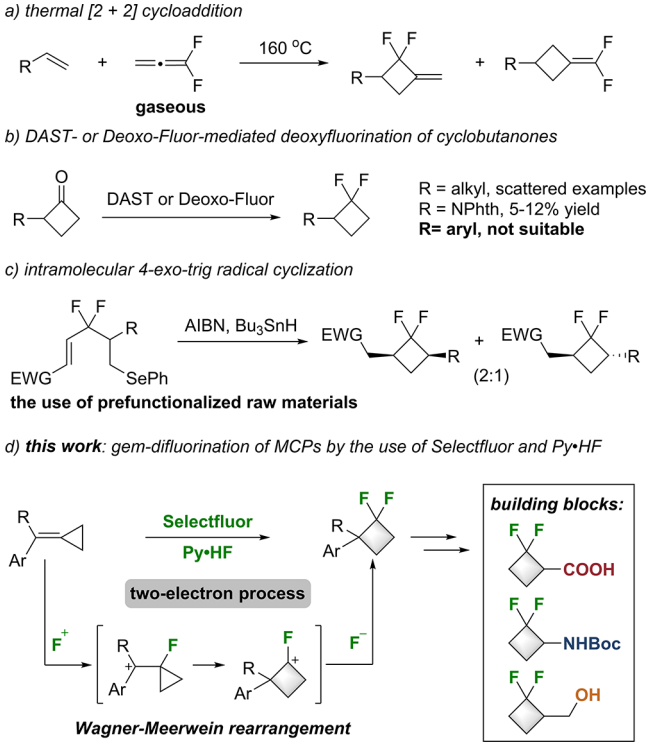
Figure 1. Representative drugs or bioactive compounds containing the fluorocyclobutane moiety.

synthetic applications. DAST or its derivative-mediated direct deoxyfluorination of 2-substituted cyclobutanones seems to be a convenient and valuable method to provide 2-substituted *gem*-difluorocyclobutanes (Scheme 1b).[9] Nevertheless, only scattered examples are successful when a 2-alkyl substrate was employed.[9a–c] The replacement of alkyl with a phthalimido group led to a drastically decreased yield of 5–12%.[9d] It should be noted that the reaction conditions of this deoxyfluorination are not compatible with 2-aryl cyclobutanones.[10] Alternatively,

Received: March 5, 2021
Published: April 1, 2021

https://doi.org/10.1021/acs.orglett.1c00767
Org. Lett. 2021, 23, 3088–3093

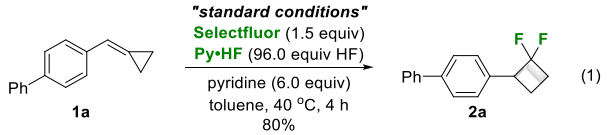
Scheme 1. Synthesis of 2-Substituted *gem*-Difluorocyclobutanes and Difunctionalizations of Methylenecyclopropanes (MCPs)



AIBN-triggered intramolecular 4-*exo-trig* radical cyclization of *gem*-difluorinated selenide was also feasible to access polysubstituted *gem*-difluorocyclobutanes, with poor diastereoselectivity being observed and prefunctionalized raw materials being needed (Scheme 1c).[11] Considering the potential applications of 2-substituted *gem*-difluorocyclobutanes and the drawbacks of their synthesis methods, it is still highly desirable to develop a new synthetic methodology for the construction of such important molecules.

Methylenecyclopropane and its derivatives (MCPs),[12] featuring an exocyclic double bond on the cyclopropane ring, have emerged as versatile synthetic building blocks in a number of intriguing transformations.[13] Among these diverse transformations, the ring expansion of MCPs via rearrangement was demonstrated to be a useful strategy to construct four-membered carbocycles.[14] In continuation of our interest in organofluorine synthesis,[15] we envisioned that 2-substituted *gem*-difluorocyclobutanes might be accessible via a Wagner−Meerwein rearrangement of MCPs in the presence of electrophilic and nucleophilic fluorine sources. Although previous reports showed that the directly ring-opened aminofluorination reaction of MCPs was observed in the presence of a strong nucleophile and an electrophilic fluorination reagent such as Selectfluor or NFSI,[16] we postulated that a weak nucleophilic fluoride ion might make the rearrangement proceed smoothly. Herein, we disclose our recognition of the migratory *gem*-difluorination of 2-arylsubstituted MCPs via Wagner−Meerwein rearrangement for the synthesis of 2-arylsubstituted *gem*-difluorocyclobutanes by using Selectfluor/Py·HF (Scheme 1d). To the best of our knowledge, the combination of Selectfluor and Py·HF as the electrophilic and nucleophilic fluorine sources for the *gem*-difluorinations of organic molecules in one system is unprecedented.[17] The reaction proceeds under mild reaction conditions with good functional group tolerance. Remarkably, further oxidation of the aryl ring of these products by $RuCl_3$/$NaIO_4$ affords 2,2-difluorocyclobutane-1-carboxylic acid, which can be readily converted to a diverse array of *gem*-difluorocyclobutane-containing compounds.

