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VISIBLE-LIGHT-ENABLED C(sp^2)-H DIFLUOROALKYLATION OF ALDEHYDE-DERIVED HYDRAZONES UNDER METAL-FREE CONDITIONS

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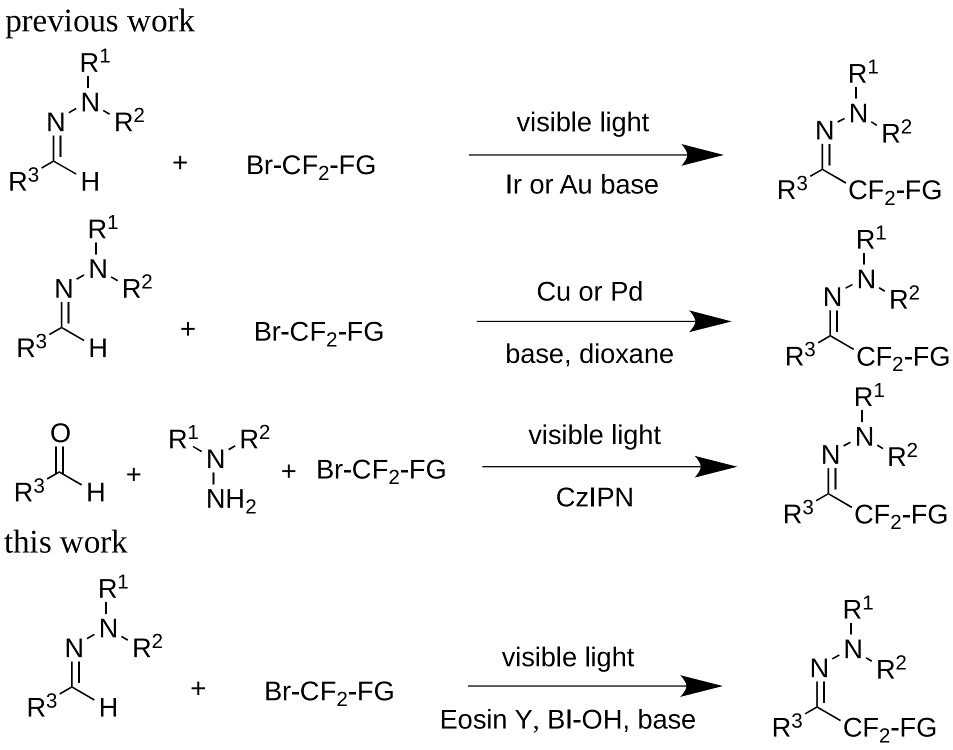
Abstract – A Eosin Y-catalyzed C(sp^2)-H difluoromethylation of aldehyde-derived hydrazones between difluoroalkyl bromides and aldehyde-derived hydrazones is reported. This reaction has a wide range of substrates and occurs under metal-free condition. A mechanism that involves a difluoroacetate radical via single electron transfer (SET) pathway is proposed for this reaction.

The introduction of CF_2 functional groups into organic molecules has great significance in organic synthesis because of the unique properties of fluorinated molecules. It can improve the lipophilicity, metabolic stability and reactivity of organic molecules.[1] Moreover, the CF_2 group can enhance the acidity of adjacent groups and change the dipole moment and conformation of the molecule.[2] On the other hand, hydrazones and its derivatives are extremely important organic synthesis intermediates with many applications.[3] Therefore, the introduction of CF_2 into the hydrazones may form some molecules with practical significance. Although considerable progress has been made in the study of fluoroalkylation of organic molecule,[4] the research of difluoroalkylation of hydrazones is relatively rare. Conceptually, it is still a very meaningful work to develop an efficient method to introduce the CF_2 group to the hydrazones. In the past few years, there have been many ways to introduce CF_2CO_2Et group into the hydrazones by transition metal catalysis. For example, (a) Xu *et al.*[5] and Xie *et al.*[6] used Ir or Au catalyst to achieve cross-coupling of hydrazones with ethyl bromodifluoroacetate under visible light. (b) Ke *et al.*[7] and Prieto *et al.*[8] have shown that Cu can also catalyze difluoroalkylation of hydrazones. Moreover, Prieto *et al.*[9] reported Pd-catalyzed difluoroalkylation of hydrazones. Although these efforts have shown great progress in the study of difluoroacetate of hydrazones, transition metal catalysis has some limitations, including the high price of some transition-metals and the environmental friendliness. Meanwhile, the pharmaceutical industry has extremely strict regulations on metal residues. However, the study of non-metal catalyzed difluoroalkylation of hydrazone is relatively rare. Only Li *et al.*[10] reported the difluoroalkylation of hydrazones using 1,2,3,5-tetrakis(carbazolyl)-4,6-dicyanobenzene (CzIPN) catalyst (non-metal catalyst).



