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Graphical Abstract

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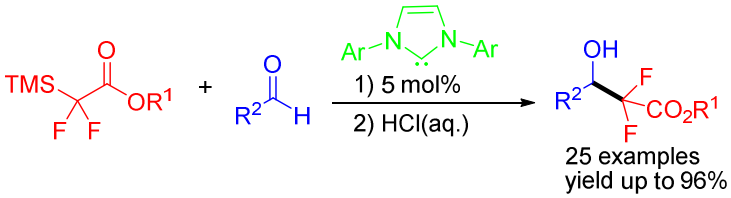

N-heterocyclic carbene-catalyzed fluorinated silyl-Reformatsky reaction of aldehydes with difluoro (trimethylsilyl) acetate

Ying Wang,[a†] Fen Xing,[a†] Cheng-Zhi Gu,[a] Wen-Juan Li,[a*] Lin He,[a] Bin Dai,[a] Guang-Fen Du [a*]

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Abstract: N-Heterocyclic carbenes (NHCs) have been employed as highly efficient organocatalysts for fluorinated silyl-Reformatsky reaction of carbonyl compounds. In the presence of 5-10 mol % NHC **A**, various aldehydes and 2,2,2–trifluoroacetophenone reacted with difluoro (trimethylsilyl) acetate to produce β–hydroxy *gem*–difluoro esters in 20–96% yields.

Keywords: N-Heterocyclic carbene; difluoro (trimethylsilyl) acetate; β–hydroxy *gem*–difluoro ester; silyl-Reformatsky reaction

1. Introduction

Fluorinated compounds have found a wide range of applications in pharmaceuticals, agrochemicals and medical chemistry.[1] Owing to the special properties of fluorine, the incorporation of fluorine atoms or fluorinated moieties into bioactive compounds has become a routine

strategy in new drug discovery. Among various fluorinated molecules, β–hydroxy *gem*–difluoro esters are particularly interesting with respect to the synthesis of bioactive compounds.[2] In the past decades, considerable efforts have been directed towards the development of efficient methods for the introduction of *gem*–difluoromethylene group into organic molecules.[3] Several fluorinating reagents such as DAST, BAST[4] and NBS-HF-amine complexes[5] can react with ketones to construct *gem*–difluoromethylene unit, but with very limited substrate scope. Mukaiyama aldol reaction[6] and Reformatsky reaction[7] can introduce *gem*–difluoromethylene into carbonyl compounds. However, the unstable fluorinated silicon enolate, harsh reaction conditions for the preparation of active organozinc reagents and the use of stoichiometric amounts of transition-metal additives restrict the applications of these methods. Therefore, the development of efficient and mild protocol for the incorporation of CF_2 group into carbonyl compounds is still highly desirable.

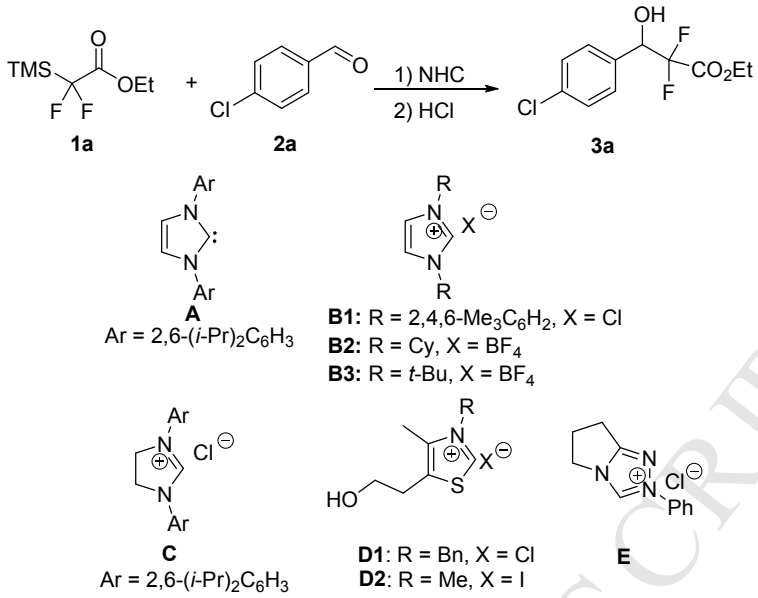
Recently, Song reported[8] that N–heterocyclic carbenes (NHCs) can be utilized as highly efficient organocatalysts[9] to mediate trifluoromethylation reaction between $TMSCF_3$ and aldehydes. But unfortunately, this protocol is not suitable for difluoromethylation reaction between $TMSCF_2H$ and carbonyl compounds.[10] We recently found that NHCs can catalyze silyl–Reformatsky reaction between

α–trimethyl silylcarbonyl compounds and aldehydes.[11] Based on this study, we envisioned that NHCs could be utilized to mediate fluorinated silyl–Reformatsky reaction of difluoro (trimethylsilyl) acetate,[12] which would provide an organocatalytic approach for nucleophilic difluoromethylenation of carbonyl compounds. Herein, we would like to report this result.

2. Results and discussion

Our research started with the reaction of 2,2–difluoro–2–trimethylsilyl acetate **1a**[13] and *p*–chlorobenzaldehyde. In the presence of 5 mol% NHC **A**,[14] the reaction smoothly proceeded in CH_3CN to furnish **3a** in 55% yield (Table 1, entry 1). With this fruitful result in hand, other common NHCs were surveyed for the reaction. NHCs generated from imidazolium can promote the reaction in moderate yields, while NHC derived from saturated imidazolinium showed relatively low reactivity (Table 1, entries 2-5). Both thiazolium and triazolium salts derived NHCs cannot promote the addition (Table 1, entries 6-8). A brief screening of reaction media indicated that the high polar DMF can afford the desired product in excellent yield (Table 1, entries 9-14). However, reduction catalyst loading to 1 mol% led to dramatic decrease of the reaction yield (Table 1, entry 15).

