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可见光诱导有机光催化合成二氟乙基苯并噁嗪

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摘要 苯并噁嗪是药物和功能分子中的重要结构. 报道了一种利用有机光催化剂在可见光诱导下合成二氟乙基苯并噁嗪的方法. 以二氟甲基亚磺酸钠作为二氟甲基化试剂, 通过烯烃的氧化二氟甲基化双官能团化反应, 可将一系列烯酰胺转化为二氟乙基苯并噁嗪类化合物, 该方法操作简单, 底物适用广泛.
关键词 氧化二氟甲基化; 苯并噁嗪; 可见光诱导反应; 有机光催化剂; 自由基

Visible-Light Induced Organophotocatalysis for the Synthesis of Difluoroethylated Benzoxazines

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Abstract Benzoxazines are important motif in pharmaceuticals and functional molecules. A visible-light induced photocatalytic strategy for the synthesis of difluoroethyl benzoxazines with organo-photocatalyst was developed. In the present protocol, a series of olefinic amides can be transferred to difluoroethylated benzoxazines via oxydifluoromethylation with CF_2HSO_2Na as difluoromethylating reagent, which is easily operated and good functional group tolerant.
Keywords oxydifluoromethylation; benzoxazine; visible light induced reaction; organophotocalyst; radical

1 Introduction

Fluorinated chemicals are regarded as important motif in pharmaceutical research and drug development.[1] Among which, the difluoromethylated compounds[2] were more significant, because it can behave as an isostere to an SH/OH group or a hydrogen donor through hydrogen bonding.[3] Therefore, difluoromethylated compounds are strong candidates for drugs giving the higher bioactivity than the CF_3 containing materials in some cases.[4] Furthermore, heterocycles such as benzoxazines present in many natural products have attracted extensive attention from chemists due to good biological activities (Scheme 1, a).[5] *N*-Acyl-(2-ene) anilines have become important starting materials for the efficient construction of functional benzoxazines via the annulation of olefinic amides with electrophiles (such as X^+)[6] and radicals (Scheme 1, b).[7] Photocatalysis as an important part of initiation of radicals is given wide attention by chemists.[8] In 2016, Fu *et al.*[9] reported the visible-light-mediated synthesis of benzoxazines from *N*-acyl-(2-ene) anilines and difluoromethyl sulfone with *fac*-Ir(ppy)$_3$ species as photocatalyst. However, expensive transition metal catalysis resulted in environmental pollution and economic burden in industrial manufacture, which could be avoided by organophotocatalytic system. Herein, we described an efficient synthesis of difluoroethylated benzoxazines via organophotocatalytic radical cascade reaction (Scheme 1, c).

2 Results and discussion

Compound **1a** and sodium difluoromethanesulfonate **2a**[10] were chosen as model substrates to investigate the reaction under photochemical system in solvent of MeCN with 4CzIPN as catalyst and Na_2CO_3 as base under radiation of 455 nm LEDs (10 W), and the target product **3aa** was obtained in 57% yield (Table 1, Entry 5). Further investigation of optimal conditions was conducted. When the base was excluded from reaction system, the yield of product raised to 79%, and isolated yield was up to 69% (Table 1, Entry 1). Other organophotocatalysts such as Eosin-Y and MesAcr showed less efficiency, affording desired compound in 32% and 70% yields (Table 1, Entry 2). The semiconductor served as catalyst led to production of **3aa**

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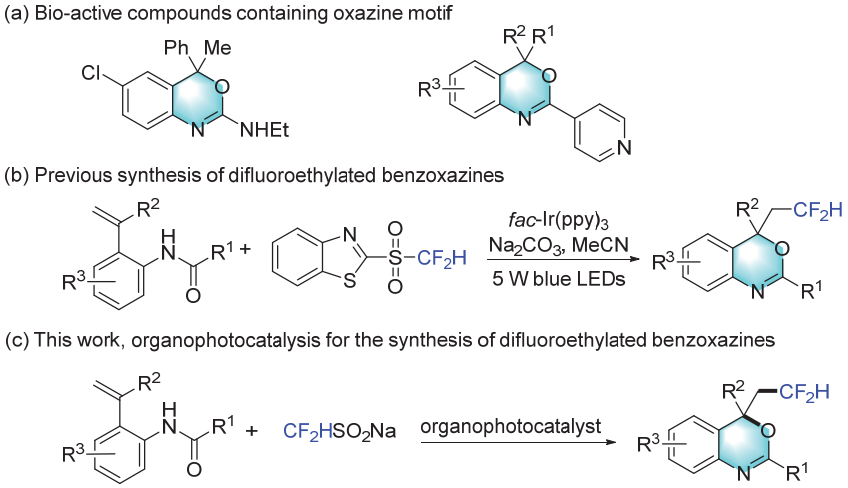
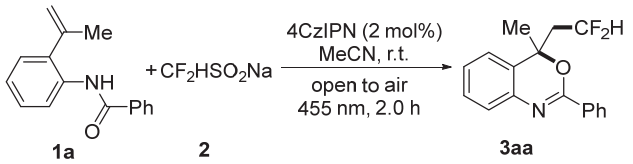


Scheme 1 Synthesis of difluoroethyl benzoxazines

with a trace amount (Table 1, Entry 3). Several solvents were tested, but no better yield was obtained (Table 1, Entry 4). After test of the wavelength for the reaction, it was found that the other light sources showed less efficiency in the reaction (Table 1, Entry 6). The product **3aa** could not formed in the absence of catalyst or light (Table 1, Entries 6, 7). O_2 was essential for the reaction, because the reaction can not run efficiently in N_2 atmosphere (Table 1, Entry 8).