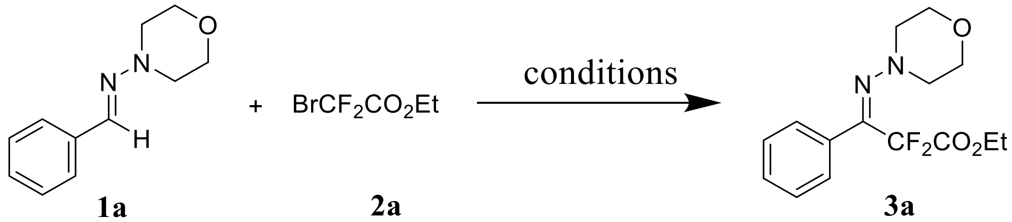
Scheme 1. Difluoroalkylation of Aldehyde-Derived Hydrazones

Here, we propose a method for the difluoroalkylation of hydrazones under metal-free conditions. The advantage of our method is that not only is Eosin Y[11] (organic dye[12]) cheaper than transition metal catalysts, but also less toxic than transition metal catalysts.

In our initial study, we used hydrazone **1a** and ethyl bromodifluoroacetate **2a** as our model substrate. We used Eosin Y as the catalyst, 2 equiv of *i*-Pr_2NEt as the base and 1 equiv of BI-OAc (1-acetoxy-1, 2-benziodoxol-3(1*H*)-one) as the additive under visible light irradiation from 15 W house blub in *t*-BuOH (2 mL). What excites us is that we had achieved the desired product in 38% isolated yield. In the oxidant screening experiment, the effect of BI-OH was better than others (BI-OAc, IBDA, IB) (Table 1, entries 1-4). Then, we tried some other photocatalysts ($Ru(bpy)_3Cl_2$, Rose Bengal) under the same conditions, Eosin Y has the highest reactivity (Table 1, entries 5-6). Next, we tried some other solvents, such as: MeCN, CH_2Cl_2, DMSO, DMF, etc (Table 1, entries 7-10). We found that *t*-BuOH was the most suitable solvent, and 69% isolation yield can be obtained using *t*-BuOH (Table 1, entries 4). Then, we screened other bases, such as: Na_2CO_3, Na_2HPO_4, KOAc, etc (Table 1, entries 11-13). The result was that *i*-Pr_2NEt

maximizes the isolated yield of the desired product. In addition, increasing the concentration of BI-OH (1-hydroxy-1,2-benziodoxol-3(1*H*)-one) can improve the efficiency of the reaction (Table 1, entries 14). Meanwhile, control experiments shown that Eosin Y, BI-OH and light were indispensable elements for this reaction (Table 1, entries 17-19). Finally, the optimal conditions for the reaction were determined as **1a** (0.2 mmol), **2a** (0.3 mmol), BI-OH (2 equiv), *i*-Pr_2NEt (2 equiv), Eosin Y (5 mol%), and *t*-BuOH (2 mL) at room temperature under Ar and 15 W house bulb for 12 h.

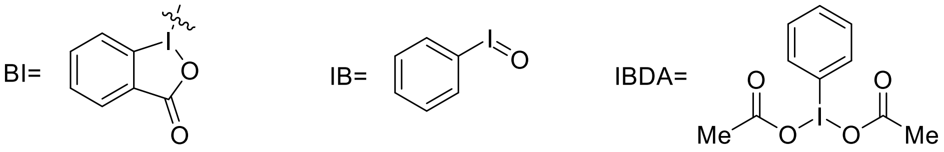
Table 1. Optimization of the Reaction Conditions[a,b]



