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PAPER

Easy access to CF_2-containing molecules based on the reaction of 2,2,3,3-tetrafluorooxetane with various nucleophiles†

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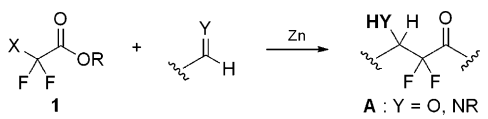
2,2,3,3-Tetrafluorooxetane reacted easily with organolithium reagents to give 1,1,3-trisubstituted 2,2-difluoropropan-1-ols in good to excellent yields. On the other hand, the reaction with Grignard reagent led to 3-bromo-1,1-disubstituted 2,2-difluoropropan-1-ols in good yields. On treating with lithium enolates, generated from enol silyl ethers and MeLi/LiBr, the corresponding 1-bromo-2,2-difluoro-3,5-dicarbonyl compounds were obtained in fair to good yields. 3-Iodo-2,2-difluoropropanoate, prepared readily from 2,2,3,3-tetrafluorooxetane and NaI, reacted successfully with various silyl enol ethers in the presence of a radical initiator to provide the corresponding coupling products in good yields.

Introduction

Incorporation of fluorine atom(s) into organic molecules often changes their structure, stability, reactivity, and biological activity, and thereby frequently leads to the discovery of novel potent applications in various domains from liquid crystalline materials to biologically active substances, peptide isosteres or enzyme inhibitors.[1] Consequently, a wide variety of synthetic methods have hitherto been developed for the preparation of various types of fluorine-incorporated compounds.[2]

Among such compounds, organic molecules containing an α,α-difluorinated carbonyl backbone have recently been recognized as one of the most important units for the application to a potent HIV protease inhibitor, *etc*.[3] Generally, it is well-known that molecules **A** having a heteroatom substituent, such as a hydroxyl or an amino group, at the β position can easily be prepared *via* the Reformatsky reaction or its variant using commercially available α-halo-α,α-difluoroacetate **1** (Scheme 1).[4] However, the fluorinated molecules **B**, without any heteroatom substituent at the β position, are very difficult to be constructed by the above methods (Scheme 2). To the best of our knowledge, there have been only a few reports on the preparation of **B** so far.[5]



Scheme 1 Reformatsky reaction.

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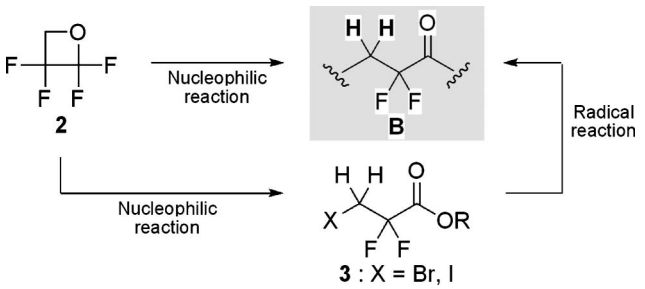


Scheme 2 Intended programs.

Therefore, the development of easy and effective synthetic methods for such molecules are highly desirable. Herein we wish to disclose easy access to various types of CF_2-containing molecules, including α,α-difluorinated carbonyl compounds without a heteroatom substituent at the β position, based on the nucleophilic reaction with 2,2,3,3-tetrafluorooxetane (**2**)[6,7] or the radical reaction of **3**, which can easily be prepared from **2**, in detail.

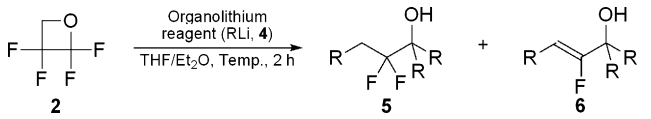
Results and discussion

Reaction of 2,2,3,3-tetrafluorooxetane with organolithium reagents

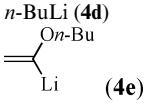
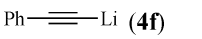
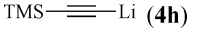
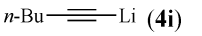
Initially, we attempted a nucleophilic ring-opening reaction of 2,2,3,3-tetrafluorooxetane (**2**) with organolithium reagents (R–Li) (**4**) as shown in Table 1.

Thus, on treating **2** with 1.1 equiv of freshly prepared PhLi (**4a**) in THF/Et_2O at −78 °C for 2 h, 2,2-difluoro-1,1,3-triphenylpropan-1-ol (**5a**) was obtained in 21% yield, together with a large amount of the unreacted starting oxetane **2** (Entry 1). As shown in Entries 2 and 3, increasing the amount of **4a** led to satisfactory results, and the best yield of **5a** (78%) was obtained when **2** was treated with 4.4 equiv of **4a** in THF at −78 °C for 2 h (Entry 3). However, (*Z*)-2-fluoroallyl alcohol **6a** was also

Table 1 Reaction of **2** with various organolithium reagents **4**



2 **5** **6**

Entry	Organolithium reagents (RLi)	Equiv of **4**	Temp./° C	Yield[a]/% of **5**	Yield[a]/% of **6**
1[b]	PhLi (**4a**)	1.1	–78	21	0
2[b]	PhLi (**4a**)	2.2	–78	41	0
3[c]	PhLi (**4a**)	4.4	–78	78	18
4[c]	PhLi (**4a**)	4.4	–20	49	43
5[c]	PhLi (**4a**)	4.4	r.t.	33	58
6[c,d]	PhLi (**4a**)	5.5	r.t.	11	71
7[c]	4-$MeOC_6H_4Li$ (**4b**)	4.4	–78	55	10
8[c]	4-$CF_3C_6H_4Li$ (**4c**)	4.4	–78	38	58
9[c]	*n*-BuLi (**4d**)	4.4	–78	25	43
10[e]	 (**4e**)	4.4	–78	—	—
11[d]	 (**4f**)	4.4	–78	6	0
12	(**4f**)	4.4	–20	91 (77)	0
13	 (**4g**)	4.4	–20	quant. (78)	0
14	 (**4h**)	4.4	–20	99 (78)	0
15	 (**4i**)	4.4	–20	99 (73)	0

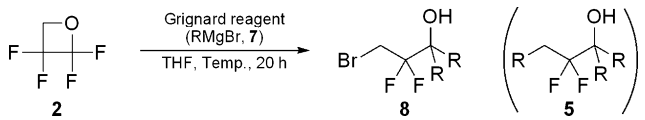
[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [b] A large amount of the starting oxetane **2** remained unreacted. [c] The products, **5** and **6** were obtained as an inseparable mixture. [d] Carried out for 20 h. [e] A complex mixture was obtained.