Table 1 Optimization of reaction conditions[a]



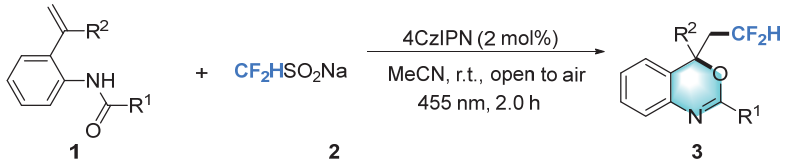
Entry	Variation from the standard reaction conditions	Yield[b]/%
1	None	77 (69)[c]
2	Eosin-Y, MesAcr	32, 70
3	g-C_3N_4, BiBrO	Trace, trace
4	THF, DMF, DMSO, DCM as solvent	33, 27, 18, 22
5	Na_2CO_3 (2.0 equiv.) as base	57
6	390, 405, 520 nm	19, 27, trace
7	Without 4CzIPN	Trace
8	Dark	0
9	N_2 atmosphere	Trace

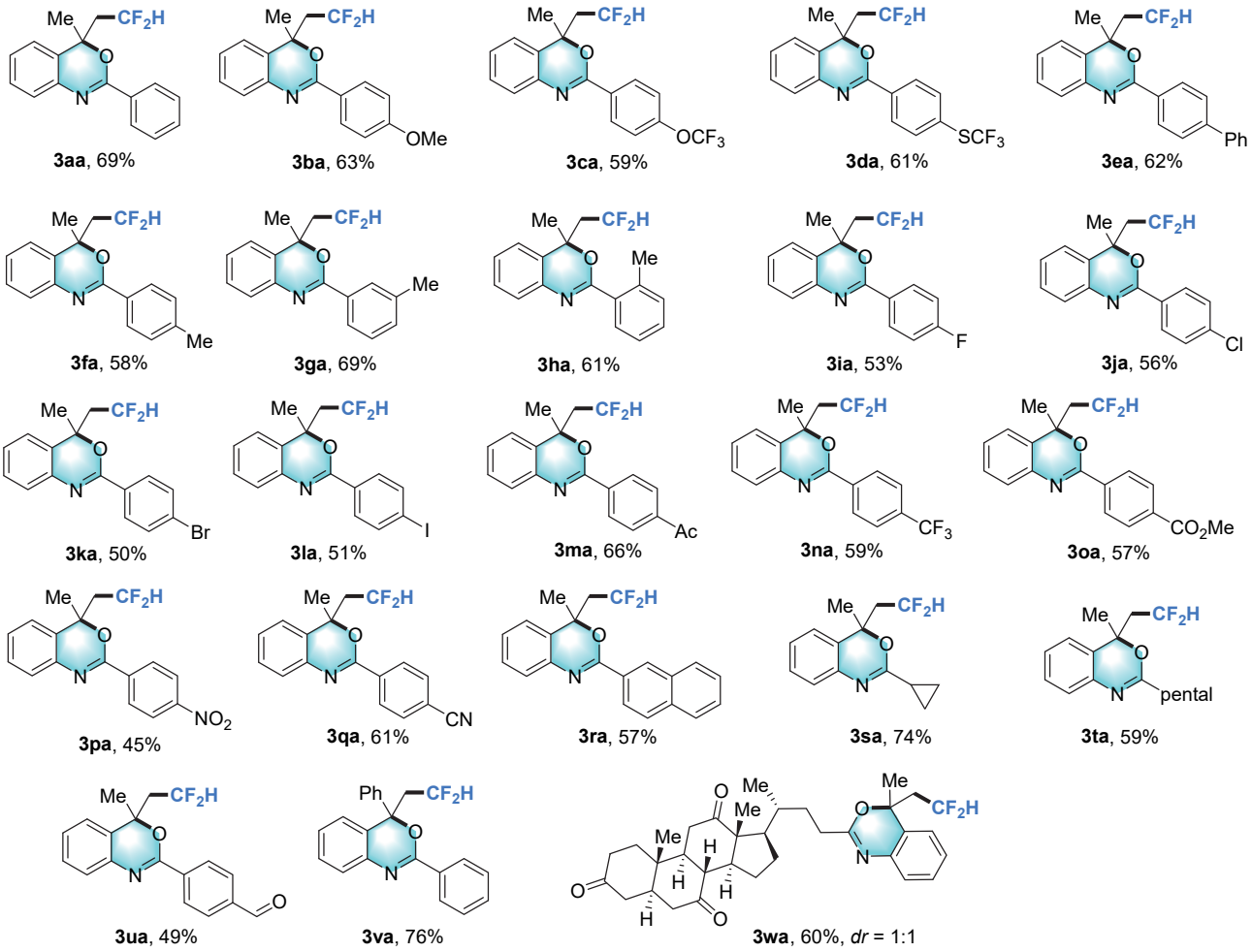
[a] Conditions: **1a** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv.), 4CzIPN (0.004 mmol, 2 mol%), MeCN (3.0 mL), r.t., open to air, under radiation of 455 nm LEDs, 2.0 h. THF: tetrahydrofuran; DMF: *N*,*N*-dimethylformamide; DMSO: dimethyl sulfoxide; DCM: dichloromethane; MesAcr: 9-mesityl-10-methylacridinium perchlorate. [b] Yield was determined with PhOMe as internal standard. [c] Isolated yield.