1a **2a** **3a**

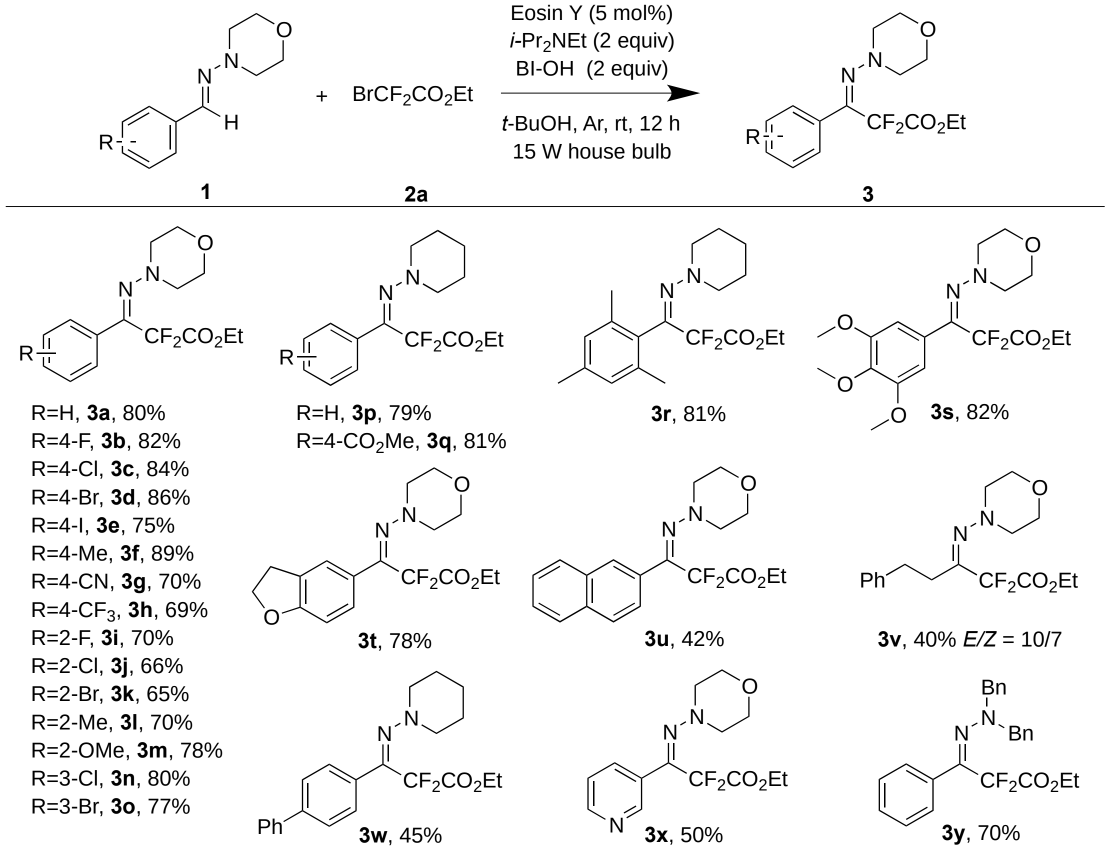
Entry	Photocatalyst	Additive	Solvent	Base	Yield (%)
1	Eosin Y	BI-OAc	*t*-BuOH	*i*-Pr_2NEt	38
2	Eosin Y	IBDA	*t*-BuOH	*i*-Pr_2NEt	0
3	Eosin Y	IB	*t*-BuOH	*i*-Pr_2NEt	0
4	Eosin Y	BI-OH	*t*-BuOH	*i*-Pr_2NEt	69
5	$Ru(bpy)_3Cl_2$	BI-OH	*t*-BuOH	*i*-Pr_2NEt	49
6	Rose Bengal	BI-OH	*t*-BuOH	*i*-Pr_2NEt	25
7	Eosin Y	BI-OH	MeCN	*i*-Pr_2NEt	41
8	Eosin Y	BI-OH	CH_2Cl_2	*i*-Pr_2NEt	33
9	Eosin Y	BI-OH	DMSO	*i*-Pr_2NEt	20
10	Eosin Y	BI-OH	DMF	*i*-Pr_2NEt	18
11	Eosin Y	BI-OH	*t*-BuOH	Na_2CO_3	15
12	Eosin Y	BI-OH	*t*-BuOH	Na_2HPO_4	23
13	Eosin Y	BI-OH	*t*-BuOH	KOAc	14
14[c]	Eosin Y	BI-OH	*t*-BuOH	*i*-Pr_2NEt	80
15[d]	Eosin Y	BI-OH	*t*-BuOH	*i*-Pr_2NEt	48
16[e]	Eosin Y	BI-OH	*t*-BuOH	*i*-Pr_2NEt	0
17	-	BI-OH	*t*-BuOH	*i*-Pr_2NEt	0
18	Eosin Y	-	*t*-BuOH	*i*-Pr_2NEt	<10
19	Eosin Y	BI-OH	*t*-BuOH	-	<10

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), BI-OH (1 equiv), *i*-Pr_2NEt (2 equiv), Eosin Y (5 mol%), and solvent (2 mL) in a sealed tube at room temperature under Ar, 15 W house bulb, 12 h. [b]Yield of the isolated product. [c]Using 2 equiv. BI-OH. [d]Reaction was conducted in the air. [e]Reaction was conducted in the dark.



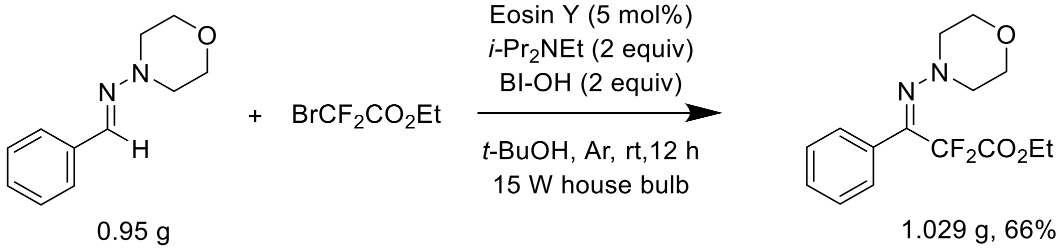
In order to determine the substrate range for this reaction, we had tried many aldehyde derived hydrazones. We had found that this method has good adaptability to substrates with electron-withdrawing groups or electron-donating groups on the aromatic rings. The result was presented in Scheme 2. The *ortho*-, *meta*- and *para*-substituted hydrazone had good adaptability to the reaction, and the desired product could be obtained in moderate yield, which meant that the spatial effects in the aromatic core had little effect on this reaction (**3b-3o**). In addition, the number of substituents on the benzene ring of the substrate had little effect on the reaction, and the disubstituted and trisubstituted substrates were produced in good yields (**3r-3t**). Moreover, heteroaromatic hydrazones compounds were also very adaptable to the reaction (**3x**). Excitingly, alkyl aldehyde hydrazone also worked well, giving the desired products with moderate yields (**3v**). To our delight, the reaction had satisfactory adaptability to hydrazones synthesized by different hydrazine (**3a**, **3p**, **3y**). However, hydrazones with (NO_2, OH and *N*,*N*-dimethyl) were not suitable for this reaction.

