OL Organic Letters

pubs.acs.org/OrgLett Letter

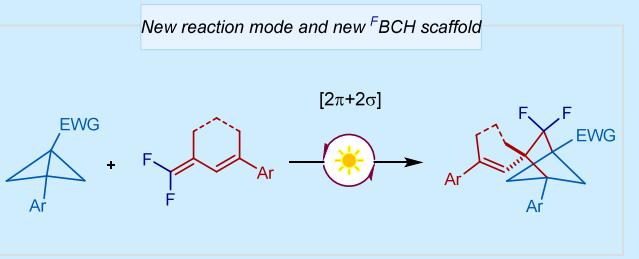
# *gem*-Difluorobicyclo[2.1.1]hexanes via Photochemical [2$\pi$ + 2$\sigma$] Cycloaddition Initiated by Oxidative Activation of *gem*-Difluorodienes

Zhenda Fu, Jianzheng Cheng, Xiao-Xi Li,* Xingwei Li,* and Songjie Yu*

Cite This: *Org. Lett.* 2024, 26, 9961−9966 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** The incorporation of fluorine atoms into three-dimensional sp$^3$-rich scaffolds represents an attractive tactic during bioisosteric evolution campaigns by endowing bioisosteric candidates with improved pharmacokinetic properties. Photo- or Lewis acid-mediated bicyclo[1.1.0]butane cycloaddition has offered an efficient approach for the construction of numerous regular bicyclo[*n*.1.1] scaffolds (*n* = 1−5) but remains a significant challenge to the synthesis of related 3D fluorinated scaffolds. Herein, we unveiled a photochemical single-electron oxidative strategy for *gem*-difluorodiene activation and subsequent [2$\pi$ + 2$\sigma$] cycloaddition with bicyclo[1.1.0]butanes to provide a broad range of *gem*-difluorobicyclo[2.1.1]hexane scaffolds containing several post-transformable handles. A combination of experimental and computational mechanistic studies suggested that the conjugated $\pi$ system of *gem*-difluorodiene plays important dual roles in promoting its preferential single-electron oxidation and stabilizing various radical-involved intermediates during the cyclization.






In medicinal chemistry, three-dimensional (3D) bicyclic structures have demonstrated to be distinguished bioisosteres of aromatic rings in pharmaceutical candidates, which often leads to improved biological activities, physicochemical properties, and metabolic profiles compared to their parent arenes.[1] In this context, structurally diverse bicyclo[1.1.1] scaffolds (BCPs)[2] have been designed for *para*-phenyl replacements of numerous lead candidates, hitherto appearing in over 700 patents.[3] Despite the progress, these well-explored regular 3D architectures are incompetent for mimicking the bond vectors and pharmacodynamics displayed in fluoro-substituted parent arenes. In contrast, their related fluorinated scaffolds are a necessary complement to the bioisosteres of fluorobenzene-like structures. Notably, increasing incorporation of fluorine atoms into the 3D sp$^3$-rich bicyclic structures can significantly modulate their pharmacokinetic properties including permeability, lipophilicity, conformation, and metabolic stability.[4] Consequently, the development of expedient strategies to synthesize such 3D fluorinated analogues has been on the urgent agenda of synthetic chemists. While there has been growing interest for synthetic chemists in the invention of new synthetic methodologies for these 3D fluorinated bicycles, the efficient preparation of such scaffolds is still in its infancy. This incongruity arises from the absence of efficient fluorinated building blocks and workable postfluorination of the regular 3D skeletons.[5] To date, only high-reactive fluorocarbenes insertion into aryl-substituted bicyclo[1.1.0]butanes (BCBs) to prepare bridge-fluorinated BCPs has been developed by Mykhailiuk et al.[6] and Ma et al.[7] (Scheme. 1a). The incorporation of fluorine atoms into other bioisosteric sp$^3$-rich structures remains conspicuously elusive. Given the promising bioisosteric application of 3D fluorinated skeletons in drug discovery, developing new strategies to access diverse fluorinated sp$^3$-rich bicycles, such as fluorobicyclo[2.1.1]-hexanes ($^F$BCHs), to replace *ortho*- or *meta*-substituted fluorobenzene is highly desirable.

Recently, bicyclo[1.1.0]butanes (BCBs) have become privileged building blocks[8] to construct a range of structurally diverse regular BCHs (Scheme. 1b) via formal cycloaddition with unsaturated $\pi$ units since the significant achievements on photoactivation of alkenyl $\pi$-bond or BCB central $\sigma$-bond to form triplet diradicals followed by [2$\pi$ + 2$\sigma$] cycloaddition independently made by Glorius et al.[9] and Brown et al.[10] So far, the BCB central $\sigma$-bond activation has emerged as a dominant strategy for BCB cycloaddition reactions through single-electron reduction[11] or oxidation,[12] and Lewis acid-assisted ionic process.[13] Inspired by those robust transformations of BCBs, we reasoned that the cycloaddition of BCBs with *gem*-difluoroalkenes would be a straightforward and

