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A Selective Synthesis of 2,2-Difluorobicyclo[1.1.1]pentane Analogues: "BCP-F_2"

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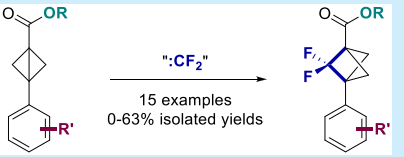
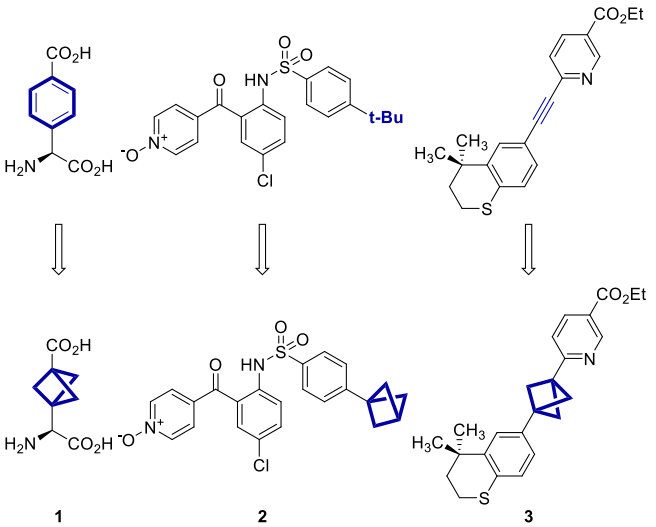
Supporting Information

ABSTRACT: The bicyclo[1.1.1]pentane (BCP) motif has been utilized as bioisosteres in drug candidates to replace phenyl, *tert*-butyl, and alkynyl fragments in order to improve physicochemical properties. However, because of the difficulty of synthesis, most BCP analogues prepared only bear 1,3-"*para*"-substituents. We report the first selective synthesis of 2,2-difluorobicyclo[1.1.1]pentanes via difluorocarbene insertion into bicyclo[1.1.0]butanes. Moreover, this methodology should inspire future studies on synthesis of other "*ortho*/*meta*-substituted" BCPs via similar mechanisms.



Bioisostere replacement is a fruitful strategy in fine-tuning the physicochemical properties of drug candidates.[1] Since the 1,3-disubstituted bicyclo[1.1.1]pentane (BCP) motif shares a similar geometry with 1,4-disubstituted benzene, BCP has been used as bioisosteres for phenyl groups.[2] The first example of such replacement was reported by Pellicciari and co-workers in 1996, using **1** (Scheme 1) as a novel mGluR1 antagonist.[3] Similar strategies have been applied to a γ-secretase inhibitor,[4] an $LpPLA_2$ inhibitor,[5] and several other central nervous system drug candidates.[6] It has been demonstrated that using BCP as the phenyl bioisostere replacement can significantly improve aqueous solubility, membrane permeability, and in vitro metabolic stability.[1a] BCP fragments also have been applied as *tert*-butyl (**2**, Scheme 1) and alkynyl isosteres (**3**, Scheme 1).

Scheme 1. Bicyclo[1.1.1]pentane Motif Used As Bioisosteres of *para*-Substituted Phenyl (1), *tert*-Butyl (2), and Alkynyl Moieties (3)



