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镍催化炔烃的立体选择性芳基-二氟烷基化反应

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摘要 报道了一种镍催化的炔烃的芳基-二氟烷基化反应. 从炔烃、溴二氟乙酸乙酯和芳基硼酸这些简单起始原料出发, 在镍络合物的催化下, 以高度立体选择性控制的方式得到一系列三取代含氟烯烃. 该方法具有催化剂成本低、反应条件温和、官能团兼容性好等优点.

关键词 镍催化; 炔烃; 立体选择性; 芳基-二氟烷基化; 氟化学

Nickel-Catalyzed Stereoselective Aryl-Difluoroalkylation of Alkynes

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Abstract A nickel-catalyzed aryl-difluoroalkylation of alkynes is developed. A series of trisubstituted fluoroalkenes can be obtained in a highly stereoselective manner by mixing of simple starting materials alkynes, ethyl bromodifluoroacetate, and arylboronic acids in the presence of nickel catalyst. This method features low-cost catalyst, mild reaction conditions, and excellent functional group compatibility.

Keywords nickel catalysis; alkynes; stereoselective; aryl-difluoroalkylation; fluorine chemistry

1 Introduction

Fluorine atom features unique chemistry properties such as the strongest electronegativity and the similar atomic radius to hydrogen atom.[1] The introduction of fluorine atoms into a compound can change the distribution of electron density inside the molecule, as well as increases the fat-solubility and membrane permeability of the compound.[1b,2] Therefore, many fluorine-containing pharmaceuticals and pesticides have the characteristics of low dosage, low toxicity, high efficacy, and strong metabolic capacity. According to statistics, more than 20% of pharmaceuticals and agricultural chemicals on the market currently contain one or more fluorine atoms.[3] Because of the excellent, valuable and unique properties of fluorinated drugs, the development of an efficient and inexpensive synthetic method has become a challenge in the field of organic chemistry. Among fluorine-containing groups, CF_2 groups were regarded as an isosteres of oxygen atom.[4] The CF_2CO_2Et group has attracted much attention due to its easy availability and easy conversion into other functional groups. The introduction of CF_2CO_2Et into organic molecules using transition metal catalysts or visible light photocatalysts has been well developed. In 2014, Zhang and his coworkers[5] introduced difluoroalkyl groups into arylboronic acids using palladium and nickel catalysts, respectively. In 2017 and beyond, our group[6] achieved the difluoroalkylation of various substituted alkynes and alkenes, respectively, using copper catalysts.

As an important synthon, alkynes play a vital role in the field of organic synthesis. The difunctionalization of alkynes has attracted extensive attention from chemists, especially the introduction of fluorine atoms into alkynes.[7] Recently, the fluoroalkylation of alkynes using fluoroalkyl halides has been developed as an attractive approach to generate C—R_f bond and C—X bond, which could be further functionalized, thus leading to difunctionalization of alkynes (Scheme 1a).[8] For example, Hu's group[8b] developed an iron-catalyzed reaction of alkynes with perfluoroalkyl iodides to give *β*-fluoroalkyl vinyl iodides, which were subsequently combined with Grignard reagents, aryl/ alkenyl boronic acids, terminal alkynes, or thiols to afford the fluorine-containing trisubstituted alkenes. In addition to the two-step coupling synthesis of trisubstituted alkenes, significant progress has been made in the one-pot synthesis of trisubstituted or tetrasubstituted fluorinated aromatic alkenes (Scheme 1b). In 2015, Nevado and his coworkers[9] reported a Pd-catalyzed three component reaction in which trisubstituted perfluoroalkylated alkenes were generated by the addition of perfluoroalkyl halides

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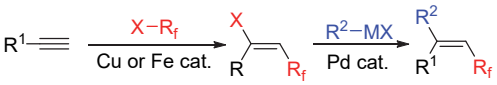
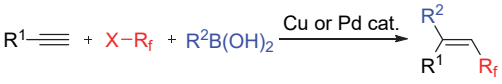
and arylboronic acids to alkynes. Shortly after, Liang,[10] Chaladaj,[11] and Wu[12] *et al.* successfully described the similar aryl-difluoro-alkylation of alkynes in the presence of copper or palladium catalyst. Herein, we disclose a Ni-catalyzed three-component reaction for the aryl-difluoroalkylation of alkynes in a highly stereoselective manner (Scheme 1c).