Initially, the migratory germinal difluorination reaction of 4-biphenylmethylenecyclopropane (**1a**) was studied in the presence of both electrophilic fluorine source Selectfluor and nucleophilic fluorine source Py·HF. To our delight, after extensive exploration, the desired product 4-(2,2-difluorocyclobutyl)-1,1′-biphenyl (**2a**) could be obtained in 80% isolated yield under the optimized reaction conditions of **1a** (0.2 mmol), Selectfluor (1.5 equiv), Py·HF (96.0 equiv HF), and pyridine (6.0 equiv) in toluene (1.0 mL) at 40 °C for 4 h (eq 1; see Supporting Information for details). It should be

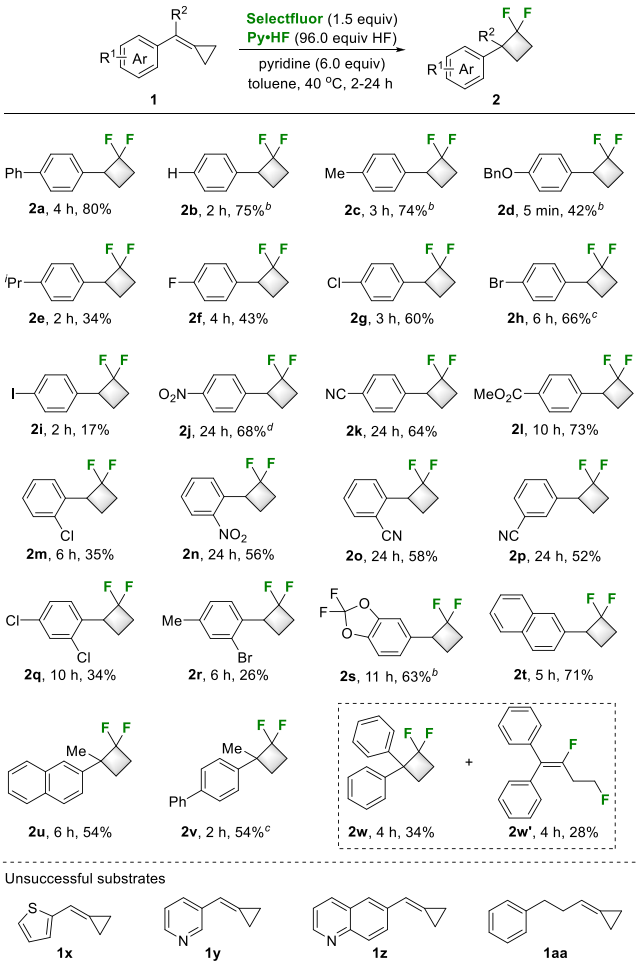


noted that no special exclusion of air and moisture is needed. With the optimized reaction conditions in hand, we next investigated the substrate scope of this migratory *gem*-difluorination reaction. As illustrated in Scheme 2, the transformation was found to be general to a diverse array of phenyl-substituted MCPs. A variety of commonly encountered functional groups, regardless of the electronic nature, at different positions of the benzene ring were well tolerated, giving the corresponding products in moderate to good yields. Substituents such as alkyl (**2c**, **2e**, **2r**), benzyloxy (**2d**), halides (**2f−i**, **2m**, **2q**, **2r**), nitro (**2j**, **2n**), cyano (**2k**, **2o**, **2p**), and ester (**2l**) were valuable functional handles for further derivatization. The lower yield of **2i** might stem from the side oxidation of aryliodides in the presence of Selectfluor.