Table 1 Optimization of reaction conditions [a]



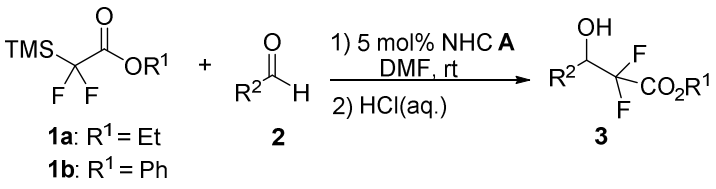
Entry	Conditions	Time (h)	Yield [b] (%)
1	5 mol% **A**, CH_3CN	12	55
2	5 mol% **B1**, DBU, CH_3CN	12	56
3	5 mol% **B2**, DBU, CH_3CN	12	53
4	5 mol% **B3**, DBU, CH_3CN	12	55
5	5 mol% **C**, DBU, CH_3CN	12	39
6	5 mol% **D1**, DBU, CH_3CN	12	< 10
7	5 mol% **D2**, DBU, CH_3CN	12	< 10
8	5 mol% **E**, DBU, CH_3CN	12	< 10
9	5 mol% **A**, toluene	24	15
10	5 mol% **A**, CH_2Cl_2	24	13
11	5 mol% **A**, $CHCl_3$	24	16
12	5 mol% **A**, Et_2O	24	22
13	5 mol% **A**, THF	24	26
14	5 mol% **A**, DMF	12	95
15	1 mol% **A**, DMF	24	65

[a] Reaction conditions: 1.5 equiv of **1a**, 0.3 mol/L of **2a**, room temperature. [b] Isolated yield.

With the optimal reaction conditions in hand (Table 1, entry 14), the scope of aldehydes was next examined and the results were summarized in Table 2. A wide range of aldehydes performed the reaction very well. Aromatic aldehydes with electron-withdrawing groups gave higher yields than those with electron-neutral or donating groups (Table 2, entries 1-8), while different positions of the substituents had no obvious effects on the

reaction (Table 2, entries 9-15). Both heliotropin and naphthaldehydes were proved to be suitable substrates, producing the corresponding products in excellent yields (Table 2, entries 16-18). Heteroaromatic aldehydes such as furfural and 2–thienyl aldehyde reacted with silylated reagent **1a** smoothly, affording the desired products in 67% and 68% yield, respectively (Table 2, entries 19 and 20). Gratifyingly, when *trans*–cinnamaldehyde was used for the reaction, the desired product **3u** can be obtained in 77% yield (Table 2, entry 21). Notably, aliphatic aldehydes, such as cyclohexanecarboxaldehyde and phenylpropyl aldehyde were also proved to be competent reactants, producing the desired product in 58% and 40% yield, respectively (Table 2, entries 22 and 23). Intriguingly, 2,2,2–trifluoroacetophenone can participate in the reaction well, producing **3x** in moderate yield (Table 2, entry 24). More interestingly, the reaction can be conducted on gram-scale and high yield maintained (Table 2, entry 25). However, when 2,2–difluoro–2–trimethylsilyl acetate **1b** was used instead of **1a**, the desired product was only isolated in 20% yield (Table 2, entry 26).

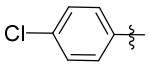
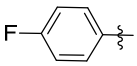
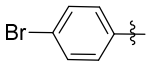
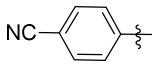
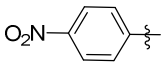
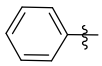
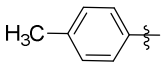
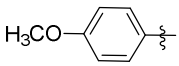
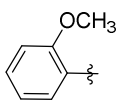
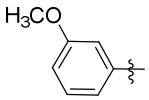
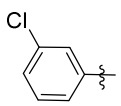
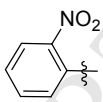
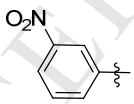
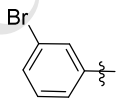
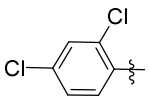
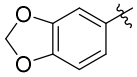
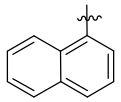
Table 2 Evaluation of substrates scope [a]

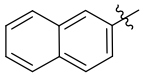
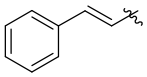
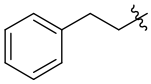
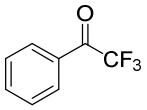
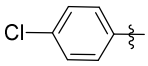
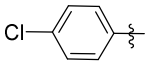