The synthesis of functionalized BCP building blocks has been challenging, because of the high ring strain of the system.[2] A successful strategy for the synthesis of functionalized BCPs employs [1.1.1]propellane (**4**) as the starting material (Scheme 2A).[2] Early works in this field dated back to the 1970s.[7] Recently, de Meijere and co-workers achieved the synthesis of iodoalkylation of **4** with ultraviolet light irradiation to provide **5**.[8] Several groups also developed coupling reactions involving **5** for further funtionalization.[8,9] In 2011, Pfizer reported the synthesis of BCP hydrazine derivative **6** using hydrogen atom transfer chemistry.[10] The BCP hydrazine derivative **6** could be further converted to 1-bicyclo[1.1.1]pentylamine.[10] Baran and co-workers reported a facile protocol achieving BCP analogues (**7**) with tertiary amine functionalities, using a strain release amination strategy.[11] Built on the radical and anionic opening of [1.1.1]propellane (**4**), the Uchiyama[12] and Knochel[13] groups developed strategies to obtain difunctionalized BCP analogues **8** and **9**, respectively. Shelp and Walsh reported the synthesis of BCP benzylamines **10** by opening **4** with 2-azaallyl anions.[14] Although these methodologies allow the access of various substituted BCP analogues, the usage of **4** as the starting material limits the functionalities on the methylene positions of the BCP moiety. In the meantime, a less-developed strategy toward the synthesis of BCP analogues involves a dichlorocarbene insertion into bicyclo[1.1.0]butanes **12** (Scheme 2B, the dichloromethylene functionality "CCl_2" is usually reduced to "CH_2" in subsequent steps).[15] The major issue of this route was the low yields in both the dichlorocarbene insertion steps (**12** → **13**) and the reduction steps (**13** → **14**).[15] However, this strategy inspired us to explore the potential of achieving BCP analogue synthesis by incorporating other carbene insertion processes. Since the incorporation of fluorine atoms can significantly modify the physicochemical properties of drug candidates,[16] we wish to prepare 2,2-difluorobicyclo[1.1.1]pentanes **16**. The additional

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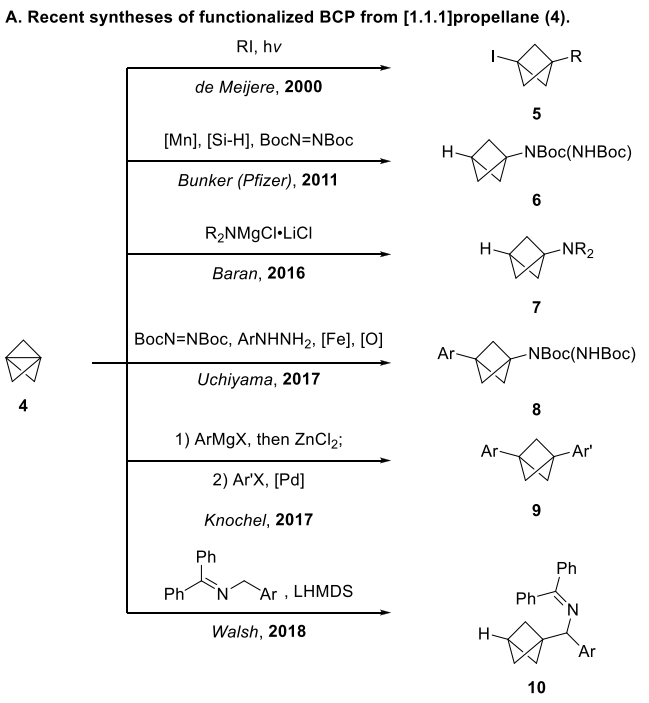
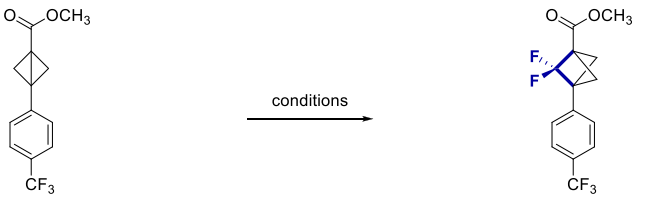
Scheme 2. (A) Recent Advances in the Syntheses of Functionalized BCP from [1.1.1]Propellane (4); (B) A Less Developed Synthesis of BCP from Bicyclo[1.1.0]butane (12); (C) This Work