[18] Notably, *ortho*-substituted substrates gave relatively lower yields, presumably for steric reasons (**2m−2o**, **2q**, and **2r**). Furthermore, decreasing the loadings of Py·HF (to 64.0 equiv) for some substrates bearing electron-neutral and electron-donating groups, such as **2b−2d**, and **2s**, was beneficial for maintaining a satisfactory yield. The *gem*-difluorination of naphthyl-substituted MCPs produced the desired products in good yields (**2t** and **2u**). However, the reaction of 2-thienyl- (**1x**), 3-pyridyl- (**1y**), or 6-quinolyl-substituted (**1z**) MCPs did not give the corresponding *gem*-difluorocyclobutanes, probably due to the strong coordination of heteroatoms (O and N) to hydrogen fluoride. The use of 1-alkyl-1-aryl-substituted MCP was also successful (**2u** and **2v**). Interestingly, when the 1,1-diphenylsubstituted substrate was subjected to the standard reaction conditions, desired product **2w** was obtained in 34% yield, accompanied by a substantial amount of direct ring-opening difluorination side product **2w′**. Unfortunately, the current reaction conditions were not compatible with simple alkylmethylenecyclopropanes. For instance, the use of (3-cyclopropylidenepropyl)benzene (**1aa**) gave no trace of the desired product, resulting in a complex mixture.

The structure of compound **2l** was unequivocally confirmed by X-ray crystallographic analysis of its derivative **4** (CCDC 1977603), which was synthesized by lithium aluminum hydride reduction of the methyl ester followed by protection of the corresponding primary alcohol with *p*-nitrobenzoyl

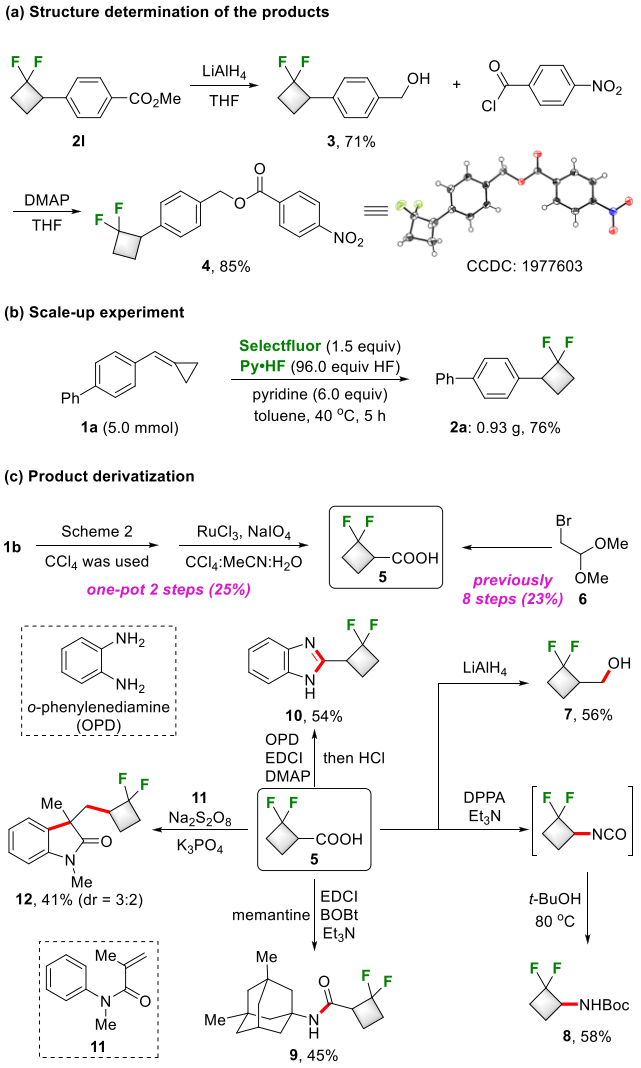
https://doi.org/10.1021/acs.orglett.1c00767
Org. Lett. 2021, 23, 3088−3093

Scheme 2. Synthesis of 2-Arylsubstituted *gem*-Difluorocyclobutanes[a]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), Selectfluor (1.5 equiv), Py·HF (96.0 equiv HF), pyridine (6.0 equiv), toluene (1 mL), air, 40 °C. [b]Py·HF (64.0 equiv HF). [c]CCl_4 was used instead of toluene. [d]AgCl (20 mol %) was used instead of pyridine, 24 h.