1a: R^1 = Et
1b: R^1 = Ph

2

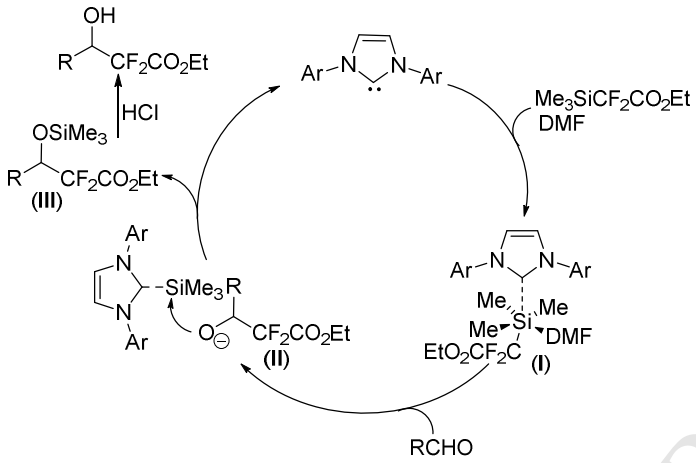
3

Entry	R	Time (h)	Product	Yield [b] (%)
1		12	**3a**	95
2		12	**3b**	92
3		15	**3c**	96
4		12	**3d**	96
5		6	**3e**	94
6[c]		24	**3f**	77
7		24	**3g**	80
8		24	**3h**	71
9[c]		24	**3i**	68
10[c]		24	**3j**	71
11[c]		15	**3k**	80
12[c]		15	**3l**	79
13[c]		15	**3m**	83
14[c]		6	**3n**	82
15[c]		6	**3o**	72
16[c]		15	**3p**	85
17		12	**3q**	90

18[c]		24	**3r**	87
19		15	**3s**	67
20		15	**3t**	68
21		12	**3u**	77
22		15	**3v**	58
23		13	**3w**	40
24		15	**3x**	45
25[d]		12	**3a**	85
26[e]		12	**3y**	20

[a] Reaction conditions: 5 mol% of NHC **A**, 1.5 equiv of **1a**, 0.3 mol/L of **2**, room temperature. [b] Isolated yield. [c] Using 10 mol% of NHC **A.** [d] 5 mol% of NHC **A**, **1** (7.5 mmol), **2a** (5.0 mmol), room temperature. [e] Using **1b** instead of **1a**.

Based on the pioneering work of NHC–mediated nucleophilic addition reactions of silicon-based nucleophiles, a plausible mechanism is proposed as depicted in Scheme 1. NHC attacks the silicon atom of $TMSCF_2COOEt$ to form a reactive hexavalent species **I** in DMF, which can initiate the following addition with aldehyde to produce intermediate **II**. The oxy anion attacks TMS group to form trimethylsilyl ether **III**, and after acidic work-up affords the final product.



Scheme 1 Proposed Mechanism

3. Conclusions

In conclusion, an NHC-catalyzed fluorinated silyl-Reformatsky reaction between carbonyl compounds and difluoro (trimethylsilyl) acetate has been described. The mild reaction conditions, simple procedure and high yields provide an efficient approach for the synthesis of β–hydroxy *gem*–difluoro esters.

4. Experimental section

4.1 General methods

Unless otherwise indicated, all reactions were conducted under nitrogen atmosphere in oven-dried glassware with magnetic stirring bar. Column chromatograph was performed with silica gel (200~300 mesh) and analytical TLC on silica gel 60-F254. ^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$), ^{19}F NMR (376 MHz, $CDCl_3$) spectra were recorded on a Bruker-DMX 400 spectrometer in $CDCl_3$, with tetramethylsilane as an internal standard and reported in ppm (δ).

N-heterocyclic carbenes **A** and **B1** were prepared according to literature procedure.[14] Silylated reagents **1** were prepared according to literature procedure.[13] All other chemicals were obtained from commercial supplies and used as received. Anhydrous THF and Et_2O, were distilled from sodium and benzophenone. DMF, CH_2Cl_2 and CH_3CN were distilled from calcium hydride. $CHCl_3$ was distilled from phosphorus pentoxide. Petroleum ether, where used, has a boiling range of 30 - 60 ^oC.

4.2 General procedure for the preparation of β–hydroxyl *gem*–difluoro esters

To a solution of IPr (NHC **A**, 6.0 mg, 0.015 mmol) in CH_3CN (1.0 mL) was added aldehyde (**2,** 0.3 mmol) and silylated reagent (**1a**, 0.45mmol, 88.2 mg). Subsequently the reaction solution was stirred at room temperature until full consume of the starting aldehyde indicated by TLC, 1.0 mL 1.0 N HCl was added at this moment and the mixture was continuously stirred for 0.5 h, then the mixture was extracted by ethyl acetate (3×10 mL). The combined organic phase was washed with saturated sodium bicarbonate and H_2O, dried by anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified through flash column chromatography (silica gel, PE/EtOAc) to give the desired products.

4.2.1 Ethyl 3-(4-chlorophenyl)-2,2-difluoro-3-hydroxypropanoate **(3a)**[15]

Light yellow liquid; IR (KBr film): 1754, 1598, 1374, 1312, 1189, 1107, 1018, 1014, 852, 830, 778, 744, 672 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.36 (m, 4H), 5.17 (dd, *J* = 15.3, 7.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.80 (s, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.4 (dd, *J* = 32.2, 30.6 Hz), 135.2, 132.9, 129.1 (t, *J* = 1.3 Hz), 128.7, 113.5 (dd, *J* = 259.7, 254.6 Hz), 73.1 (dd, *J* = 28.2, 24.6 Hz), 63.3, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.3 (d, *J* = 264.2 Hz), -120.5 (d, *J* = 264.2 Hz); GC-MS (EI): m/z 264.0 (M^{+}).