difluoromethylene functionality in **16** can both finely tune the physicochemical properties of the BCP fragment and introduce additional interactions (e.g., fluorine−dipole interaction and hydrogen bonding interaction)[16] with the target protein that is not available with traditional BCP moieties. To our knowledge, there has been only two reports of fluorinated BCP analogues prior to our work.[17] The reported BCP fluorination conditions were harsh and mixtures of multifluorinated BCP analogues were synthesized.[17] Michl and co-workers also reported the synthesis of chlorinated BCP analogues in 2019.[18] Numerous attempts for selective synthesis of fluorinated BCP analogues have been ongoing for decades in medicinal chemistry research; however, success was scarce. Herein, we report the first selective synthesis of 2,2-difluorobicyclo[1.1.1]pentane analogues, which we named BCP-F_2, as an exotic functional group for potential applications in medicinal chemistry.

Bicyclo[1.1.0]butane **15a** was prepared as the standard substrate for condition optimizations, because of the ease of analysis by ^{19}F NMR. Since sodium trichloroacetate was employed as the dichlorocarbene precursor in reported syntheses of **13**,[15] we first evaluated the analogous difluorocarbene precursors (Table 1, entries 1 and 2). Sodium

Table 1. Condition Optimization for BCP-F_2 Synthesis



entry	conditions[a]	yield[b] (%)
1	ClF_2CO_2Na, diglyme, 177 °C	(34)
2	BrF_2CO_2Na, diglyme, 150 °C	13
3	$FSO_2CF_2CO_2TMS$, NaF, toluene, 150 °C	3
4	$FSO_2CF_2CO_2TMS$, NaF, MeOBz, 105 °C	40
5	$FSO_2CF_2CO_2TMS$, NaF, tBuOAc, 90 °C	56
6	$FSO_2CF_2CO_2TMS$, NaF, EtOAc, 75 °C	45
7	$FSO_2CF_2CO_2TMS$, NaF, CH_3CN, 90 °C	61
8	$FSO_2CF_2CO_2TMS$, NaF, dioxane, 90 °C	66

[a]For each reaction, **15a** (20 mg) was employed. For detailed reaction conditions, see the Supporting Information. [b]Yields determined by ^{19}F NMR using hexafluorobenzene as the internal standard. Isolated yields are shown in parentheses.

chlorodifluoroacetate afforded the desired product **16a** in 34% isolated yield (entry 1), which is superior than sodium bromodifluoroacetate (13% NMR yield, Table 1, entry 2). The usage of diglyme as the reaction solvent and the difficulties in reaction operations (addition of slurries of the sodium salts into the starting material at high temperatures) encouraged us to explore the possibility of utilizing other difluorocarbene precursors.[19] Although only 3% of the desired product was observed by ^{19}F NMR when using trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA) as the difluorocarbene precursor in toluene at 150 °C (Table 1, entry 3), a systematic decrease of reaction temperature by changing the reaction solvent showed that 90 °C was the optimal reaction temperature (Table 1, entries 3−8). Finally, the optimized conditions, using TFDA as the difluorocarbene precursor, activated by a substoichiometric amount of sodium fluoride in dioxane at 90 °C, afforded the desired product **16a** in 66% yield by ^{19}F NMR (Table 1, entry 8).

We explored the preliminary substrate scope of BCP-F_2 synthesis on preparative scales (Scheme 3, 100 mg scales). The standard product **16a** was obtained in 56% isolated yield under optimized conditions (Table 1, entry 8). The lower yield of the unsubstituted product **16b** (34%), compared to **16a** was attributed to the lower stability of the corresponding bicyclo[1.1.0]butane starting material at the reaction temperature. A variety of substituents at the aromatic ring have been examined. Generally, substrates with electron-withdrawing groups on the aromatic ring exhibited superior reactivities, compared to those with electron-donating groups. As shown, substrates with *para*-trifluoromethyl (**16a**, 56%), *para*-bromo (**16c**, 41%), *para*-fluoro (**16d**, 53%), and *para*-methoxycarbonyl (**16e**, 63%) functionalities were obtained with higher yields than the unsubstituted analogue **16b** (35%). For *para*-methoxy analogue **16f**, complicated decompositions of the starting material were observed under reaction conditions. This