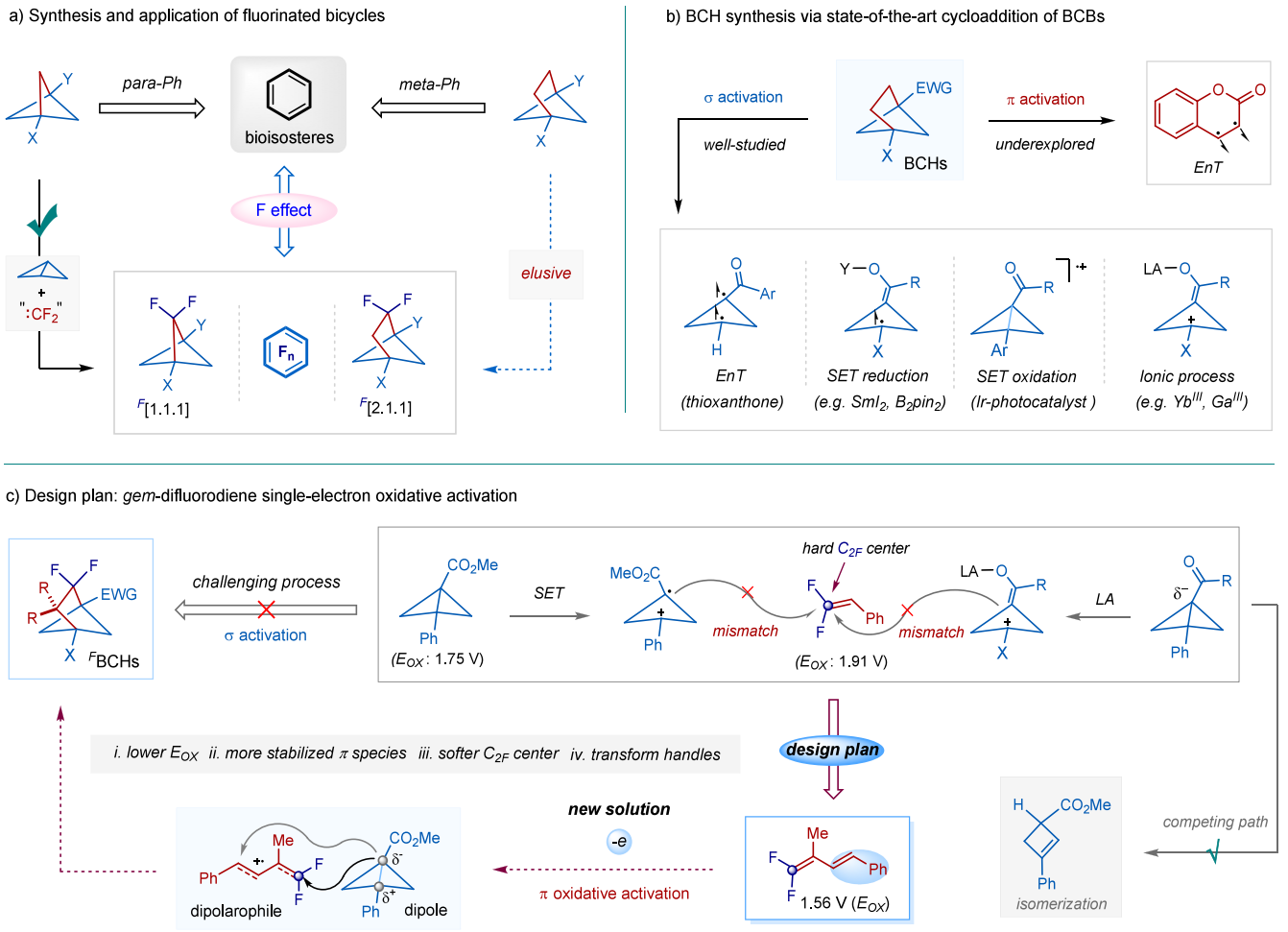
**Received:** October 9, 2024
**Revised:** November 9, 2024
**Accepted:** November 13, 2024
**Published:** November 15, 2024