4.2.2 Ethyl 2,2-difluoro-3-(4-fluorophenyl)-3-hydroxypropanoate (**3b**)[16]

Light yellow liquid, IR (KBr film): 3488, 2991, 2943, 1754, 1650, 1511, 1447, 1397, 1375, 1312, 1225, 1189, 1101, 1069, 1014, 944, 853, 795, 781, 740, 729, 694, 636 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.38 (m, 2H), 7.14 – 7.05 (m, 2H), 5.17 (dd, *J* = 15.3, 7.8 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.99 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.5 (dd, *J* = 32.3, 30.8 Hz), 163.2 (d, *J* = 248.0 Hz), 130.3 (d, *J* = 2.6 Hz), 129.6 (dt, *J* = 8.4, 1.3 Hz), 115.4 (d, *J* = 21.9 Hz), 113.6 (dd, *J* = 259.7, 254.5 Hz), 73.1 (dd, *J* = 27.9, 24.5 Hz), 63.3, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.6 (d, *J* = 262.7 Hz), -120.5 (d, *J* = 263.0 Hz); GC-MS (EI): m/z 248.0 (M^{+}).

4.2.3 Ethyl 3-(4-bromophenyl)-2,2-difluoro-3-hydroxypropanoate **(3c)**[7d]

Light yellow liquid, IR (KBr film): 3502, 2989, 2964, 1914, 1769, 1593, 1490, 1464, 1393, 1371, 1344, 1308, 1289, 1267, 1205, 1182, 1118, 1050,

1008, 865, 833, 787, 772, 734, 701, 657, 627 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.50 (m, 2H), 7.38 – 7.30 (m, 2H), 5.15 (dd, *J* = 15.4, 7.6 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.98 (s, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.4 (dd, *J* = 32.4, 30.7 Hz), 133.4 (d, *J* = 1.9 Hz), 131.6, 129.4 (t, *J* = 1.1 Hz), 123.4, 113.4 (dd, *J* = 258.7, 253.6 Hz), 73.1 (dd, *J* = 28.0, 24.5 Hz), 63.3, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.1 (d, *J* = 263.7 Hz), -120.6 (d, *J* = 263.7 Hz); GC-MS (EI): m/z 307.9 (M^{+}).

4.2.4 Ethyl 3-(4-cyanophenyl)-2,2-difluoro-3-hydroxypropanoate **(3d)**[7d]

Light yellow liquid, IR (KBr film): 1755, 1611, 1505, 1399, 1374, 1299, 1190, 1105, 1070, 1019, 855, 883, 782, 687 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.67 (m, 2H), 7.66 – 7.55 (m, 2H), 5.27 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.10 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.1 (dd, *J* = 32.1, 30.9 Hz), 139.6 (dd, *J* = 1.3, 0.7 Hz), 132.1, 128.5 (t, *J* = 1.4 Hz), 118.4, 113.2 (dd, *J* = 261.2, 254.9 Hz), 113.0, 73.0 (dd, *J* = 28.3, 24.6 Hz), 63.5, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.0 (d, *J* = 267.7 Hz), -120.7 (d, *J* = 267.5 Hz); GC-MS (EI): m/z 255.0 (M^{+}).

4.2.5 Ethyl 2,2-difluoro-3-hydroxy-3-(4-nitrophenyl)propanoate **(3e)**

Light yellow liquid, IR (KBr film): 3502, 3078, 2916, 2848, 1758, 1608, 1522, 1495, 1464, 1448, 1372, 1352, 1448, 1372, 1352, 1308, 1201, 1177, 1118, 1061, 1014, 996, 866, 850, 829, 796, 745, 726, 691, 655 cm^{-1}; ^{1}H

NMR (400 MHz, Chloroform-*d*) δ 8.31 – 8.18 (m, 2H), 7.75 – 7.62 (m, 2H), 5.34 (dd, *J* = 15.6, 6.7 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.38 (s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.2 (dd, *J* = 32.3, 30.6 Hz), 148.4, 141.5, 128.7 (t, *J* = 1.3 Hz), 123.4, 113.2 (dd, *J* = 261.9, 256.0 Hz), 72.8 (dd, *J* = 28.5, 24.3 Hz), 63.6, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.7 (d, *J* = 266.5 Hz), -120.7 (d, *J* = 266.8 Hz); GC-MS (EI): m/z 275.0 (M^+). HRMS (ESI) m/z calcd for $C_{11}H_{12}F_2NO_5$ $[M+H]^+$ 276.0678, found 276.0676.

4.2.6 **Ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (3f)**[16]

Light yellow liquid, IR (KBr film): 3502, 2988, 2964, 2900, 1755, 1496, 1455, 1394, 1375, 1318, 1191, 1065, 1027, 922, 856, 836, 802, 782, 742, 718, 698, 629 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.38 (m, 5H), 5.17 (dd, *J* = 15.5, 8.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.85 (s, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.6 (dd, *J* = 32.3, 30.8 Hz), 134.5 (d, *J* = 2.1 Hz), 129.2, 128.4, 127.7, 113.8 (dd, *J* = 259.4, 254.2 Hz), 73.8 (dd, *J* = 27.7, 24.4 Hz), 63.2, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.8 (d, *J* = 261.6 Hz), -120.4 (d, *J* = 261.6 Hz); GC-MS (EI): m/z 230.0 (M^+).