Scheme 3. Structure Determination of the Products, Gram-Scale Synthesis, and Product Derivatization

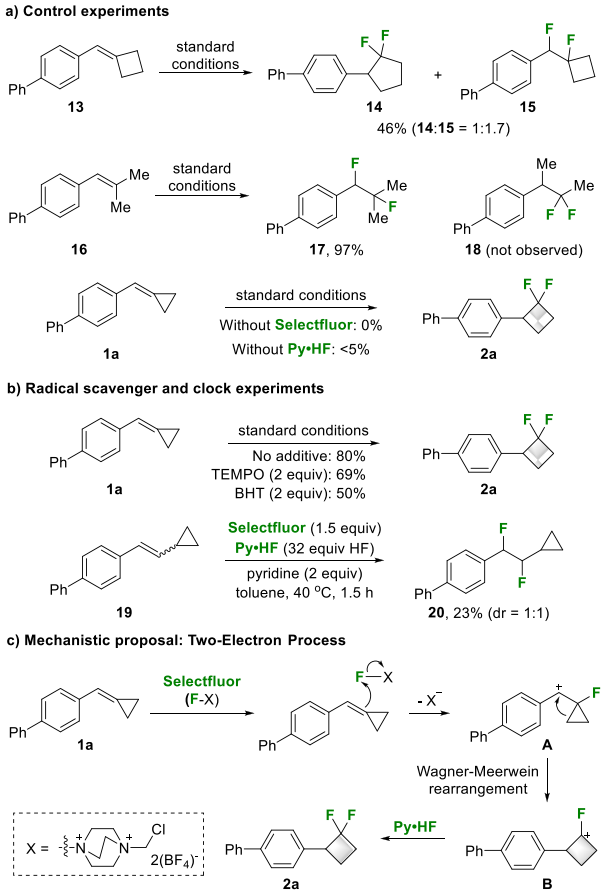


chloride/DMAP in an overall yield of 60% (Scheme 3a). To demonstrate the synthetic practicality of this protocol, a scale-up synthesis of *gem*-difluorocyclobutane **2a** was performed (Scheme 3b). And, 0.93 g of **2a** was obtained in 76% yield under the standard reaction conditions with a prolonged reaction time (to 5 h). The synthetic utility of this methodology was evidenced by a rapid preparation of 2,2-difluorocyclobutane-1-carboxylic acid **5**, a potential fluorinated building block for medicinal chemistry (Scheme 3c). Previously, Grygorenko and co-workers reported the synthesis of compound **5** in a total yield of 23% via 8 steps starting from 2-bromo-1,1-dimethoxyethane (**6**).[9a] By using our developed new methodology, carboxylic acid **5** could be easily accessible with a 25% total yield starting from a 25.0 mmol scale of **1b** through a one-pot two-step sequence, involving migratory *gem*-difluorination and following by oxidation[19] of the phenyl ring of **2b** to carboxyl by $RuCl_3/NaIO_4$. Remarkably, the obtained acid **5** can be used as a versatile building block to access various *gem*-difluorocyclobutane-containing compounds. Reduction of **5** with $LiAlH_4$ smoothly delivered alcohol **7**, and the carboxyl group within **5** could be converted to the corresponding amine derivative **8** via Curtius rearrangement[20] with good efficiency. On the other hand, through EDCI/HOBt-mediated amidation of carboxylic acid with amine, the *gem*-difluorocyclobutane moiety could be introduced into bioactive molecules, such as the antisenile dementia drug memantine,[21] affording the corresponding drug-derived compound **9** with an unoptimized 45% yield. In addition, treatment of acid **5** with *o*-phenylenediamine (OPD) in the presence of EDCI and DMAP followed by hydrochloric acid produced the condensation product 2-*gem*-difluorocyclobutyl benzimidazole **10** with a 54% yield. Finally, the oxidation of **5** with $Na_2S_2O_8$ triggered a metal-free decarboxylative radical alkylation[22] of *N*-acrylamide **11** and a C−H functionalization cascade to provide *gem*-difluorocyclobutane-containing oxindole **12** in 41% yield with a diastereometric ratio of 3:2.