observed in 18% yield as byproduct, and we found that both were inseparable. Raising the reaction temperature caused an increase in the amount of **6a** (Entries 3–5). When **2** was treated with 5.5 equiv of **4a** at room temperature for 20 h, the corresponding (*Z*)-**6a** was formed in 71% yield (Entry 6). In this case, 11% of **5a** still remained unreacted. Various sorts of organolithium reagents were also applied to this reaction under the conditions as described in Entry 3. 4-Methoxyphenyllithium (**4b**) was found to be effective for this reaction, leading to 2,2-difluoropropanol derivative **5b** in 55% yield, along with 10% of (*Z*)-2-fluoroallyl alcohol **6b** (Entry 7). By contrast, 4-(trifluoromethyl)phenyllithium (**4c**) and *n*-BuLi (**4d**) provided the corresponding (*Z*)-2-fluoroallyl alcohols **6c** and **6d** in 58% and 43% yields as a major product, respectively (Entries 8 and 9). The use of alkenyllithium **4e** did not result in a satisfactory result (Entry 10). While phenylethynyllithium (**4f**) also did not react with the oxetane **2** at –78 °C (Entry 11), a higher reaction temperature (–20 °C) resulted in a quantitative formation of **5f** (Entry 12). Various lithium acetylides **4g**, **4h** and **4i** could also participate successfully in the nucleophilic ring-opening reaction to give the corresponding 2,2-difluoropropanol derivatives **5g**, **5h** and **5i** in excellent yields, respectively (Entries 13–15).

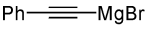
Reaction of 2,2,3,3-tetrafluorooxetane with Grignard reagents

Similarly, we examined the reaction of 2,2,3,3-tetrafluorooxetane (**2**) with Grignard reagents (**7**) as tabulated in Table 2.

Table 2 Reaction of **2** with various Grignard reagents **7**



2 **8** **5**

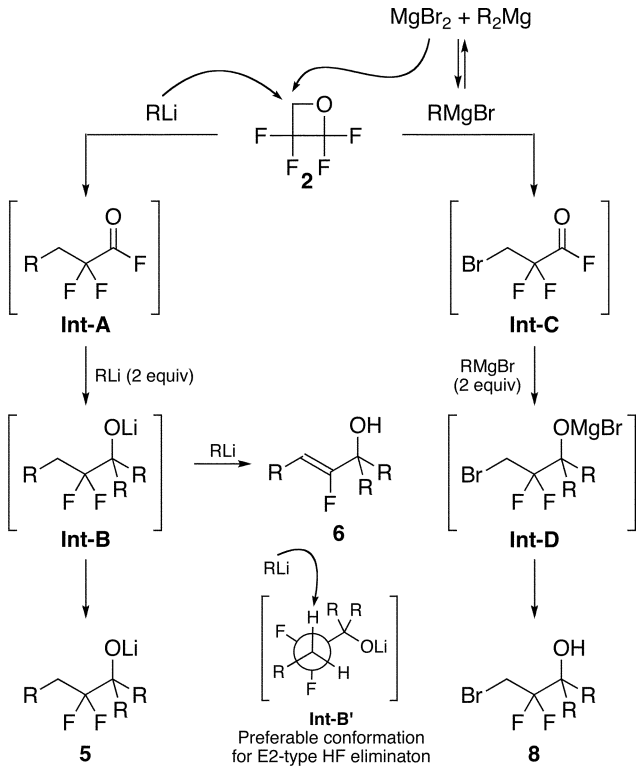
Entry	Grignard reagents (RMgBr)	Equiv of **7**	Temp./° C	Yield[a]/% of **8**
1	PhMgBr (**7a**)	2.2	0	18
2	PhMgBr (**7a**)	2.2	r.t.	16
3	PhMgBr (**7a**)	4.4	r.t.	87 (78)
4	PhMgBr (**7a**)	4.4	reflux	24
5	4-$MeOC_6H_4MgBr$ (**7b**)	4.4	r.t.	69 (69)
6	4-$CH_3C_6H_4MgBr$ (**7c**)	4.4	r.t.	92 (78)
7[b]	1-NpMgBr (**7d**)	4.4	r.t.	—
8[b]	*n*-BuMgBr (**7e**)	4.4	r.t.	—
9[b]	*s*-BuMgBr(**7f**)	4.4	r.t.	—
10[b]	*c*-HexMgBr(**7g**)	4.4	r.t.	—
11	 (**7h**)	4.4	r.t.	33
12	(**7i**)	4.4	r.t.	(91)

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [b] A complex mixture was obtained.

Thus, treatment of **2** with 2.2 equiv of freshly prepared phenylmagnesium bromide (**7a**) in THF at 0 °C or room temperature for 20 h did not provide any trace of 2,2-difluoropropanol derivative **5a**, but led to 3-bromo-2,2-difluoropropanol derivative **8a** in low yield (Entries 1 and 2). The reaction with 4.4 equiv of **7a** in THF at room temperature for 20 h took place smoothly to give **8a** in 87% yield as a sole product (Entry 3), though the reaction at the reflux temperature did not afford a satisfactory result (Entry 4). Aromatic Grignard reagents, such as 4-methoxyphenyl- (**7b**) and 4-methylphenylmagnesium bromide (**7c**), could participate nicely in the reaction, leading to the corresponding **8b** and **8c** in good to excellent yields (Entries 5 and 6). However, neither 1-naphthylmagnesium bromide (**7d**) nor alkylmagnesium bromides (**7e**, **7f** and **7g**) were found to be effective for the present reaction (Entries 7–10). While alkenylmagnesium bromide **7h** was somewhat less reactive (Entry 11), alkynylmagnesium bromide **7i** reacted well with **2** to afford **8i** in 91% yield (Entry 12).

A possible reaction mechanism

As shown in Scheme 3, 2,2,3,3-tetrafluorooxetane (**2**) may be opened by nucleophilic attack of the organolithium reagent at the methylene carbon to form 3-substituted 2,2-difluoropropanoyl fluoride (**Int-A**), which undergoes double nucleophilic attack by the organolithium reagent, followed by hydrolysis, affording 3-substituted 2,2-difluoropropanol derivative **5**. (*Z*)-2-Fluoroallyl alcohol **6** would be obtained by E2-type H–F elimination from lithium alkoxide **Int-B** through a preferable conformation **Int-B′**. In the case of the Grignard reaction, $MgBr_2$ species, which would be formed from RMgBr *via* Schlenk equilibrium, might attack the methylene carbon of **2** much faster than RMgBr, leading to 3-bromo-2,2-difluoropropanoyl fluoride (**Int-C**). The resulting **Int-C** would be immediately transformed into the alkoxide **Int-D**



Scheme 3 A possible reaction mechanism.

by double nucleophilic attack of the Grignard reagent, providing the 3-bromo-2,2-difluoropropanol derivative **8** after hydrolysis.