(a) Stepwise difunctionalization of alkynes.

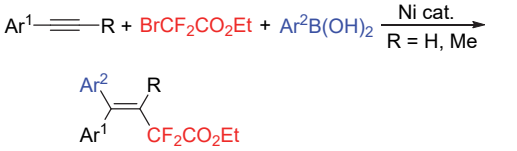


M = Mg, B, Zn, Sn, Si, *etc.*

(b) One-pot difunctionalization of alkynes.



(c) This work: Ni-catalyzed aryl-difluoroalkylation of alkynes.



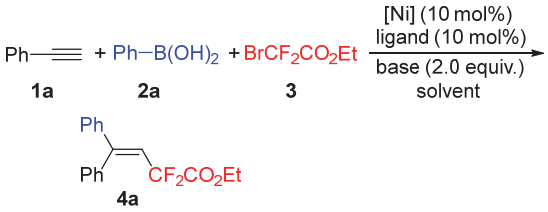
Scheme 1 Strategies for the synthesis of fluorine-containing trisubstituted alkenes

2 Results and discussion

Initially, phenylacetylene (**1a**), phenylboronic acid (**2a**), and ethyl bromodifluoroacetate (**3**) were used as template substrates to react at 100 ℃ under argon atmosphere with $NiCl_2$(dppe) as a catalyst, terpyridine (tpy) as a ligand, K_3PO_4 as base, and *N*,*N*-dimethylformamide (DMF) as solvent. However, only trace amount of ethyl 2,2-difluoro-4,4-diphenylbut-3-enoate (**4a**) was detected (Table 1, Entry 1). When $NiCl_2(PPh_3)_2$ and $NiCl_2(py)_4$ were used as a catalyst, the yields were still very low (Table 1, Entries 2 and 3). Subsequently, different bases were screened and it is gratifying that the reaction could proceed successfully in the presence of K_2CO_3 as a base in DMF, leading to the desired product **4a** in 51% yield (Table 1, Entry 5). The replacement of tpy by other ligands such as 2,2'-bipyridine (bpy), 8-aminoquinoline, and 1,10-phenanthroline (1,10-phen) did not increase the yield of product **4a** (Table 1, Entries 6～8). Finally, other solvents were screened (Table 1, Entries 9～12). When dichloroethane (DCE) was used as solvent, the yield of **4a** could be significantly improved to 90% (Table 1, Entry 9). Eventually, the conditions in Entry 9 were chosen as the optimized conditions, which involved $NiCl_2(py)_4$ as catalyst in the presence of K_2CO_3 in DCE at 100 ℃ under argon.

With the optimized conditions in hand, the scope of substrates was explored. Firstly, the scope of alkynes was investigated as depicted in Table 2. In general, the phenylacetylenes containing electron-rich groups at the *para*-position were well tolerated and afforded the products (**4a** and **4b**) in moderate yields. The difluoroalkyl group is in the

Table 1 Optimization of reaction conditions[a]