To gain insight into the current migratory *gem*-difluorination reaction, several mechanistic experiments were carried out (Scheme 4). The reaction of 4-biphenylmethylenecyclobutane (**13**) under standard conditions gave the desired migratory *gem*-difluorination product **14** along with major 1,2-difluorinated product **15**, while the reaction of acyclic alkene **16** completely produced 1,2-difluorination product **17** (97% yield), and no trace of rearrangement product was observed (Scheme 4a). These results indicated that the existence of a

https://doi.org/10.1021/acs.orglett.1c00767
Org. Lett. 2021, 23, 3088−3093

Scheme 4. Mechanistic Studies and Proposed Reaction Mechanism



strained cyclopropyl moiety on the substrate is important for the Wagner–Meerwein rearrangement reactivity. In addition, further control experiments were carried out to trace the source of two incorporated fluorine atoms within the products (Scheme 4a). When **1a** was subjected to the standard reaction conditions with omission of Selectfluor or Py·HF, no or only trace amount of the desired **2a** was isolated, indicating that the two fluorine atoms arise from both Selectfluor and Py·HF. Typically, two possible processes have been proposed for Selectfluor-mediated fluorination of alkenes, including the single-electron transfer (SET)[23] and two-electron process.[24] To determine whether a radical intermediate was formed via a SET process in such reactions, the radical trapping and clock experiments were conducted. The employment of TEMPO or BHT as a radical scavenger in the reaction of **1a** only slightly decreased the reactivity (Scheme 4b). Furthermore, the reaction of a radical clock substrate **19** under our conditions mainly afforded the 1,2-difluorinated product **20**, without the detection of a ring-opening product (Scheme 4b). These results, along with the use of toluene as the reaction media, suggested that a possible single-electron transfer pathway might not be involved in the reaction.

On the basis of the above observations and the preceding literatures,[24] a plausible reaction mechanism for this migratory *gem*-difluorination of MCPs is proposed and outlined in Scheme 4c. Initially, the interaction between the double bond within **1a** and the electrophilic fluorinating reagent Selectfluor delivers the β-fluorinated cyclopropylcarbinyl cation species **A** through a two-electron process. The regioselectivity of this electrophilic fluorination might stem from the capability of the aryl group to stabilize the formed benzylic cation. Thereafter, in the presence of the weak nucleophilic fluoride ion, Wagner–Meerwein rearrangement takes place preferentially to forge an α-fluorinated cyclobutyl cation **B**, which is then attacked by the fluoride to provide the 2-arylsubstituted *gem*-difluorocyclobutane product **2a**. The driving force of this rearrangement is the release of the high strain energy of cyclopropane and a stabilizing effect of the fluorine atom to its bound carbocation.

In summary, we have developed a migratory *gem*-difluorination reaction of aryl-substituted methylenecyclopropanes (MCPs) via Wagner–Meerwein rearrangement by using Selectfluor and Py·HF as fluorine sources. The protocol enables a facile and efficient construction of 2-aryl *gem*-difluorocyclobutane derivatives, which would be otherwise challenging to be prepared. Broad substrate scope, good functional group tolerance, and moderate to good yields were observed. Mechanistic studies suggest that the electrophilic fluorination of double bonds with Selectfluor involves a two-electron transfer process. The synthetic utility of the reaction was demonstrated by further transformations of the products to several useful *gem*-difluorocyclobutane-containing building blocks such as carboxylic acid, amine, and alcohol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00767.

Detailed experimental procedures, spectroscopic characterization of all reported compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1977603 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Qingjiang Li − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China; State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, P. R. China;* orcid.org/0000-0001-5535-6993; Email: liqingj3@mail.sysu.edu.cn

Authors

Peng-Peng Lin − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China*

Long-Ling Huang − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China*

Si-Xin Feng − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of*

https://doi.org/10.1021/acs.orglett.1c00767
Org. Lett. 2021, 23, 3088−3093

Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China

Shuang Yang − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China*

Honggen Wang − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China;* orcid.org/0000-0002-9648-6759

Zhi-Shu Huang − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China;* orcid.org/0000-0002-6211-5482

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00767

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Guangdong Basic and Applied Basic Research Foundation (2019A1515011322 and 2020A1515010624), the Fundamental Research Funds for the Central Universities (19ykpy124), the National Natural Science Foundation of China (81930098), the Key-Area Research and Development Program of Guangdong Province (2020B1111110003), the Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery (2019B030301005), and the State Key Laboratory of Natural and Biomimetic Drugs, Peking University (K20170210).

■ REFERENCES

(1) For a selected review, see: Fan, Y.-Y.; Gao, X.-H.; Yue, J.-M. Attractive Natural Products with Strained Cyclopropane and/or Cyclobutane Ring Systems. *Sci. China: Chem.* **2016**, *59*, 1126−1141.