To further investigate the application of the reaction in synthesis, we conducted a gram scale experiment, and the reaction result (66% yield) was also satisfactory when the reaction was extended to the gram scale.



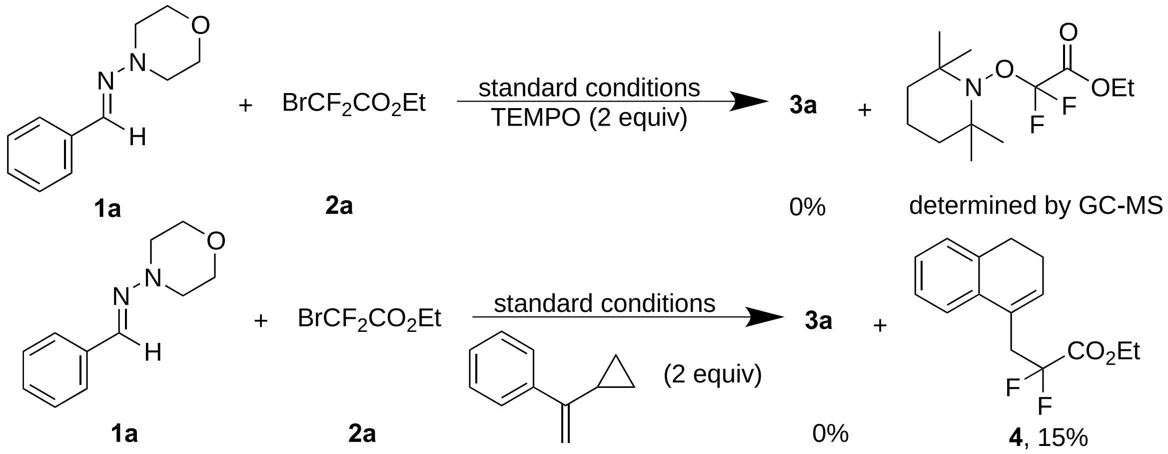
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), BI-OH (2 equiv), *i*-Pr_2NEt (2 equiv), Eosin Y (5 mol%), and solvent (2 mL) in a sealed tube at room temperature under Ar, 15 W house bulb, 12 h.

Scheme 2. Substrate Scope of Hydrazone[a]



