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Silver-promoted decarboxylative radical addition/annulation of oxamic acids with *gem*-difluoroolefins: concise access to CF_2-containing 3,4-dihydroquinolin-2-ones†

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Described is a silver-promoted decarboxylative radical addition/annulation of oxamic acids with *gem*-difluoroalkenes. This reaction proceeded under mild reaction conditions with broad functional group compatibility, enabling the convenient synthesis of various structurally diverse CF_2-containing 3,4-dihydroquinolin-2-ones that might find applications in medical chemistry.

Fluorinated compounds usually occupy an important place in the fields of medicinal chemistry, agrochemistry, and functional materials science, as the biological and physicochemical properties of parent molecules change significantly upon the introduction of fluorine atom or fluorinated substructures.[1] As a typical representative of fluorine-containing groups, difluoromethylene functionality (CF_2) has appeared as a versatile and superior structural motif in many medicinal agents (Fig. 1). The CF_2 group can not only serve as a chemically and metabolically inert bioisosteres for hydroxy, thiol, and carbonyl units, but also affect electronic and chemical properties of its neighbouring group.[2] Thus, exploration of innovative synthetic methods for the introduction of this moiety into target molecules is of great interest, and substantial research efforts have been devoted to its preparation.[3]

3,4-Dihydroquinolin-2-one ring system is an important heterocyclic skeleton and often occurs in biologically active natural products and pharmacologically relevant therapeutic agents.[4] Representative examples include partial dopamine agonist aripiprazole (**I**),[4a] insecticidal yaequinolone E (**II**),[4b] spirocyclic acetylcholinesterase inhibitor trigolutesin A (**III**),[4c] and HIV-1 reverse transcriptase inhibitor (**IV**) (Fig. 2).[4d] In this context, various synthetic approaches toward the construction of this intriguing skeleton have been documented.[5] However, only limited protocols are available for the incorporation of a fluorine-containing unit into this skeleton,[6] such as electrophilic fluorination of 3,4-dihydroquinolin-2-one derivatives with NFSI,[6a] and the addition of molecular fluorine to heterocyclic enone systems.[6b] Another method involves a two-step procedure consisting of S_N2 reaction of diethyl fluoromalonate with *ortho*-nitrobenzyl bromide derivatives followed by one-pot reduction/lactamization.[6c] There is therefore a great demand to develop general and practical methods for the assembly of this scaffold with the concurrent incorporation of a CF_2-containing group from readily available reagents.

Radical-triggered cascade annulation is a well-established powerful methodology for rapid assembly of various carbocyclic and heterocyclic frameworks in an economically favourable way.[7,8] It should be noted that this methodology has also demonstrated its synthetic utility in the construction of CF_2-containing ring systems.[8] In 2015, Zhu and co-workers pre-

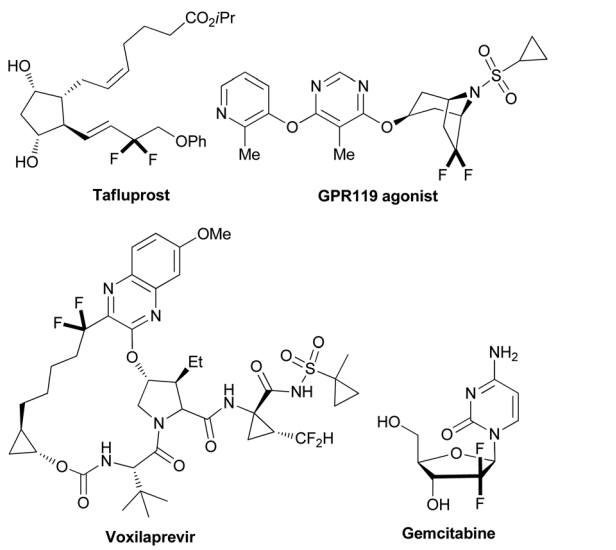

Fig. 1 Examples of bioactive compounds bearing a CF_2 moiety.