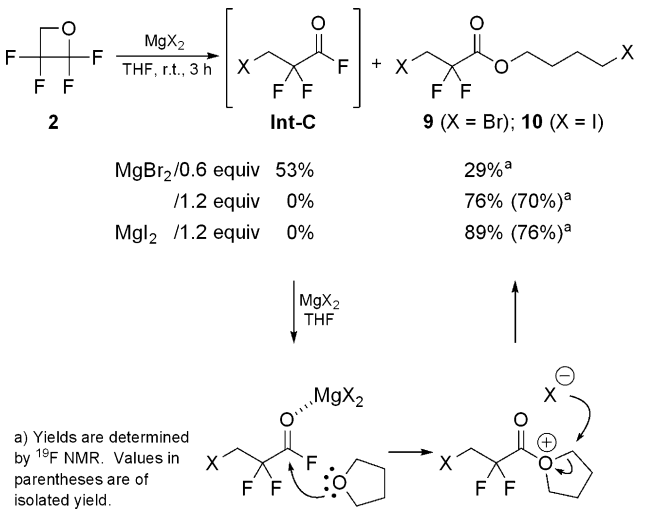
MgX_2-induced ring-opening reaction of 2

The above results of the reaction with Grignard reagents led us to be interested in the MgX_2-induced ring-opening reaction of **2**.

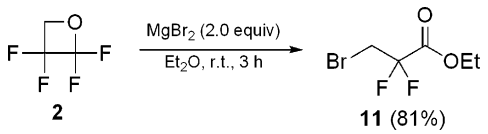
On treatment of **2** with 0.6 equiv of $MgBr_2$ in THF at room temperature for 3 h, not only 3-bromo-2,2-difluoropropanoyl fluoride (**Int-C**) but also 4-bromobutyl 3-bromo-2,2-difluoropropanoate (**9**) were observed in 53% and 29% yields, respectively. The use of 1.2 equiv of $MgBr_2$ caused a significant improvement of the yield, **9** being obtained in 76% yield. MgI_2 was also found to be very effective for this reaction, the corresponding iodinated ester **10** being afforded in 89% yield. These esters would be formed as shown in Scheme 4. Thus, MgX_2 activates the carbonyl group of acid fluoride **Int-C**, followed by simultaneous nucleophilic attack by THF–oxygen, leading to an oxonium ion intermediate, which may be attacked by X^- to form the corresponding ester **9** or **10**.

This ring-opening reaction could also be employed for the one-pot preparation of ethyl 3-bromo-2,2-difluoropropanoates **11**. Thus, treatment of 2,2,3,3-tetrafluorooxetane (**2**) with 2.0 equiv of $MgBr_2$ in Et_2O at room temperature for 3 h provided the corresponding ethyl ester in 81% yield (Scheme 5).

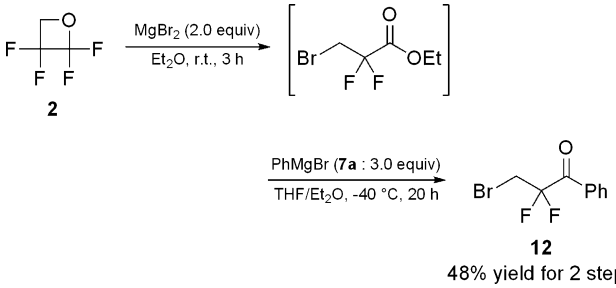
Additionally, the $MgBr_2$-induced ring-opening reaction was applied to the one-pot preparation of 2,2-difluoroketones as illustrated in Scheme 6. Thus, on treating **2** with $MgBr_2$ in Et_2O at room temperature for 3 h, followed by addition of 3.0 equiv of PhMgBr (**7a**) at –40 °C, 3-bromo-2,2-difluoropropiophenone (**12**) was obtained in 48% a two-step yield.



Scheme 4 MgX_2-induced ring-opening reaction of **2**.



Scheme 5 $MgBr_2$-induced ring-opening/nucleophilic attack sequence leading to 3-bromo-2,2-difluoropropanoates.



Scheme 6 One-pot preparation of 2,2-difluorinated carbonyl compound from **2**.

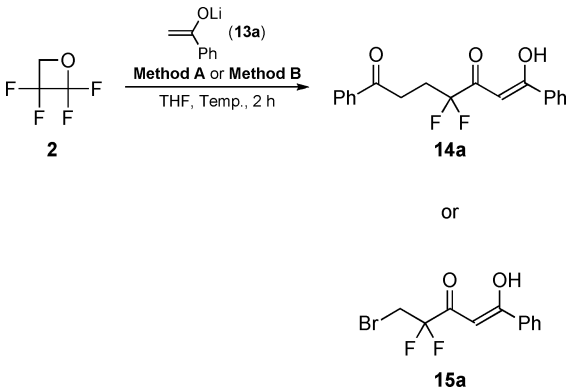
Reaction of 2,2,3,3-tetrafluorooxetane with enolates

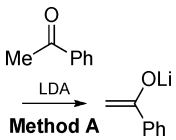
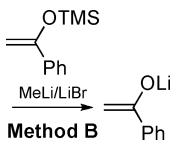
Next, we attempted to address the reaction of 2,2,3,3-tetrafluorooxetane (**2**) with enolates. The results are summarized in Table 3.

Thus, treatment of **2** with 2.0 equiv of lithium enolate **13a**, prepared from LDA and acetophenone, in THF at room temperature for 2 h gave the enol **14a** in only 19% yield (Entry 1). Prolonged reaction time (20 h) did not lead to a dramatic change (Entry 2). Additionally, the use of 3.0–4.0 equiv of **14a** caused only a slight increase of the yield of **15a** (Entries 3 and 4).