4.2.7 Ethyl 2,2-difluoro-3-hydroxy-3-(p-tolyl)propanoate **(3g)**[16]

Light yellow liquid, IR (KBr film): 2988, 2957, 1756, 1653, 1616, 1558, 1516, 1447, 1394, 1374, 1316, 1190, 1104, 1069, 1043, 1020, 856, 828, 774, 723, 696, 622 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 –

7.30 (m, 2H), 7.25 – 7.16 (m, 2H), 5.14 (dd, *J* = 15.6, 8.1 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 2.78 (s, 1H), 2.39 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.6 (dd, *J* = 32.5, 31.4 Hz), 139.2, 131.5 (d, *J* = 2.1 Hz), 129.2, 127.6 (t, *J* = 1.1 Hz), 113.8 (dd, *J* = 258.4, 252.9 Hz), 73.7 (dd, *J* = 27.8, 24.4 Hz), 63.1, 21.2, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.9 (d, *J* = 261.0 Hz), -120.5 (d, *J* = 261.0 Hz); GC-MS (EI): m/z 244.0 (M^+).

4.2.8 Ethyl 2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)propanoate **(3h)**[17]

Light yellow liquid, IR (KBr film): 3675, 3502, 2988, 2961, 1755, 1612, 1586, 1514, 1465, 1395, 1374, 1305, 1249, 1176, 1066, 1028, 835, 786, 740, 697, 637, 603 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.34 (m, 2H), 6.95 – 6.89 (m, 2H), 5.11 (dd, *J* = 15.4, 8.3 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.90 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.7 (dd, *J* = 32.6, 30.9 Hz), 160.3, 129.1 (t, *J* = 1.1 Hz), 126.6 (d, *J* = 2.2 Hz), 113.9, 113.8 (dd, *J* = 259.6, 253.5 Hz), 73.4 (dd, *J* = 27.8, 24.4 Hz), 63.1, 55.3, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -114.2 (d, *J* = 260.5 Hz), -120.5 (d, *J* = 260.4 Hz); GC-MS (EI): m/z 260.0 (M^+).

4.2.9 Ethyl 2,2-difluoro-3-hydroxy-3-(2-methoxyphenyl)propanoate **(3i)**

Light yellow liquid, IR (KBr film): 3502, 2998, 2964, 1757, 1603, 1589, 1493, 1464, 1441, 1394, 1374, 1310, 1288, 1245, 1184, 1118, 1066, 1044,

1025, 943, 856, 836, 801, 784, 754, 708, 627 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.32 (m, 2H), 7.07 – 6.91 (m, 2H), 5.36 (dd, *J* = 18.0, 7.5 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.8 (dd, *J* = 32.9, 30.5 Hz), 157.9, 130.3, 129.9 (t, *J* = 1.2 Hz), 122.2 (d, *J* = 1.6 Hz), 121.0, 114.4 (dd, *J* = 259.4, 254.9 Hz), 111.3, 71.8 (dd, *J* = 28.4, 24.5 Hz), 63.0, 55.8, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.9 (d, *J* = 256.2 Hz), -121.5 (d, *J* = 256.1 Hz); GC-MS (EI): m/z 260.0 (M^+); HRMS (ESI) m/z calcd for $C_{12}H_{15}F_2O_4$ $[M+H]^+$ 261.0932, found 261.0929.

4.2.10 Ethyl 2,2-difluoro-3-hydroxy-3-(3-methoxyphenyl)propanoate **(3j)**[18]

Light yellow liquid, IR (KBr film): 3675, 3502, 2988, 2961, 1755, 1602, 1587, 1491, 1456, 1457, 1394, 1374, 1309, 1257, 1189, 1158, 1096, 1067, 1039, 927, 850, 767, 716, 696, 641 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.28 (m, 1H), 7.08 – 7.00 (m, 2H), 6.97 – 6.88 (m, 1H), 5.15 (dd, *J* = 14.2, 7.2 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 2.96 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.6 (dd, *J* = 32.6, 30.8 Hz), 159.6, 136.0 (d, *J* = 2.1 Hz), 129.4, 120.0 (t, *J* = 1.1 Hz), 114.9, 113.7 (dd, *J* = 259.9, 254.4 Hz), 113.1 (t, *J* = 1.2 Hz), 73.7 (dd, *J* = 27.8, 24.3 Hz), 63.2, 55.3, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.7 (d, *J* = 261.5 Hz), -120.4 (d, *J* = 261.5 Hz); GC-MS (EI): m/z 260.1 (M^+).

4.2.11 Ethyl 3-(3-chlorophenyl)-2,2-difluoro-3-hydroxypropanoate (**3k**)

Light yellow liquid, IR (KBr film): 1754, 1656, 1599, 1576, 1475, 1432, 1374, 1306, 1191, 1101, 1067, 1009, 900, 848, 772, 748, 692, 664 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.44 (m, 1H), 7.41 – 7.30 (m, 3H), 5.16 (dd, *J* = 15.3, 7.5 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.23 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.4 (dd, *J* = 33.0, 30.4 Hz), 136.5 (dd, *J* = 1.8, 0.6 Hz), 134.4, 129.7, 129.3, 127.9 (t, *J* = 1.2 Hz), 125.9 (t, *J* = 1.3 Hz), 113.5 (dd, *J* = 259.8, 256.2 Hz), 73.1 (dd, *J* = 28.0, 24.6 Hz), 63.4, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.0 (d, *J* = 263.6 Hz), -120.4 (d, *J* = 263.4 Hz); GC-MS (EI): 263.9 (M^+). HRMS (ESI) m/z calcd for $C_{11}H_{12}ClF_2O_3$ $[M+H]^+$ 265.0437, found 265.0438.