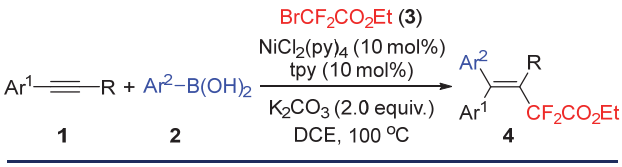
Entry	[Ni]	Ligand	Base	Solvent	Yield[b]/%
1	$NiCl_2$(dppe)	tpy	K_3PO_4	DMF	3
2	$NiBr_2(PPh_3)_2$	tpy	K_3PO_4	DMF	2
3	$NiCl_2(py)_4$	tpy	K_3PO_4	DMF	15
4	$NiCl_2(py)_4$	tpy	Na_2CO_3	DMF	24
5	$NiCl_2(py)_4$	tpy	K_2CO_3	DMF	51
6	$NiCl_2(py)_4$	bpy	K_2CO_3	DMF	8
7	$NiCl_2(py)_4$	1,10-phen	K_2CO_3	DMF	3
8	$NiCl_2(py)_4$	xantphos	K_2CO_3	DMF	7
9	**$NiCl_2(py)_4$**	**tpy**	**K_2CO_3**	**DCE**	**90 (72)**
10	$NiCl_2(py)_4$	tpy	K_2CO_3	THF	52
11	$NiCl_2(py)_4$	tpy	K_2CO_3	MeCN	13
12	$NiCl_2(py)_4$	tpy	K_2CO_3	Tol	3

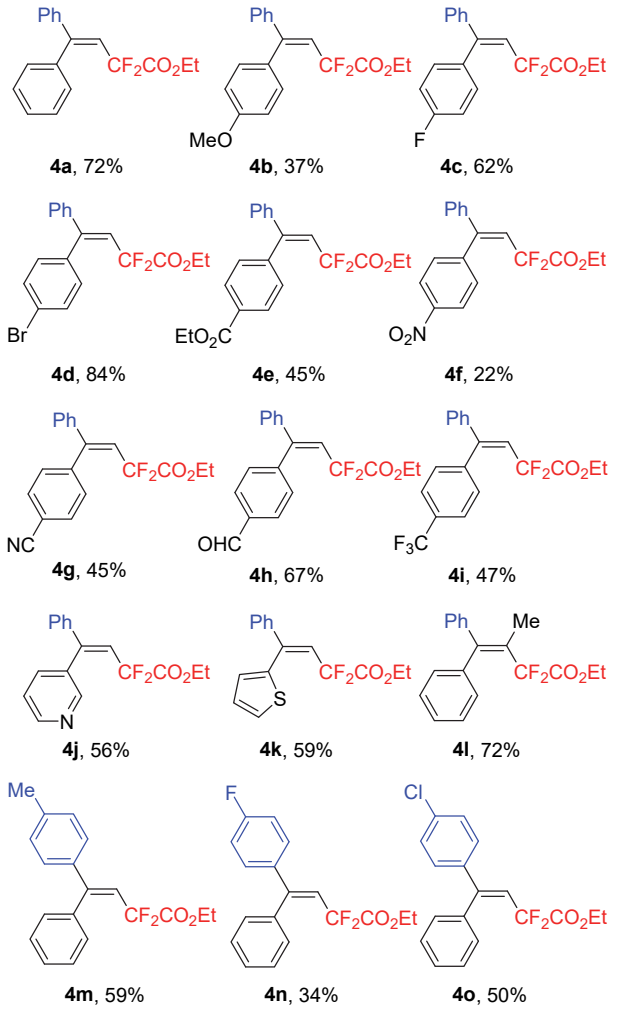
[a] Reaction conditions: Unless otherwise noted, all reactions were performed with **1a** (0.20 mmol), **2a** (0.3 mmol, 1.5 equiv.), **3a** (0.3 mmol, 1.5 equiv.), catalyst (0.10 equiv.), ligands (0.10 equiv.), base (0.40 mmol, 2.0 equiv.), in solvent (1.0 mL) at 100 ℃ under Ar for 12 h; [b] Yields were determined by GC with mesitylene as an internal standard. The value in parentheses is isolated yield.