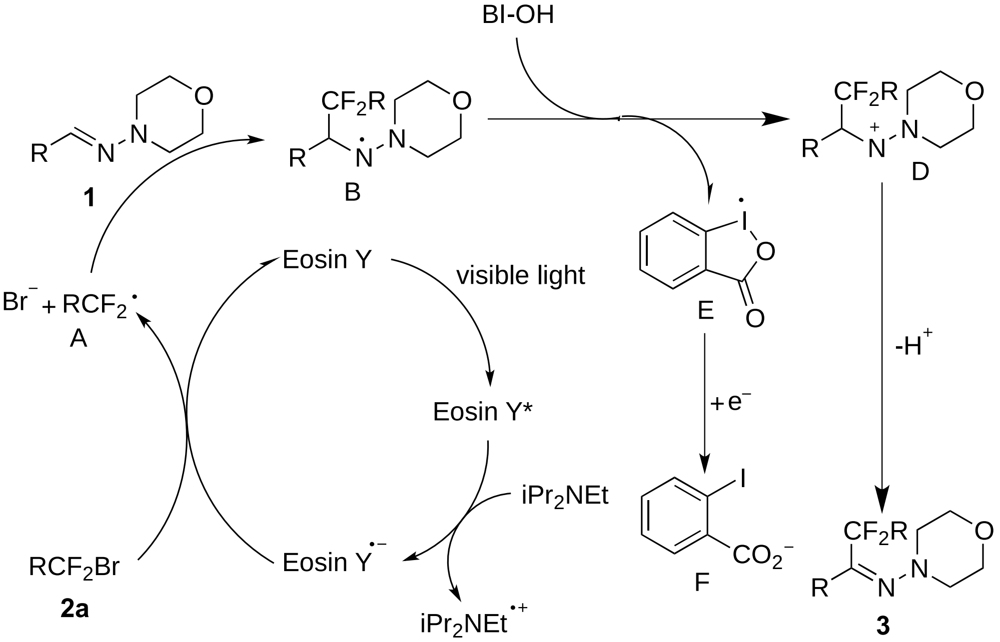
Scheme 3. Gram-Scale Experiment

In order to understand the mechanism of the reaction, we conducted radical trapping experiments. When the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinoxyl) is added to this reaction, the desired product was inhibited and TEMPO-CF_2CO_2Et adduct appears as a substitute product detected by GC-MS. This result indicated that a radical pathway exists in the course of this reaction. Then, we did another radical capture experiment using *α*-cyclopropylstyrene as a radical scavenger. When *α*-cyclopropylstyrene was present in the reaction system, product **4** was detected (GC-MS), and thus confirming that this reaction involves a process of a free CF_2CO_2Et radical production.



Scheme 4. Radical-Trapping Experiments

According to the above experimental results and previous studies,[13] a possible mechanism for this reaction is proposed in Scheme 5. Initially, the reaction proceeds by the formation of the key intermediate ethyl *α,α*-difluoroacetate radical A, which undergoes a single electron transfer process between Eosin Y radical anion and $BrCF_2CO_2Et$. Subsequently, the radical A was added to the carbon-nitrogen π bond of hydrazone **1** to form aminyl radical intermediate B. Then, the aminyl radical intermediate B was oxidized to an amino-cation D by BI-OH, and a benziodoxole radical E was formed. Finally, the benziodoxole radical E was reduced to the 2-iodobenzoic acid anion F, and the desired product **3** was obtained by proton removal.



Scheme 5. Proposed Mechanism

In conclusion, we have developed an efficient, practical, and environmentally friendly way to synthesize difluoroalkylated hydrazones using readily prepared hydrazones and inexpensive ethyl bromodifluoroacetate as raw materials under metal-free conditions. A series of aldehyde-derived hydrazones were adapted to this reaction conditions and were capable of obtaining the corresponding difluoroalkylated hydrazones in good yields. Further work on this reaction is underway in our laboratory.

EXPERIMENTAL

General considerations. All the reactions were performed in Schlenk tubes under argon atmosphere. Various hydrazones were prepared by reacting the corresponding aldehydes with 1,1-disubstituted hydrazines in CH_2Cl_2 in the presence of $MgSO_4$. Compounds (**3a-3p**, **3t-3v**, **3x-3y**) had been reported in the literature, ethyl difluoroacetate was purchased from Energy Chemical and used without further purification. All the solvents used in this study were obtained from commercial suppliers and used without further purification. Flash column chromatographic purification of products was performed over silica gel (200−300 mesh). ^{1}H NMR (600 MHz), ^{13}C NMR (150 MHz) and ^{19}F NMR (564 MHz) were recorded in $CDCl_3$ using TMS as internal standard. Data for ^{1}H NMR are reported as follows: chemical shift (ppm, scale), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift (ppm, scale), multiplicity, and coupling constant (Hz).

General Procedure for Difluoroalkylation of Aldehyde-Derived Hydrazones. The aldehyde-derived hydrazone (0.2 mmol), Eosin Y (5 mol%, 6.5 mg), and 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (BI-OH, 2 equiv, 0.4 mmol) were added to a 25 mL Schlenk tube in air. Then the mixture was evacuated and backfilled with Ar (three times). $BrCF_2CO_2Et$ (0.3 mmol), *i*-Pr_2NEt (2 equiv, 0.4 mmol) and *t*-BuOH were added successively. The mixture was stirred at ambient temperature for 12 h while irradiated by 15 W house bulb. After the reaction, the mixture was extracted with EtOAc (EA), and then the organic layer was concentrated and purified by column chromatography to afford the product.

Spectral data for products

Following general procedure, the product **3a**[7] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (50.1 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.44 – 7.37 (m, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.61 – 3.58 (m, 4H), 2.94 – 2.91 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.63 (t, *J* = 31.6 Hz), 140.59 (t, *J* = 31.9 Hz), 131.20, 129.68, 128.62, 128.57, 114.26 (t, *J* = 249.6 Hz), 65.93, 62.53, 54.08, 14.03. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.53.

Following general procedure, the product **3b**[7] was purified by flash chromatography (PE/EA = 10:1) as a colorless oil (54.1 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.12 (t, *J* = 8.7 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.62 – 3.59 (m, 4H), 2.94 – 2.91 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.48 (t, *J* = 31.6 Hz), 163.22 (d, *J* = 250.9 Hz), 139.92 (t, *J* = 31.7 Hz), 130.68 (d, *J* = 8.3 Hz), 127.03 (d, *J* = 3.7 Hz), 115.94 (d, *J* = 21.6 Hz), 114.17 (t, *J* = 249.7 Hz), 65.92, 62.63, 54.08, 14.05. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.49, -109.74.