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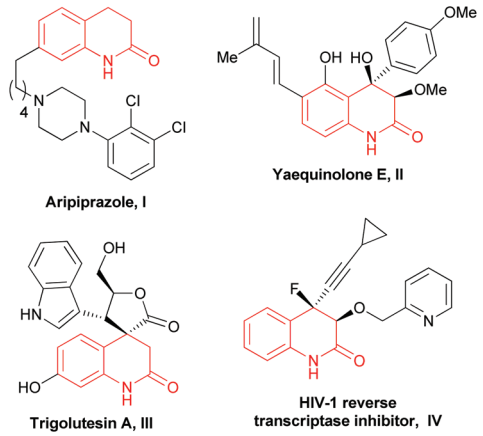
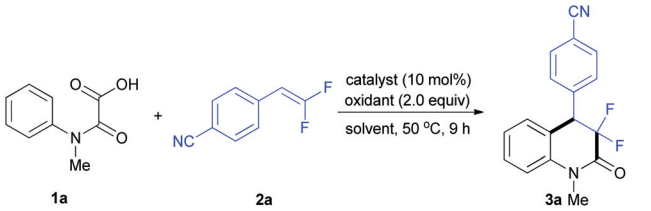


Fig. 2 Examples of biologically important molecules containing 3,4-dihydroquinolin-2-one motifs.

sented a visible light-mediated tandem radical cyclization of enol lactone with difluoroacylarenes to produce difluoroalkylated heterocyclic skeletons.[8a] A recent report on a novel silver-catalyzed intramolecular decarboxylative cyclization of 5-aryl-2,2-difluoropentanoic acids was described by Zhu's group.[8b] Very recently, Wang's group reported a novel and efficient protocol for desulfonylation-initiated distal alkenyl migration and its application to the elusive alkenylation of unactivated alkenes.[8c] Owing to their distinct electronic properties and reactivity, *gem*-difluoroalkenes have recently emerged as versatile synthetic intermediates for a variety of C–F functionalization reactions.[9] On the other hand, examples employing these building blocks for difluoroalkylation are poorly documented so far.[10] Herein, we describe a new silver-promoted decarboxylative radical addition/annulation of oxamic acids with *gem*-difluoroolefins under mild conditions. This protocol features the employment of *gem*-difluoroolefins as the CF_2 source, thus providing a wide range of CF_2-containing 3,4-dihydroquinolin-2-ones in moderate to good yields.

Our initial efforts focused on the silver-promoted decarboxylative cascade cyclization of *N*-methyl-*N*-phenyloxamic acid **1a** with *gem*-difluoroalkene **2a** (Table 1). To our delight, the reaction proceeded smoothly to furnish the desired product **3a** in 66% yield when $AgNO_3$ (10 mol%) was used as a catalyst in the presence of $K_2S_2O_8$ (2.0 equiv.) in CH_3CN/H_2O (1 : 1) at 50 °C under an argon atmosphere (entry 1). The structure of **3a** was unambiguously confirmed by spectroscopic data and X-ray diffraction analysis of a single crystal.[11] A subsequent decrease or increase of the oxidant amount reduced the yield slightly (entries 2 and 3). Replacing $K_2S_2O_8$ with $(NH_4)_2S_2O_8$ or $Na_2S_2O_8$ proved not to be beneficial (entries 4 and 5), and no reaction occurred with DTBP (di-*tert*-butyl peroxide) as the oxidant (entry 6). Further experiments indicated that other silver catalysts, such as AgOTf, Ag_2SO_4, and AgOAc, were inferior to $AgNO_3$ (entries 7–9). With the confirmation of the optimal loading of $AgNO_3$ as 10 mol% (entries 10 and 11), several other solvent mixtures were then surveyed. The results revealed that a mixture of acetone/H_2O was superior to other

Table 1 Optimization of the reaction conditions[a]