trans-position with the phenyl group from phenylboronic acid. In addition, aryl alkynes containing halogens on the phenyl ring were also competent substrates, leading to the expected products **4c** and **4d** in good yields (62% and 84%), respectively. On the other hand, other electron-withdrawing groups on the phenyl ring, such as ester (**4e**), cyano (**4g**), and trifluoromethyl (**4i**), have little effect on the reaction yields, except the nitro group leading to a low yield. Besides, aldehydes can be tolerated under the standard conditions, resulting in the target compound **4h** with 67% yield. For heteroaromatic alkyne substrates, such as 3-ethynylpyridine and 2-ethynylthiophene, the corresponding aryl-difluoroalkylation products can be obtained in moderate or good yields (**4j** and **4k**). It is noteworthy that besides terminal alkynes, internal alkynes also afforded the tetrasubstituted alkenes in good yield (**4l**). Then the scope of arylboronic acids was also investigated. Electronic properties of substituents on the benzene ring of arylboronic acids have little effect on this transformation. Electron-donating groups, such as methyl, gave the target product with 59% yield (**4m**). In addition, it was found that arylboronic acids with halogen atom could undergo the desired transformation smoothly to give the corresponding products in moderate yields (**4n** and **4o**).

In order to clarify the mechanism, a control experiment was carried out. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.5 equiv.) was added under the standard reaction conditions, GC analysis of reaction aliquots showed that no product **4a** was obtained and TEMPO-

Table 2 Scope of alkynols[a]

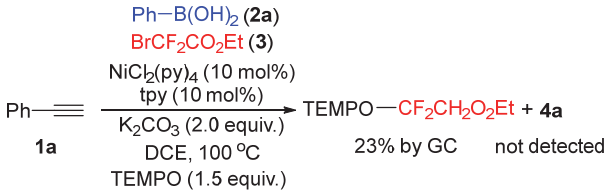




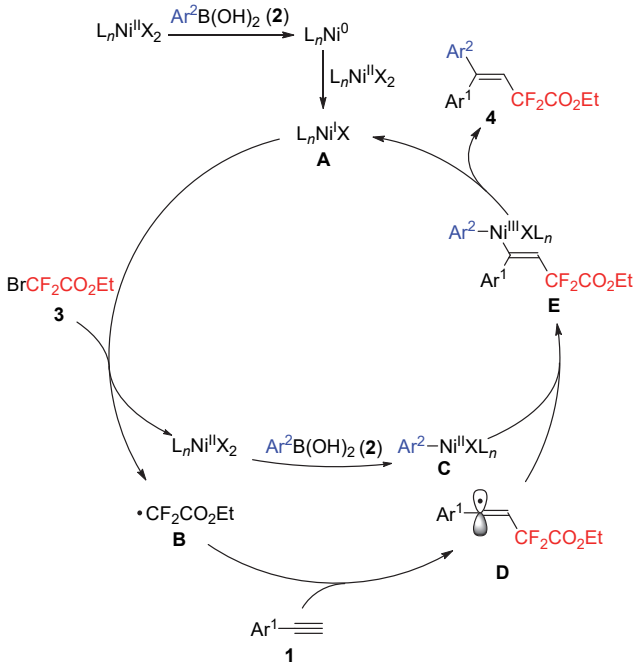
[a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv.), **2** (1.5 mmol, 1.5 equiv.), **3** (1.5 mmol, 1.5 equiv.), $NiCl_2(py)_4$ (10 mol%), tpy (10 mol%), K_2CO_3 (2.0 mmol, 2.0 equiv.), DCE (5.0 mL), under Ar at 100 ℃ for 12 h.

CF_2COOEt adduct was detected with 23% yield (Scheme 2). Thus, the reaction was inhibited completely by TEMPO and a radical pathway might be involved in the reaction.

Based on the above experiments and relevant reported results,[9,10b] a plausible mechanism was proposed as shown in Scheme 3. The catalytic cycle began with the partial reduction of L_nNiCl_2 by phenyl boronic acid, affording nickel(0) species, which then react with remaining Ni(II) to result Ni(I) intermediate **A**. Then, the reaction of ethyl difluorobromoacetate with **A** led to difluoroalkyl radical **B** and Ni(II) species, which further transmetallate with aryl boronic acid to afford aryl nickel **C**. The addition of difluoroalkyl radical **B** on the alkyne generated the vinyl radical intermediate **D**. Subsequently, the radical intermediate **D** could capture the key nickel species **C** to afford