4.2.12 Ethyl 2,2-difluoro-3-hydroxy-3-(2-nitrophenyl)propanoate **(3l)**[19]

Light brown liquid, IR (KBr film): 3568, 3003, 2954, 2840, 1743, 1716, 1600, 1586, 1528, 1492, 1463, 1437, 1352, 1290, 1243, 1119, 1080, 1053, 1025, 924, 853, 830, 796, 751, 691, 673 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 – 7.89 (m, 2H), 7.76 – 7.66 (m, 1H), 7.60 – 7.50 (m, 1H), 6.25 (dd, *J* = 15.3, 6.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.55 (s, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.1 (dd, *J* = 32.6, 30.8 Hz), 148.8, 133.3, 130.1 (t, *J* = 1.5 Hz), 129.8, 129.5 (d, *J* = 1.4 Hz), 124.7, 113.4 (dd, *J* = 260.7, 255.5 Hz), 67.7 (dd, *J*

= 28.7, 23.6 Hz), 63.6, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.8 (d, *J* = 266.2 Hz), -120.4 (d, *J* = 265.7 Hz); GC-MS (EI): 275.0 (M^+).

4.2.13 Ethyl 2,2-difluoro-3-hydroxy-3-(3-nitrophenyl)propanoate (**3m**)

Light brown liquid, IR (KBr film): 1751, 1585, 1536, 1471, 1411, 1351, 1322, 1194, 1056, 930, 909, 858, 825, 726, 680, 671, 628 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 – 8.34 (m, 1H), 8.30 – 8.22 (m, 1H), 7.90 – 7.80 (m, 1H), 7.66 – 7.57 (m, 1H), 5.34 (dd, *J* = 15.4, 6.8 Hz, 1H), 4.37 (q, *J* = 7.6 Hz, 2H), 3.23 (s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.1 (dd, *J* = 32.5, 30.8 Hz), 148.2, 136.6, 133.8 (t, *J* = 1.3 Hz), 129.4, 124.1, 122.8 (t, *J* = 1.3 Hz), 113.2 (dd, *J* = 261.4, 254.8 Hz), 72.7 (dd, *J* = 28.7, 24.7 Hz), 63.6, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.9 (d, *J* = 267.7 Hz), -120.8 (d, *J* = 267.0 Hz); GC-MS (EI): m/z 275.0 (M^+); HRMS (ESI) m/z calcd for $C_{11}H_{11}F_2NO_5$ $[M+H]^+$ 275.0605, found 275.0609.

4.2.14 Ethyl 3-(3-bromophenyl)-2,2-difluoro-3-hydroxypropanoate (**3n**)

Light yellow liquid, IR (KBr film): 3675, 3411, 2988, 2923, 2851, 1762, 1676, 1593, 1578, 1489, 1449, 1387, 1318, 1125, 1205, 1176, 1084, 1027, 1002, 973, 855, 753, 672, 645 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.60 (m, 1H), 7.57 – 7.50 (m, 1H), 7.42 – 7.36 (m, 1H), 7.31 – 7.26 (m, 1H), 5.15 (dd, *J* = 15.3, 7.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.10 (s, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.4 (dd, *J* = 32.4, 31.0 Hz), 136.7, 132.3, 130.8 (t, *J* = 1.3 Hz), 129.9,

126.4 (t, *J* = 1.3 Hz), 122.5, 113.5 (dd, *J* = 259.9, 254.5 Hz), 73.0 (dd, *J* = 28.1, 24.7 Hz), 63.4, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.0 (d, *J* = 263.5 Hz), -120.4 (d, *J* = 263.5 Hz); GC-MS (EI): m/z 307.9 (M^+). HRMS (ESI) m/z calcd for $C_{11}H_{12}BrF_2O_3$ $[M+H]^+$ 308.9932, found 308.9934.

4.2.15 Ethyl 3-(2,4-dichlorophenyl)-2,2-difluoro-3-hydroxypropanoate (**3o**)

Light yellow liquid, IR (KBr film): 3675, 3502, 2988, 2959, 1754, 1590, 1563, 1563, 1534, 1473, 1376, 1309, 1184, 1108, 1070, 1042, 1010, 847, 830, 780, 741, 689, 659 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.55 (m, 1H), 7.46 – 7.40 (m, 1H), 7.38 – 7.31 (m, 1H), 5.73 (dd, *J* = 15.9, 6.5 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.02 (s, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.4 (dd, *J* = 32.5, 30.6 Hz), 135.7, 134.5, 131.2 (d, *J* = 1.5 Hz), 130.7 (dd, *J* = 2.1, 1.2 Hz), 129.3, 127.5, 113.5 (dd, *J* = 260.8, 255.3 Hz), 69.1 (dd, *J* = 28.9, 23.7 Hz), 63.5, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.7 (d, *J* = 265.5 Hz), -120.9 (d, *J* = 265.6 Hz); GC-MS (EI): m/z 297.5 (M^+). HRMS (ESI) m/z calcd for $C_{11}H_{11}Cl_2F_2O_3$ $[M+H]^+$ 299.0047, found 299.0042.

4.2.16Ethyl3-(benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-3-hydroxypropanoate (**3p**)[7d]

Light yellow liquid; IR (KBr film): 3502, 2992, 2908, 1754, 1610, 1505, 1489, 1445, 1375, 1396, 1307, 1244, 1187, 1095, 1067, 1-34, 925, 853, 778, 711, 633 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 – 6.94 (m, 0H), 6.93 – 6.88 (m, 1H), 6.85 – 6.80 (m, 1H), 6.00 (s, 2H), 5.10 (dd, *J* = 15.2, 8.1 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.81 (s, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.5 (dd, *J* = 32.5, 30.8 Hz), 148.4, 147.9, 128.1 (t, *J* = 1.8 Hz), 121.7 (t, *J* = 1.1 Hz), 113.6 (dd, *J* = 259.2, 253.9 Hz), 108.1, 108.0 (t, *J* = 1.5 Hz), 101.3, 73.6 (dd, *J* = 27.8, 24.3 Hz), 63.2, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -114.1 (d, *J* = 261.5 Hz), -120.5 (d, *J* = 261.5 Hz); GC-MS (EI): 274.0(M^{+}).