With the optimized condition in hand, the scope of synthesis of benzoxazines via organophotocatalystic oxydifluoromethylation was explored. It was found that a variety of 2-vinylacetamides bearing different groups could be used as precursors of benzyl radical, affording 4-difluoroethyl benzoxazines **3aa**～**3wa** in 45%～76% yields (Table 2). Many functional groups could be tolerated in the current protocol. C(sp^2)—X (X=F, Cl, Br, I) bond on carbamyl substituted aryl ring was retained in the reaction, affording products **3ia**～**3la** in isolated yields from 50% to 56%. Not only electron donating groups (OMe, OCF_3, SCF_3) but also electron withdrawing groups (Ac, CO_2Me, CF_3, NO_2) substituted substrates **1** could be transformed to the corresponding benzoxazines in 45%～63% yields. Furthermore, alkyl and cyclic alkyl amides could be used under current protocol to afford desired product (**3sa**, 84%; **3ta**, 79%; **3ua**, 80%). Heterocyclic ring, such as pyridine ring is also tolerated (**3ra**, 61%). Groups at each position of the aryl ring of substrate **1** were well compatible under standard conditions, delivering the desired products in good yields (**3fa**, 58%; **3ga**, 69%; **3ha**, 61%). To further evaluate the efficiency of the reaction, we applied this protocol in late-stage synthesis, substrate **1w** which was made from the natural compound dehydrocholic acid could also be successfully used under the present condition, and the corresponding oxazine **3wa** was obtained in 60% yield. Diaryl olefin substrate **1v** could also be transformed into the desired oxazine **3va** in 76% yield. To our delight, substrate with group CHO, which is unstable under oxidative condition, could also generate the desired oxazine **3ua** in 49% yield. From an industrial practicality viewpoint, the scalability is significant important aspects for the application of a synthetic methodology.

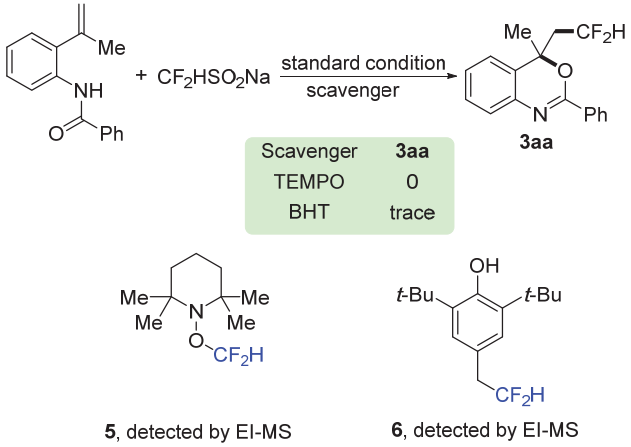
To gain mechanistic insight into the organophotocatalystic reaction, both the radical trapping experiments were carried out. As shown in Scheme 2, the present reactions were completely inhibited in the presence of the radical scavenger [2,2,6,6-tetramethylpiperidoxyl (TEMPO) or butylated hydroxytoluene (BHT)] and compounds **5** and **6** were detected by EI-MS. The results indicated that the radical process was presumably involved in the organophotocatylic transformation. The light turn-on/off experiment resulted that continuous light radiation was indispensable for this transformation, likely ruling out the radical chain reaction pathway (Figure 1).

Table 2 Scope of substrates





[a] Conditions: **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv.), 4CzIPN (0.004 mmol, 2 mol%), MeCN (3.0 mL), r.t., open to air, under radiation of 455 nm LEDs, 2.0 h, isolated yield.



Scheme 2 Control experiments

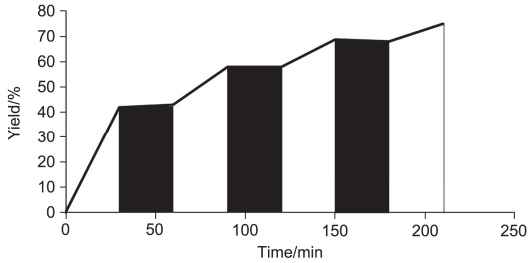
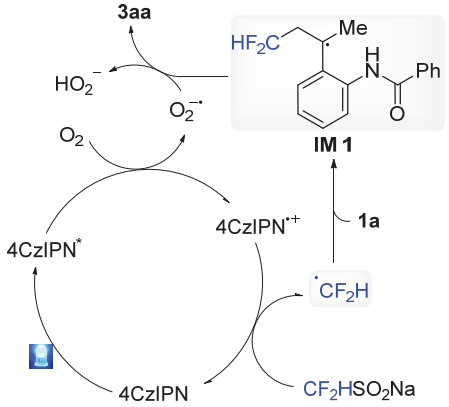


Figure 1 Light turn on/off experiments

Based on the above-mentioned experimental results and previously reported results,[11] a plausible mechanism for the organophotocatalysis was proposed and shown in Scheme 3. First, 4CzIPN was excited by blue light and oxidized by oxygen to form its radical cation. Then,

CF_2HSO_2Na was oxdized by 4CzIPN radical cation, generating $\bullet CF_2H$ radical, which reacted with **1a** via radical addition reaction to form reacting intermediate **IM 1**. **IM 1** was oxidized by superoxide radical to benzyl cation and cyclized via intramolecular nucleophilic attack to form the final product **3aa**.



Scheme 3 Proposed reaction mechanism

3 Conclusions

In conclusion, a green and efficient organophotochemical annulation for synthesis of difluoroethylated benzoxazines was realized, providing a practical method to prepare various N,O-six membered cyclochemicals. The present transformation can be achieved via organophotocatalysis without addition of base under visible light radiation. With the optimal conditions, a variety of difluoroethylated benzoxazines were obtained in good to excellent yields. And late-stage synthesis highlighted the application of present protocol.

4 Experimental sections

4.1 General information

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200～300 mesh silica gel. ^{1}H NMR spectra were recorded at 500 MHz, ^{13}C NMR spectra were recorded at 125 MHz and ^{19}F NMR spectra were recorded at 471 MHz by using a Bruker Avance 400 spectrometer. Chemical shifts were calibrated using residual undeuterated solvent as an internal reference (^{1}H NMR: $CDCl_3$ δ 7.26, ^{13}C NMR: $CDCl_3$ δ 77.16).

4.2 General experimental procedure for compounds 3

In a quartz reactor equipped with a stir bar, olefinic acyl amides **1** (0.2 mmol), CF_2HSO_2Na (0.3 mmol, 48.7 mg, ω＝85%, 1.5 equiv.), 4CzIPN (0.004 mmol, 3.5 mg, 2 mol%) and MeCN (3 mL) were added. The reaction tube was under radiation with 455 nm LEDs at room temperature. After completion, the reaction medium was concentrated under reduced pressure, and the pure products **3aa**～**3wa** were obtained by flash chromatography on silica gel.

