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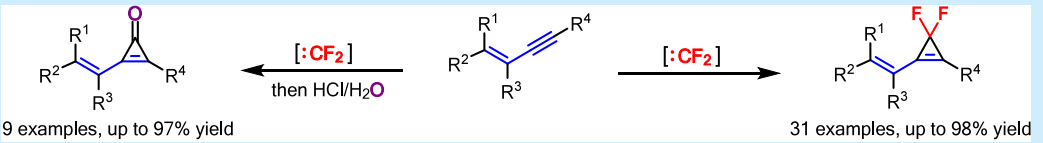
Chemoselective [2+1] Cycloaddition of Difluorocarbene with Conjugated Enynes: Synthesis of Alkenyl Difluorocyclopropenes

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ABSTRACT: The chemoselective [2+1] cycloaddition of difluorocarbene with conjugated enynes has been achieved. Using $TMSCF_2Br$ as the difluorocarbene precursor in the presence of a catalytic amount of *n*-$Bu_4N^+Br^-$, the reaction proceeded smoothly in THF at 110 °C, affording a series of alkenyl-substituted difluorocyclopropenes. Subsequently, these products could be hydrolyzed in one pot to furnish the corresponding alkenyl-substituted cyclopropenones.

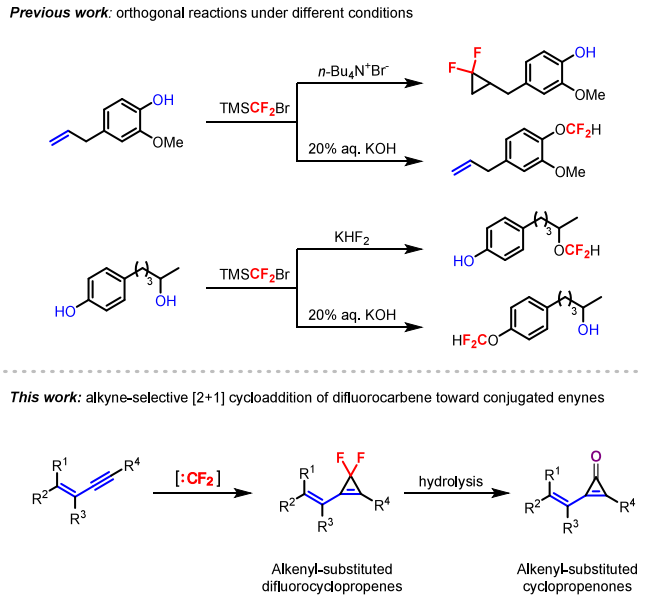
The selective introduction of a fluorine atom(s) or fluorinated moieties into organic compounds is a crucial synthetic strategy in drug and materials science.[1,2] Given this, difluorocarbene serves as a key reactive intermediate for fluorine-containing organic compounds.[3] Its conventional reactions primarily fall into four categories: (1) [2+1] cycloaddition with alkenes or alkynes,[4] (2) difluoromethylation of nucleophiles,[5] (3) acting as a bridging unit between nucleophiles and electrophiles,[6] and (4) ylide formation with amines or phosphines.[7]

Difluorocyclopropenes, which can be accessed via the [2+1] cycloaddition of alkynes with difluorocarbene, constitute an important class of synthetic intermediates and versatile building blocks for complex (fluorinated) molecules.[8] They also serve as efficient deoxyfluorinating agents, leveraging the aromaticity of cyclopropenium cations.[9] Their hydrolysis product, cyclopropenone, finds broad utility in transition-metal catalysis,[10] organocatalysis,[11] polymerization,[12] and bioorthogonal chemistry.[13] However, the high reactivity of difluorocarbene often limits the use of structurally complex alkynes to avoid side reactions at multiple reactive sites,[14] making the synthesis of elaborate difluorocyclopropenes via this route a significant challenge.

Previously, we achieved orthogonal reactivities between difluorocarbene and different functional groups within the same molecule by exploiting different reaction conditions (Scheme 1).[15] However, achieving orthogonal reactions with two similar functional groups, particularly selective addition to alkenes versus alkynes, presents a more formidable challenge. Herein, we report the chemoselective [2+1] cycloaddition of difluorocarbene with the alkyne moiety of conjugated enynes, compounds bearing both alkenyl and alkynyl groups.