(2) For a review, see: Marson, C. M. New and Unusual Scaffolds in Medicinal Chemistry. *Chem. Soc. Rev.* **2011**, *40*, 5514−5533.

(3) For a review, see: Namyslo, J. C.; Kaufmann, D. E. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1485−1538.

(4) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 1st ed.; Wiley: 2004.

(5) (a) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822−5880. (b) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. CF_2H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017**, *139*, 9325−9332. (c) Cahard, D.; Ma, J. *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications*, 1st ed. Eds.; Wiley, 2020.

(6) (a) Yu, W.; Williams, L.; Camp, V. M.; Malveaux, E.; Olson, J. J.; Goodman, M. M. Stereoselective Synthesis and Biological Evaluation of Syn-1-Amino-3-[^{18}F]Fluorocyclobutyl-1-Carboxylic Acid as a Potential Positron Emission Tomography Brain Tumor Imaging Agent. *Bioorg. Med. Chem.* **2009**, *17*, 1982−1990. (b) Frost, J. M.; Dart, M. J.; Tietje, K. R.; Garrison, T. R.; Grayson, G. K.; Daza, A. V.; El-Kouhen, O. F.; Yao, B. B.; Hsieh, G. C.; Pai, M.; Zhu, C. Z.; Chandran, P.; Meyer, M. D. Indol-3-Ylcycloalkyl Ketones: Effects of N1 Substituted Indole Side Chain Variations on CB_2 Cannabinoid Receptor Activity. *J. Med. Chem.* **2010**, *53*, 295−315. (c) Popovici-Muller, J.; Lemieux, R. M.; Artin, E.; Saunders, J. O.; Salituro, F. G.; Travins, J.; Cianchetta, G.; Cai, Z.; Zhou, D.; Cui, D.; Chen, P.; Straley, K.; Tobin, E.; Wang, F.; David, M. D.; Penard-Lacronique, V.; Quivoron, C.; Saada, V.; de Botton, S.; Gross, S.; Dang, L.; Yang, H.; Utley, L.; Chen, Y.; Kim, H.; Jin, S.; Gu, Z.; Yao, G.; Luo, Z.; Lv, X.; Fang, C.; Yan, L.; Olaharski, A.; Silverman, L.; Biller, S.; Su, S.-S. M.; Yen, K. Discovery of AG-120 (Ivosidenib): A First-in-Class Mutant IDH1 Inhibitor for the Treatment of IDH1Mutant Cancers. *ACS Med. Chem. Lett.* **2018**, *9*, 300−305. (d) Knutsen, L. J. S.; Kelly, N. M.; Pedersen, T. H.; Olesen, C. E.; Labelle, M.; Little, P. B.; Cooper, M. E.; Saraswat, N.; Dudekula, D.; Taj, R. A. Compounds For The Treatment of Neuromuscular Disorders. US 2019183812A1, June 20, 2019.

(7) For selected recent examples, see: (a) Song, P.; Zhu, S. Nickel-Catalyzed Hydrofluorination of Unactivated Alkenes through a HAT Pathway. *ACS Catal.* **2020**, *10*, 13165−13170. (b) Webb, E. W.; Park, J. B.; Cole, E. L.; Donnelly, D. J.; Bonacorsi, S. J.; Ewing, W. R.; Doyle, A. G. Nucleophilic (Radio)Fluorination of Redox-Active Esters via Radical-Polar Crossover Enabled by Photoredox Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 9493−9500. (c) Giustra, Z. X.; Yang, X.; Chen, M.; Bettinger, H. F.; Liu, S.-Y. Accessing 1,2-Substituted Cyclobutanes through 1,2-Azaborine Photoisomerization. *Angew. Chem., Int. Ed.* **2019**, *58*, 18918−18922. (d) Bafaluy, D.; Georgieva, Z.; Muñiz, K. Iodine Catalysis for C(Sp^3)−H Fluorination with a Nucleophilic Fluorine Source. *Angew. Chem., Int. Ed.* **2020**, *59*, 14241−14245. (e) Nielsen, M. K.; Ahneman, D. T.; Riera, O.; Doyle, A. G. Deoxyfluorination with Sulfonyl Fluorides: Navigating Reaction Space with Machine Learning. *J. Am. Chem. Soc.* **2018**, *140*, 5004−5008. (f) Melnykov, K.; Granat, D.; Volochnyuk, D.; Ryabukhin, S.; Grygorenko, O. Multigram Synthesis of C_4/C_5 3,3-Difluorocyclobutyl-Substituted Building Blocks. *Synthesis* **2018**, *50*, 4949−4957.