The reaction with lithium enolate **13a**, generated from α-silyloxystyrene and MeLi/LiBr, was also performed as listed in Entries 5–9. On treating **2** with 1.1 equiv of **13a**, generated from 1.1 equiv each of α-silyloxystyrene and MeLi/LiBr, in THF at 0 °C for 2 h, β-brominated adduct **15a** was given in 39% yield, instead of **14a** (Entry 5). Increasing the amount of lithium enolate as well as raising the reaction temperature resulted in a significant improvement of the yield (Entries 6 and 7), and the best result was

Table 3 Reaction of **2** with lithium enolate derived from acetophenone



Entry	Method[a]	Equiv of **13a**	Temp/° C	Time/ h	Yield[b]/% of **14a**	Yield[b]/% of **15a**
1[c]		2.0	r.t.	2	19	0
2[c]		2.0	r.t.	20	21	0
3[c]		3.0	r.t.	2	39	0
4[c]		4.0	r.t.	2	43	0
5[c,d]		1.1	0	2	0	39
6[d]		2.2	0	2	0	49
7[d]		2.2	r.t.	2	0	70
8[d]		2.2	r.t.	20	0	73
9		3.3	r.t.	2	0	79 (66)

[a] Method A: Lithium enolate was generated from LDA and acetophenone in THF. Method B: Lithium enolate was generated from α-silyloxystyrene and MeLi/LiBr in Et_2O. [b] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [c] The unreacted starting oxetane **2** was observed. [d] Unknown product was observed.

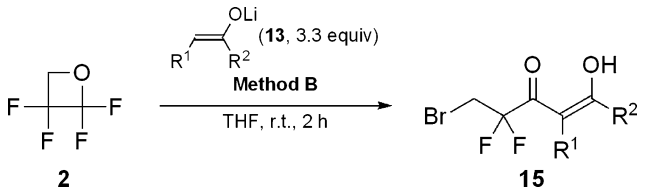
obtained (79% yield) when **2** was subjected to 3.3 equiv of **13a** at room temperature for 2 h (Entry 9).

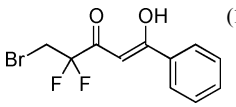
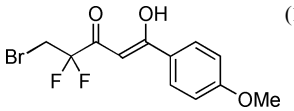
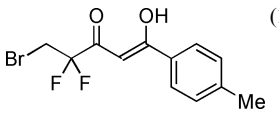
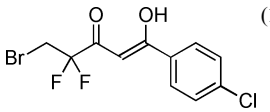
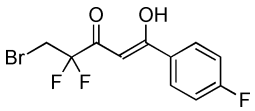
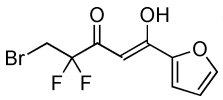
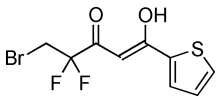
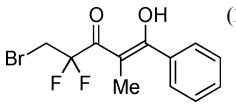
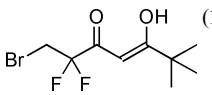
As shown in Entries 2–5 of Table 4, lithium enolates **13**, prepared from various types of acetophenone derivatives having an electron-donating as well as an electron-withdrawing group, were found to be very effective for this reaction, the corresponding products **15b–e** being provided in 83–93% yields. 2-Acetyl furan or thiophene-derived enolates could also participate successfully in the reaction, giving the corresponding furan- or thiophene-containing product **15f** and **15g** in almost quantitative yields (Entries 6 and 7). However, the lithium enolates derived from propiophenone and pinacolone were somewhat less reactive, the desired adducts being afforded in moderate yields (Entries 8 and 9).

Additionally, the reaction of **2** with various stabilized carbanions were also attempted as shown in Fig. 1.

Thus, treatment of **2** with 3.3 equiv of sodium diethyl malonate in THF at room temperature for 2 h, followed by the addition of sat. NH_4Cl aqueous solution, led to 2,2-difluorinated amide **16a** in 81% yield as the sole product. In sharp contrast, the use of other stabilized carbanions, such as the carbanions derived from

Table 4 Reaction of **2** with various lithium enolates **13** using Method B



Entry	Product	Yield[a]/% of **15**
1	 (**15a**)	79 (66)
2	 (**15b**)	86 (45)
3	 (**15c**)	83 (60)
4	 (**15d**)	84 (65)
5	 (**15e**)	93 (40)
6[b]	 (**15f**)	95 (59)
7[c]	 (**15g**)	quant. (64)
8[c]	 (**15h**)	40
9[c]	 (**15i**)	35

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [b] Carried out at 0 °C. [c] Unknown product was observed.

ethyl benzoylacetate and ethyl diethylphosphonoacetate, brought about a preferential formation of the bis-adducts **17a** and **17b** in 13% and 42% yields, together with a small amount of **16b** and **16c**. Unfortunately, these products were found to be inseparable from unknown products.

Radical reaction using 2,2-difluoro-3-iodopropanoate

We next investigated the radical reaction[8] of methyl 2,2-difluoro-3-iodopropanoate (**18**),[9] which could easily be prepared *via* the ring-opening reaction of 2,2,3,3-tetrafluorooxetane (**2**). The results are collated in Table 5.

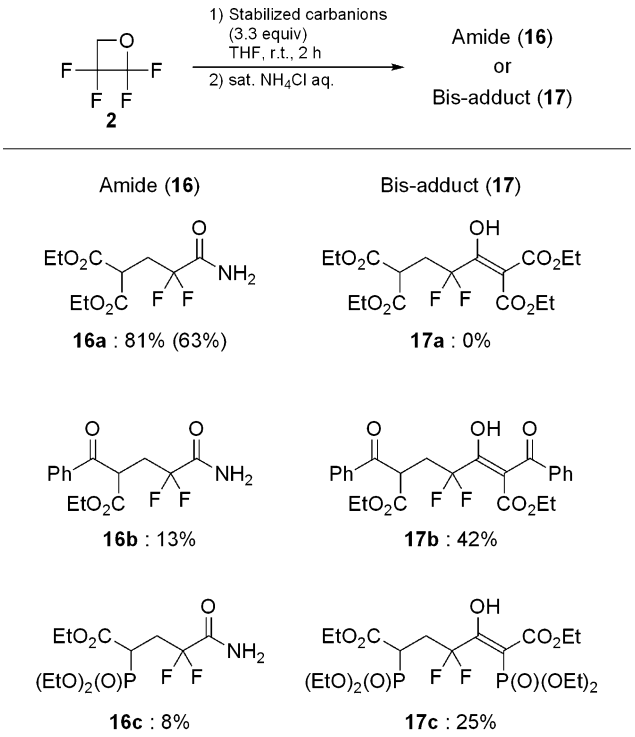
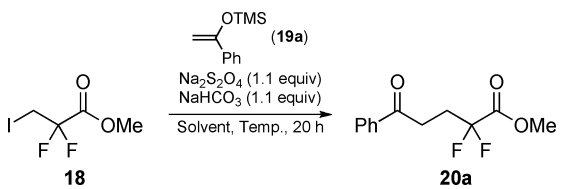


Fig. 1 Reaction of **2** with various stabilized carbanions.