4-(2,2-Difluoroethyl)-4-methyl-2-phenyl-4*H*-benzo[*d*]-[1,3]oxazine (**3aa**):[11a] Colorless oil, 69% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18～8.10 (m, 2H), 7.54～7.49 (m, 1H), 7.46 (dd, J＝8.3, 6.6 Hz, 2H), 7.34 (d, J＝4.3 Hz, 2H), 7.26～7.20 (m, 1H), 7.12 (d, J＝7.6 Hz, 1H), 6.15～5.86 (m, 1H), 2.69～2.44 (m, 2H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.9, 138.4, 132.5, 131.7, 129.3, 128.5, 128.5, 127.9, 127.1, 125.7, 122.7, 115.0 (t, J＝239.3 Hz), 77.6 (t, J＝5.5 Hz), 45.0 (t, J＝21.3 Hz), 27.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ: －112.6 (d, J＝67.6 Hz, 2F).

4-(2,2-Difluoroethyl)-2-(4-methoxyphenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (**3ba**):[11a] Colorless oil, 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13～8.03 (m, 2H), 7.36～7.29 (m, 2H), 7.21 (ddd, J＝7.6, 6.4, 2.2 Hz, 1H), 7.11 (dd, J＝7.4, 1.2 Hz, 1H), 6.99～6.93 (m, 2H), 6.01 (tdd, J＝55.7, 5.2, 4.0 Hz, 1H), 3.87 (s, 3H), 2.67～2.43 (m, 2H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 162.6, 155.9, 138.8, 129.8, 129.3, 128.5, 126.6, 125.5, 124.9, 122.7, 115.1 (t, J＝239.3 Hz), 113.8, 77.6～77.4 (m), 55.5, 44.9 (t, J＝21.3 Hz), 27.3; ^{19}F NMR (471 MHz, Chloroform-*d*) δ: －110.4～－113.6 (m, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(4-(trifluoromethoxy)-phenyl)-4*H*-benzo[*d*][1,3]oxazine (**3ca**):[11a] Colorless oil, 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.22～8.13 (m, 2H), 7.38～7.31 (m, 2H), 7.28 (d, J＝8.5 Hz, 2H), 7.27～7.22 (m, 1H), 7.12 (dd, J＝7.7, 1.2 Hz, 1H), 5.97 (tdd, J＝55.7, 5.2, 4.0 Hz, 1H), 2.71～2.38 (m, 2H), 1.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.7, 151.7, 138.2, 131.0, 129.7, 129.4, 128.3, 127.4, 125.9, 122.8, 120.5 (q, J＝258.0 Hz), 120.5, 115.0 (t, J＝239.4 Hz), 78.0 (t, J＝6.0 Hz), 45.1 (t, J＝21.4 Hz), 27.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: －57.6 (s, 3F), －112.7 (d, J＝16.7 Hz, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(4-((trifluoromethyl)-thio)phenyl)-4*H*-benzo[*d*][1,3]oxazine (**3da**):[11a] Colorless oil, 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (d, J＝8.2 Hz, 2H), 7.73 (d, J＝8.1 Hz, 2H), 7.39～7.31 (m, 2H), 7.26 (td, J＝7.0, 2.2 Hz, 1H), 7.13 (d, J＝7.6 Hz, 1H), 5.97 (tt, J＝55.7, 4.6 Hz, 1H), 2.69～2.42 (m, 2H), 1.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.7, 138.1, 135.9, 134.9, 129.5 (q, J＝308.4 Hz), 129.5, 128.8, 128.3, 128.0 (q, J＝2.1 Hz), 127.7, 126.0, 122.8, 115.0 (t, J＝239.5 Hz), 78.1 (t, J＝6.1 Hz), 45.1 (t, J＝21.4 Hz), 27.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: －42.1 (s, 3F), －112.6～－112.8 (m, 2F).

2-([1,1'-Biphenyl]-4-yl)-4-(2,2-difluoroethyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (**3ea**):[11a] Colorless oil, 62% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.20 (d, J＝8.3 Hz, 2H), 7.68 (d, J＝8.3 Hz, 2H), 7.66～7.62 (m, 2H), 7.47 (t, J＝7.6 Hz, 2H), 7.41～7.31 (m, 3H), 7.26～7.20 (m, 1H), 7.12 (d, J＝7.6 Hz, 1H), 6.03 (tt, J＝55.7, 4.6 Hz, 1H), 2.71～2.43 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.8, 144.4, 140.3, 138.5, 131.3, 129.3, 129.0, 128.5, 128.4, 128.0, 127.3, 127.1, 127.1, 125.7, 122.7, 115.1 (t, J＝239.4 Hz), 77.6 (t, J＝6.0 Hz), 45.0 (t, J＝21.3 Hz), 27.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ: －111.7～－113.6 (m, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(*p*-tolyl)-4*H*-benzo[*d*]-