(8) (a) Dolbier, W. R.; Wicks, G. E. Reactivity and Stereochemical Studies of the [2 + 2] Cycloaddition of 1,1-Difluoroallene and Styrene. *J. Am. Chem. Soc.* **1985**, *107*, 3626−3631. (b) Dolbier, W. R.; Seabury, M.; Daly, D.; Smart, B. E. The [2 + 2] and [2 + 4] Cycloadditions of Difluoromethylenecyclopropanes. *J. Org. Chem.* **1986**, *51*, 974−979. (c) Jin, F.; Xu, Y.; Huang, W. 1,1-Difluoro-2-Triphenylsiloxybuta-1,3-Diene as a Potentially Useful Fluorine-Containing Building Block: Preparation and [4 + 2] and [2 + 2] Cycloadditions. *J. Chem. Soc., Chem. Commun.* **1993**, *10*, 814−816.

(9) (a) Chernykh, A. V.; Melnykov, K. P.; Tolmacheva, N. A.; Kondratov, I. S.; Radchenko, D. S.; Daniliuc, C. G.; Volochnyuk, D. M.; Ryabukhin, S. V.; Kuchkovska, Y. O.; Grygorenko, O. O. Last of the *gem*-Difluorocycloalkanes: Synthesis and Characterization of 2,2-Difluorocyclobutyl-Substituted Building Blocks. *J. Org. Chem.* **2019**, *84*, 8487−8496. (b) Chernykh, A. V.; Feskov, I. O.; Chernykh, A. V.; Daniliuc, C. G.; Tolmachova, N. A.; Volochnyuk, D. M.; Radchenko, D. S. Synthesis of Fluorinated Building Blocks Based on Spiro[3.3]-Heptane Scaffold. *Tetrahedron* **2016**, *72*, 1036−1041. (c) Chernykh, A. V.; Tkachenko, A. N.; Feskov, I. O.; Daniliuc, C. G.; Tolmachova, N. A.; Volochnyuk, D. M.; Radchenko, D. S. Practical Synthesis of Fluorinated Piperidine Analogues Based on the 2-Azaspiro[3.3]-Heptane Scaffold. *Synlett* **2016**, *27*, 1824−1827. (d) Ishii, S.; Niwa, Y.; Watanabe, S. Deoxyfluorination of α-N-Phthaloyl Cycloalkanones with Bis(2-Methoxyethyl)Aminosulfur Trifluoride (Deoxo-Fluor). *J. Fluorine Chem.* **2016**, *182*, 41−46.

(10) Grygorenko and co-workers pointed out that the direct deoxofluorination of 2-phenyl-, 2-methoxyphenyl-, and 2-furyl-substituted cyclobutanones with Morph-DAST was unfruitful; see ref 9a.

(11) Kumamoto, H.; Kawahigashi, S.; Wakabayashi, H.; Nakano, T.; Miyaike, T.; Kitagawa, Y.; Abe, H.; Ito, M.; Haraguchi, K.; Balzarini, J.; Baba, M.; Tanaka, H. Tuning Efficiency of the 4-Exo-Trig Cyclization by the Electronic Effect: Ring Closure of 3,3-Difluoro-4-Pentenyl Carbon Radicals and Synthesis of a *gem*-Difluorocyclobutane Nucleoside. *Chem. Commun.* **2012**, *48*, 10993−10995.

(12) Methylenecyclopropanes (MCPs) are conveniently accessible in one step by the Wittig olefination of commercially available 3-bromo-triphenylphosphonium bromide with corresponding carbonyl compounds. See: Utimoto, K.; Tamura, M.; Sisido, K. Preparation and Reaction of Cyclopropyltriphenylphosphonium Salt. *Tetrahedron* **1973**, *29*, 1169−1171.