Following general procedure, the product **3c**[7] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow liquid (58.1 mg, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.60 (m, 4H), 2.96 – 2.92 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.41 (t, *J* = 31.5 Hz), 139.36 (t, *J* = 31.7 Hz), 135.89, 130.00, 129.47, 129.04, 114.13 (t, *J* = 249.6 Hz), 65.91, 62.66, 54.09, 14.05. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.37.

Following general procedure, the product **3d**[7] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow liquid (67.0 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.62 – 3.60 (m, 4H), 2.95 – 2.92 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.37 (t, *J* = 31.6 Hz), 139.30 (t, *J* = 31.9 Hz), 131.97, 130.21, 129.97, 124.18, 114.07 (t, *J* = 249.7 Hz), 65.89, 62.64, 54.10, 14.04. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.41.

Following general procedure, the product **3e**[10] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow liquid (65.7 mg, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.60 (d, *J* = 4.4 Hz, 4H), 2.94 (br s, 4H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.33 (t, *J* = 31.5 Hz), 139.29 (t, *J* = 31.6 Hz), 137.86, 130.56, 130.23, 114.03 (t, *J* = 249.7 Hz), 96.12, 65.85, 62.60, 54.09, 14.01. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.32.

Following general procedure, the product **3f**[7] was purified by flash chromatography (PE/EA = 10:1) as a pale yellow solid (58.0 mg, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.0

Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.62 – 3.58 (m, 4H), 2.95 – 2.91 (m, 4H), 2.38 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.73 (t, *J* = 31.7 Hz), 141.08 (t, *J* = 31.7 Hz), 139.87, 129.34, 128.40, 128.08, 114.34 (t, *J* = 249.7 Hz), 65.99, 62.52, 54.04, 21.44, 14.06. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.57.

Following general procedure, the product **3g**[7] was purified by flash chromatography (PE/EA = 10:1) as a yellow solid (47.2 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.60 (m, 4H), 2.96 – 2.92 (m, 4H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.03 (t, *J* = 31.5 Hz), 137.56 (t, *J* = 31.5 Hz), 135.91, 132.34, 129.50, 117.90, 113.94 (t, *J* = 250.1 Hz), 113.60, 65.76, 62.77, 54.22, 14.00. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.03.

Following general procedure, the product **3h**[7] was purified by flash chromatography (PE/EA = 10:1) as a yellow solid (52.4 mg, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.60 (m, 4H), 2.96 – 2.92 (m, 4H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.28 (t, *J* = 31.4 Hz), 138.37 (t, *J* = 30.9 Hz), 135.00, 131.69 (q, *J* = 32.9 Hz), 129.21, 125.64 (q, *J* = 3.7 Hz), 124.51 (t, *J* = 272.4 Hz), 114.11 (t, *J* = 249.7 Hz), 65.87, 62.74, 54.21, 14.05. ^{19}F NMR (564 MHz, $CDCl_3$) δ -63.04, -101.17.

Following general procedure, the product **3i**[10] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (46.2 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 13.4, 6.4 Hz, 1H), 7.30 (t, *J* = 6.9 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 8.7 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.56 – 3.53 (m, 4H), 2.96 – 2.89 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.50 (t, *J* = 31.9 Hz), 159.86 (d, *J* = 250.2 Hz), 131.82 (d, *J* = 8.0 Hz), 131.57 (t, *J* = 31.6 Hz), 130.75 (d, *J* = 3.0 Hz), 124.28 (d, *J* = 3.5 Hz), 119.47 (d, *J* = 18.4 Hz), 115.78 (d, *J* = 21.4 Hz), 113.98 (t, *J* = 249.3 Hz), 65.98, 62.54, 53.40, 13.98. ^{19}F NMR (564 MHz, $CDCl_3$) δ -102.11, -109.87.

Following general procedure, the product **3j**[10] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (45.7 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.55 (t, *J* = 4.9 Hz, 4H), 2.99 – 2.88 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.60 (t, *J* = 30.5 Hz), 134.53, 132.50 (dd, *J* = 35.1, 30.3 Hz), 131.17, 131.01, 130.90, 129.48, 126.67, 114.22 (t, *J* = 247.5 Hz), 66.18, 62.49, 53.28, 14.01. ^{19}F NMR (564 MHz, $CDCl_3$) δ -99.99 (d, *J* = 266.4 Hz), -103.11 (d, *J* = 266.3 Hz).

Following general procedure, the product **3k**[10] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow liquid (50.7 mg, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.31 – 7.26 (m, 1H), 4.39 (q, *J* = 6.9 Hz, 2H), 3.62 (t, *J* = 4.9 Hz, 4H), 3.09 – 3.03 (m, 2H), 3.01 – 2.94 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.66 (t, *J* = 31.1 Hz), 133.43, 133.27 (d, *J* = 6.0 Hz), 131.29, 130.97, 130.35, 127.20, 124.26, 114.24 (dd, *J* = 250.9, 248.0 Hz), 66.29, 62.52, 53.35, 14.07. ^{19}F NMR (564 MHz, CDCl$_3$) δ -99.75 (d, *J* = 265.9 Hz), -102.92 (d, *J* = 265.9 Hz).

