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Synthesis of Difluorinated Heterocyclics through Metal-Free [8+1] and [4+1] Cycloaddition of Difluorocarbene

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Cite This: *Org. Lett.* 2021, 23, 2670–2675 Read Online

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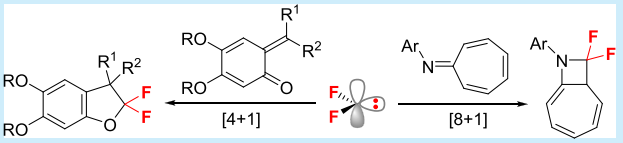
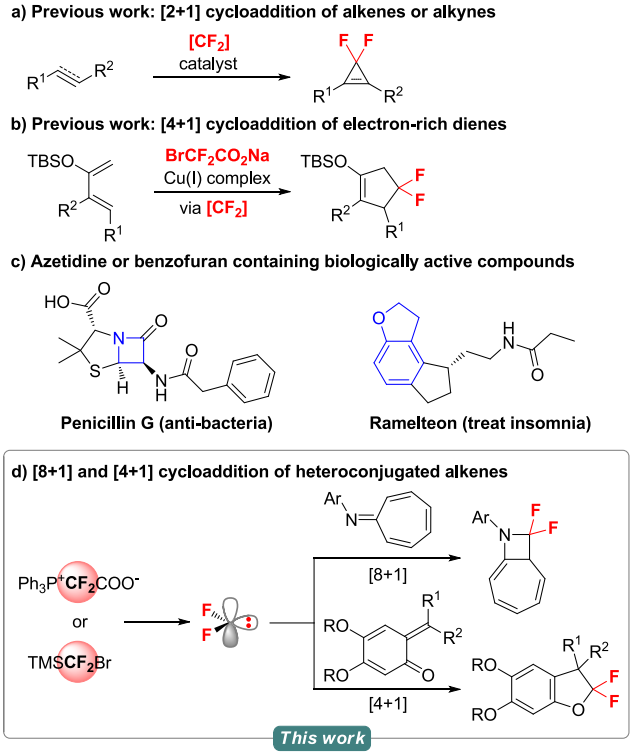
ABSTRACT: With $Ph_3P^+CF_2COO^-$ or $TMSCF_2Br$ as the difluorocarbene sources, a facile metal-free cycloaddition between heteroconjugated alkenes and difluorocarbene was developed for the highly convergent synthesis of novel difluorinated heterocyclics, including *gem*-difluorinated azetidines and 2,3-dihydrobenzofurans. The cycloaddition features high reactivity and regioselectivity, as well as good tolerance of various electron-donating or electron-withdrawing substituents on azaheptafulvenes and *o*-quinone methides.



Given their unique electron-deficient characteristics and physical, chemical, and biochemical properties, difluoroalkylated compounds are not only extensively present in drugs, agrochemicals, and functional materials but also commonly utilized as a class of industrial raw materials in various synthetic transformations.[1] As a consequence, significant progress in the selective introduction of a CF_2 motif into small molecules has been achieved by employing nucleophilic or electrophilic difluoromethylation reagents over the past several decades.[2,3] Among them, difluoromethylation involving the difluorocarbene pathway has recently attracted considerable attention.[4]

As an electron-deficient carbene species,[5] difluorocarbene is a high-reactivity intermediate that can be trapped by heteroatom nucleophiles (N, O, S, Se, P, and X)[4,6] or activated carbon nucleophiles[7] to generate difluoromethylated compounds. In addition, valuable strategies based on metal difluorocarbene ($[M]{=}CF_2$) involving catalytic coupling have recently been developed by Zhang and co-workers.[8] Although significant advances in this field have been achieved in the past several years, the existing processes for the cyclization between unsaturated compounds and difluorocarbene are rather limited. Most of the examples have focused on the development of efficient methods for the [2+1] cycloaddition between difluorocarbene and alkenes or alkynes (Scheme 1a).[6b,9] Recently, a [4+1] cycloaddition of silyl dienol ethers via a difluorocarbene pathway has been reported, in which electron-rich dienes and a phenanthroline-based Cu(I) complex are employed (Scheme 1b).[10] However, these strategies have been demonstrated to be inefficient for the electron-deficient polyenes. In particular, the direct [8+1] and [4+1] cycloaddition of heteroconjugated alkenes involving metal-free difluorocarbene has been a long-standing challenge, and the potential side reaction on [2+1] cycloaddition between difluorocarbene and the alkenyl moiety of an unsaturated compound may pose significant competition. Notably, cycloaddition on electron-deficient polyenes has not been