https://doi.org/10.1021/acs.orglett.4c03798
*Org. Lett.* 2024, 26, 9961−9966

**Scheme 1. 3D Scaffolds via Catalytic Cyclization of BCBs**

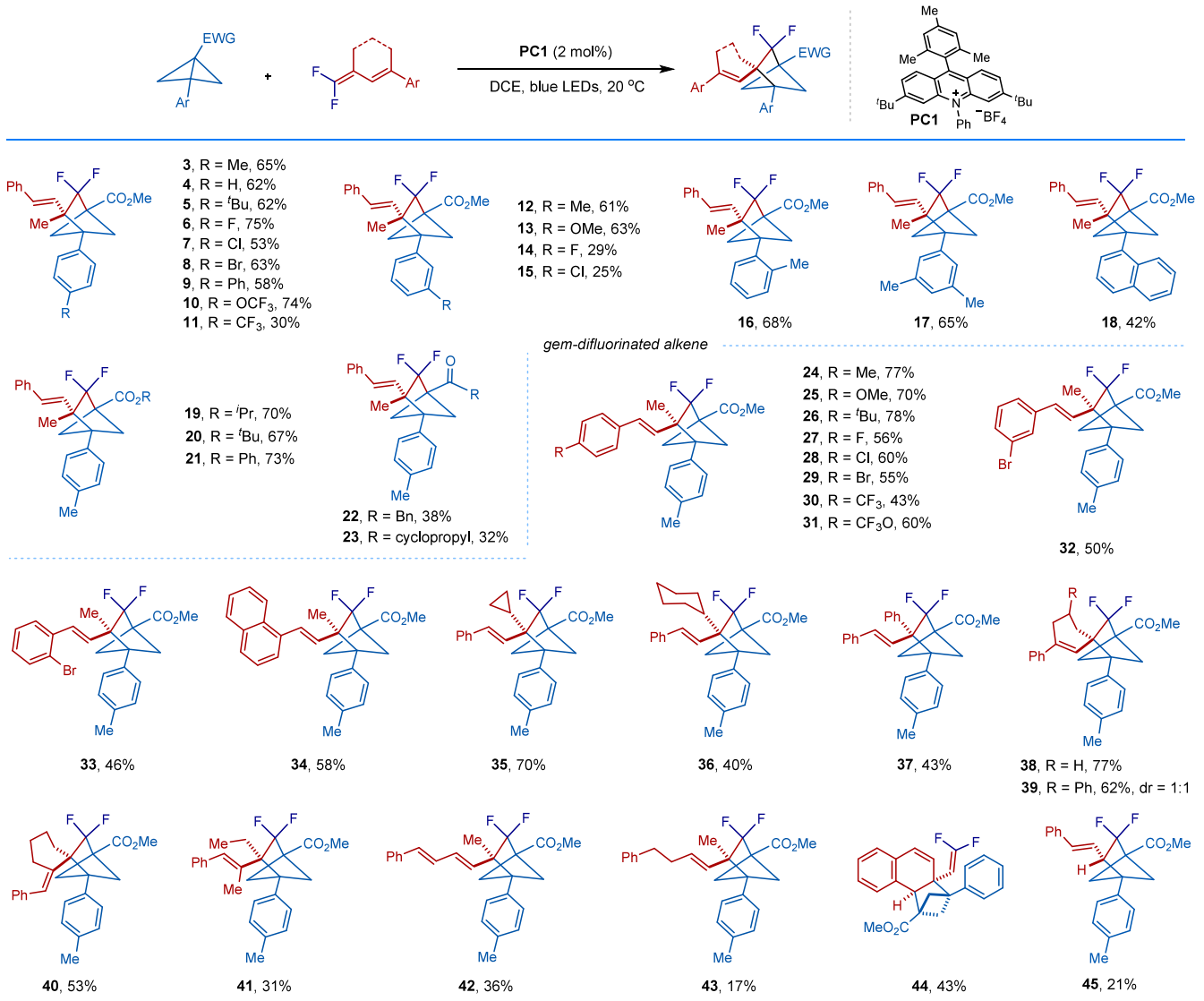



atom-economical strategy to furnish $^{F}$BCHs. However, as noteworthy issues, the mismatched hard *gem*-difluorinated carbon ($C_{2F}$) and facile fluorine elimination of the formed *gem*-difluorinated *β*-carbanion intermediates[14] pose great challenges during the addition of the generated BCB-involved radical or ionic species to *gem*-difluoroalkenes, which has also been demonstrated by our unsuccessful initial attempts with (2,2-difluorovinyl)benzene as a substrate. To avoid these issues, new cyclization modes are required where the oxidative activation of *gem*-difluoroalkenes[15] may offer a great advantage. However, because of the higher oxidative potential of (2,2-difluorovinyl)benzene ($E_{OX}$ = 1.91 V versus SCE) than that of BCBs ($E_{OX}$ = 1.75 V versus SCE), single-electron oxidation of BCBs often occurs preferentially to form a distonic radical cation via a *σ*-bond-cleaved electron transfer event (Scheme. 1c, top). The mismatched electronic properties between BCB radical and the $C_{2F}$ center will lead to isomerization or dimerization of BCBs. To overcome this limitation, we determined to design new fluorinating reagents that could undergo more facile single-electron oxidative process. We reasoned that the conjugated *gem*-difluorodienes feature a lower oxidative potential ($E_{OX}$ = 1.56 V versus SCE), a relatively softer $C_{2F}$ center, an extended *π* system for stabilizing radical or ionic intermediates, and several transform handles for further derivatizations, all of which may make *gem*-difluorodiene *π*-oxidative activation and subsequent cyclization with BCBs be a promising and intriguing strategy (Scheme. 1c, bottom). Upon formation of the *gem*-difluorodiene radical cation via single-electron oxidation, [2*π* + 2*σ*] cycloaddition with BCBs would take place to provide a unique class of functionalized $^{F}$BCHs containing several diversifiable transform handles,[16] which largely expands the synthetic and bioisosteric space of $^{F}$BCHs.

After a careful condition screening (see details in the Supporting Information), the optimal conditions were established: 3,6-di-*tert*-butyl-substituted acridinium-based **PC1** (2 mol %), DCE solvent, and blue LEDs. With a set of optimal reaction conditions in hand, the scope of this cycloaddition was first evaluated on a range of BCBs. As depicted in Scheme 2, this photochemical cycloaddition proceeded efficiently with a variety of BCBs. Various electron-donating substituents on the phenyl groups were tolerated, including methyl (**3**, **12**, **16**, and **17**), *tert*-butyl (**5**), and methoxy (**13**) groups, at the *para*-, *meta*-, and *ortho*-positions, leading to the formation of the corresponding $^{F}$BCHs in 61−68% yields. Halogens (such as fluoro, chloro, and bromo) (**6**−**8**), as well as phenyl and trifluoromethoxy groups (**9** and **10**) at the *para*-position of phenyl rings, were also tolerated well to give the desired $^{F}$BCHs in good yields. In addition, the BCBs equipped with a 4-(trifluoromethyl)phenyl group (**11**) also reacted with **2**, albeit in modest yield potentially because of the reduced BCB nucleophilicity caused by the highly electron-withdrawing trifluoromethyl group. Installation of fluoro and chloro groups into the *meta*-position


https://doi.org/10.1021/acs.orglett.4c03798
Org. Lett. 2024, 26, 9961−9966

**Scheme 2. Reaction Conditions: 1 (0.1 mmol), 2 (0.3 mmol), PC1 (2 mol %), DCE (1 mL), and Blue LEDs (455 nm, 10 W) under Nitrogen Atmosphere at 20 °C for 10 h in Isolated Yield**