Initially, we used **1a** as a model substrate, using $TMSCF_2Br$ (1.5 equiv) as the difluorocarbene source with 3 mol % *n*-$Bu_4N^+Br^-$ as the initiator in toluene at 80 °C, and the desired

Scheme 1. Orthogonal Reactivity of Difluorocarbene with Multiple Functional Groups



alkyne-selective [2+1] cycloadduct was obtained in 36% yield with substantial starting material recovery (Table 1, entry 1). Increasing the temperature to 110 °C increased the yield to

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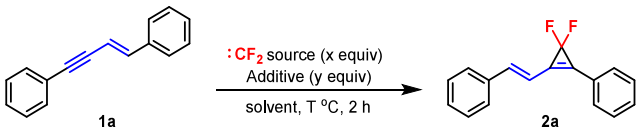


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Table 1. Optimization of the Reaction Conditions[a]



entry	:CF_2 source (equiv)	additive (equiv)	T (°C)	solvent	yield of **2a** (%)
1	$TMSCF_2Br$ (1.5)	TBAB (0.03)	80	toluene	36
2	$TMSCF_2Br$ (1.5)	TBAB (0.03)	110	toluene	66
3	$TMSCF_2Br$ (1.5)	TBAB (0.03)	110	THF	90
4[b]	$ClCF_2CO_2Na$ (2.0)	–	120	diglyme	ND[c]
5[b]	$BrCF_2CO_2Na$ (2.0)	–	120	diglyme	ND[c]

[a]Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), solvent (2.0 mL). Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b]**1a** (0.1 mmol, 1.0 equiv), solvent (1.0 mL). [c]Not detected.

66%, albeit with concomitant formation of hydrolysis byproducts (entry 2). We suspected that these byproducts stemmed from the decomposition of the target compound by TMSBr generated *in situ*. Notably, switching the solvent to THF increased the yield to 90% (entry 3), which we attribute to THF consuming TMSBr via a ring-opening reaction.[16] In contrast, no desired product was observed when using sodium chlorodifluoroacetate or sodium bromodifluoroacetate as the difluorocarbene source, with **1a** remaining largely intact (entry 4 or 5, respectively).

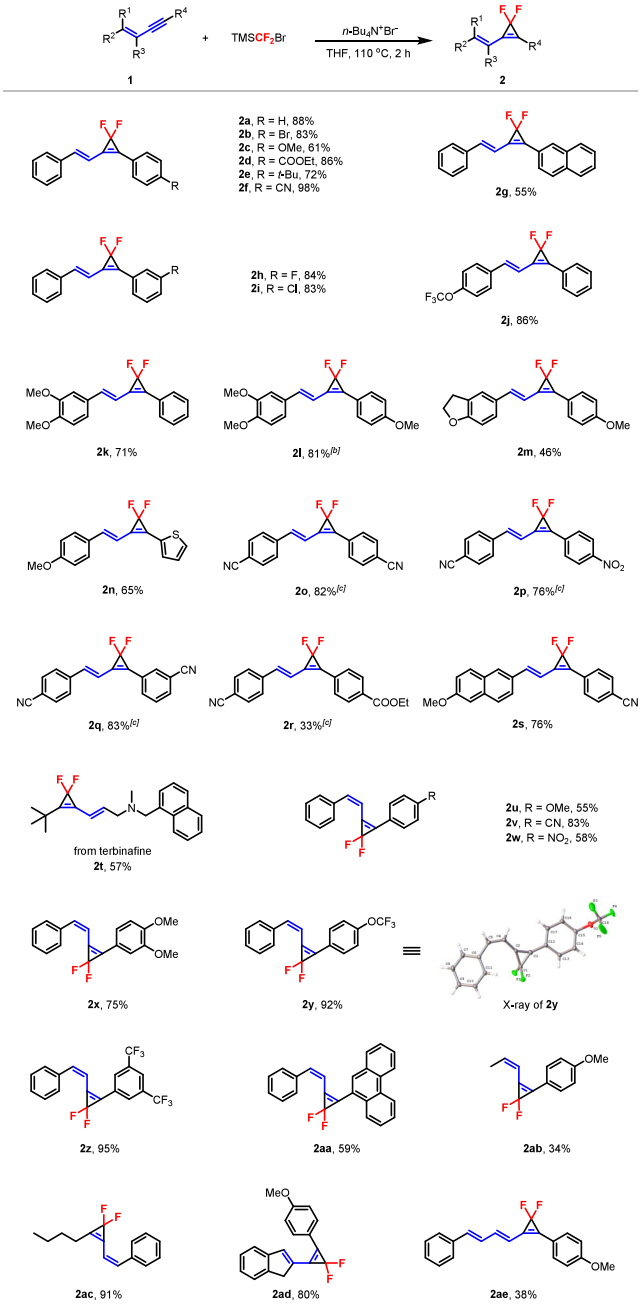
The substrate scope was subsequently evaluated under the optimized conditions (Table 1, entry 3; Scheme 2). A variety of conjugated enynes bearing different substituents on the aromatic ring, including halogens (**2b**, **2h**, and **2i**), ethers (**2c**, **2k**−**2n**, **2s**, and **2x**), an ester (**2d** and **2r**), a *tert*-butyl group (**2e**), nitrile (**2f**, **2o**−**2s**, and **2v**), nitro (**2p** and **2w**), trifluoromethyl (**2z**), and trifluoromethoxy (**2j** and **2y**), were well tolerated, affording the desired products in moderate to high isolated yields (33−98%). Substrates with naphthalene or anthracene rings also proceeded smoothly, delivering the corresponding products in good yields (**2g** or **2aa**, respectively).