Scheme 1. Cyclizations Involving Difluorocarbene



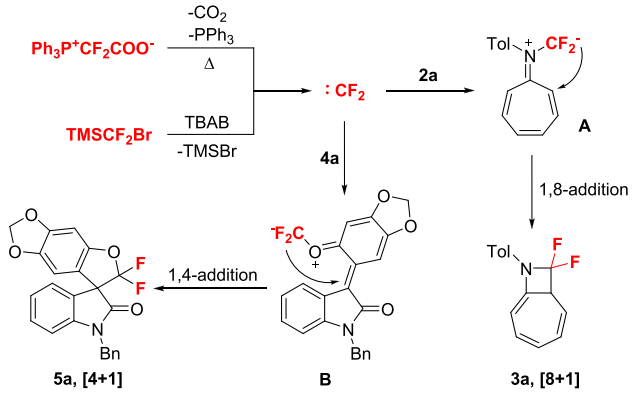
Received: February 17, 2021
Published: March 16, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00577
Org. Lett. 2021, 23, 2670–2675

successfully demonstrated. The azetidine and benzofuran are important heterocyclic skeletons, which widely exist in many natural products, drugs, and drug candidates (Scheme 1c).[11,12] It is noteworthy that fluorinated bioactive compounds play important roles in drug discovery, which account for >20% of marketed drugs.[1] *gem*-Difluorinated azetidines and benzofurans may have novel bioactivity and molecular mechanisms of action. As part of our ongoing research on fluoroalkylation,[13] we herein report an unprecedented [8+1] and [4+1] cycloaddition of difluorocarbene with electron-deficient heteroconjugated alkenes (Scheme 1d). The method facilitates the formation of *gem*-difluorinated azetidine and 2,3-dihydrobenzofuran derivatives with high efficiency and excellent functional-group tolerance from azaheptafulvenes and *o*-quinone methides, respectively.[14]

Theoretically, difluorocarbene (:CF_2) may be released from $Ph_3P^+CF_2CO_2^-$ or $TMSCF_2Br$ through a thermodynamic decarboxylation or in the presence of TBAB, respectively. It would be trapped by the N or O atom in heteroconjugated alkene 8-azaheptafulvene **2a** or *o*-quinone methide **4a** to deliver the carbanion-containing intermediate **A** or **B**, which served as an active carbon nucleophile. Finally, *gem*-difluorinated azetidine **3a** was formed through an intramolecular 1,8-conjugate addition reaction of species **A**. Similarly, species **B** underwent an intramolecular 1,4-nucleophilic attack to deliver the corresponding *gem*-difluorinated 2,3-dihydrobenzofuran **5a** (Scheme 2). The

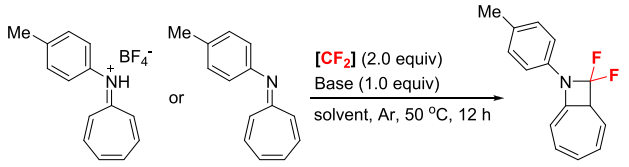
Scheme 2. Working Hypothesis of Cycloaddition of Difluorocarbene



significant challenge in this strategy is to trap the difluorocarbene intermediate by the heteroatom (C═N or C═O) of heteroconjugated alkenes. If the difluorocarbene species cannot be captured, the cyclization reaction is difficult.

At the outset of our preliminary investigation, 8-azaheptafulvenium fluoroborate **1a** was selected as a model heteroconjugated alkene for preliminary studies, which could readily transform into 8-azaheptafulvene **2a** *in situ* under basic conditions. Subsequently, $TMSCF_2Br$ or HCF_2Cl was employed as a difluorocarbene source and reacted with **1a** in CH_3CN at 50 °C using Cs_2CO_3 as a base under an argon atmosphere for 12 h (Table 1, entries 1 and 2). Unfortunately, no *gem*-difluorinated azetidine **3a** was observed under these conditions. Fortunately, **3a** was obtained in 25% yield when $BrCF_2COOEt$ was used as the difluorocarbene source (Table 1, entry 3). Then, other commonly used difluorocarbene sources, including $BrCF_2COOK$ and difluoromethylene phosphobetaine $Ph_3P^+CF_2CO_2^-$ (PDFA),[4c,15] have been