Following general procedure, the product **3l**[10] was purified by flash chromatography (PE/EA = 10:1) as a colorless liquid (45.6 mg, 70%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.31 (t, *J* = 6.8 Hz, 2H), 7.21 (t, *J* = 8.9 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.58 (td, *J* = 6.3, 3.8 Hz, 4H), 2.95 – 2.92 (m, 2H), 2.91 – 2.86 (m, 2H), 2.29 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 163.89 (t, *J* = 31.8 Hz), 138.69 (dd, *J* = 34.9, 29.8 Hz), 138.06, 131.19, 129.95, 129.68, 128.81, 125.73, 114.43 (t, *J* = 249.0 Hz), 66.26, 62.45, 53.81, 19.65, 14.08. ^{19}F NMR (564 MHz, CDCl$_3$) δ -100.98 (d, *J* = 268.8 Hz), -103.32 (d, *J* = 268.6 Hz).

Following general procedure, the product **3m**[10] was purified by flash chromatography (PE/EA = 5:1) as a colorless liquid (53.4 mg, 78%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.38 (td, *J* = 8.4, 1.7 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 6.97 (td, *J* = 7.5, 0.7 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.62 – 3.56 (m, 4H), 3.05 – 2.94 (m, 4H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 164.02 (t, *J* = 32.2 Hz), 157.58, 134.77 (t, *J* = 32.9 Hz), 131.14, 130.40, 120.78, 120.48, 114.15 (t, *J* = 249.4 Hz), 111.04, 66.13, 62.37, 55.70, 53.32, 14.04. ^{19}F NMR (564 MHz, CDCl$_3$) δ -105.15, -105.91.

Following general procedure, the product **3n**[10] was purified by flash chromatography (PE/EA = 10:1) as a pale yellow liquid (55.4 mg, 80%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.49 (s, 1H), 7.41 – 7.35 (m, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.64 – 3.58 (m, 4H), 2.97 – 2.93 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 163.36 (t, *J* = 31.5 Hz), 138.44 (t, *J* = 32.0 Hz), 134.73, 132.87, 129.97, 129.94, 128.66, 126.87, 114.09 (t, *J* = 249.6 Hz), 65.89, 62.67, 54.14, 14.05. ^{19}F NMR (564 MHz, CDCl$_3$) δ -101.28.

Following general procedure, the product **3o**[10] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (60.0 mg, 77%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.65 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.64 – 3.60 (m, 4H), 2.97 – 2.93 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 163.35 (t, *J* = 31.6 Hz), 138.29 (t, *J* = 32.0 Hz), 133.12, 132.85, 131.49, 130.19, 127.30, 122.74, 114.08 (t, *J* = 249.9 Hz), 65.89, 62.67, 54.15, 14.05. ^{19}F NMR (564 MHz, CDCl$_3$) δ -101.24.

Following general procedure, the product **3p**[6] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (49.0 mg, 79%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.49 – 7.43 (m, 2H), 7.42 – 7.36 (m, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.95 – 2.91 (m, 4H), 1.49 – 1.41 (m, 6H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 164.11 (t, *J* = 31.8 Hz), 136.76 (t, *J* = 31.8 Hz), 131.95, 129.23, 128.68, 128.41, 114.99 (t, *J* = 248.5 Hz), 62.42, 54.70, 24.68, 23.83, 14.07. ^{19}F NMR (564 MHz, CDCl$_3$) δ -100.58.

Following general procedure, the product **3q** was purified by flash chromatography (PE/EA = 10:1) as a yellow solid (59.6 mg, 81%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 2.95 – 2.91 (m, 4H), 1.50 – 1.42 (m, 6H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 166.43, 163.79 (t, *J* = 31.7 Hz), 136.68, 134.91 (t, *J* = 32.0 Hz), 130.68, 129.55, 128.83, 114.82 (t, *J* = 248.7 Hz), 62.51, 54.85, 52.27, 24.66, 23.67, 14.04. ^{19}F NMR (564

MHz, CDCl$_3$) δ -100.16.

Following general procedure, the product **3r** was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (57.0 mg, 81%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.86 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.97 – 2.94 (m, 4H), 2.28 (s, 3H), 2.26 (s, 6H), 1.43 (dt, J = 9.0, 7.8 Hz, 6H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 164.58 (t, J = 32.7 Hz), 138.71, 137.82, 133.98 (t, J = 33.0 Hz), 128.91, 128.20, 115.31 (t, J = 248.9 Hz), 62.20, 53.62, 25.54, 23.93, 21.12, 20.29, 14.07. ^{19}F NMR (564 MHz, CDCl$_3$) δ -101.08 (d, J = 4.4 Hz).