Scheme 2 Probe of the reaction mechanism by trapping the radical intermediates



Scheme 3 Proposed mechanism

Ni(III) aryl intermediate **E**, reductive elimination of which resulted the product **4** and regenerated Ni(I). The high stereoselectivity can be attributed to the low energetic requirement for the rapidly *E*/*Z* interconversion of vinyl radical and the low steric requirement for the *Z*-vinyl radical to recombine with the external aryl-Ni(III) radical from the opposite side of the difluoroalkyl group.[13]

3 Conclusions

In conclusion, a nickel catalyzed one-pot aryl-difluoroalkylation of alkynes with ethyl difluorobromoacetate and arylboronic acids was reported. Through this protocol, two new C—C bonds were constructed with high stereoselectivity. A variety of terminal alkynes and arylboronic acids were tolerated in this reaction, making it a general method for the synthesis of such fluorine-containing trisubstituted or tetrasubstituted alkenes. Preliminary mechanistic investigations indicated that a possible nickel initiated radical addition of alkyne was involved in this transformation. Further investigations on reaction mechanism and synthetic application of this transformation are currently underway in our laboratory.

4 Experimental section

4.1 General information

All experiments were carried out under argon atmosphere. DMF, tetrahydrofuran (THF), DCE, and acetonitrile were dried and distilled by the standard methods. Other commercially available reagents were purchased and used without further purification, unless otherwise stated. Commercially unavailable alkynes were prepared according to the known procedure of Sonogashira coupling.[14] Flash chromatographic separations were carried out on 200～300 mesh silica gel. Reactions were monitored by TLC and GC analysis of reaction aliquots. GC analysis was performed on an Agilent 7890 gas chromatography using a HP-5 capillary column (30 m×0.32 mm, 0.5 μm film) with appropriate hydrocarbons as internal standards. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE III spectrometer and calibrated using residual undeuterated solvent ($CDCl_3$ at δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR). High resolution mass spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI) through a Bruker Daltonics-micrOTOF-QII.

4.2 General procedure for difunctionalization of alkynes.

To a 25 mL of sealed tube was added **1** (1.0 mmol, 1.0 equiv.), **2** (1.5 mmol, 1.5 equiv.), $NiCl_2(py)_4$ (0.1 mmol, 10 mol%), tpy (0.1 mmol, 10 mol%) and K_2CO_3 (2.0 mmol, 2.0 equiv.) under argon atmosphere. DCE (5 mL) and **3** (1.5 mmol, 1.5 equiv.) were added subsequently. The reaction was stirred at 100 ℃ for 12 h. The reaction mixture was diluted with EtOAc and filtered with a pad of celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography to give the target molecule.

Ethyl 2,2-difluoro-4,4-diphenylbut-3-enoate (**4a**):[9b] Light yellow oil (217.1 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36～7.21 (m, 10H), 6.27 (t, J=11.7 Hz, 1H), 3.90 (q, J=6.6 Hz, 2H), 1.16 (t, J=6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.5 (t, J=33.9 Hz), 151.1 (t, J=9.4 Hz), 140.6, 137.2, 129.9, 129.2, 128.7, 128.5, 128.1, 128.0, 119.6 (t, J=28.4 Hz), 112.7 (t, J=245.0 Hz), 62.8, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −90.9 (d, J=11.8 Hz).

(*E*)-Ethyl-2,2-difluoro-4-(4-methoxyphenyl)-4-phenylbut-3-enoate (**4b**):[9b] Light yellow oil (122.3 mg, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32～7.24 (m, 5H), 7.13 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.7 Hz, 2H), 6.20 (t, J=11.7 Hz, 1H), 3.92 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 1.16 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.7 (t, J=33.9 Hz), 160.0, 151.0 (t, J=9.6 Hz), 141.1, 131.5, 129.5, 129.2, 128. 5, 128.2, 119.2 (t, J=28.4 Hz), 113.5, 112.8 (t, J=244.3 Hz), 62.9, 55.4, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −90.2 (d, J=11.8 Hz).