Table 1. Investigation of the Reaction Conditions[a]



1a 2a 3a

entry	1a or 2a	base	[CF_2]	solvent	3a (%)[b]
1[c]	1a	Cs_2CO_3	$TMSCF_2Br$	CH_3CN	0
2	1a	Cs_2CO_3	HCF_2Cl	CH_3CN	0
3	1a	Cs_2CO_3	$BrCF_2COOEt$	CH_3CN	25
4	1a	Cs_2CO_3	$BrCF_2COOK$	CH_3CN	37
5	1a	Cs_2CO_3	PDFA[e]	CH_3CN	40
6	2a	–	PDFA[e]	CH_3CN	66
7	2a	–	PDFA[e]	DMF	50
8	2a	–	PDFA[e]	NMP	46
9	2a	–	PDFA[e]	Et_2O	14
10	2a	–	PDFA[e]	CH_2Cl_2	78
11	2a	–	PDFA[e]	EtOAc	65
12	2a	–	PDFA[e]	toluene	57
13	2a	–	PDFA[e]	dioxane	79
14	2a	–	PDFA[e]	THF	80
15[d]	2a	–	PDFA[e]	THF	86

[a]Reaction conditions: **1a** or **2a** (0.1 mmol), CF_2 reagent (2.0 equiv), and Cs_2CO_3 (1.0 equiv) in solvent (1.0 mL) at 50 °C for 12 h. [b]Yields determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c]With 20 mol % TBAB as a catalyst. [d]Reaction time of 1 h. [e]$Ph_3P^+CF_2CO_2^-$.

employed, which deliver **3a** in 37% and 40% yields, respectively (Table 1, entries 4 and 5, respectively). To our delight, when 8-azaheptafulvene **2a** was used instead of **1a**, the reaction yield was increased to 66% (Table 1, entry 6). Solvent screening showed that CH_2Cl_2 and dioxane were the preferred solvents in terms of reactivity and yield, whereas poorer yields were found when using DMF, NMP, Et_2O, EtOAc, or toluene as the solvent (Table 1, entries 7–13). An even higher yield (80%) was obtained when THF was chosen as the solvent (Table 1, entry 14). Finally, decreasing the reaction time to 1 h improved the yield to 86% (Table 1, entry 15), indicating the high reactivity of the current cycloaddition and insufficient stability of the *gem*-difluorinated azetidine under the reaction conditions. As a comparison, when linear aza-conjugated alkene *N*-tosyl imine of chalcone was employed as the substrate, no cyclization product was detected.

With the optimized conditions in hand (Table 1, entry 15), the cyclization was then extended to a variety of 8-azaheptafulvenes **2** with different substitution patterns (Scheme 3). First, the electronical nature of the substituents was investigated. 8-Azaheptafulvenes (**2a–k**) with different substituents at the *para* position on the phenyl ring, including electron-donating and electron-withdrawing groups, can be readily converted into the corresponding *gem*-difluorinated azetidines **3a–k** in good to excellent yields. A series of functional groups, such as alkyl, phenyl, alkoxy, halogen, nitrile, ester, and even trifluoromethyl groups, are quite compatible with the reaction conditions. Then, multisubstituted aniline-derived substrates were surveyed. The 8-azaheptafulvene derivatives bearing phenyl rings disubstituted with 3,4-dimethyl (**2l**) or 3-chloro-4-methyl (**2m**) as well as 3,4-dihalo (**2n** and **2o**) groups were cyclized in good to high yields. Likewise, the substrate with a sterically hindered *o*- and *p*-