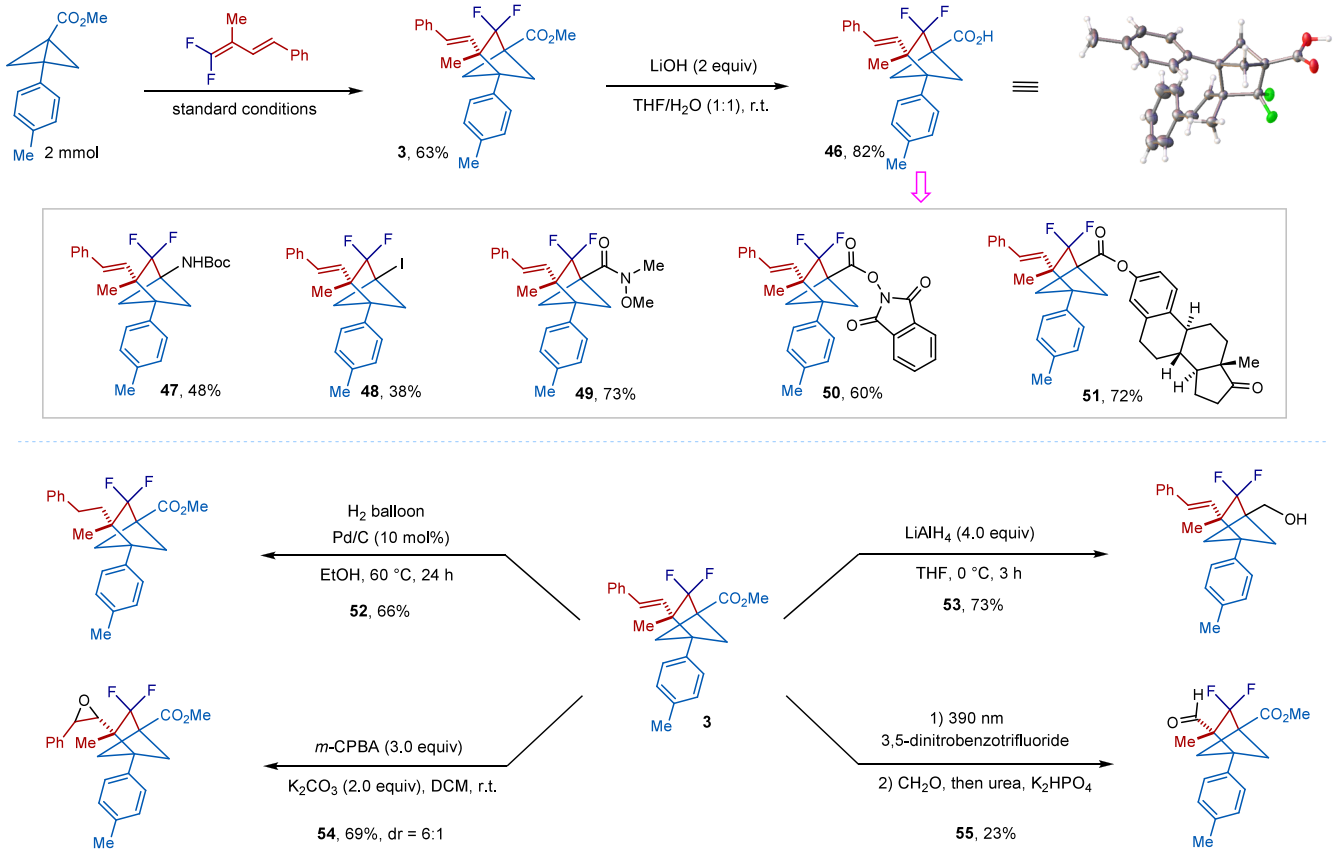

of benzene rings afforded the cyclized skeletons in 25−29% yields in which isomerization of BCBs to methyl cyclobut-2-ene-1-carboxylates was observed (**14** and **15**). The cyclization of *iso*-propyl-, *tert*-butyl-, or phenyl carboxylate-substituted BCBs were also examined to provide the desired *gem*-fluorinated skeletons in decent yields (**19**−**21**). Beyond an ester group in the BCB backbone, success was found with 2-phenylacetyl- and cyclopropanecarbonyl-substituted BCBs (**22** and **23**), albeit in moderate yields.

Next, the scope was further extended to the *gem*-difluorodienes. The transformations worked well with electron-donating groups including methyl, *tert*-butyl, and methoxy groups, at the *para*-position of the aryl rings of (*E*)-(4,4-difluoro-3-methylbuta-1,3-dien-1-yl)benzene (**24**−**26**). Acceptable reactivities toward formation of the desired $^{F}$BCHs were observed when halogens such as fluoro, chloro, and bromo groups were introduced to various positions of the benzene rings in the diene substrates (**27**−**29**, **32**, and **33**). Naphthalene motif was well tolerated and provided the desired product in a 58% yield (**34**). The incorporation of a strong electron-withdrawing trifluoromethyl group (**30**) gave the corresponding $^{F}$BCH in 43% yield. The presence of a medicinally relevant trifluoromethoxy group at the *para*-position of the phenyl ring in the substrate afforded product **31** in 60% yield. Beyond the methyl substituent at the 3-position of *gem*-difluorodienes, sterically demanding cyclopropyl, cyclohexyl, and phenyl groups did not greatly diminish the reaction efficiency and gave the desired products in good yields (**35**−**37**). The functional group compatibility of this protocol was further demonstrated by exploring cyclic *gem*-difluorodienes as substrates, which afforded cyclopropagative complex three-dimensional scaffolds in 53−77% yields (**38**−**40**). 2,3-Disubstituted *gem*-difluorodiene also showed good reactivity to provide product **41** in modest yield. To our delight, a conjugated *gem*-difluorotriene was subjected to the standard conditions, and the desired product bearing a conjugated diene group was obtained in 36% yield (**42**). At the current stage, aromatic substituents are essential to the high reactivity as an alkyl-substituted *gem*-difluorodiene offered the desired cycloaddition product in a low yield (**43**). Although using 2-(2,2-difluorovinyl)naphthalene as a substrate failed to give the desired $^{F}$BCHs, *ortho*-selective dearomative