Table 5 Radical coupling reaction of **18** with silyl enol ether **19a**

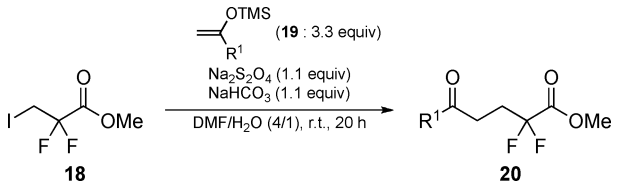


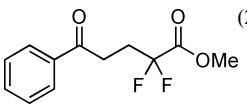
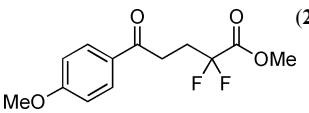
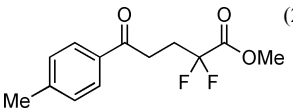
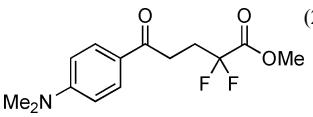
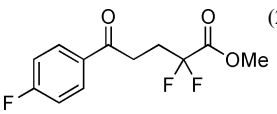
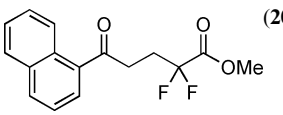
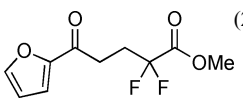
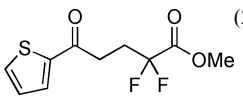
Entry	Equiv of **19a**	Solvent[a]	Temp/°C	Yield[b]/% of **20a**	Recovery[b]/% of **18**
1[c]	1.1	DMF/H_2O	r.t.	52	34
2	2.2	DMF/H_2O	r.t.	55	43
3	2.2	DMF	r.t.	0	quant.
4[c]	2.2	DMF/H_2O	40	55	0
5	3.3	DMF/H_2O	r.t.	73 (65)	23
6	3.3	DMF/H_2O	40	61	0

[a] Ratio of DMF/H_2O was 4 : 1. [b] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [c] 2-Fluoroacrylate was observed in the reaction mixture.

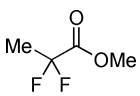
Reaction of 1.1 equiv of silyl enol ether **19a** in the presence of 1.1 equiv each of $Na_2S_2O_4$ and $NaHCO_3$ in DMF/H_2O (4 : 1) at room temperature for 20 h proceeded relatively smoothly to give the corresponding coupling product **20a** in 52% yield, together with 34% recovery of the starting ester **18** (Entry 1). The use of 2.2 equiv of **19a** did not improve the yield at all. As can be seen in Entry 3, H_2O was found to be crucial. Though increasing the temperature did not lead to a satisfactory result (Entry 4), the reaction using 3.3 equiv of **19a** at room temperature gave the best yield, the coupling adduct **20a** being obtained in 73% yield (Entry 5).

Table 6 Radical coupling reaction of **18** with various silyl enol ethers **19**



Entry	Product	Yield[a]/% of **20**	Recovery[a]/% of **18**
1	(**20a**) 	73 (65)	23
2[b]	(**20b**) 	52 (44)	30
3	(**20c**) 	77 (58)	22
4[b]	(**20d**) 	22	33
5	(**20e**) 	76 (34)	23
6[b]	(**20f**) 	48 (40)	40
7	(**20g**) 	80 (54)	18
8	(**20h**) 	54 (20)	45

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [b] In Entries 2, 4 and 6, reduction product **21** was obtained in 17%, 38% and 10% yields, respectively.


21

Subsequently, various types of silyl enol ethers were applied to the present radical coupling reaction under the conditions of Entry 5 in Table 5, and the results are summarized in Table 6.

As shown in Entries 1–3, 5 and 6, various silyl enol ethers derived from acetophenones containing an electron-donating as well as an electron-withdrawing group at the 4-position, like 4-methoxy (**19b**), 4-methyl- (**19c**), or 4-fluoroacetophenone

(**19e**), could participate well in the reaction, giving rise to the corresponding adducts **20b**, **20c**, and **20e** in 52–77% yields. Additionally, the silyl enol ethers derived from 1-acetonaphthone, 2-acetylfuran, and 2-acetylthiophene were also found to be good radical coupling partners, the desired adducts **20f**, **20g**, and **20h** being obtained in good to high yields. However, incorporation of a dimethylamino group into the phenyl ring of the acetophenone led to a decrease in the reactivity of the corresponding silyl enol ether, the coupling product **20d** being provided in only 22% yield.

Similarly, the radical coupling reaction of **18** with alkenes, like 1-octene, vinylcyclohexane, and 5-hexen-1-ol was attempted (Fig. 2). Thus, the reaction of **18** with 3.3 equiv of 1-octene in DMF/H_2O (4 : 1) at room temperature for 20 h did not lead to a satisfactory result (the coupling product **22a** was obtained in only 5%), while the reaction using Et_3B (10 mol%, 3 times) as a radical initiator in hexane at 0 °C for 4.5 h resulted in a significant improvement of the yield of **22a** (64% yield). The reaction with vinylcyclohexane or 5-hexen-1-ol also gave the corresponding adducts **22b**, **22c** in fair to good yields.

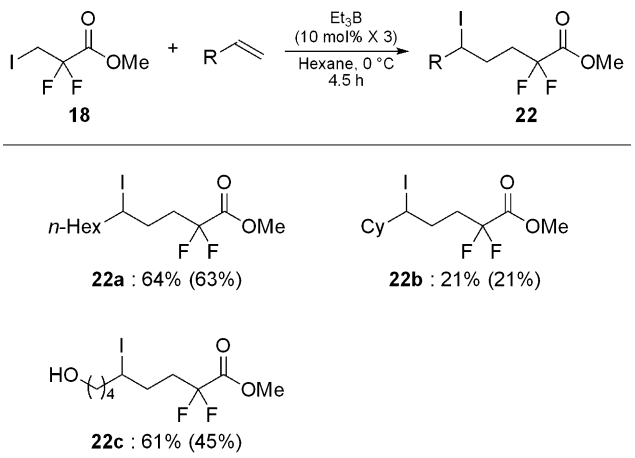


Fig. 2 Radical coupling reaction of **18** with various alkenes.