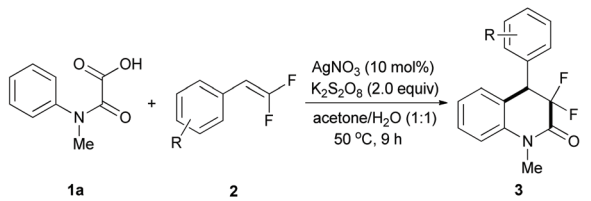
Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	$AgNO_3$	$K_2S_2O_8$	$CH_3CN : H_2O$	66
2[c]	$AgNO_3$	$K_2S_2O_8$	$CH_3CN : H_2O$	52
3[d]	$AgNO_3$	$K_2S_2O_8$	$CH_3CN : H_2O$	57
4	$AgNO_3$	$(NH_4)_2S_2O_8$	$CH_3CN : H_2O$	59
5	$AgNO_3$	$Na_2S_2O_8$	$CH_3CN : H_2O$	47
6	$AgNO_3$	DTPB	$CH_3CN : H_2O$	0
7	AgOTf	$K_2S_2O_8$	$CH_3CN : H_2O$	32
8	Ag_2SO_4	$K_2S_2O_8$	$CH_3CN : H_2O$	18
9	AgOAc	$K_2S_2O_8$	$CH_3CN : H_2O$	0
10[e]	$AgNO_3$	$K_2S_2O_8$	$CH_3CN : H_2O$	13
11[f]	$AgNO_3$	$K_2S_2O_8$	$CH_3CN : H_2O$	56
12	$AgNO_3$	$K_2S_2O_8$	1,4-Dioxane : H_2O	34
13	$AgNO_3$	$K_2S_2O_8$	DMF : H_2O	38
14	$AgNO_3$	$K_2S_2O_8$	DMSO : H_2O	27
15	$AgNO_3$	$K_2S_2O_8$	EtOH : H_2O	35
16	**$AgNO_3$**	**$K_2S_2O_8$**	**Acetone : H_2O**	**79**
17[g]	$AgNO_3$	$K_2S_2O_8$	Acetone : H_2O	68
18[h]	$AgNO_3$	$K_2S_2O_8$	Acetone : H_2O	0
19	—	$K_2S_2O_8$	Acetone : H_2O	0
20	$AgNO_3$	—	Acetone : H_2O	0

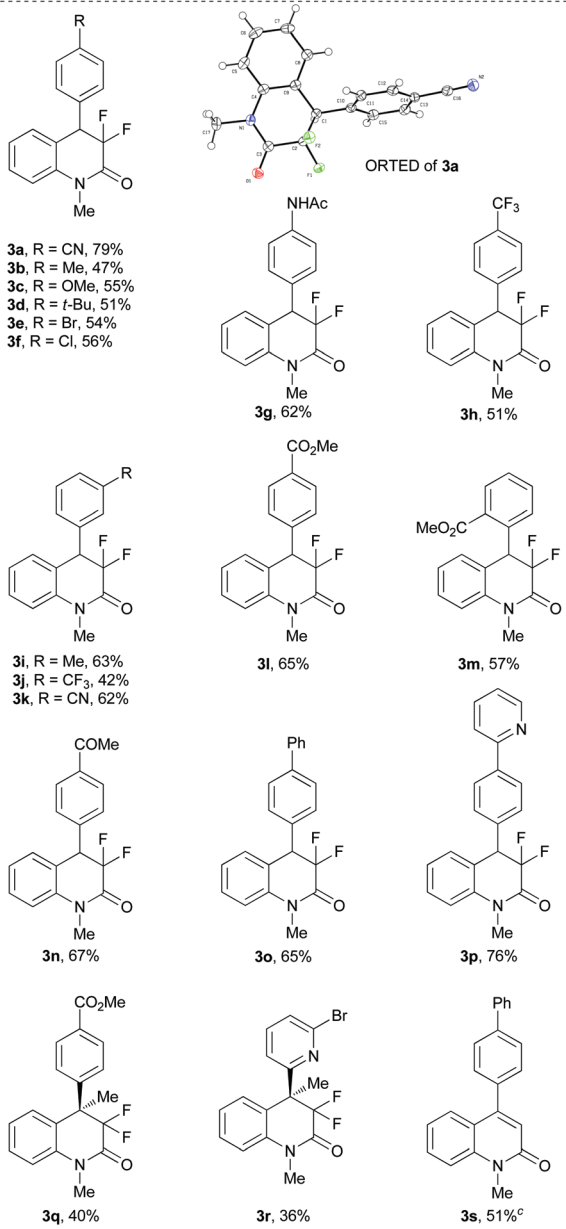
[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.50 mmol), catalyst (10 mol%), oxidant (1.0 mmol), solvent (v/v = 1 : 1, 3 mL), argon, 50 °C, and 9 h. [b] Yield of isolated product. [c] $K_2S_2O_8$ (0.75 mmol). [d] $K_2S_2O_8$ (1.50 mmol). [e] $AgNO_3$ (5 mol%). [f] $AgNO_3$ (15 mol%). [g] Reaction at 70 °C. [h] Reaction at 30 °C.