https://doi.org/10.1021/acs.orglett.4c03798
Org. Lett. 2024, 26, 9961−9966

**Scheme 3. Large-Scale Reaction and Product Transformations**

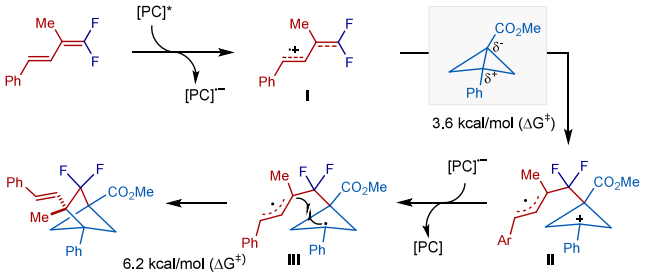



cycloaddition of naphthalene and BCBs proceeded to prepare complex bicyclic scaffold **44** with a synthetically useful *gem*-difluorinated group in 43% yield. Interestingly, two competing pathways between 1,2-addition and 3,4-addition were observed when using (*E*)-(4,4-difluorobuta-1,3-dien-1-yl)benzene as a substrate where the desired product **45** was obtained in 21% yield with a side product in 44% yield via a 1,2-addition fashion (see details in the Supporting Information).

The reaction was easily scaled up to 2.0 mmol to allow for the isolation of compound **3** in 63% yield (Scheme. 3). The $^{F}$BCHs offer several multiple transform handles, such as olefinic and ester groups, for further downstream modifications. Hydrolysis of an ester in the $^{F}$BCH backbone led to the formation of the corresponding carboxylic acid **46** in 82% yield. The carboxyl group has long been recognized as a highly adaptable transform handle in organic synthesis. Thus, further derivatizations were performed on the carboxyl group of compound **46**. Decarboxylative amination and iodination produced amino-$^{F}$BCH **47** and iodo-$^{F}$BCH **48**, respectively. Moreover, the carboxyl group could be steadily transformed to Weinreb amide **49** and redox-active ester **50**, both of which are synthetically useful precursors in further diversified $^{F}$BCH synthesis. In addition, sewing the $^{F}$BCH core on the estrone scaffold was achieved in a good yield via a simple esterification (**51**). Reduction of the double bond via Pd/C-catalyzed selective hydrogenation generated saturated sp$^3$-rich scaffold **52** in 66% yield, while reduction of the ester moiety with $LiAlH_4$ produced hydroxylated $^{F}$BCH **53** in 73% yield. Subjecting the product to *m*-CPBA gave epoxide **54** in 69% yield with a 6:1 dr. Finally, we successfully managed to cleave the double bond via photochemical oxidation to provide formyl-substituted $^{F}$BCH scaffold **55** in modest yield.[17]

Given our experimental and computational studies (see the details in Supporting Information), a possible mechanistic pathway for the photochemical $^{F}$BCH synthesis is postulated in Scheme 4. The *gem*-difluorodiene radical cation **I** is

**Scheme 4. Proposed Mechanism**




generated by a single-electron oxidative event. Subsequent electrophilic addition of this reactive intermediate to dipolar BCB furnishes $\pi$-stabilized distonic radical cation **II** where the positive charge is localized at the tertiary benzylic position. Then, the single-electron reduction of intermediate **II** and successive cyclization via radical−radical coupling would generate the desired product.

In summary, we have established a unified strategy for the catalytic preparation of *gem*-difluorobicyclo[2.1.1]hexanes through well-orchestrated photochemical cycloaddition of BCBs and *gem*-difluorodienes. This protocol regioselectively furnished a library of unprecedented *gem*-difluorinated



https://doi.org/10.1021/acs.orglett.4c03798
Org. Lett. 2024, 26, 9961−9966

bicyclo[2.1.1]hexanes containing a wide range of synthetically useful groups. The synthetic applicability of this methodology was further verified by a wide array of structurally diversified transformations of *gem*-difluorobicyclo[2.1.1]hexanes. Mechanistic studies suggested that a crucial radical cation is generated by the initial single-electron oxidative activation of *gem*-difluorodienes followed by electrophilic addition to dipolar BCBs. We anticipate that this activation strategy of *gem*-difluorodienes, as well as these new *gem*-difluorinated $sp^3$-rich scaffolds, will find broad synthetic and bioisosteric applications in drug discovery and related fields.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03798.

Experimental details, characterization of all new compounds, the X-ray crystal structure, computational results, and NMR spectra (PDF)

### Accession Codes

Deposition Numbers 2348514−2348515 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Xiao-Xi Li** − *Institute of Frontier Chemistry, School of Chemistry and Chemical Engineering, Shandong University, Qingdao 266237, China;* orcid.org/0000-0002-3593-7536; Email: lixiaoxi@sdu.edu.cn

**Xingwei Li** − *Institute of Frontier Chemistry, School of Chemistry and Chemical Engineering, Shandong University, Qingdao 266237, China*; Email: lixw@snnu.edu.cn

**Songjie Yu** − *Institute of Frontier Chemistry, School of Chemistry and Chemical Engineering, Shandong University, Qingdao 266237, China;* orcid.org/0000-0001-9156-8774; Email: yusongjie23@sdu.edu.cn

### Authors

**Zhenda Fu** − *Institute of Frontier Chemistry, School of Chemistry and Chemical Engineering, Shandong University, Qingdao 266237, China;* orcid.org/0000-0001-9406-5048

**Jianzheng Cheng** − *Institute of Frontier Chemistry, School of Chemistry and Chemical Engineering, Shandong University, Qingdao 266237, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.4c03798


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Key R&D Program of China (No. 2022YFA1503104) and National Natural Science Foundation of China (No. 22371029 and 22371175) for financial support. S.Y. thanks the Taishan Scholar of Shandong Province (tsqnz20221108) and the Qilu Young Scholar of Shandong University for funding.