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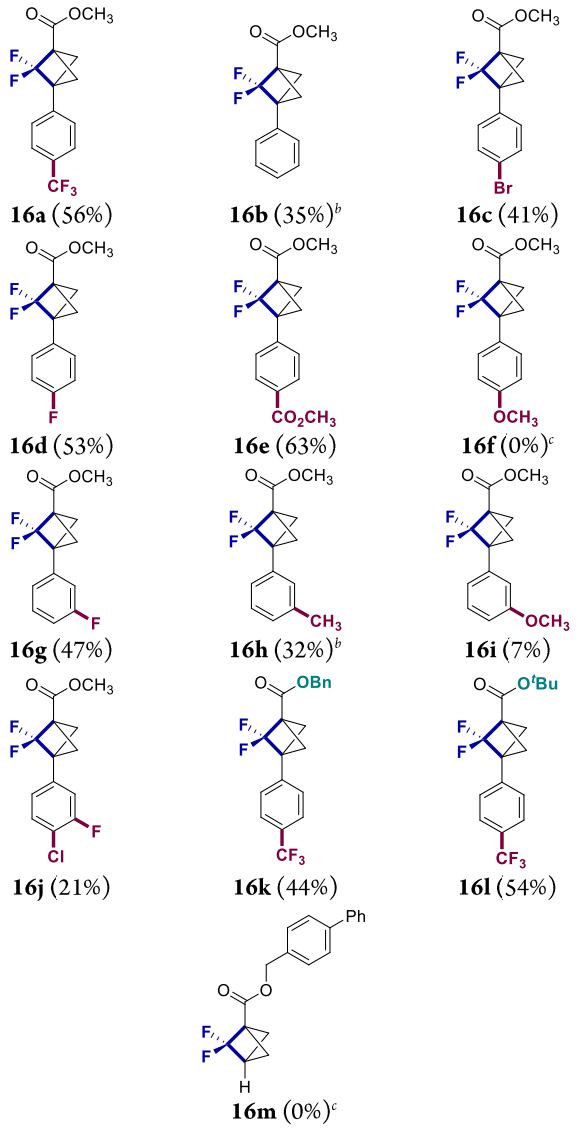
Scheme 3. Preliminary Substrate Scope[a]

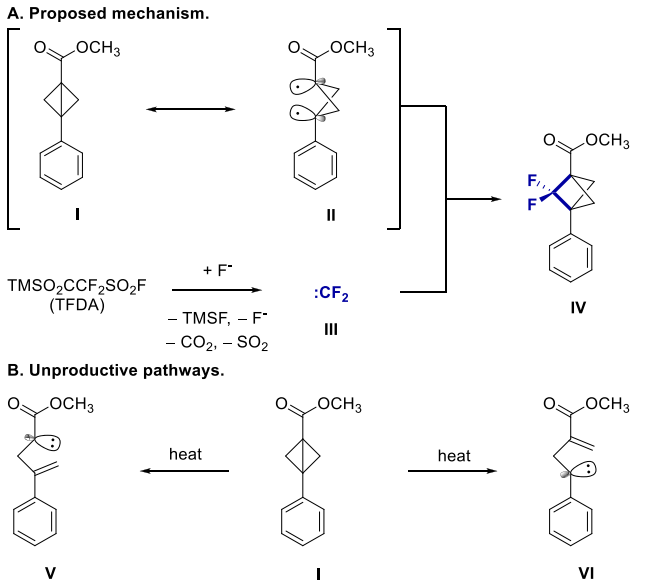


[a]All yields are isolated yields. Bicyclo[1.1.0]butane (100 mg), NaF (50 mol %), TFDA (3.00 equiv), dioxane (0.33 M), 90 °C, unless otherwise noticed. [b]Reaction conducted on a 700 mg scale. [c]Complex decomposition of the corresponding bicyclo[1.1.0]butane starting material was observed.