Following general procedure, the product **3s** was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (65.6 mg, 82%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.71 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 6H), 3.64 – 3.61 (m, 4H), 2.99 – 2.95 (m, 4H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 163.58 (t, J = 31.5 Hz), 153.24, 139.56 (t, J = 31.8 Hz), 138.81, 125.93, 114.39 (t, J = 249.4 Hz), 105.54, 66.05, 62.56, 60.86, 56.13, 53.90, 14.01. ^{19}F NMR (564 MHz, CDCl$_3$) δ -101.37 (d, J = 5.0 Hz).

Following general procedure, the product **3t**[7] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (34.7 mg, 45%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.34 (s, 1H), 7.27 (d, J = 7.7 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 4.61 (t, J = 8.7 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.64 – 3.58 (m, 4H), 3.23 (t, J = 8.7 Hz, 2H), 3.00 – 2.89 (m, 4H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 163.70 (t, J = 31.8 Hz), 161.12, 141.71 (t, J = 31.4 Hz), 128.86, 127.58, 125.01, 122.63, 114.36 (t, J = 249.5 Hz), 109.45, 71.50, 65.94, 62.44, 53.96, 29.33, 14.00. ^{19}F NMR (564 MHz, CDCl$_3$) δ -101.51.

Following general procedure, the product **3u**[7] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (30.2 mg, 42%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.38 – 8.25 (m, 1H), 7.98 (s, 1H), 7.89 – 7.81 (m, 2H), 7.64 – 7.43 (m, 3H), 4.40 (q, J = 7.1 Hz, 3H), 3.64 – 3.53 (m, 4H), 3.03 – 2.91 (m, 4H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 163.68 (t, J = 31.9 Hz), 140.67 (t, J = 32.5 Hz), 133.45, 132.79, 131.30, 128.48, 128.35, 128.35, 127.76, 127.33, 126.75, 125.38, 114.43 (t, J = 249.3 Hz), 65.97, 62.59, 54.19, 14.07. ^{19}F NMR (564 MHz, CDCl$_3$) δ -101.19.

Following general procedure, the product **3v**[7] (*E/Z* = 10/7) was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (27.2 mg, 40%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.32 – 7.28 (m, 2H × 1 + 2H × 0.7), 7.25 – 7.18 (m, 3H × 1 + 3H × 0.7), 4.35 (q, J = 7.1 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H × 0.7), 3.77 – 3.73 (m, 4H), 3.71 – 3.67 (m, 4H × 0.7), 2.98 – 2.94 (m, 2H × 1 + 2H × 0.7), 2.84 – 2.81 (m, 2H × 1 + 2H × 0.7), 2.79 – 2.74 (m, 4H), 2.64 – 2.59 (m, 4H × 0.7), 1.38 – 1.32 (m, 3H × 1 + 3H × 0.7). ^{13}C NMR (151 MHz, CDCl$_3$) δ 167.83 (t, J = 25.3 Hz), 162.87 (t, J = 31.3 Hz), 161.72 (t, J = 31.2 Hz), 158.07 (t, J = 29.3 Hz), 140.48, 140.39, 128.56, 128.50, 128.39, 128.25, 126.43, 126.23, 113.78 (t, J = 251.7 Hz), 107.91 (t, J = 253.5 Hz), 65.90, 65.33, 62.68, 62.34, 54.92, 54.65, 32.91, 32.04, 31.72, 28.80, 13.99, 13.98. ^{19}F NMR (564 MHz, CDCl$_3$) δ -105.14, -105.92.

Following general procedure, the product **3w** was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (55.5 mg, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.7, 5.8 Hz, 4H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.01 – 2.94 (m, 4H), 1.51 – 1.42 (m, 6H), 1.40 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.11 (t, *J* = 31.8 Hz), 141.87, 140.12, 136.63 (t, *J* = 31.8 Hz), 130.67, 129.04, 128.83, 127.71, 127.03, 127.02, 115.09 (t, *J* = 248.5 Hz), 62.46, 54.75, 24.69, 23.83, 14.08. ^{19}F NMR (564 MHz, $CDCl_3$) δ -100.36.

Following general procedure, the product **3x**[7] was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (31.3 mg, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.67 (d, *J* = 4.7 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 7.5, 5.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.64 – 3.59 (m, 4H), 2.98 – 2.94 (m, 4H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.16 (t, *J* = 31.4 Hz), 150.62, 149.37, 136.12, 127.60, 123.49, 114.02 (t, *J* = 249.8 Hz), 65.82, 62.75, 54.21, 14.03. ^{19}F NMR (564 MHz, $CDCl_3$) δ -101.33.

Following general procedure, the product **3y** was purified by flash chromatography (PE/EA = 10:1) as a slight yellow oil (59.1 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 11H), 7.04 (d, *J* = 7.2 Hz, 4H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.17 (s, 4H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.12 (t, *J* = 31.8 Hz), 136.88, 134.87 (t, *J* = 32.7 Hz), 131.08, 129.41, 129.14, 128.38, 127.95, 127.67, 127.23, 114.95 (t, *J* = 247.9 Hz), 62.43, 58.75, 13.97. ^{19}F NMR (564 MHz, $CDCl_3$) δ -100.03.

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