Several general trends emerged. (1) *E*-Alkene isomers gave slightly higher yields than their *Z*-counterparts (cf. **2c** vs **2u** and **2f** vs **2v**). (2) Electron-rich enynes generally provided lower yields compared with their electron-deficient analogues (cf. **2c** vs **2f** and **2u** vs **2v**). (3) Excellent yields were maintained even with multiple electron-donating or electron-withdrawing substituents on the arene (**2k**−**2m**, **2o**−**2q**, **2x**, and **2z**). The structure of **2y** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 2505930).

Notably, the chemoselectivity for the alkyne over the alkene remained intact regardless of the electronic nature of the substituents on both unsaturated units (**2ab** and **2ac**). Furthermore, neither extending the conjugated system (**2ae**) nor introducing a sterically demanding group on the alkyne (**2t**) compromised the regioselectivity, with the [2+1] cycloaddition occurring exclusively at the alkynyl moiety.

Subsequently, we developed a one-pot synthesis of alkenyl-substituted cyclopropenones directly from conjugated enynes (Scheme 3). For most substrates, the yields of cyclopropenones were substantially improved compared to difluorocyclopropenes obtained via the [2+1] cycloaddition with difluorocarbene (e.g., **2h** vs **3e**, **2g** vs **3f**, and **2n** vs **3h**). We ascribe this improvement to the partial hydrolytic loss of difluorocyclopropenes during the reaction and isolation steps. However, when the arene ring of the conjugated enyne bears strong electron-withdrawing groups such as a cyano substituent, the cyclopropenone yield was lower than that of the corresponding [2+1] cycloadduct (e.g., **2f** vs **3b**). This result is consistent with the higher stability of the electron-deficient

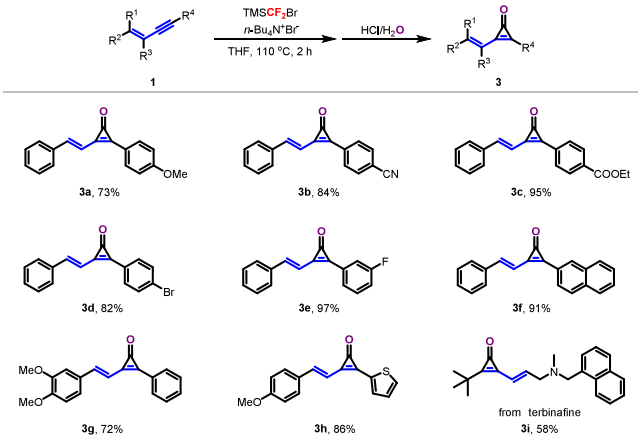
Scheme 2. Substrate Scope for the Synthesis of Alkenyl Difluorocyclopropenes[a]



[a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv), $TMSCF_2Br$ (0.75 mmol, 1.5 equiv), n-$Bu_4N^+Br^-$ (0.015 mmol, 3 mol %), THF (2.0 mL). Isolated yields. [b]**1l** (0.25 mmol, 1.0 equiv), $TMSCF_2Cl$ (0.5 mmol, 2.0 equiv), n-$Bu_4N^+Cl^-$ (0.005 mmol, 2 mol %), toluene (2.0 mL). [c]**2** (1.5 mmol, 3.0 equiv), 4 h.