Conclusions

In summary, we have demonstrated easy access to various sorts of the CF_2-containing molecules including α,α-difluorinated carbonyl compounds without a heteroatom substituent at the β position. Fluorinated oxetane **2** reacted easily with organolithium reagents to give 1,1,3-trisubstituted 2,2-difluoropropanols **5** in good to excellent yields. On the other hand, the reaction with Grignard reagents led to 3-bromo-1,1-disubstituted 2,2-difluoropropanols **8** in good yields. Additionally, lithium enolates from silyl enol ethers were found to be a good nucleophiles. Furthermore, it was revealed that methyl 3-iodo-2,2-difluoropropanoate (**18**) also reacted successfully with various types of alkenes in the presence of a radical initiator to afford the corresponding radical coupling products **20** and **22** in fair to good yields.

Experimental section

Typical procedure for the preparation of 2,2-difluoro-1,1,3-triphenylpropan-1-ol (5f)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with a solution of 4.4 equiv of phenylacetylene in THF. To this solution was added 4.4 equiv of *n*-BuLi in hexane at –20 °C, and the solution was stirred for 15 min. Then, 0.130 g (1.0 mmol) of 2,2,3,3-tetrafluorooxetane (**2**) in THF (4.0 mL) was slowly added to the mixture *via* a syringe at –20 °C, and the solution was stirred for additional 2 h at –20 °C. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl (30 mL), followed by extraction with ether (20 mL, 5 times). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography of the residue using hexane/ethyl acetate gave the pure product, 2,2-difluoro-1,1,3-tris(2-phenylethynyl)propan-1-ol (**5f**) in 77% yield.

2,2-Difluoro-1,1,3-tris(2-phenylethynyl)propan-1-ol (5f)

^{1}H NMR ($CDCl_3$) δ 3.12 (s, 1H), 3.53 (t, J = 16.9 Hz, 2H), 7.25–7.53 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 24.62 (t, J = 25.2 Hz), 67.51 (t, J = 30.9 Hz), 80.20, 83.30, 84.10, 86.34, 119.17 (t, J = 255.8 Hz), 120.93, 122.81, 128.14, 128.28, 129.35, 131.75, 132.01; ^{19}F NMR ($CDCl_3$) δ –110.01 (t, J = 16.9 Hz, 2F); IR (neat) 3543, 3061, 1495, 1448, 1217, 1192, 1167, 1042 cm^{-1}; HRMS (FAB) m/z (M^+) Calcd for $C_{27}H_{18}F_2O$ 396.1326, found 396.1328.

2,2-Difluoro-1,1,3-tris(3-benzyloxypropyn-1-yl)propan-1-ol (5g)

^{1}H NMR ($CDCl_3$) δ 3.22 (t, J = 16.9 Hz, 2H), 4.13 (s, 2H), 4.14 (s, 4H), 4.54 (s, 4H), 4.57 (s, 2H), 4.96 (s, 1H), 7.22–7.33 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 23.41 (t, J = 24.6 Hz), 56.52, 56.90, 65.97 (t, J = 31.1 Hz), 70.95, 71.41, 77.47, 79.57, 81.18, 82.02, 118.84 (t, J = 255.4 Hz), 127.22, 127.60, 127.77, 127.96, 128.13, 128.21, 136.52, 136.93; ^{19}F NMR ($CDCl_3$) δ –110.52 (brs, 2F); IR (neat) 3310, 3065, 3032, 2934, 2856, 1497, 1456, 1354, 1258, 1184, 1088, 1028 cm^{-1}; HRMS (FAB) m/z (M^+) Calcd for $C_{33}H_{29}F_2O_4$ 527.2034, found: 527.2040.

2,2-Difluoro-1,1,3-tris(2-trimethylsilylethynyl)propan-1-ol (5h)

^{1}H NMR ($CDCl_3$) δ 0.15 (s, 9H), 0.17 (s, 18H), 3.12 (t, J = 16.9 Hz, 2H), 3.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ –0.61, –0.20, 24.52 (t, J = 24.7 Hz), 66.78 (t, J = 30.8 Hz), 89.12, 91.82, 96.54, 98.70, 118.41 (t, J = 256.2 Hz); ^{19}F NMR ($CDCl_3$) δ –111.60 (t, J = 16.9 Hz); IR (neat) 3472, 2963, 2901, 2189, 1418, 1337, 1252, 1151, 1067, 1030, 937 cm^{-1}; HRMS (FAB) m/z (M^+) Calcd for $C_{18}H_{31}F_2OSi_3$ 385.1651, found 385.1654.

2,2-Difluoro-1,1,3-trihexyn-1-ylpropan-1-ol (5i)

^{1}H NMR ($CDCl_3$) δ 0.83–0.87 (m, 9H), 1.35–1.47 (m, 12H), 2.12–2.20 (m, 6H), 2.99–3.05 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.22, 13.27, 18.07, 18.19, 21.65, 23.37 (t, J = 25.1 Hz), 29.92, 30.56, 66.44 (t, J = 31.0 Hz), 70.45, 75.52, 83.87, 86.58, 118.98 (t, J = 254.5 Hz); ^{19}F NMR ($CDCl_3$) δ –112.22 (t, J = 16.9 Hz, 2F); IR (neat) 3479, 2959, 2936, 2864, 2241, 1697, 1466, 1086 cm^{-1}; HRMS (FAB) m/z (M^+) Calcd for $C_{21}H_{39}F_2O$ 335.2186, found 335.2188.

Typical procedure for the preparation of 3-bromo-2,2-difluoro-1,1-diphenylpropan-1-ol (8a)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with a solution of 4.4 equiv of phenylmagnesium bromide in THF. To this solution, 0.130 g (1.0 mmol) of 2,2,3,3-tetrafluorooxetane (**2**) in THF (4.0 mL) was slowly added *via* a syringe at −20 °C. After being stirred for 20 h at room temperature, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (30 mL), followed by extraction with ether (20 mL, 5 times). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography of the residue using hexane/benzene (5 : 1) gave pure product **8a**.