[1,3]oxazine (**3fa**):[11a] Colorless oil, 58% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05～7.99 (m, 2H), 7.36～7.30 (m, 2H), 7.25 (d, J=7.9 Hz, 2H), 7.23～7.18 (m, 1H), 7.13～7.08 (m, 1H), 6.00 (tdd, J=55.8, 5.3, 3.9 Hz, 1H), 2.66～2.45 (m, 2H), 2.41 (s, 3H), 1.78 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.1, 142.2, 138.6, 129.7, 129.3, 129.2, 128.6, 127.9, 126.9, 125.6, 122.7, 115.1 (t, J=239.3 Hz), 77.5～77.5 (m), 44.9 (t, J=21.3 Hz), 27.4, 21.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −111.9～−113.3 (m, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(*m*-tolyl)-4*H*-benzo[*d*]-[1,3]oxazine (**3ga**):[11a] Colorless oil, 69% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, J=2.1 Hz, 1H), 7.93～7.89 (m, 1H), 7.37～7.30 (m, 4H), 7.22 (dt, J=8.4, 4.3 Hz, 1H), 7.11 (d, J=7.6 Hz, 1H), 6.00 (tdd, J=55.7, 5.2, 3.9 Hz, 1H), 2.67～2.44 (m, 2H), 2.43 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.2, 138.5, 138.2, 132.6, 132.4, 129.3, 128.5, 128.5, 128.4, 127.0, 125.7, 125.1, 122.7, 115.1 (t, J=239.3 Hz), 77.6 (d, J=6.0 Hz), 45.0 (t, J=21.3 Hz), 27.5, 21.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −111.5～−113.6 (m, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(*o*-tolyl)-4*H*-benzo[*d*]-[1,3]oxazine (**3ha**):[11a] Colorless oil, 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (dd, J=7.8, 1.5 Hz, 1H), 7.37～7.29 (m, 3H), 7.29～7.22 (m, 3H), 7.11 (dd, J=7.7, 1.2 Hz, 1H), 5.96 (tdd, J=55.8, 5.2, 4.0 Hz, 1H), 2.68～2.52 (m, 5H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.7, 138.3, 132.4, 131.6, 130.6, 129.6, 129.3, 127.8, 127.2, 125.9, 125.8, 122.7, 115.2 (d, J=239.7 Hz), 78.0 (d, J=6.2 Hz), 45.1 (t, J=21.5 Hz), 28.1, 21.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.7 (d, J=38.2 Hz, 2F).

4-(2,2-Difluoroethyl)-2-(4-fluorophenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (**3ia**):[11a] Colorless oil, 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17～8.10 (m, 2H), 7.37～7.29 (m, 2H), 7.27～7.20 (m, 1H), 7.12 (td, J=8.3, 2.1 Hz, 3H), 5.98 (tt, J=55.7, 4.6 Hz, 1H), 2.65～2.41 (m, 2H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 165.0 (d, J=252.3 Hz), 155.0, 138.3, 130.1 (d, J=9.0 Hz), 129.3, 128.6 (d, J=3.0 Hz), 128.2, 127.1, 125.6, 122.7, 115.5 (d, J=22.0 Hz), 114.9 (t, J=239.4 Hz), 77.7 (t, J=6.0 Hz), 44.9 (t, J=21.3 Hz), 27.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −108.0 (s, 1F), −112.7 (d, J=25.8 Hz, 2F).

2-(4-Chlorophenyl)-4-(2,2-difluoroethyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (**3ja**):[11a] Colorless oil, 56% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10～8.03 (m, 2H), 7.44～7.39 (m, 2H), 7.37～7.30 (m, 2H), 7.27～7.21 (m, 1H), 7.11 (dd, J=7.7, 1.3 Hz, 1H), 6.14～5.78 (m, 1H), 2.69～2.38 (m, 2H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.0, 138.3, 137.9, 131.0, 129.4, 129.3, 128.7, 128.4, 127.3, 125.8, 122.8, 115.0 (t, J=239.4 Hz), 77.9 (t, J=6.0 Hz), 45.1 (t, J=21.4 Hz), 27.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.6 (d, J=24.0 Hz, 2F).

2-(4-Bromophenyl)-4-(2,2-difluoroethyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (**3ka**):[11a] Colorless oil, 50% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 (d, J=8.6 Hz, 2H), 7.50 (d, J=8.6 Hz, 2H), 7.29～7.22 (m, 2H), 7.19～7.14 (m, 1H), 7.03 (dd, J=7.6, 1.3 Hz, 1H), 5.89 (tdd, J=55.7, 5.2, 4.0 Hz, 1H), 2.65～2.25 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.1, 138.2, 132.5, 131.7, 131.4, 129.5, 129.4, 128.3, 127.4, 126.5, 125.8, 122.8, 115.0 (t, J=239.4 Hz), 77.9 (t, J=6.0 Hz), 45.0 (t, J=21.4 Hz), 27.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.6 (d, J=20.8 Hz, 2F).

4-(2,2-Difluoroethyl)-2-(4-iodophenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (**3la**):[11a] Colorless oil, 51% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (d, J=8.6 Hz, 2H), 7.79 (d, J=8.4 Hz, 2H), 7.38～7.29 (m, 2H), 7.24 (td, J=7.6, 7.2, 2.0 Hz, 1H), 7.11 (dd, J=7.7, 1.3 Hz, 1H), 6.11～5.82 (m, 1H), 2.67～2.38 (m, 2H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.3, 138.2, 137.7, 132.0, 129.5, 129.4, 128.4, 127.4, 125.8, 122.8, 115.0 (t, J=239.5 Hz), 98.9, 77.9 (t, J=6.1 Hz), 45.0 (t, J=21.3 Hz), 27.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −111.7～−113.7 (m, 2F).

1-(4-(4-(2,2-Difluoroethyl)-4-methyl-4*H*-benzo[*d*][1,3]-oxazin-2-yl)phenyl)ethan-1-one (**3ma**):[11a] Colorless oil, 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.22 (d, J=8.3 Hz, 2H), 8.03 (d, J=8.4 Hz, 2H), 7.39～7.33 (m, 2H), 7.27 (ddd, J=8.5, 5.5, 3.2 Hz, 1H), 7.14 (d, J=7.6 Hz, 1H), 6.14～5.84 (m, 1H), 2.66 (s, 3H), 2.64～2.45 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.9, 154.9, 139.1, 138.1, 136.6, 129.5, 128.4, 128.3, 128.1, 127.7, 126.0, 122.8, 115.0 (t, J=239.5 Hz), 78.0 (t, J=6.1 Hz), 45.1 (t, J=21.4 Hz), 27.7, 27.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.7 (d, J=25.8 Hz, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(4-(trifluoromethyl)-phenyl)-4*H*-benzo[*d*][1,3]oxazine (**3na**):[11a] Colorless oil, 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.25 (d, J=8.2 Hz, 2H), 7.71 (d, J=8.2 Hz, 2H), 7.39～7.33 (m, 2H), 7.27 (ddd, J=8.5, 6.0, 2.8 Hz, 1H), 7.13 (d, J=7.6 Hz, 1H), 5.97 (tt, J=55.7, 4.6 Hz, 1H), 2.76～2.36 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.5, 138.0, 135.9, 133.1 (q, J=32.6 Hz), 129.5, 128.3, 128.2, 127.7, 126.0, 124.0 (q, J=272.4 Hz), 125.4 (q, J=3.8 Hz), 122.8, 115.0 (t, J=239.5 Hz), 78.1 (t, J=6.0 Hz), 45.2 (t, J=21.4 Hz), 27.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −62.8 (s, 3F), −112.7 (d, J=11.1 Hz, 2F).