(*E*)-Ethyl-2,2-difluoro-4-(4-fluorophenyl)-4-phenylbut-3-enoate (**4c**):[8] Light yellow oil (198.2 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28～7.21 (m, 3H), 7.18～7.14 (m, 2H), 7.14～7.09 (m, 2H), 7.01～6.94 (m, 2H), 6.18 (t, J=12.0 Hz, 1H), 3.91 (q, J=7.2 Hz, 2H), 1.12 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.6 (t, J=33.9 Hz), 163.0 (d, J=248.5 Hz), 150.2 (t, J=9.1 Hz), 140.5, 133.2 (d, J=3.5 Hz), 131.8 (d, J=8.3 Hz), 129.4, 128.6, 128.0, 119.9 (t, J=28.0 Hz), 115.2 (d, J=21.2 Hz), 112.6 (t, J=245.7 Hz), 63.0, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −91.4 (d, J=11.8 Hz, 2F), −112.5～−112.6 (m, 1F).

(*E*)-Ethyl-4-(4-bromophenyl)-2,2-difluoro-4-phenylbut-3-enoate (**4d**):[9b] Light yellow oil (319.5 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51～7.49 (m, 2H), 7.35～7.30 (m, 3H), 7.24～7.22 (m, 2H), 7.08 (d, J=8.3 Hz, 2H), 6.27 (t, J=12.0 Hz, 1H), 4.01 (q, J=7.1 Hz, 2H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.6 (t, J=34.0 Hz), 150.0 (t, J=8.8 Hz), 140.1, 136.2, 131.6, 131.3, 129.4, 128.6, 128.0, 123.0, 119.8 (t, J=27.8 Hz), 112.5 (t, J=246.4 Hz), 63.1, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −91.8 (d, J=12.2 Hz, 2F).

(*E*)-Ethyl-4-(4-ethoxy-3,3-difluoro-4-*oxo*-1-phenylbut-1-en-1-yl) benzoate (**4e**): Light yellow oil (168.0 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J=8.0 Hz, 2H), 7.24～7.19 (m, 5H), 7.14～7.12 (m, 2H), 6.22 (t, J=12.2 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 3.90 (q, J=7.1 Hz, 2H), 1.31 (t, J=7.1 Hz, 3H), 1.11 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.2, 163.5 (t, J=34.0 Hz), 150.1 (t, J=8.7 Hz), 141.8, 139.8, 130.6, 129.8, 129.5, 129.3, 128.6, 127.9, 119. 9 (t, J=27.8 Hz), 112.4 (t, J=246.6 Hz), 63.1, 61.2, 14.4, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −90.6 (d, J=11.3 Hz, 2F); HRMS (ESI) calcd for $C_{21}H_{20}F_2NaO_4^+$ [M+Na$^+$] 397.1222, found 397.1229.

(*E*)-Ethyl-2,2-difluoro-4-(4-nitrophenyl)-4-phenylbut-3-enoate (**4f**): Light yellow oil (76.4 mg, 22% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35～8.08 (m, 2H), 7.49～7.31 (m, 5H), 7.23～7.12 (m, 2H), 6.34 (t, J=12.9 Hz, 1H), 4.14 (q, J=7.2 Hz, 2H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.2 (t, J=33.8 Hz), 144.4 (t, J=10.1 Hz), 140.7, 138.2, 131.3, 129.6, 128.9, 128.5, 128.3, 126.9, 121.3 (t, J=29.2 Hz), 112.5 (t, J=243.8 Hz), 63.0, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −94.0 (d, J=12.9 Hz); HRMS (ESI) calcd for $C_{18}H_{15}F_2NNaO_4^+$ [M+Na$^+$] 370.0861, found 370.0860.