4.2.17 Ethyl 2,2-difluoro-3-hydroxy-3-(naphthalen-1-yl)propanoate (**3q**)[16]

Light yellow liquid; IR (KBr film): 3523, 2988, 2958, 1755, 1635, 1653, 1598, 1558, 1540, 1514, 1471, 1446, 1395, 1374, 1306, 1193, 1170, 1080, 1066, 998, 953, 845, 787, 753, 718, 640, 625 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 – 8.08 (m, 1H), 7.95 – 7.87 (m, 2H), 7.85 – 7.77 (m, 1H), 7.61 – 7.49 (m, 3H), 6.08 (dd, *J* = 15.7, 7.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.95 (s, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.8 (dd, *J* = 32.7, 30.6 Hz), 133.6, 131.4, 130.7 (d, *J* = 1.6 Hz), 129.9, 128.9, 126.6, 126.2 (d, *J* = 1.5 Hz), 125.8, 125.2, 123.2 (dd, *J* = 2.4, 1.3 Hz), 114.3 (dd, *J* = 260.3, 254.3 Hz), 69.7 (dd, *J* = 28.5,

24.3 Hz), 63.3, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.2 (d, *J* = 260.3 Hz), -119.6 (d, *J* = 260.6 Hz); GC-MS (EI) 280.0 (M^+).

4.2.18 Ethyl 2,2-difluoro-3-hydroxy-3-(naphthalen-2-yl)propanoate (**3r**)[16]

Light yellow liquid, IR (KBr film): 3484, 2988, 2940, 1753, 1596, 1572, 1474, 1429, 1397, 1308, 1189, 1089, 1099, 1070, 998, 855, 770, 742, 691, 668, 630 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 – 7.81 (m, 4H), 7.62 – 7.49 (m, 3H), 5.35 (dd, *J* = 15.4, 8.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.23 (s, 1H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.7 (dd, *J* = 32.5, 30.9 Hz), 133.7, 132.9, 132.0 (d, *J* = 2.2 Hz), 128.2, 128.2, 127.7, 127.5, 126.7, 126.4, 124.8 (t, *J* = 1.4 Hz), 114.0 (dd, *J* = 260.0, 253.6 Hz), 73.9 (dd, *J* = 27.9, 24.5 Hz), 63.2, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.3 (d, *J* = 261.6 Hz), -120.0 (d, *J* = 261.6 Hz); GC-MS (EI) 280.0 (M^+).

4.2.19 Ethyl 2,2-difluoro-3-(furan-2-yl)-3-hydroxypropanoate (**3s**)[16]

Light yellow liquid; IR (KBr film): 3675, 3469, 2988, 2900, 1755, 1646, 1502, 1448, 1394, 1375, 1308, 1198, 1147, 1080, 1065, 1012, 944, 928, 886, 854, 789, 708, 645 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.54 – 6.51 (m, 1H), 6.44 – 6.41 (m, 1H), 5.22 (dd, *J* = 14.6, 8.2 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.01 (s, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.0 (dd, *J* = 32.1, 30.8 Hz), 143.5, 113.0 (dd, *J* = 258.8, 255.7 Hz), 110.7, 110.1 (t, *J* = 1.4 Hz), 68.3 (dd, *J* = 28.5, 25.8 Hz), 63.3, 13.9; ^{19}F NMR (376 MHz,

Chloroform-*d*) δ -114.5 (d, *J* = 262.9 Hz), -119.7 (d, *J* = 263.0 Hz); GC-MS (EI): m/z 220.0 (M^+).

4.2.20 Ethyl 2,2-difluoro-3-hydroxy-3-(thiophen-2-yl)propanoate (**3t**)[16]

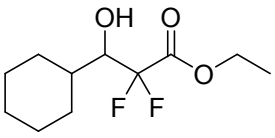
Light yellow liquid; IR (KBr film): 3675, 2988, 2958, 1755, 1653, 1558, 1537, 1471, 1436, 1394, 1375, 1305, 1183, 1164, 1066, 1041, 854, 755, 742, 705, 644 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.39 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.22 – 7.15 (m, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.44 (dd, *J* = 14.8, 7.8 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.98 (s, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.3 (dd, *J* = 32.5, 30.8 Hz), 136.8 (d, *J* = 2.3 Hz), 127.5 (t, *J* = 1.2 Hz), 127.0, 126.9, 113.2 (dd, *J* = 259.6, 255.0 Hz), 70.3 (dd, *J* = 28.8, 25.5 Hz), 63.3, 13.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -114.0 (d, *J* = 261.7 Hz), -120.2 (d, *J* = 261.7 Hz); GC-MS (EI): m/z 236.0 (M^+).