https://dx.doi.org/10.1021/acs.orglett.1c00577
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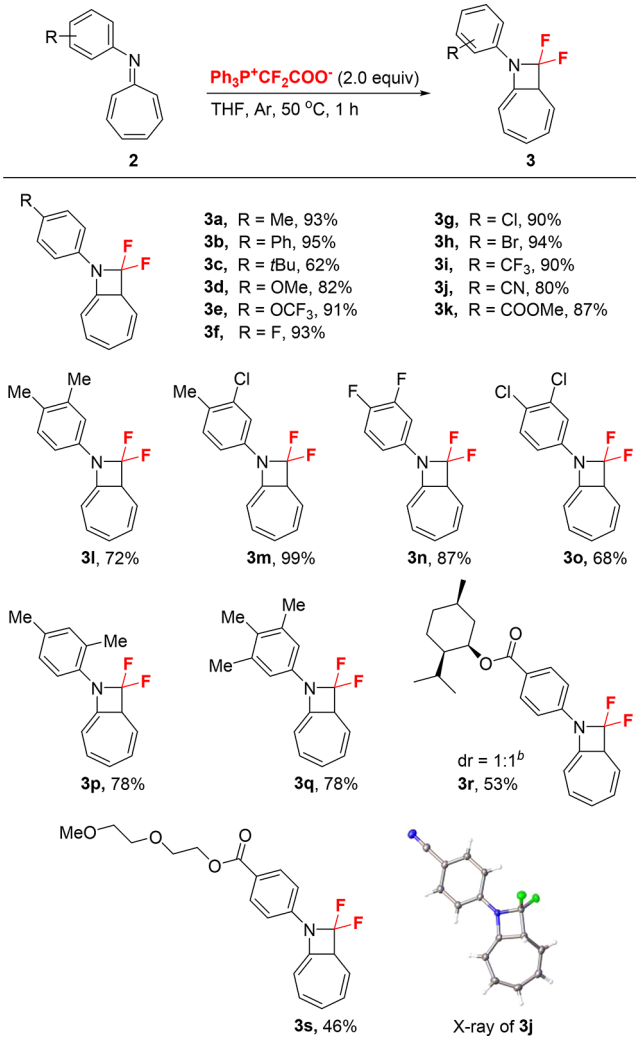
Scheme 3. Substrate Scope of the [8+1] Cycloaddition Reaction[a]

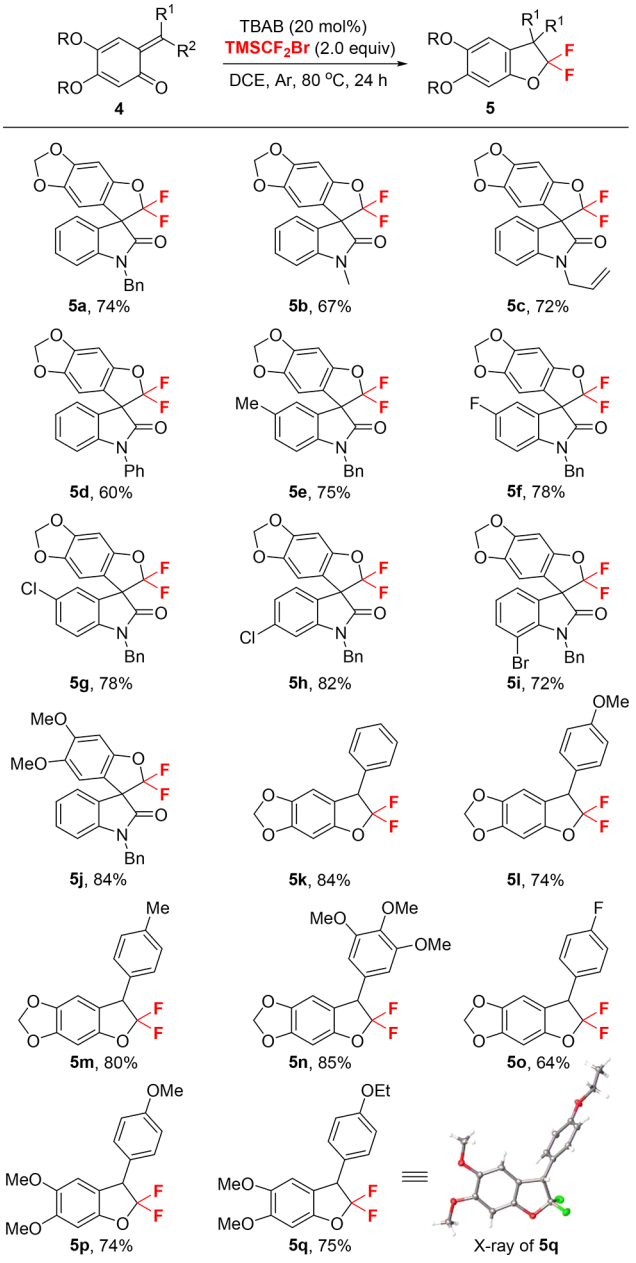


[a]Reaction conditions: 8-azaheptafulvene **2** (0.5 mmol) and $Ph_3P^+CF_2COO^-$ (1.0 mmol, 2.0 equiv) in THF at 50 °C for 1 h. Yields are isolated yields. [b]Diastereoselectivity was determined by ^1H NMR and ^{19}F NMR analysis of the crude product.