3-Bromo-2,2-difluoro-1,1-diphenylpropan-1-ol (8a)

^{1}H NMR ($CDCl_3$) δ 2.96 (brs, 1H), 3.66 (t, J = 16.11 Hz, 2H), 7.33–7.38 (m, 6H), 7.57–7.58 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 31.35 (t, J = 26.32 Hz), 79.59 (t, J = 26.53 Hz), 120.77 (t, J = 254.79 Hz), 127.30 (t, J = 2.26 Hz), 128.21, 128.28, 140.78; ^{19}F NMR ($CDCl_3$) δ −108.08 (t, J = 16.94 Hz, 2F); IR (neat) 3543, 3061, 3038, 2991, 1601, 1495, 1423, 1340, 1271, 1126; HRMS (FAB) m/z (M^+) Calcd for $C_{15}H_{13}BrF_2O$ 326.0118, found 326.0129.

3-Bromo-2,2-difluoro-1,1-bis(4-methoxyphenyl)propan-1-ol (8b)

^{1}H NMR (CD_3COCD_3) δ 2.67 (brs, 1H), 3.66 (s, 6H), 3.66 (m, 2H), 6.74–6.78 (m, 4H), 7.32–7.36 (m, 4H); ^{13}C NMR (CD_3COCD_3) δ 32.74 (t, J = 26.46 Hz), 55.46, 79.65 (t, J = 24.80 Hz), 113.83, 121.96 (t, J = 253.76 Hz), 129.55, 134.71, 159.91; ^{19}F NMR (CD_3COCD_3) δ −105.18 (t, J = 15.80 Hz, 2F); IR (neat) 3437, 3001, 2958, 2636, 2837, 1706, 1582, 1442, 1419, 1128, 1111; HRMS (FAB) m/z (M^+) Calcd for $C_{17}H_{17}BrF_2NaO_3$ 409.0227, found 409.0218.

3-Bromo-2,2-difluoro-1,1-bis(4-methylphenyl)propan-1-ol (8c)

^{1}H NMR (CD_3COCD_3) δ 2.12 (s, 6H), 2.62 (brs, 1H), 3.61 (t, J = 16.19 Hz, 2H), 6.95–7.00 (m, 4H), 7.23–7.30 (m, 4H); ^{13}C NMR (CD_3COCD_3) δ 21.08, 32.80 (t, J = 26.06 Hz), 80.04 (t, J = 25.20 Hz), 122.01 (t, J = 253.76 Hz), 128.30, 129.47, 138.27, 139.94; ^{19}F NMR (CD_3COCD_3) δ −105.16 (t, J = 15.99 Hz, 2F); IR (neat) 3535, 3030, 2923, 1707, 1670, 1511, 1426, 1364, 1270, 1111.

3-Bromo-2,2-difluoro-1,1-bis(phenylethynyl)propan-1-ol (8i)

^{1}H NMR ($CDCl_3$) δ 3.22 (s, 1H), 4.09 (t, J = 15.68 Hz, 2H), 7.34–7.42 (m, 6H), 7.52–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ = 29.20 (t, J = 25.89 Hz), 66.94 (t, J = 31.26 Hz), 82.88, 86.74, 117.24 (t, J = 254.54 Hz), 120.72, 128.39, 129.57, 132.07; ^{19}F NMR ($CDCl_3$) δ −111.99 (t, J = 16.94 Hz, 2F); IR (neat) 3408, 3057, 2926, 2853, 2361, 2235, 1599, 1576, 1491, 1445, 1360, 1329, 1269, 1229, 1217, 1043; HRMS (FAB) m/z (M^+) Calcd for $C_{19}H_{14}BrF_2O$ 375.0196, found 375.0197.

Typical procedure for the preparation of 4-bromobutyl 3-bromo-2,2-difluoropropanoate (9)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with a suspension of 1.2 equiv of $MgBr_2$ in THF. To this suspension, 0.130 g (1.0 mmol) of 2,2,3,3-tetrafluorooxetane (**2**) in THF (2 mL) was added slowly *via* a syringe at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (30 mL). The resultant mixture was extracted with ether (50 mL, 3 times) and the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography of the residue using hexane/benzene (1 : 2) gave pure product **9**.

4-Bromobutyl 3-bromo-2,2-difluoropropanoate (9)

^{1}H NMR ($CDCl_3$) δ 1.89–2.00 (m, 4H), 3.44 (t, J = 6.29 Hz, 2H), 3.73 (t, J = 12.88 Hz, 2H), 4.35 (t, J = 6.23 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.88, 28.37 (t, J = 30.16 Hz), 28.79, 32.64, 66.38, 112.44 (t, J = 253.15 Hz), 161.87 (t, J = 31.94 Hz); ^{19}F NMR ($CDCl_3$) δ −105.58 (t, J = 12.41 Hz, 2F); IR (neat) 3042, 2966, 2851, 1774, 1422, 1331, 1223, 1169, 1051, 881, 772, 716.

4-Iodobutyl 3-iodo-2,2-difluoropropanoate (10)

^{1}H NMR ($CDCl_3$) δ 1.78–1.92 (m, 4H), 3.18 (t, J = 6.57 Hz, 2H), 3.56 (t, J = 14.72 Hz, 2H), 4.29 (t, J = 6.29 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 0.00 (t, J = 27.30 Hz), 5.77, 28.90, 29.28, 65.98, 112.42 (t, J = 252.02 Hz), 161.15 (t, J = 32.95 Hz); ^{19}F NMR ($CDCl_3$) δ −100.49 (t, J = 15.59 Hz, 2F); IR (neat) 3523, 3033, 2962, 2844, 1767, 1414, 1295, 1228, 1163, 1058, 909, 768, 730; HRMS (FAB) m/z (M+Na) Calcd for $C_7H_{10}F_2I_2NaO_2$ 440.8631, found 440.8638.

Ethyl 3-bromo-2,2-difluoro propanoate (11)

^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.18 Hz, 3H), 3.73 (t, J = 13.01 Hz, 2H), 4.38 (q, J = 7.11 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.88, 28.47 (t, J = 30.12 Hz), 63.54, 112.39 (t, J = 252,90 Hz), 161.91 (t, J = 32.07 Hz); ^{19}F NMR ($CDCl_3$) δ −105.80 (t, J = 12.03, 2F); IR (neat) 3580, 3399, 1763, 1703, 1420, 1375, 1225, 1051.

Typical procedure for the preparation of 3-bromo-2,2-difluoro-1-phenyl-propane-1-one (12)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with a suspension of 1.2 equiv of $MgBr_2$ in THF. To this suspension, 0.130 g (1.0 mmol) of 2,2,3,3-tetrafluorooxetane (**2**) in THF (2 mL) was added slowly *via* a syringe at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was allowed to cool to −40 °C, then 3.0 equiv of PhMgBr, which was prepared from PhBr and Mg in THF, was added to this mixture. After being stirred for 20 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (30 mL). The solution was extracted with ether (50 mL, 3 times) and the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography of the residue using hexane/EtOAc gave the product **12**.