## ■ REFERENCES


(1) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756. Selected Reviews: (b) Mykhailiuk, P. K. Saturated Bioisosteres of Benzene: Where to Go Next? *Org. Biomol. Chem.* **2019**, *17*, 2839−2849. (c) Locke, G. M.; Bernhard, S. S. R.; Senge, M. O. Nonconjugated Hydrocarbons as Rigid-Linear Motifs: Isosteres for Material Sciences and Bioorganic and Medicinal Chemistry. *Chem.—Eur. J.* **2019**, *25*, 4590−4647. (d) Tsien, J.; Hu, C.; Merchant, R. R.; Qin, T. Three-dimensional Saturated C($sp^3$)-Rich Bioisosteres for Benzene. *Nat. Rev. Chem.* **2024**, *8*, 605−627.

(2) (a) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. M.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Amination. *Science* **2016**, *351*, 241−246. (b) Caputo, D. F. J.; Arroniz, C.; Dürr, A. B.; Mousseau, J. J.; Stepan, A. F.; Mansfield, S. J.; Anderson, E. A. Synthesis and Applications of Highly Functionalized 1-Halo-3-substituted Bicyclo[1.1.1]pentanes. *Chem. Sci.* **2018**, *9*, 5295−5300. (c) Shelp, R. A.; Walsh, P. J. Synthesis of BCP Benzylamines from 2-Azaallyl Anions and [1.1.1]Propellane *Angew. Chem. Int. Ed.* **2018**, *57*, 15857−15861. (d) Makarov, I. S.; Brocklehurst, C. E.; Karaghiosoff, K.; Koch, G.; Knochel, P. Synthesis of Bicyclo[1.1.1]pentane Bioisosteres of Internal Alkynes and *para*-Disubstituted Benzenes from [1.1.1]Propellane *Angew. Chem. Int. Ed.* **2017**, *56*, 12774−12777. (e) Yu, S.; Jing, C.; Noble, A.; Aggarwal, V. K. 1,3-Difunctionalizations of [1.1.1]Propellane via 1,2-Metallate Rearrangements of Boronate Complexes. *Angew. Chem., Int. Ed.* **2020**, *59*, 3917−3921. (f) Zhang, X.; Smith, R. T.; Le, C.; McCarver, S. J.; Shireman, B. T.; Carruthers, N. I.; MacMillan, D. W. C. Copper-Mediated Synthesis of Drug-like Bicyclopentanes. *Nature* **2020**, *580*, 220−226. (g) Dong, W.; Yen-Pon, E.; Li, L.; Bhattacharjee, A.; Jolit, A.; Molander, G. A. Exploiting the $sp^2$ Character of Bicyclo[1.1.1]-pentyl Radicals in the Transition-Metal-Free Multi-Component Difunctionalization of [1.1.1]propellane. *Nat. Chem.* **2022**, *14*, 1068−1077.

(3) (a) Pellicciari, R.; Raimondo, M.; Marinozzi, M.; Natalini, B.; Costantino, G.; Thomsen, C. (*S*)-(+)-2-(3′-Carboxybicyclo[1.1.1]-pentyl)-glycine, a Structurally New Group I Metabotropic Glutamate Receptor Antagonist. *J. Med. Chem.* **1996**, *39*, 2874−2876. (b) Hewings, D. S.; Jaeschke, G.; Kuhn, B.; Nagel, Y. A.; Ricci, A. EGFR Inhibitors. WO 2021/123087 A1, 2021.

(4) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359.

(5) (a) Shtarev, A. B.; Pinkhassik, E.; Levin, M. D.; Stibor, I.; Michl, J. Partially Bridge-Fluorinated Dimethyl Bicyclo[1.1.1]pentane-1,3-dicarboxylates: Preparation and NMR Spectra. *J. Am. Chem. Soc.* **2001**, *123*, 3484−3492. (b) Bychek, R.; Mykhailiuk, P. K. A Practical and Scalable Approach to Fluoro-Substituted Bicyclo[1.1.1]pentanes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202205103.

(6) Bychek, R. M.; Hutskalova, V.; Bas, Y. P.; Zaporozhets, O. A.; Zozulya, S.; Levterov, V. V.; Mykhailiuk, P. K. Difluoro-Substituted Bicyclo[1.1.1]pentanes for Medicinal Chemistry: Design, Synthesis, and Characterization. *J. Org. Chem.* **2019**, *84*, 15106−15117.

(7) Ma, X.; Sloman, D. L.; Han, Y.; Bennett, D. J. A Selective Synthesis of 2,2-Difluorobicyclo[1.1.1]pentane Analogues: "BCP-$F_2$. *Org. Lett.* **2019**, *21*, 7199−7203.

(8) (a) Kelly, C. B.; Milligan, J. A.; Tilley, L. J.; Sodano, T. M. Bicyclobutanes: from Curiosities to Versatile Reagents and Covalent Warheads. *Chem. Sci.* **2022**, *13*, 11721−11737. (b) Tyler, J. L.; Aggarwal, V. K. Synthesis and Applications of Bicyclo[1.1.0]butyl and Azabicyclo[1.1.0]butyl Organometallics. *Chem.—Eur. J.* **2023**, *29*, No. e202300008. (c) Golfmann, M.; Walker, J. C. L. Bicyclobutanes