solvent mixtures, providing the desired product **3a** in 79% yield (entries 12–16). In addition, the yield of **3a** was slightly decreased at higher temperature (entry 17). However, the reaction failed to proceed at lower temperature (entry 18). Finally, the reaction was unfruitful in the absence of silver catalyst or persulfate salt (entries 19 and 20).

Having developed the optimum reaction conditions, we turned our attention to exploring the scope of this cascade reaction with respect to various *gem*-difluoroolefins (Table 2). Substrates bearing electron-donating (such as Me, OMe, *t*-Bu, and AcNH) or electron-withdrawing substituents (such as CN, Br, Cl, CF_3, CO_2Me, and CH_3CO) at the *para*-position of the benzene ring were all accommodated in this cascade process, providing the corresponding products in moderate to good yields (**3a–h**, **3l**, **3n–o**). As expected, the substituents at the *meta*- or *ortho*-position of the benzene ring also worked well and moderate yields of the corresponding products were obtained (**3i–k**, **3m**). Among them, substrates with electron-withdrawing substituents at the *para*-position of the benzene ring furnished higher yields than those at the *meta*-positions (**3a** *vs.* **3k**, **3h** *vs.* **3j**). Substitution of the *ortho*-position with an ester group reduced the yield slightly (**3l** *vs.* **3m**), which might be caused by steric hindrance effect of the *ortho*-substituent. Interestingly, 2-(4-(2,2-difluorovinyl)phenyl)pyridine **2p** was

Table 2 Substrate scope of gem-difluoroolefins[a,b]



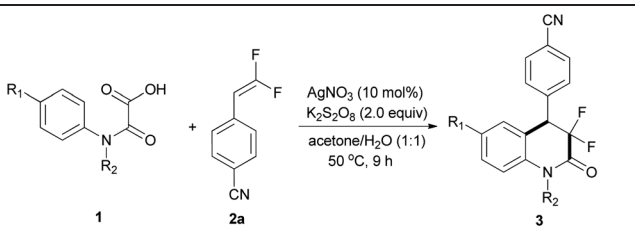


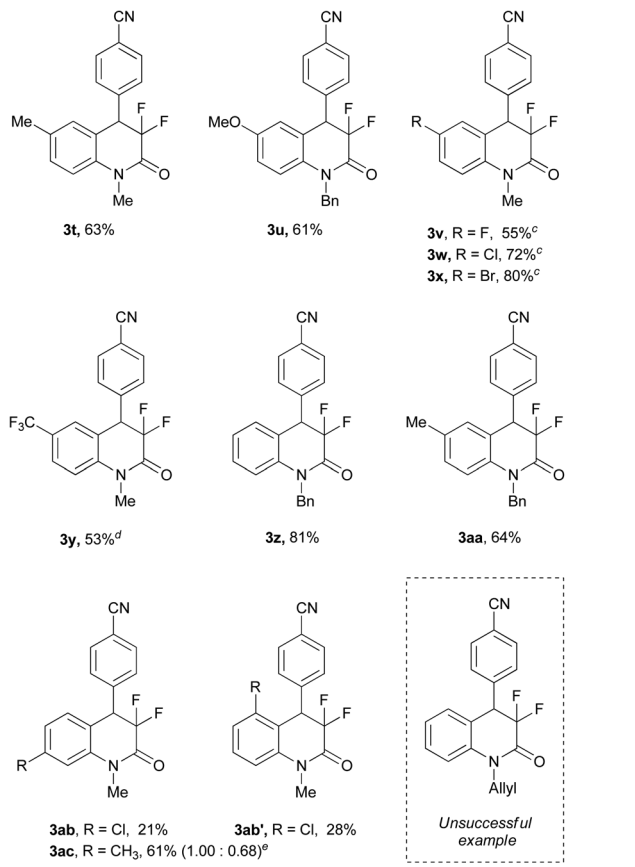
[a] Reaction conditions: **1a** (0.75 mmol), **2** (0.50 mmol), $AgNO_3$ (10 mol%), $K_2S_2O_8$ (1.0 mmol), acetone (1.5 mL), H_2O (1.5 mL), 50 °C, under an argon atmosphere for 9 h. [b] Yield of isolated product. [c] Monofluoro-substituted 4-(1-fluorovinyl)-1,1′-biphenyl **2s** was used as the substrate.