dimethyl-substituted aryl was well tolerated under the same reaction conditions, providing the desired product **3p** in 78% yield. The aromatic ring containing three methyl groups was also a suitable substrate (**2q**) for the [8+1] reaction to furnish the desired product **3q** in 78% yield. Finally, to probe the application of the current approach in organic synthesis, 8-azaheptafulvenes derived from biological activity relevant molecules, including L-menthol (**2r**) and polyethylene glycol (PEG, **2s**) motifs, were examined. The reactions proceeded smoothly to produce target products **3r** and **3s**, which provided a straightforward pathway toward the late-stage modification of complex compounds. The structure of **3j** was confirmed by X-ray diffraction.

Encouraged by the results with 8-azaheptafulvenes, we turned our attention to the construction of oxygen-containing *gem*-difluorinated heterocycles, which are also attracting considerable attention in life science and functional materials. In this reaction, $TMSCF_2Br$ is used as the difluorocarbene source for the formation of compound **5**. As shown in Scheme 4, the substrate scope of [4+1] cycloaddition reaction

Scheme 4. Substrate Scope of the [4+1] Cycloaddition Reaction[a]



[a]Reaction conditions: TBAB (20 mol %), *o*-quinone methide **4** (0.2 mmol), and $TMSCF_2Br$ (0.4 mmol, 2.0 equiv) in DCE at 80 °C for 24 h. Yields are isolated yields.

involving difluorocarbene was evaluated by using *o*-quinone methides as the heteroconjugated alkenes in the presence of tetrabutylammonium bromide (TBAB). First, an oxindole-embedded *o*-quinone methide **4a** was subjected to the *gem*-difluorinated cyclization reaction under the optimized conditions (see the Supporting Information for details). The corresponding difluorinated 2,3-dihydrobenzofuran **5a** was isolated in 74% yield. The nitrogen atom of the oxindole moiety bearing methyl, allyl, and phenyl substituents was found to be compatible with the cyclization conditions, delivering difluorinated 2,3-dihydrobenzofurans **5b**−**d** as the sole products in 60−72% yields. Interestingly, no *gem*-difluorocyclopropanated byproduct was detected, even in the

https://dx.doi.org/10.1021/acs.orglett.1c00577
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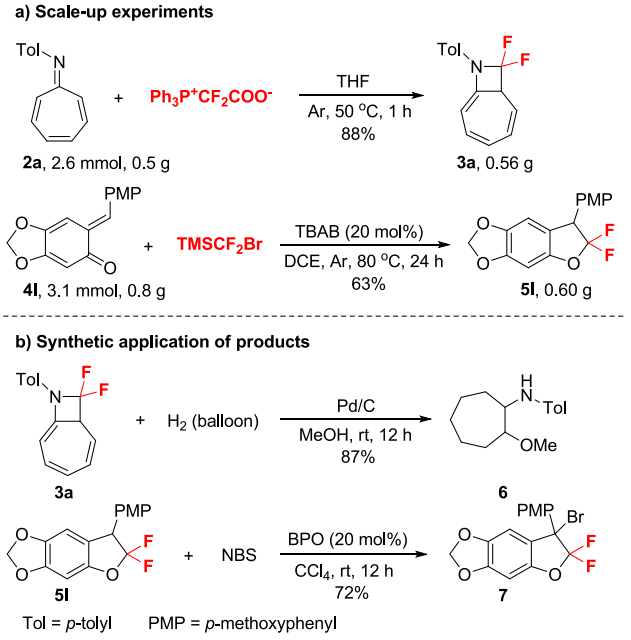
case of allyl-substituted substrate **4c**.[9] Furthermore, methyl- or halogen-functionalized oxindoles **4e−i** are suitable substrates for the reaciotn, and the expected products **5e−i** were obtained in good yields. In addition, 4,5-dimethoxyphenol-derived substrate **4j** was efficiently converted to targeted product **5j** in 84% yield. Similarly, other *o*-quinone methides derived from aromatic aldehydes underwent the [4+1] cycloaddition smoothly, giving cyclizated products **5k−q** in good to excellent yields. The structure of difluorinated 2,3-dihydrobenzofuran **5q** was further characterized by an X-ray crystallographic analysis. However, linear oxa-conjugated alkenes such as chalcone and *trans*-methyl 2-oxo-4-phenylbut-3-enoate were not suitable substrates for the reaction.