as Unusual Building Blocks for Complexity Generation in Organic Synthesis. *Commun. Chem.* **2023**, *6*, 9. (d) Bellotti, P.; Glorius, F. Strain-Release Photocatalysis. *J. Am. Chem. Soc.* **2023**, *145*, 20716−20732. (e) Wipf, P.; Walczak, M. A. A. Pericyclic Cascade Reactions of (Bicyclo-[1.1.0]butylmethyl)amines. *Angew. Chem., Int. Ed.* **2006**, *45*, 4172−4175. (f) Fu, Q.; Cao, S.; Wang, J.; Lv, X.; Wang, H.; Zhao, X.; Jiang, Z. Enantioselective [2$\pi$ + 2$\sigma$] Cycloadditions of Bicyclo[1.1.0]butanes with Vinylazaarenes through Asymmetric Photoredox Catalysis. *J. Am. Chem. Soc.* **2024**, *146*, 8372−8380. (g) Dutta, S.; Lu, Y.-L.; Erchinger, J. E.; Shao, H.; Studer, E.; Schäfer, F.; Wang, H.; Rana, D.; Daniliuc, C. G.; Houk, K. N.; Glorius, F. Double Strain-Release [2$\pi$ + 2$\sigma$]-Photocycloaddition. *J. Am. Chem. Soc.* **2024**, *146*, 5232−5241. (h) Zheng, Y.; Huang, W.; Dhungana, R. K.; Granados, A.; Keess, S.; Makvandi, M.; Molander, G. A. Photochemical Intermolecular [3$\sigma$ + 2$\sigma$]-Cycloaddition for the Construction of Aminobicyclo[3.1.1]heptanes. *J. Am. Chem. Soc.* **2022**, *144*, 23685−23690. (i) Nguyen, T. V. T.; Bossonnet, A.; Wodrich, M. D.; Waser, J. Photocatalyzed [2$\sigma$ + 2$\sigma$] and [2$\sigma$ + 2$\pi$] Cycloadditions for the Synthesis of Bicyclo[3.1.1]heptanes and 5- or 6-Membered Carbocycles. *J. Am. Chem. Soc.* **2023**, *145*, 25411−25421. (j) Wang, H.; Shao, H.; Das, A.; Dutta, S.; Chan, H. T.; Daniliuc, C.; Houk, K. N.; Glorius, F. Dearomative Ring Expansion of Thiophenes by Bicyclobutane Insertion. *Science* **2023**, *381*, 75−81. (k) Woelk, K. J.; Dhake, K.; Schley, N. D.; Leitch, D. C. Enolate Addition to Bicyclobutanes Enables Expedient Access to 2-Oxo-bicyclohexane Scaffolds. *Chem. Commun.* **2023**, *59*, 13847−13850. (l) Liang, Y.; Nematswerani, R.; Daniliuc, C. G.; Glorius, F. Silver-Enabled Cycloaddition of Bicyclobutanes with Isocyanides forthe Synthesis of Polysubstituted 3-Azabicyclo[3.1.1]heptanes. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202402730. (m) Zhou, J.-L.; Xiao, Y.; He, L.; Gao, X.-Y.; Yang, X.-C.; Wu, W.-B.; Wang, G.; Zhang, J.; Feng, J.-J. Palladium-Catalyzed Ligand-Controlled Switchable Hetero-(5 + 3)/Enantioselective [2$\sigma$+2$\sigma$] Cycloadditions of Bicyclobutanes with Vinyl Oxiranes. *J. Am. Chem. Soc.* **2024**, *146*, 19621−19628. (n) Xiao, Y.; Wu, F.; Tang, L.; Zhang, X.; Wei, M.; Wang, G.; Feng, J.-J. Divergent Synthesis of Sulfur-Containing Bridged Cyclobutanes by Lewis Acid Catalyzed Formal Cycloadditions of Pyridinium 1,4-Zwitterionic Thiolates and Bicyclobutanes. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202408578. (o) Wu, F.; Wu, W.-B.; Xiao, Y.; Li, Z.; Tang, L.; He, H.-X.; Yang, X.-C.; Wang, J.-J.; Cai, Y.; Xu, T.-T.; Tao, J.-H.; Wang, G.; Feng, J.-J. Zinc-Catalyzed Enantioselective Formal (3 + 2) Cycloadditions of Bicyclobutanes with Imines: Catalytic Asymmetric Synthesis ofAzabicyclo[2.1.1]hexanes. *Angew. Chem., Int. Ed.* **2024**, No. e202406548.

(9) (a) Kleinmans, R.; Pinkert, T.; Dutta, S.; Paulisch, T. O.; Keum, H.; Daniliuc, C. G.; Glorius, F. Intermolecular [2$\pi$ + 2$\sigma$]-Photocycloaddition Enabled by Triplet Energy Transfer. *Nature* **2022**, *605*, 477−482.

(10) Guo, R.; Chang, Y.-C.; Herter, L.; Salome, C.; Braley, S. E.; Fessard, T. C.; Brown, M. K. Strain-Release [2$\pi$ + 2$\sigma$] Cycloadditions for the Synthesis of Bicyclo[2.1.1]hexanes Initiated by Energy Transfer. *J. Am. Chem. Soc.* **2022**, *144*, 7988−7994.

(11) (a) Liu, Y.; Lin, S.; Li, Y.; Xue, J.-H.; Li, Q.; Wang, H. Pyridine-Boryl Radical-Catalyzed [2$\pi$ + 2$\sigma$] Cycloaddition of Bicyclo[1.1.0]-butanes with Alkenes. *ACS Catal.* **2023**, *13*, 5096−5103. (b) Yan, H.; Liu, Y.; Feng, X.; Shi, L. Hantzsch Esters Enabled [2$\pi$+2$\sigma$] Cycloadditions of Bicyclo[1.1.0]butanes and Alkenes under Photo Conditions. *Org. Lett.* **2023**, *25*, 8116−8120. (c) Yu, T.; Yang, J.; Wang, Z.; Ding, Z.; Xu, M.; Wen, J.; Xu, L.; Li, P. Selective [2$\sigma$ + 2$\sigma$] Cycloaddition Enabled by Boronyl Radical Catalysis: Synthesis of Highly Substituted Bicyclo[3.1.1]heptanes. *J. Am. Chem. Soc.* **2023**, *145*, 4304−4310. (d) Agasti, S.; Beltran, F.; Pye, E.; Kaltsoyannis, N.; Crisenza, G. E. M.; Procter, D. J. A Catalytic Alkene Insertion Approach to Bicyclo[2.1.1]hexane Bioisosteres. *Nat. Chem.* **2023**, *15*, 535−541.