also amenable to this reaction, delivering the desired product **3p** in good yield (76%). With respect to fully substituted *gem*-difluoralkenes, the reactions proceeded smoothly to provide the corresponding products in moderate yields (**3q–r**). When 4-(1-fluorovinyl)-1,1′-biphenyl **2s** was used as a cyclization partner, a tandem annulation followed by elimination of a HF occurred to afford quinolin-2-one **3s** in 51% yield. However, *gem*-difluoroalkenes derived from aliphatic aldehydes proved incompetent in this reaction (see the ESI† for details).

To further examine the applicability of the protocol, we screened different oxamic acids **1** in reactions with *gem*-difluoroolefin **2a** (Table 3). A series of *para*-substituted oxamic acids bearing electron-donating or electron-withdrawing groups proved to be efficient partners in these transform-

Table 3 Substrate scope of oxamic acids[a,b]



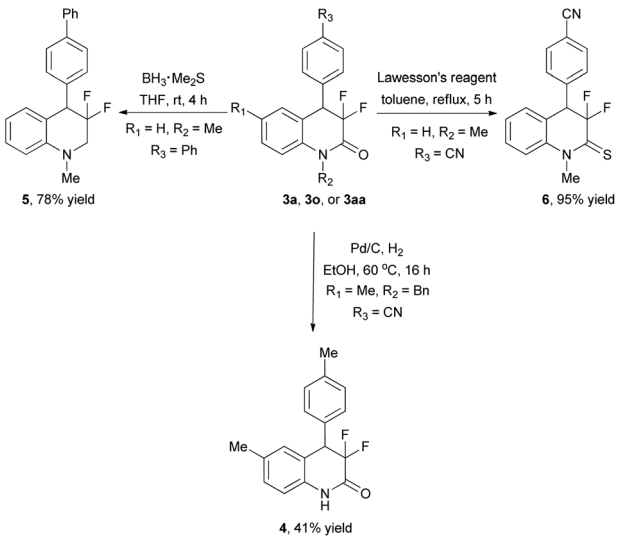


[a] Reaction conditions: **1** (0.75 mmol), **2a** (0.50 mmol), $AgNO_3$ (10 mol%), $K_2S_2O_8$ (1.0 mmol), acetone (1.5 mL), H_2O (1.5 mL), 50 °C, under an argon atmosphere for 9 h. [b] Yield of isolated product. [c] Reaction at 60 °C. [d] Reaction at 70 °C. [e] A mixture of regioisomers (4-(3,3-difluoro-1,7-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)benzonitrile and 4-(3,3-difluoro-1,5-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)benzonitrile) in a ratio of 1.00 : 0.68.

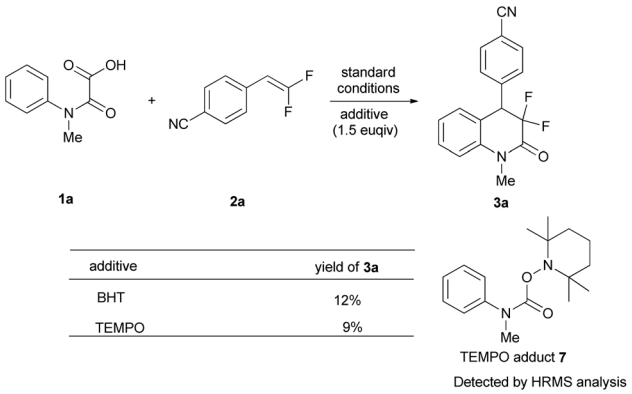
ations, affording the corresponding products in moderate to good yields (**3t–y**). The compatibility of halogen substituents provides the potential for further derivatization through C–C or C–heteroatom bond-forming reactions (**3v–x**). Furthermore, *N*-benzyl substituted oxamic acids were also applicable substrates in the reaction, with corresponding products obtained in good yields (**3u**, **3z–aa**). And a mixture of two regioisomers was observed with respect to *meta*-substituted oxamic acids with poor regioselectivity, which might attributed to relatively less steric hindrance (**3ab–ac**). Unfortunately, the reaction using *N*-allyl substituted oxamic acid as the partner failed to give the desired cyclization product.