(13) For a review, see: Zhang, D.-H.; Tang, X.-Y.; Shi, M. Gold-Catalyzed Tandem Reactions of Methylenecyclopropanes and Vinylidenecyclopropanes. *Acc. Chem. Res.* **2014**, *47*, 913−924.
(14) For a very recent review, see: Cao, H.; Chen, F.; Su, C.; Yu, L. Construction of Carbocycles from Methylenecyclopropanes. *Adv. Synth. Catal.* **2020**, *362*, 438−461.
(15) (a) Lv, W.-X.; Li, Q.; Li, J.-L.; Li, Z.; Lin, E.; Tan, D.-H.; Cai, Y.-H.; Fan, W.-X.; Wang, H. *gem*-Difluorination of Alkenyl N-Methyliminodiacetyl Boronates: Synthesis of α- and β-Difluorinated Alkylborons. *Angew. Chem., Int. Ed.* **2018**, *57*, 16544−16548. (b) Zhang, Q.-Q.; Chen, S.-Y.; Lin, E.; Wang, H.; Li, Q. Regio- and Stereoselective Alkenylation of Allenoates with *gem*-Difluoroalkenes: Facile Access to Fluorinated 1,4-Enynes Bearing an All-Carbon Quaternary Center. *Org. Lett.* **2019**, *21*, 3123−3126. (c) Li, J.-L.; Lin, E.; Han, X.-L.; Li, Q.; Wang, H. Synthesis of α-Fluorinated Imides via Direct Fluorohydroxylation of Ynamides. *Org. Lett.* **2019**, *21*, 4255−4258.
(16) (a) Fu, W.; Zou, G.; Zhu, M.; Hong, D.; Deng, D.; Xun, C.; Ji, B. Stereoselective Fluorination of Methylenecyclopropanes with N-F Reagents: A Modular Entry to γ-Fluorohomoallylic Sulfonimides and γ-Fluorohomoallylic Amides. *J. Fluorine Chem.* **2009**, *130*, 996−1000. (b) Jiang, M.; Shi, M. Reactions of Methylenecyclopropanes and Vinylidenecyclopropanes with N-Fluorodibenzenesulfonimide. *Tetrahedron* **2009**, *65*, 5222−5227.
(17) Reddy, V. P.; Alleti, R.; Perambuduru, M. K.; Welz-Biermann, U.; Buchholz, H.; Prakash, G. K. S. *gem*-Difluorination of 2,2-Diaryl-1,3-Dithiolanes by Selectfluor® and Pyridinium Polyhydrogen Fluoride. *Chem. Commun.* **2005**, *5*, 654−656.
(18) Ye, C.; Twamley, B.; Shreeve, J. M. Straightforward Syntheses of Hypervalent Iodine(III) Reagents Mediated by Selectfluor. *Org. Lett.* **2005**, *7*, 3961−3964.
(19) Nunez, M. T.; Martin, V. S. Efficient Oxidation of Phenyl Groups to Carboxylic Acids with Ruthenium Tetraoxide. A Simple Synthesis of (*R*)-γ-Caprolactone, the Pheromone of Trogoderma Granarium. *J. Org. Chem.* **1990**, *55*, 1928−1932.
(20) Curtius, Th Ueber Stickstoffwasserstoffsäure (Azoimid) N_3H. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023−3033.
(21) Ataie, A.; Ataee, R.; Shadifar, M.; Shahabi, S.; Aghajanpour, S. M.; Hosseinpour, Y. Interaction of Memantine with Homocysteine on the Apoptosis in the Rat Hippocampus Cells. *Int. J. Mol. Cell. Med.* **2012**, *1*, 145−152.
(22) Shi, Y.; Xiao, H.; Xu, X.-H.; Huang, Y. Transition Metal Free Decarboxylative Fluoroalkylation of N-Acrylamides with 3,3,3-Trifluoro-2,2-Dimethylpropanoic Acid (TFDMPA). *Org. Biomol. Chem.* **2018**, *16*, 8472−8476.
(23) For selected examples, see: (a) Zhang, X.; Liao, Y.; Qian, R.; Wang, H.; Guo, Y. Investigation of Radical Cation in Electrophilic Fluorination by ESI-MS. *Org. Lett.* **2005**, *7*, 3877−3880. (b) Wu, S.-W.; Liu, F. Synthesis of α-Fluoroketones from Vinyl Azides and Mechanism Interrogation. *Org. Lett.* **2016**, *18*, 3642−3645.
(24) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. Selectfluor: Mechanistic Insight and Applications. *Angew. Chem., Int. Ed.* **2005**, *44*, 192−212.

https://doi.org/10.1021/acs.orglett.1c00767
Org. Lett. 2021, 23, 3088−3093