(12) (a) Dutta, S.; Lee, D.; Ozols, K.; Daniliuc, C. G.; Shintani, R.; Glorius, F. Photoredox-Enabled Dearomative [2$\pi$+2$\sigma$] Cycloaddition of Phenols. *J. Am. Chem. Soc.* **2024**, *146*, 2789−2797. (b) Tyler, J. L.; Schäfer, F.; Shao, H.; Stein, C.; Wong, A.; Daniliuc, C. G.; Houk, K. N.; Glorius, F. Bicyclo[1.1.0]butyl Radical Cations: Synthesis and AppliCation to [2$\pi$+2$\sigma$] Cycloaddition Reactions. *J. Am. Chem. Soc.* **2024**, *146*, 16237.

(13) (a) Radhoff, N.; Daniliuc, C. G.; Studer, A. Lewis Acid Catalyzed Formal (3 + 2)-Cycloaddition of Bicyclo[1.1.0]butanes with Ketenes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202304771. (b) Zhang, J.; Su, J.-Y.; Zheng, H.; Li, H.; Deng, W.-P. Eu(OTf)$_3$-Catalyzed Formal Dipolar [4$\pi$ + 2$\sigma$] Cycloaddition of Bicyclo-[1.1.0]butanes with Nitrones: Access to Polysubstituted 2-Oxa-3-azabicyclo[3.1.1]heptanes. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202318476. (c) Dhake, K.; Woelk, K. J.; Becica, J.; Un, A.; Jenny, S. E.; Leitch, D. C. Beyond Bioisosteres: Divergent Synthesis of Azabicyclohexanes and Cyclobutenyl Amines from Bicyclobutanes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202204719. (d) Liang, Y.; Paulus, F.; Daniliuc, C. G.; Glorius, F. Catalytic Formal [2$\pi$ + 2$\sigma$] Cycloaddition of Aldehydes with Bicyclobutanes: Expedient Access to Polysubstituted 2-Oxabicyclo[2.1.1]hexanes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202305043. (e) Ni, D.; Hu, S.; Tan, X.; Yu, Y.; Li, Z.; Deng, L. Intermolecular Formal Cycloaddition of Indoles with Bicyclo[1.1.0]butanes by Lewis Acid Catalysis. *Angew. Chem. Int. Ed* **2023**, *62*, No. e202308606. (f) Tang, L.; Xiao, Y.; Wu, F.; Zhou, J.-L.; Xu, T.-T.; Feng, J.-J. Silver-Catalyzed Dearomative [2$\pi$+2$\sigma$] Cycloadditions of Indoles with Bicyclobutanes: Access to Indoline Fused Bicyclo[2.1.1]hexanes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202310066.

(14) (a) Xu, W.; Jiang, H.; Leng, J.; Ong, H.-W.; Wu, J. Visible-Light-Induced Selective Defluoroborylation of Polyfluoroarenes, *gem*-Difluoroalkenes, and Trifluoromethylalkenes. *Angew. Chem., Int. Ed.* **2020**, *59*, 4009−4016. (b) Li, Y.; Li, X.; Li, X.; Shi, D. Visible-Light-Promoted *E*-selective Synthesis of $\alpha$-Fluoro-$\beta$-arylalkenyl Sulfides via the Deoxygenation/Isomerization Process. *Chem. Commun.* **2021**, *57*, 2152−2155.

(15) (a) Wang, J.; Gao, H.; Shi, C.; Chen, G.; Tan, X.; Chen, X.; Xu, L.; Cai, X.; Huang, B.; Li, H. Recent Advances in Radical-based C−F Bond Activation of Polyfluoroarenes and *gem*-Difluoroalkenes. *Chem. Commun.* **2021**, *57*, 12203−12217. (b) Tu, Y.; Shi, P.; Bolm, C. Visible-Light-Mediated $\alpha$-Ketoacylations of *NH*-Sulfoximines with *gem*-Difluoroalkenes. *Org. Lett.* **2022**, *24*, 907−911. (c) Liu, H.; Ge, L.; Wang, D.-X.; Chen, N.; Feng, C. Photoredox-Coupled F-Nucleophilic Addition: Allylation of gem-Difluoroalkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 3918−3922. (d) Yu, X.; Maity, A.; Studer, A. Cooperative Photoredox and N-Heterocyclic Carbene Catalyzed Fluoroaroylation for the Synthesis of $\alpha$-Trifluoromethyl-Substituted Ketones. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202310288.

(16) During our submission, Feng et al. reported an intramolecular cyclization of difluorinated hexa-1,5-dienes via energy transfer photocatalysis: Wu, M.; Ren, K.; Zou, C.; Chen, J.; Ma, R.; Zhu, C.; Feng, C. A general synthesis of *gem*-difluorobicyclo[2.1.1]hexanes. *Chin. Chem. Lett.* **2024**, 110213.

(17) Ruffoni, A.; Hampton, C.; Simonetti, M.; Leonori, D. Photoexcited Nitroarenes for the Oxidative Cleavage of Alkenes. *Nature* **2022**, *610*, 81−86.



https://doi.org/10.1021/acs.orglett.4c03798
*Org. Lett.* 2024, 26, 9961−9966