Methyl 4-(4-(2,2-difluoroethyl)-4-methyl-4*H*-benzo[*d*]-[1,3]oxazin-2-yl)benzoate (**3oa**):[11a] Colorless oil, 57% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.20 (d, J=8.3 Hz, 2H), 8.11 (d, J=8.3 Hz, 2H), 7.39～7.33 (m, 2H), 7.26 (td, J=6.4, 5.6, 2.9 Hz, 1H), 7.13 (d, J=7.6 Hz, 1H), 5.99 (tt, J=55.7, 4.6 Hz, 1H), 3.95 (s, 3H), 2.69～2.44 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 166.7, 155.0, 138.1, 136.6, 132.6, 129.6, 129.5, 128.4, 127.8, 127.6, 126.0, 122.8, 115.0 (t, J=239.5 Hz), 78.0 (t, J=6.1 Hz), 52.5, 45.1 (t, J=21.3 Hz), 27.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.7 (d, J=29.6 Hz, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (**3pa**):[11a] Colorless oil, 45% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (d, J=8.5 Hz, 2H), 8.11 (d, J=8.5 Hz, 2H), 7.35 (d, J=4.0 Hz, 2H), 7.28～7.22 (m, 1H), 7.12 (d, J=7.6 Hz, 1H), 5.98 (tdd, J=55.7, 5.1, 4.1 Hz, 1H), 3.95 (s, 3H), 2.68～2.42 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 153.8, 149.7, 138.4, 137.8, 129.6, 128.8, 128.2, 128.2, 126.3, 123.6, 122.9,

114.9 (t, J=239.6 Hz), 78.4 (d, J=6.2 Hz), 45.3 (t, J=21.5 Hz), 28.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.6～−112.9 (m, 2F).

4-(4-(2,2-Difluoroethyl)-4-methyl-4*H*-benzo[*d*][1,3]-oxazin-2-yl)benzonitrile (**3qa**):[11a] Colorless oil, 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.24 (d, J=8.3 Hz, 2H), 7.74 (d, J=8.3 Hz, 2H), 7.39～7.32 (m, 2H), 7.28 (td, J=7.6, 2.1 Hz, 1H), 5.96 (tt, J=55.6, 4.6 Hz, 1H), 2.71～2.43 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.0, 137.8, 136.6, 132.2, 129.6, 128.3, 128.2, 128.0, 126.1, 122.9, 118.6, 114.9 (t, J=239.6 Hz), 114.7, 78.3 (t, J=6.0 Hz), 45.2 (t, J=21.4 Hz), 27.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.7 (d, J=3.1 Hz, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-(naphthalen-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**3ra**):[11a] Colorless oil, 57% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.59 (d, J=1.6 Hz, 1H), 8.26 (dd, J=8.7, 1.6 Hz, 1H), 7.98 (dd, J=7.3, 2.0 Hz, 1H), 7.90 (dd, J=12.0, 8.4 Hz, 2H), 7.56 (tt, J=7.2, 5.4 Hz, 2H), 7.41～7.34 (m, 2H), 7.28～7.23 (m, 1H), 7.15 (d, J=7.6 Hz, 1H), 6.22～5.91 (m, 1H), 2.74～2.47 (m, 2H), 1.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.0, 138.6, 135.1, 132.9, 129.8, 129.4, 129.2, 128.6, 128.5, 128.2, 127.9, 127.8, 127.2, 126.6, 125.8, 124.5, 122.8, 115.1 (t, J=239.4 Hz), 77.8 (d, J=6.0 Hz), 45.0 (t, J=21.3 Hz), 27.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.4～−112.8 (m, 2F).

2-Cyclopropyl-4-(2,2-difluoroethyl)-4-methyl-4*H*-benzo-[*d*][1,3]oxazine (**3sa**):[11a] Colorless oil, 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (td, J=7.6, 1.4 Hz, 1H), 7.14 (t, J=7.1 Hz, 2H), 7.05～6.98 (m, 1H), 5.84 (tdd, J=55.8, 5.3, 3.8 Hz, 1H), 2.57～2.29 (m, 2H), 1.71 (tt, J=8.3, 4.8 Hz, 1H), 1.63 (s, 3H), 1.04 (dt, J=6.9, 3.3 Hz, 2H), 0.87 (dq, J=7.1, 3.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 162.5, 138.3, 129.3, 127.8, 126.3, 124.5, 122.6, 115.1 (t, J=239.1 Hz), 45.0 (t, J=21.4 Hz), 27.7, 14.7, 7.0, 6.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.4～−112.8 (m, 2F).

4-(2,2-Difluoroethyl)-4-methyl-2-pentyl-4*H*-benzo[*d*]-[1,3]oxazine (**3ta**):[11a] Colorless oil, 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31～7.25 (m, 1H), 7.21～7.11 (m, 2H), 7.04 (d, J=7.6 Hz, 1H), 5.88 (tt, J=56.2, 4.4 Hz, 1H), 2.42 (dqd, J=52.1, 15.0, 4.5 Hz, 2H), 2.12 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 159.5, 137.9, 129.3, 127.6, 126.9, 124.9, 122.8, 115.1 (t, J=239.1 Hz), 77.2 (t, J=6.2 Hz), 45.7 (t, J=21.2 Hz), 28.0, 21.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.7 (d, J=12.3 Hz, 2F).