Further synthetic transformations of the products were also explored (Scheme 1). The deprotection of the benzylamide product **3aa**, accompanied by reduction of the cyano group,[12] provided the corresponding free secondary amide **4** in 41% yield. The reduction of **3o** with $BH_3{\cdot}Me_2S$ gave the tetrahydroquinoline core **5** in 78% yield. Furthermore, the thiolactam **6** could be obtained in excellent yield upon by the treatment of **3a** with Lawesson's reagent.

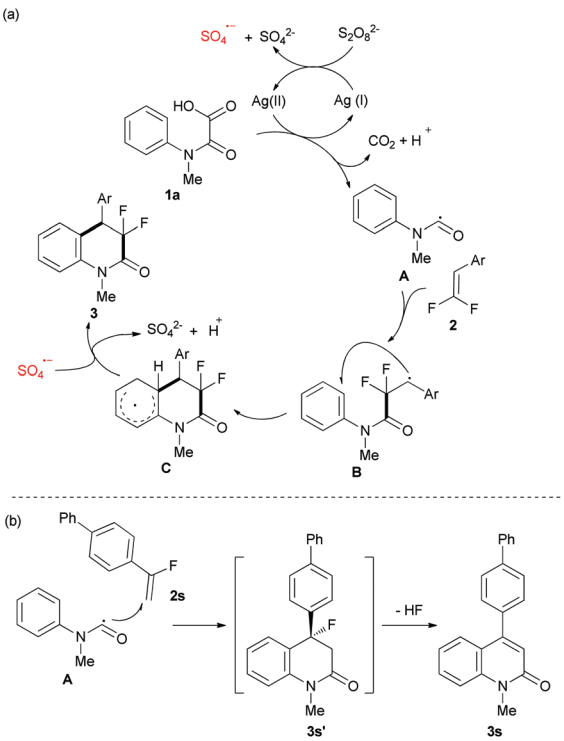
As shown in Scheme 2, a significantly reduced yield of **3a** was observed when stoichiometric amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the catalytic system. Importantly, a carbamoyl-captured TEMPO **7** was detected by HRMS analysis (for the details, see the ESI†). These findings suggest that the reaction might proceed through a radical pathway. On the basis of the present results and previous works,[5c,13] a plausible reaction mechanism is illustrated in Scheme 2. Initially, an oxidation of Ag(I) by persulfate anion occurs to generate the Ag(II) species, which triggers a single electron-transfer process (SET) of **1a** to deliver a carbamoyl radical **A** along with the regeneration of the Ag(I) catalyst and release of CO_2. Subsequent intermolecular radical addition of **A** to *gem*-difluoroalkene **2** affords a benzyl radical **B**, which then undergoes an intramolecular 6-



Scheme 1 Derivatization of the products.



Scheme 2 Control experiments.



Scheme 3 Proposed reaction mechanism.

endo-trig cyclization to produce the radical **C**. Finally, a dehydroaromatization occurs *via* an oxidative single electron-transfer process to furnish the desired product **3**. On the other hand, for the reaction of **2s**, the addition of species **A** to **2s** followed by intramolecular cyclization/dehydroaromatization provides the intermediate **2s'**. As a consequence of elimination of a HF,[14] the final product **3s** is formed (Scheme 3).

Conclusions

In summary, we have successfully developed a novel silver-promoted decarboxylative radical addition/annulation of oxamic

acids with *gem*-difluoroolefins, thereby enabling efficient access to various CF_2-containing 3,4-dihydroquinolin-2-ones under mild reaction conditions. This reaction presents a new strategy for introduction of the CF_2 moiety to organic molecules through a radical cyclization process of *gem*-difluoroolefins. Further application of the protocol in the preparation of a variety of novel and potentially useful CF_2-containing compounds is underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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