4.2.21 Ethyl (E)-2,2-difluoro-3-hydroxy-5-phenylpent-4-enoate (**3u**)[16]

Light yellow liquid; IR (KBr film): 3467, 3028, 2940, 1754, 1654, 1578, 1491, 1456, 1437, 1394, 1374, 1309, 1257, 1189, 1158, 1096, 1067, 1039, 927, 850, 767, 716, 696, 641 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.41 (m, 2H), 7.40 – 7.29 (m, 3H), 6.83 (d, *J* = 16.0 Hz, 1H), 6.26 (dd, *J* = 16.0, 6.7 Hz, 1H), 4.88 – 4.69 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.4 (dd, *J* = 32.2, 30.9 Hz), 135.9, 135.7, 128.7, 128.6, 126.9, 121.5 (dd, *J* = 3.5, 2.3 Hz), 113.9 (dd, *J* = 258.0, 255.6 Hz), 73.0 (dd, *J* = 27.9,

25.2 Hz), 63.2, 14.0; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -114.2 (d, *J* = 263.6 Hz), -120.6 (d, *J* = 263.1 Hz); GC-MS (EI): m/z 256.1 (M^+).

4.2.22 Ethyl 3-cyclohexyl-2,2-difluoro-3-hydroxypropanoate (**3v**)[17,20]



Light yellow liquid; IR (KBr film): 3523, 2990, 2926, 2854, 1757, 1535, 1450, 1395, 1374, 1314, 1209, 1181, 1093, 1062, 1041, 957, 924, 895, 855, 842, 781, 741, 715, 658 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.37 (q, *J* = 7.1 Hz, 2H), 3.84 (dt, *J* = 17.8, 6.7 Hz, 1H), 2.15 (s, 1H), 1.99 – 1.89 (m, 1H), 1.83 – 1.65 (m, 5H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.32 – 1.11 (m, 5H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.9 (dd, *J* = 33.0, 31.0 Hz), 115.4 (dd, *J* = 258.3, 255.6 Hz), 75.2 (dd, *J* = 26.1, 23.8 Hz), 63.0, 38.2 (d, *J* = 1.5 Hz), 29.6 (dd, *J* = 2.3, 1.2 Hz), 27.3 (dd, *J* = 1.7, 0.9 Hz), 26.1, 26.0, 25.8, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.6 (d, *J* = 263.5 Hz), -120.1 (d, *J* = 263.2 Hz); GC-MS (EI): m/z 236.0 (M^+).

4.2.23 Ethyl 2,2-difluoro-3-hydroxy-5-phenylpentanoate (**3w**)[20]

Colorless liquid, IR (KBr film): 1755, 1603, 1486, 1454, 1373, 1307, 1307, 1216, 1172, 1067, 1030, 856, 781, 698, 654 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.27 (m, 2H), 7.21 – 7.18 (m, 3H), 4.32 (dd, *J* = 7.1, 14.2 Hz, 2H), 4.60-4.97 (m, 1H), 2.97-2.89 (m, 1H), 2.80-2.69 (m, 1H), 2.15(s, 1H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.5 (dd, *J* = 31.3, 33.3 Hz), 140.7, 128.5, 128.4，126.2， 114.52 (dd, *J* = 255.5, 257.5 Hz), 70.9 (dd, *J* = 25.2, 27.2 Hz),

63.1, 31.2, 30.75 – 30.70 (m), 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -114.8 (d, *J* = 266.9 Hz), -121.8 (d, *J* = 266.9 Hz), -121.7 (dd, *J* = 3.7, 266.9 Hz); GC-MS (EI): m/z 297.9 (M^+).

4.2.24 Ethyl 2,2,4,4,4-pentafluoro-3-hydroxy-3-phenylbutanoate (**3x**)

Colorless liquid; IR (KBr film): 3575, 3467, 2988, 2923, 2851, 1731, 1647, 1447, 1393, 1374, 1317, 1251, 1198, 1075, 1026, 956, 891, 820, 796, 734, 662 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.71 (m, 2H), 7.50 – 7.42 (m, 3H), 4.28 (s, 1H), 4.23 (qd, *J* = 7.1, 1.4 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.4, 130.3 (d, *J* = 1.1 Hz), 130.0, 128.4, 127.0 (q, *J* = 2.0 Hz), 124.6, 121.7, 112.0 (t, *J* = 266.2 Hz), 64.0, 13.5; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -74.1 (t, *J* = 10.2 Hz), -113.7 (dq, *J* = 19.9, 10.1 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{12}F_5O_3$ $[M+H]^+$ 299.0701, found 299.0700.

4.2.25 Phenyl 3-(4-chlorophenyl)-2,2-difluoro-3-hydroxypropanoate (**3y**)[21]

White solid; m.p. 92.1-93.2 ^{o} C; IR (KBr film): 1733, 1637, 1492, 1289, 1067, 1015, 764, 749,687,571cm-1;1HNMR (400 MHz, Chloroform-d) δ 7.6 – 7.4 (m, 6H) , 7.4 – 7.3 (m, 1H), 7.2– 7.1 (m, 2H), 5.3 (dd,J= 15.1, 7.8 Hz, 1H), 2.8 (s, 1H);13CNMR (101 MHz, Chloroform-d) δ 161.8 (dd,J= 33.5, 31.7 Hz),1 49.6 , 135.5 , 132.6 , 129.8 , 129.2 , 128.8 , 126.9 , 120.8 , 113.7 (dd,J= 2 60.4, 254.9 Hz), 73.4 (dd,J= 28.0, 24.5 Hz);19F NMR(376 MHz, Chlorof

orm-d) δ -113.2 (d,J= 263.1 Hz), -119.9 (d,J= 263.1 Hz); GC-MS (EI): m/z 311.9 (M^+).

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Notes and references

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Graphical Abstract

N-heterocyclic carbene-catalyzed fluorinated silyl-Reformatsky reaction of aldehydes and difluoro (trimethylsilyl) acetate.