is because the bicyclo[1.1.0]butane substrate **15f** (not shown, see the Supporting Information) was highly unstable, even at room temperature in solutions. This electronic trend was also observed with *meta*-substituted analogues, as the yields decrease with the increasing electron density of the aromatic substituent on the bicyclo[1.1.0]butane starting material [*meta*-fluoro analogue **16g** (47%) > *meta*-methyl analogue **16h** (32%) > *meta*-methoxy analogue **16i** (7%)]. The 4-chloro-3-fluoro analogue **16j** was obtained in 21% yield. We also examined the nature of the ester group and both benzyl (**16k**, 44%) and *tert*-butyl esters (**16l**, 54%) were obtained in synthetically useful yields. To demonstrate the necessity of the aromatic group, we prepared the monosubstituted bicyclo[1.1.0]butane substrate **15m** (not shown; see the Supporting Information). Under optimized conditions, the desired product **16m** was not observed.

These results led to the mechanistic proposal that is described in Scheme 4A. The bicyclo[1.1.0]butane starting

Scheme 4. (A) Proposed Mechanism for BCP-F_2 Synthesis; (B) Unproductive Pathways of I under Heat



material **I** is in resonance to the diradical intermediate **II**. Meanwhile, fluoride-catalyzed decomposition of TFDA provided difluorocarbene **III**, releasing trimethylsilyl fluoride (TMSF), carbon dioxide (CO_2), and sulfur dioxide (SO_2). The desired product **IV** could be afforded either via direct insertion of the difluorocarbene **III** into the C−C bond in **I** or by stepwise radical addition with **II**. The overall moderate yields of the BCP-F_2 synthesis are attributed to the potential unproductive decomposition pathways of **I** (Scheme 3B; see Scheme S1 in the Supporting Information).[2]

To study the chemostability of the BCP-F_2 functionality, we prepared bicyclo[1.1.0]butane analogue **15n** (Scheme 5). The BCP-F_2 analogue **16n** could be obtained in 47% isolated yield; however, for the ease of operation, we subjected the crude reaction mixture after BCP-F_2 synthesis directly to further functionalization without purification. We first tested the stability of BCP-F_2 fragment under extreme conditions, i.e., strongly acidic environment to achieve **17a** and strongly reductive conditions to achieve **17b**. Treating the crude reaction mixture with anhydrous hydrochloric acid provided the corresponding BCP-F_2 carboxylic acid **17a** in 40% isolated yield. Reducing BCP-F_2 intermediate **16n** by lithium aluminum hydride ($LiAlH_4$) in refluxing tetrahydrofuran (THF) provided the corresponding alcohol **17b** in 32% isolated yield. We then tested the compatibility of BCP-F_2 functionality in three of the most commonly used transformations in medicinal chemistry (i.e., palladium-catalyzed C−N coupling, Suzuki coupling, and Stille coupling reactions). Tandem BCP-F_2 formation and C−N cross coupling provided the azetidine derivative **17c** in 39% yield. Telescoping BCP-F_2 formation and Suzuki coupling with 4-pyridylboronic acid provided **17d** in 31% yield over two steps. The Stille coupling product **17e** was obtained in 29% isolated yield when coupled with 2-(tributylstannyl)oxazole in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], copper(I) iodide (CuI), and cesium fluoride (CsF) in refluxing *N*,*N*-