(*E*)-Ethyl-4-(4-cyanophenyl)-2,2-difluoro-4-phenylbut-3-enoate (**4g**): Light yellow oil (147.1 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68～7.66 (m, 2H), 7.38～7.32 (m, 5H), 7.21～7.19 (m, 2H), 6.32 (t, J=12.8 Hz, 1H), 4.11 (q, J=7.2 Hz, 2H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.4 (t, J=33.9 Hz), 149.3 (t, J=7.8 Hz), 142.3, 139.4, 131.9, 130.5 (t, J=2.4 Hz), 129.7, 128.8, 127.8, 120.2 (t, J=26.8 Hz), 118.5, 112.5, 112.2 (t, J=248.0 Hz), 63.2, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −92.8 (s, J=11.3 Hz, 2F); HRMS (ESI) calcd for $C_{19}H_{15}F_2NNaO_2^+$ [M + Na$^+$] 350.0963, found 350.0957.

(*E*)-Ethyl-2,2-difluoro-4-(4-formylphenyl)-4-phenylbut-3-enoate (**4h**): Light yellow oil (220.3 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.06 (s, 1H), 7.91 (d, J=8.1

Hz, 2H), 7.34～7.42 (m, 5H), 7.17～7.07 (m, 2H), 6.34 (t, J=12.5 Hz, 1H), 4.06 (q, J=7.1 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 191.8, 163.5 (t, J=34.0 Hz), 149.8 (t, J=8.2 Hz), 143.7, 139.7, 136.2, 130.5, 129.6, 129.4, 128.7, 127.8, 120.0 (t, J=27.2 Hz), 112.3 (t, J=247.4 Hz), 63.1, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −90.9 (s, J=11.2 Hz, 2F); HRMS (ESI) calcd for $C_{19}H_{17}F_2O_3^+$ [M+H$^+$] 353.0960, found 353.0964.

(*E*)-Ethyl-2,2-difluoro-4-phenyl-4-(4-(trifluoromethyl)-phenyl)but-3-enoate (**4i**):[9b] Light yellow oil (173.4 mg, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, J=8.0 Hz, 2H), 7.43～7.31 (m, 5H), 7.29～7.13 (m, 2H), 6.33 (t, J=12.3 Hz, 1H), 4.02 (q, J=7.1 Hz, 2H), 1.21 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.6 (t, J=33.8 Hz), 149.8 (t, J=8.3 Hz), 141.1, 139.8, 130.7 (q, J=32.6 Hz), 130.3 (t, J=2.3 Hz), 129.6, 128.8, 127.9, 125.1 (q, J=3.8 Hz), 124.0 (q, J=272.7 Hz), 120.2 (t, J=27.5 Hz), 112.4 (t, J=247.2 Hz), 63.2, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.8 (s, 3F), −96.15 (d, J=11.2 Hz, 2F).

(*E*)-Ethyl-2,2-difluoro-4-phenyl-4-(pyridin-3-yl)but-3-enoate (**4j**): Light yellow oil (169.6 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, J=4.8 Hz, 1H), 7.56 (td, J=7.7, 1.7 Hz, 1H), 7.27～7.19 (m, 5H), 7.15 (t, J=6.2 Hz, 1H), 7.08 (d, J=7.9 Hz, 1H), 6.12 (t, J=13.3 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 1.16 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.6 (t, J=34.4 Hz), 155.5, 148.9 (t, J=8.9 Hz), 148.6, 139.3, 136.3, 129.2, 128.7, 128.5, 124.8, 123.4, 123.2 (t, J=28.6 Hz), 112.7 (t, J=246.4 Hz), 62.6, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −94.3 (d, J=13.3 Hz); HRMS (ESI) calcd for $C_{17}H_{15}F_2NNaO_2^+$ [M+Na$^+$] 326.0963, found 326.0953.

(*E*)-Ethyl-2,2-difluoro-4-phenyl-4-(thiophen-2-yl)but-3-enoate (**4k**): Light yellow oil (182.0 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, J=5.1 Hz, 1H), 7.31～7.27 (m, 5H), 7.16 (d, J=4.3 Hz, 1H), 6.98～6.95 (m, 1H), 6.12 (t, J=11.4 Hz, 1H), 3.91 (q, J=7.2 Hz, 2H), 1.10 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.2 (t, J=33.8 Hz), 144.4 (t, J=10.1 Hz), 140.7, 138.2, 131.3, 129.6, 128.9, 128. 5, 128.3, 126.9, 121.3 (t, J=29.2 Hz), 112.5 (t, J=243.8 Hz), 63.0, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −89.4 (d, J=11.3 Hz, 2F); HRMS (ESI) calcd for $C_{16}H_{14}F_2NaO_2S^+$ [M+Na$^+$] 331.0575, found 331.0574.