4-(4-(2,2-Difluoroethyl)-4-methyl-4*H*-benzo[*d*][1,3]-oxazin-2-yl)benzaldehyde (**3ua**): Colorless oil, 49% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.09 (s, 1H), 8.29 (d, J=8.1 Hz, 2H), 7.95 (d, J=8.1 Hz, 2H), 7.36 (d, J=4.2 Hz, 2H), 7.27 (dt, J=8.5, 4.2 Hz, 1H), 7.13 (d, J=7.6 Hz, 1H), 5.98 (tt, J=55.7, 4.6 Hz, 1H), 2.66～2.47 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.9, 154.7, 138.3, 138.1, 138.0, 129.6, 129.5, 128.5, 128.4, 127.8, 126.2, 122.8, 115.0 (t, J=239.5 Hz), 78.2 (t, J=6.0 Hz), 45.3 (t, J=21.5 Hz), 27.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −112.5～−112.9 (m, 2F).

4-(2,2-Difluoroethyl)-2,4-diphenyl-4*H*-benzo[*d*][1,3]-oxazine (**3va**): Colorless oil, 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28～8.20 (m, 2H), 7.51 (t, J=7.2 Hz, 1H), 7.46 (dd, J=8.3, 6.4 Hz, 2H), 7.39～7.35 (m, 2H), 7.34～7.31 (m, 2H), 7.30～7.21 (m, 5H), 6.05 (tt, J=55.6, 4.3 Hz, 1H), 3.01 (td, J=15.1, 4.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.0, 142.1, 139.2, 132.2, 131.8, 129.6, 128.7, 128.5, 128.5, 128.0, 126.8, 126.6, 125.9, 125.6, 124.5, 115.4 (t, J=240.0 Hz), 81.0 (t, J=6.5 Hz), 44.9 (t, J = 22.4 Hz); ^{19}F NMR (471 MHz, Chloroform-*d*) δ: −110.2～−112.3 (m, 2F).

(5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((*R*)-4-((*S*)-4-(2,2-Difluoroethyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)-butan-2-yl)-10,13-dimethyldodecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,7,12(2*H*,4*H*)-trione (**3wa**): Colorless oil, 60% yield, *dr*=1∶1. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29～7.25 (m, 1H), 7.20～7.13 (m, 2H), 7.03 (d, J=7.6 Hz, 1H), 6.01～5.75 (m, 1H), 2.95～2.82 (m, 3H), 2.56～2.39 (m, 3H), 2.34 (ddt, J=18.1, 9.0, 4.9 Hz, 4H), 2.28～2.20 (m, 3H), 2.18 – 2.12 (m, 2H), 2.11～2.02 (m, 3H), 2.00～1.94 (m, 1H), 1.86 (tt, J=11.6, 4.9 Hz, 2H), 1.67 (d, J=2.9 Hz, 4H), 1.62 (td, J=14.4, 4.7 Hz, 1H), 1.48 (q, J=10.9, 7.8 Hz, 1H), 1.40 (s, 3H), 1.36 (tt, J=5.8, 2.2 Hz, 2H), 1.08 (s, 3H), 0.91 (d, J=6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 212.0, 209.1, 208.8, 162.5, 162.4 (C'), 138.0, 129.2, 127.8, 127.8 (C'), 126.8, 125.0, 122.7, 115.6 (d, J=239.6 Hz), 115.6 (d, J=239.6 Hz, C') 57.1, 51.9, 49.2, 47.0, 45.9, 45.9 (C'), 45.7, 45.5 (t, J=21.5 Hz), 45.1, 42.9, 38.8, 36.6, 36.2, 36.0, 36.0 (C'), 35.4, 32.7, 31.7, 31.7 (C'), 28.1, 28.0 (C'), 27.8, 27.8 (C'), 25.3, 22.0, 18.9, 18.9 (C'), 12.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −111.9～−113.6 (m, 2F).

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of compounds **3aa**～**3wa**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

References

[1] (a) Kirsch, P. *Modern Fluoroorganic Chemistry*: *Synthesis*, *Reactivity*, *Applications*, Wiley-VCH, Weinheim, **2013**.
(b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

[2] (a) Shi, L.; An, D.; Mei, G.-J. *Org. Chem. Front.* **2022**, *9*, 4192.
(b) Feng, J.; Jia, X.; Zhang, S.; Lu, K.; Cahard, D. *Org. Chem. Front.* **2022**, *9*, 3598.
(c) Gui, Q.-W.; Teng, F.; Li, Z.-C.; Xiong, Z.-Y.; Jin, X.-F.; Lin, Y.-W.; Cao, Z.; He, W.-M. *Chin. Chem. Lett.* **2021**, *32*, 1907.
(d) Zhang, S.; Li, L.; Zhang, J.; Zhang, J.; Xue, M.; Xu, K. *Chem. Sci*. **2019**, *10*, 3181.
(e) Xiong, P.; Xu, H.-H.; Song, J.; Xu, H.-C. *J. Am. Chem. Soc.* **2018**, *140*, 2460.
(f) Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342.
(g) Ren, X.; Liu, Q.; Wang, Z.; Chen, X. *Chin. Chem. Lett.* **2023**, *34*, 107473.
(h) Qin, W. B.; Xiong, W.; Zhao, Y. S.; Fu, K. Z.; Su, L.; Liu, G. K. *Org. Lett.* **2021**, *23*, 8482.

[3] (a) Meanwell, N. A. *J. Med. Chem*. **2011**, *54*, 2529.
(b) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626.

[4] Gauthier, J. Y.; Belley, M.; Deschenes, D.; Fournier, J. F.; Gagne, S.; Gareau, Y.; Hamel, M.; Henault, M.; Hyjazie, H.; Kargman, S.; Lavallee, G.; Levesque, J. F.; Li, L.; Mamane, Y.; Mancini, J.; Morin, N.; Mulrooney, E.; Robichaud, J.; Therien, M.; Tranmer, G.;

Wang, Z.; Wu, J.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2836.