To further demonstrate their synthetic potential, the current [8+1] and [4+1] cycloadditions were evaluated on gram scales. Under the standard reaction conditions, **2a** (0.5 g, 2.6 mmol) and **4l** (0.8 g, 3.1 mmol) reacted smoothly with difluorocarbene reagents, providing the corresponding cyclized products **3a** and **5l**, respectively, without a significant loss of efficiency (Scheme 5a). The synthetic utility of *gem*-

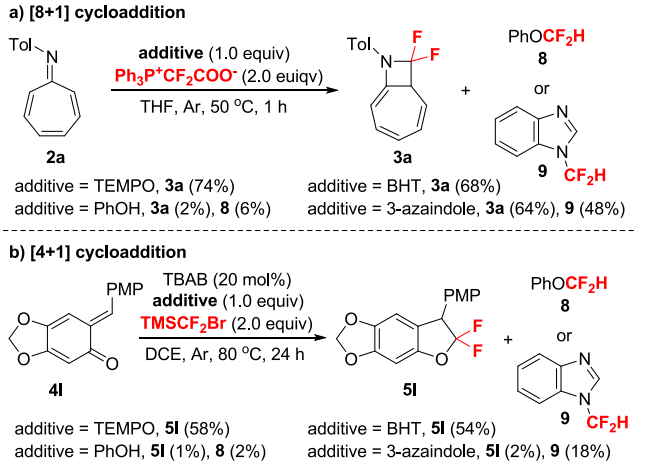
Scheme 5. Scale-up and Derivatization Experiments



difluorinated azetidine and 2,3-dihydrobenzofuran was next investigated. As illustrated in Scheme 5b, when *gem*-difluorinated azetidine **3a** underwent hydrogenation in methanol in the presence of Pd/C and H_2 (balloon) at room temperature for 12 h, product **6** without a difluoromethylene group was obtained in excellent yield. This reveals that this four-membered ring is unstable. For *gem*-difluorinated 2,3-dihydrobenzofuran **5l**, the benzylic carbon center adjacent to the difluoromethyl group has high nucleophilic reactivity. It could readily react with *N*-bromosuccinimide (NBS) at room temperature to give brominated product **7** in 72% yield, which facilitated further transformation.

Several control experiments have been performed to gain insight into the cycloaddition reaction mechanism (Scheme 6). When [8+1] or [4+1] cyclization was carried out in the presence of radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT)

Scheme 6. Control Experiments



under the standard conditions, the reactivities were slightly affected and thus the free radical pathway could be ruled out. Subsequently, carbene-trapping reagents phenol and 3-azaindole were individually subjected to the [8+1] cycloaddition systems, the cyclization reaction was partly inhibited, and difluorocarbene-captured adducts **8** and **9** were detected by ^{19}F NMR in 6% and 48% yields, respectively. When similar experiments were carried out for the [4+1] cyclization of *o*-quinone methide, the cyclization reaction was almost stopped and the corresponding trapped adduct **8** or **9** was also detected. These results clearly revealed that both [8+1] and [4+1] cycloaddition proceeded through the difluorocarbene process.

In summary, we have discovered the first [8+1] and [4+1] cycloaddition of a heteroconjugated alkene with an *in situ*-produced difluorocarbene, delivering the azetidine and 2,3-dihydrobenzofuran analogues with a wide substrate scope and high efficiency. This approach represents an unprecedented construction of *gem*-difluorinated four- or five-membered heterocyclics through a carbene cyclization strategy without a metal catalyst. This transformation is readily scaled up and likely to find broad synthetic applications, which provides a straightforward and versatile avenue for the late-stage modification of biologically relevant compounds. Further development of other kinds of *gem*-difluorinated cyclization reactions involving difluorocarbene is presently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00577.

Experimental procedures, screening of reaction conditions, characterization data, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 2052766 and 2054601 contain 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.

https://dx.doi.org/10.1021/acs.orglett.1c00577
Org. Lett. 2021, 23, 2670−2675

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are thankful for the financial support from the National Key Research and Development Program of China (Grant 2018YFA0704000) and the National Natural Science Foundation of China (Grant 22077098). The authors are grateful to Dr. Guofu Qiu and Dr. Jianli Duan of the School of Pharmaceutical Sciences at Wuhan University for the NMR and HRMS analyses, respectively.

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https://dx.doi.org/10.1021/acs.orglett.1c00577
Org. Lett. 2021, 23, 2670−2675