(*E*)-Ethyl-2,2-difluoro-3-methyl-4,4-diphenylbut-3-enoate (**4l**): Light yellow oil (227.2 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46～7.18 (m, 6H), 7.15～7.13 (m, 4H), 3.79 (q, J=7.1 Hz, 2H), 1.95 (s, 3H), 1.16 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.8 (t, J=33.6 Hz), 146.5 (t, J=7.3 Hz), 141.6, 139.9, 130.0, 129.0, 128.4, 128.0, 127. 9, 127. 7, 127.3 (t, J=24.0 Hz), 114.1 (t, J=248.1 Hz), 62.7, 16.1 (t, J=18.0 Hz), 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −90.9 (d, J=11.3 Hz, 2F); HRMS (ESI) calcd for $C_{19}H_{18}F_2NaO_2^+$ [M+Na$^+$] 339.1167, found 339.1161.

(*Z*)-Ethyl-2,2-difluoro-4-phenyl-4-(*p*-tolyl)but-3-enoate (**4m**):[9b] Light yellow oil (186.1 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42～7.34 (m, 3H), 7.23～7.20 (m, 2H), 7.18～7.10 (m, 4H), 6.26 (t, J=11.8 Hz, 1H), 3.90 (q, J=7.1 Hz, 2H), 2.36 (s, 3H), 1.17 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.6 (t, J=34.0 Hz), 150.9 (t, J=9.5 Hz), 139.4, 137.7, 137.3, 129.9, 129.2, 128.6, 128.1, 127.9, 118.7 (t, J=28.4 Hz), 112.8 (t, J=244.7 Hz), 62.8, 21.3, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −90.7 (d, J=11.6 Hz, 2F).

(*Z*)-Ethyl-2,2-difluoro-4-(4-fluorophenyl)-4-phenylbut-3-enoate (**4n**):[9b] Light yellow oil (108.8 mg, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39～7.35 (m, 3H), 7.25～7.17 (m, 4H), 7.02～6.98 (m, 2H), 6.21 (t, J=11.7 Hz, 1H), 3.89 (q, J=7.2 Hz, 2H), 1.16 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.6 (t, J=34.0 Hz), 162.9 (d, J=248.5 Hz), 150.2 (t, J=9.1 Hz), 140.4, 133.1 (d, J=3.5 Hz), 131.7 (d, J=8.3 Hz), 129.3, 128.5, 127.9, 119.8 (t, J=28.0 Hz), 115.1 (d, J=21.2 Hz), 112.5 (t, J=245.7 Hz), 63.0, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −90.9 (d, J=11.8 Hz, 2F), −112.2～−112.3 (m, 1F).

(*Z*)-Ethyl-4-(4-chlorophenyl)-2,2-difluoro-4-phenylbut-3-enoate (**4o**):[9b] Light yellow oil (167.7 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39～7.36 (m, 3H), 7.30～7.28 (m, 2H), 7.20～7.17 (m, 4H), 6.25 (t, J=11.6 Hz, 1H), 3.90 (q, J=7.2 Hz, 2H), 1.17 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.4 (t, J=33.7 Hz), 149.9 (t, J=9.4 Hz), 139.0, 136.7, 135.3, 129.9, 129.3, 128.9, 128.7, 128.3, 119.9 (t, J=28.4 Hz), 112.5 (t, J=245.0 Hz), 62.9, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −91.05 (d, J=11.6 Hz, 2F).

Supporting Information The detailed procedure for the synthesis of **4** and radical capture experiment, copies of ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR of **4a**～**4o**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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