[5] (a) Gromachevskaya, E. V.; Kvitkovskii, F. V.; Kosulina, T. P.; Kul'nevich, V. G. *Chem. Heterocycl. Compd.* **2003**, *39*, 137.
(b) Zhang, P.; Terefenko, E. A.; Fensome, A.; Wrobel, J.; Winneker, R.; Lundeen, S.; Marschke, K. B.; Zhang, Z. *J. Med. Chem.* **2002**, *45*, 4379.
(c) Lu, Y.-H.; Zhang, Z.-T.; Wu, H.-Y.; Zhou, M.-H.; Song, H.-Y.; Ji, H.-T.; Jiang, J.; Chen, J.-Y.; He, W.-M. *Chin. Chem. Lett.* **2023**, *34*, 108036.
(d) Jiang, J.; Wang, K.-L.; Li, X.; Wu, C.; Ji, H.-T.; Chen, X.; He, W.-M. *Chin. Chem. Lett.* **2023**, *34*, 108699.

[6] (a) Xie, Q.; Long, H.-J.; Zhang, Q.-Y.; Tang, P.; Deng, J. *J. Org. Chem.* **2020**, *85*, 1882.
(b) Cao, T.-T.; Zhang, W.-K.; Qin, F.-H.; Kang, Q.-Q.; Dong, Y.; Li, Q.; Kang, C.; Wei, W.-T. *ACS Sustainable Chem. Eng.* **2020**, *8*, 16946.
(c) Zhang, X.; Cao, W.-B.; Xu, X.-P.; Ji, S.-J. *Synthesis* **2019**, *51*, 3805.
(d) Zhao, J.-F.; Duan, X.-H.; Yang, H.; Guo, L.-N. *J. Org. Chem.* **2015**, *80*, 11149.

[7] (a) Babu, S. S.; Varma, A. A.; Gopinath, P. *Chem. Commun.* **2022**, *58*, 1990.
(b) Wu, J.; Zong, Y.; Zhao, C.; Yan, Q.; Sun, L.; Li, Y.; Zhao, J.; Ge, Y.; Li, Z. *Org. Biomol. Chem.* **2019**, *17*, 794.
(c) Liu, T.; Zheng, D.; Li, Z.; Wu, J. *Adv. Synth. Catal.* **2018**, *360*, 865.
(d) Wang, J.; Sang, R.; Chong, X.; Zhao, Y.; Fan, W.; Li, Z.; Zhao, J. *Chem. Commun.* **2017**, *53*, 7961.
(e) Yang, H.; Duan, X. H.; Zhao, J. F.; Guo, L. N. *Org. Lett.* **2015**, *17*, 1998.
(f) Jana, S.; Ashokan, A.; Kumar, S.; Verma, A.; Kumar, S. *Org. Biomol. Chem.* **2015**, *13*, 8411.
(g) Deng, Q.-H.; Chen, J.-R.; Wei, Q.; Zhao, Q.-Q.; Lua, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2015**, *51*, 3537.
(h) Chu, X.-Q.; Xu, X.-P.; Meng, H.; Ji, S.-J. *RSC Adv.* **2015**, *5*, 67829.

[8] (a) Marzo, L.; Pagire, S. K.; Reiser, O.; Konig, B. *Angew. Chem., Int. Ed.* **2018**, *57*, 10034.
(b) Wang, Z.; Liu, Q.; Liu, R.; Ji, Z.; Li, Y.; Zhao, X.; Wei, W. *Chin. Chem. Lett.* **2022**, *33*, 1479.
(c) Song, H.-Y.; Jiang, J.; Wu, C.; Hou, J.-C.; Lu, Y.-H.; Wang, K.-L.; Yang, T.-B.; He, W.-M. *Green Chem.* **2023**, *25*, 3292.
(d) Lu, Y.-H.; Mu, S.-Y.; Li, H.-X.; Jiang, J.; Wu, C.; Zhou, M.-H.; Ouyang, W.-T.; He, W.-M. *Green Chem.* **2023**, *25*, 5539.
(e) Gui, Q.-W.; Teng, F.; Yu, P.; Wu, Y.-F.; Nong, Z.-B.; Yang, L.-X.; Chen, X.; Yang, T.-B.; He, W.-M. *Chin. J. Catal.* **2023**, *44*, 111.
(f) Chen, J. Y.; Wu, H. Y.; Song, H. Y.; Li, H. X.; Jiang, J.; Yang, T. B.; He, W. M. *J. Org. Chem.* **2023**, *88*, 8360.
(g) Lu, Y.-H.; Wu, C.; Hou, J.-C.; Zhou, M.-H.; Huang, X.-J.; He, W.-M. *ACS Catal.* **2023**, *13*, 13071.

[9] Fu, W.; Han, X.; Zhu, M.; Xu, C.; Wang, Z.; Ji, B.; Hao, X.-Q.; Song, M.-P. *Chem. Commun.* **2016**, *52*, 13413.

[10] (a) Zou, Z.; Li, H.; Huang, M.; Zhang, W.; Zhi, S.; Wang, Y.; Pan, Y. *Org. Lett.* **2021**, *23*, 8252.
(b) Wang, H.; Zhang, J.; Shi, J.; Li, F.; Zhang, S.; Xu, K. *Org. Lett.* **2019**, *21*.
(c) Ruan, Z.; Huang, Z.; Xu, Z.; Mo, G.; Tian, X.; Yu, X. Y.; Ackermann, L. *Org. Lett.* **2019**, *21*, 1237.

[11] (a) Chen, X.; Jiang, J.; Huang, X.-J.; He, W.-M. *Org. Chem. Front.* **2023**, *10*, 3839.
(b) Natarajan, P.; Chuskit, D.; Priya; Manjeet *New J. Chem.* **2022**, *46*, 322.

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