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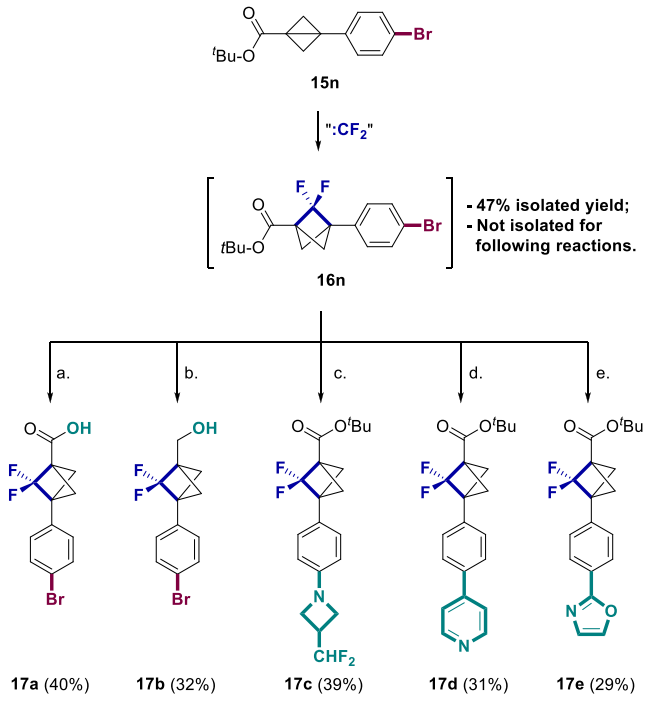
Scheme 5. Further Functionalization of BCP-F_2 Analogues:[a,b]

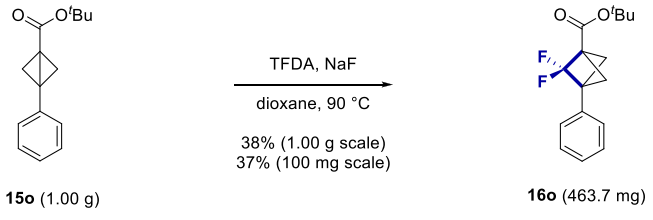


[a]Yields over two steps. [b]Mechanism routes: (a) HCl (10.0 equiv), dioxane, 24 °C, 12 h, 40%; (b) $LiAlH_4$ (1.00 equiv), THF, reflux, 15 min, 32%. (c) XantPhos Pd G3 (10 mol %), 3-(difluoromethyl)-azetidine hydrochloride (3.00 equiv), cesium carbonate (5.00 equiv), dioxane, 120 °C, 4 h, 39%; (d) XPhos Pd G2 (10 mol %), 4-pyridylboronic acid (3.00 equiv), sodium carbonate (3.00 equiv), dimethoxyethane, 90 °C, 1.5 h, 31%; and (e) $Pd(PPh_3)_4$ (10 mol %), CuI (10 mol %), CsF (2.00 equiv), 2-(tributylstannyl)oxazole (2.00 equiv), DMF, 130 °C, 1 h, 29%.

dimethyl formamide (DMF). These apparently harsh reaction conditions were intentionally chosen to establish the stability of the BCP-F_2 functionality under forced conditions.

Finally, to demonstrate the scalability of this methodology, we conducted the synthesis of **16o** with 1.00 g of **15o** under the optimized conditions (Scheme 6). BCP-F_2 analogue **16o** was obtained in 38% isolated yield (463.7 mg), which is comparable to the 37% isolated yield of **16o** obtained on a 100-mg-scale reaction.

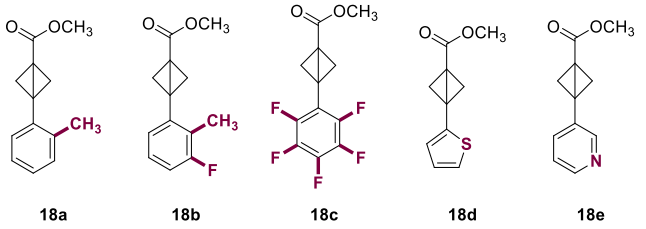
Scheme 6. Gram-Scale Reaction



Currently, we are investigating further scale-up procedures for **16o**. We are also in the process of developing optimal conditions to oxidatively convert the phenyl group in **16o** to the carboxylic acid functionality to achieve derivatives with broader application for medicinal chemistry.