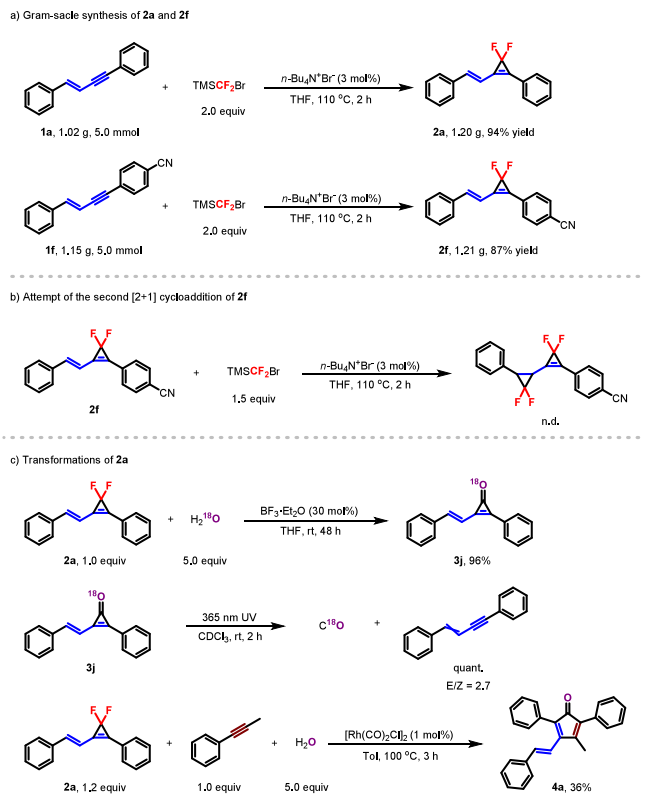
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Scheme 3. Substrate Scope for the One-Pot Synthesis of Alkenyl-Substituted Cyclopropenones[a]



[a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv), $TMSCF_2Br$ (0.75 mmol, 1.5 equiv), n-$Bu_4N^+Br^-$ (0.015 mmol, 3 mol %), THF (2.0 mL). Isolated yields.

Scheme 4. Gram-Scale Synthesis and Synthetic Applications of 2a and 2f



difluorocyclopropene derivatives, which consequently undergo hydrolysis less readily. Furthermore, the cyclopropenone derivative of terbinafine could also be synthesized in good yield using this method (**3i**).

To further demonstrate the utility of this synthetic method, we explored gram-scale synthesis and subsequent transformations of the resulting difluorocyclopropenes. The syntheses of **2a** and **2f** could be readily scaled up to 5.0 mmol. While the yield of **2f** slightly decreased due to losses during recrystallization, efficient multigram preparation was achieved (Scheme 4a). When **2f** was subjected to the standard [2+1] cycloaddition conditions with $TMSCF_2Br$, no product arising from a second cycloaddition at the alkenyl group was observed. This result indicates that the energy barrier for a subsequent [2+1] cycloaddition between the conjugated enyne and difluorocarbene is significantly higher than that of the first one (Scheme 4b).

Furthermore, hydrolysis of **2a** with $H_2{}^{18}O$ catalyzed by $BF_3{\cdot}Et_2O$ (30 mol %) proceeded smoothly to deliver ^{18}O-labeled cyclopropenone **3j** in 96% yield (Scheme 4c). Notably, **3j** quantitatively releases $C^{18}O$ upon irradiation with 365 nm UV light, suggesting its potential as a versatile precursor for the synthesis of diverse ^{18}O-labeled carbonyl compounds. In a distinct transformation, **2a** underwent a [3+2] cycloaddition with 1-phenyl-1-propyne in the presence of catalyst $[Rh(CO)_2Cl]_2$ and water, affording cyclopentadienone **4a** in 36% yield (Scheme 4c).

In summary, a chemoselective [2+1] cycloaddition of difluorocarbene with conjugated enynes has been developed, facilitating the synthesis of diverse alkenyl-substituted difluorocyclopropenes and cyclopropenones. This method represents the first example of achieving chemoselectivity with difluorocarbene between two similarly reactive functional groups. The methodology offers a valuable strategy for the late-stage functionalization of drug molecules and the construction of novel organic synthons.

■ 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.6c00865.

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

Accession Codes

Deposition Number 2505930 contains 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.

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Notes

The authors declare no competing financial interest.

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