A major limitation of this transformation is the potential difficulty in accessing the bicyclo[1.1.0]butane starting material. Representative examples of bicyclo[1.1.0]butanes that failed in preparation are summarized in Scheme 7. The *ortho*-

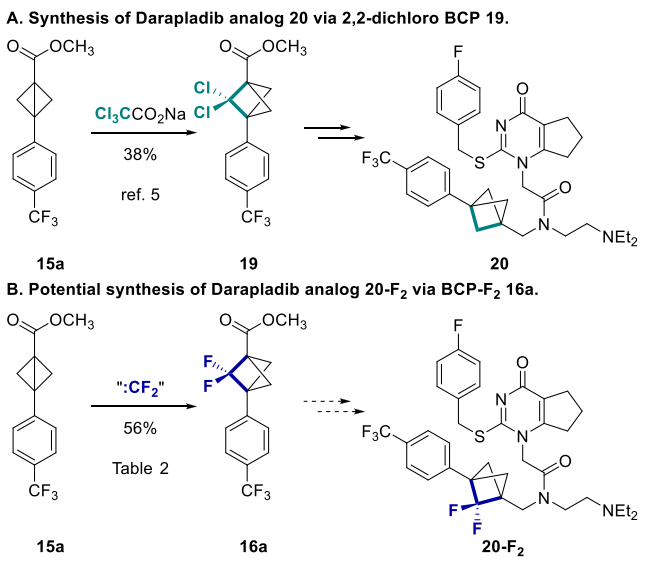
Scheme 7. Substrates That Failed in Preparation



substituted analogues (e.g., **18a** and **18b**) were not suitable for the synthetic route. Electron-poor aryl analogues (e.g., **18c**) also failed because of low nucleophilicity of the corresponding organometallic reagents in the addition reaction into the ketone functionality of **11**. Another major limitation for the synthesis of bicyclo[1.1.0]butanes is the incompatibility with heteroaryl substituents (e.g., **18d** and **18e**).

Note that the yield for this transformation (formation of **16a**; see Scheme 8) is similar to the analogue obtained with dichlorocarbene analogue **19**.[5]

Scheme 8. Comparison of Dichlorocarbene and Difluorocarbene Insertion Results Toward the Synthesis of Darapladib Analogues (A) 20 and (B) 20-F_2



We also conducted some preliminary in silico profiling of BCP-F_2 analogue **21**, compared to its analogue **22**. The selective data that are summarized in Table 2 are predicted properties that have been calculated using proprietary models.[20] This table shows that, although the log *D* and polar surface area (PSA) values are similar between BCP-F_2 analogue **21** (log *D* = 0.63, PSA = 44.6) and BCP analogue **22** (log *D* = 0.50, PSA = 44.9), the *c* log *P* value of **21** (*c* log *P* = 1.59) is more than 0.5 log units lower than **22** (*c* log *P* = 2.11). The difluorosubstituents on **21** also rendered a lower pK_a of the carboxylic acid functionality (pK_a = 3.17), compared to **22** (pK_a = 4.81). Further in vitro and in vivo profilings of BCP-F_2 analogues are underway in our laboratory.

To conclude, we report the first selective synthesis of 2,2-difluorobicyclo[1.1.1]pentane analogues, which we have

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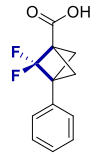
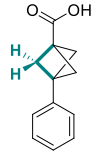
Table 2. Predicted Properties

structure	logD	PSA	clogP	pKa
 **21**	0.63	44.6	1.59	3.17
 **22**	0.50	44.9	2.11	4.81

named BCP-F_2. The reaction proceeds rapidly under mild conditions with commercially available reagents. We proposed a diradical−carbene combination mechanism. The desired products were obtained with synthetically useful yields on 100-mg scales. We further demonstrated that the BCP-F_2 functionality is stable under harsh reaction conditions. We believe this BCP-F_2 work should find application as an exotic functional group in medicinal chemists' journey to escape the "flatland."[1a] Currently, further studies to broaden the substrate scope as well as using other carbene precursors to provide 2-substituted and/or 2,2-disubstituted bicyclo[1.1.1]pentane analogues are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02026.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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