3-Bromo-2,2-difluoro-1-phenyl-propane-1-one (12)

^{1}H NMR ($CDCl_3$) δ 3.92 (t, J = 14.57 Hz, 2H), 7.52 (t, J = 7.98 Hz, 2H), 7.67 (t, J = 8.78 Hz, 1H), 8.11 (d, J = 7.38 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.14 (t, J = 28.02 Hz), 115.14 (t, J = 256.57 Hz),

128.83, 130.17 (t, J = 3.40 Hz), 131.44 (t, J = 2.64 Hz), 134.80, 187.54 (t, J = 30.94 Hz); ^{19}F NMR ($CDCl_3$) δ –100.27 (t, J = 12.03 Hz, 2F) IR (neat) 3379, 3062, 2987, 2929, 2854, 1971, 1913, 1773, 1697, 1598, 1450, 1422, 1309, 1206, 1033, 929, 898, 713, 686, 578; HRMS (FAB) m/z (M+H) Calcd for $C_9H_8BrF_2O$ 248.9751, found 248.9727.

Typical procedure for the preparation of 5-bromo-4,4-difluoro-1-hydroxy-1-phenylpent-1-en-3-one (15a)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with 3.3 equiv. of 1-phenyl-1-(trimethylsilyloxy)ethylene, prepared from acetophenone in THF. To this solution, 3.32 mL (3.30 mmol) of 1.04 M methyl-lithium in ether was slowly added *via* a syringe at –78 °C. After being stirred for 0.5 h at 0 °C, to this solution 0.130 g (1.0 mmol) of **2** was slowly added *via* a syringe at –78 °C. After being stirred for 2 h at room temperature, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (30 mL), followed by extraction with ether (20 mL × 5). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated with a rotary evaporator. Column chromatography of the residue using hexane/benzene (5 : 1) gave pure product, 5-bromo-4,4-difluoro-1-hydroxy-1-phenylpent-1-ene-3-one (**15a**).

5-Bromo-4,4-difluoro-1-hydroxy-1-phenylpent-1-en-3-one (15a)

M.P. 31–33 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (t, J = 13.66 Hz, 2H), 6.67 (s, 1H), 7.47 (t, J = 6.67 Hz, 2H), 7.60 (t, J = 6.67 Hz, 1H), 7.94 (d, J = 6.91 Hz, 2H), 15.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.49 (t, J = 29.29 Hz), 92.79 (t, J = 2.55 Hz), 114.39 (t, J = 250.77 Hz), 127.50, 128.84, 133.21, 133.65, 183.34 (t, J = 29.29 Hz), 185.43; ^{19}F NMR ($CDCl_3$) δ –107.21 (t, J = 13.66 Hz, 2F); IR (KBr) 3140, 3033, 2971, 1811, 1600, 1227, 1050, 1035, 927, 775; HRMS (FAB) m/z (M^+) Calcd for $C_{11}H_{10}{}^{79}BrF_2O_2$ 290.9833, found 290.9838.

5-Bromo-4,4-difluoro-1-hydroxy-1-(4-metoxyphenyl)-pent-1-en-3-one (15b)

M.P. 49–50 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (t, J = 13.60 Hz, 2H), 3.88 (s, 3H), 6.58 (s, 1H), 6.96 (d, J = 8.95 Hz, 2H), 7.93 (d, J = 8.95 Hz, 2H), 15.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.74 (t, J = 30.74 Hz), 55.50, 91.99 (t, J = 2.91 Hz), 114.47 (t, J = 250.01 Hz), 114.21, 125.71, 129.86, 164.24, 181.52 (t, J = 30.74 Hz), 185.59; ^{19}F NMR ($CDCl_3$) δ –107.31 (t, J = 8.95 Hz, 2F); IR (KBr) 3046, 2984, 2844, 1600, 1509, 1423, 1315, 1261, 1171, 1030, 792; HRMS (FAB) m/z (M+H) Calcd for $C_{12}H_{12}BrF_2O_3$ 320.9940, found 320.9939.

5-Bromo-4,4-difluoro-1-hydroxy-1-(4-methylphenyl)-pent-1-en-3-one (15c)

M.P. 53–54 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.79 (t, J = 13.61 Hz, 2H), 6.61 (s, 1H), 7.26 (d, J = 7.99 Hz, 2H), 7.82 (d, J = 7.99 Hz, 2H), 15.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.59, 28.59 (t, J = 30.36 Hz), 92.33 (t, J = 2.33 Hz), 114.37 (t, J = 250.26 Hz), 127.54, 139.53, 130.43, 144.82, 182.73 (t, J = 30.36 Hz), 185.60; ^{19}F NMR ($CDCl_3$) δ –107.26 (t, J = 13.61 Hz, 2F); IR (KBr) 3037, 2977, 1606, 1504, 1421, 1229, 1187, 1050, 1029, 800; HRMS (FAB) m/z (M+H) Calcd for $C_{12}H_{12}BrF_2O_2$ 304.9988, found 304.9989.

5-Bromo-4,4-difluoro-1-hydroxy-1-(4-chlorophenyl)-pent-1-en-3-one (15d)

M.P. 46–47 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (t, J = 13.44 Hz, 2H), 6.62 (s, 1H), 7.46 (d, J = 8.45 Hz, 2H), 7.88 (d, J = 8.45 Hz, 2H), 15.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.35 (t, J = 30.43 Hz), 92.81 (t, J = 3.61 Hz), 114.37 (t, J = 250.77 Hz), 128.82, 129.32, 131.69, 140.11, 183.39 (t, J = 30.43 Hz), 184.15; ^{19}F NMR ($CDCl_3$) δ –107.05 (t, J = 13.44 Hz, 2F); IR (KBr) 3124, 3037, 2980, 1922, 1795, 1592, 1489, 1217, 1094, 1044, 845, 807; HRMS (FAB) m/z (M+H) Calcd for $C_{11}H_9BrClF_2O_2$ 324.9443, found 324.9443.

5-Bromo-4,4-difluoro-1-hydroxy-1-(4-fluorophenyl)-pent-1-en-3-one (15e)

M.P. 39–41 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (t, J = 13.45 Hz, 2H), 6.61 (s, 1H), 7.17 (t, J = 8.65 Hz, 2H), 7.98 (dd, J = 8.65, 8.65 Hz, 2H), 15.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.41 (t, J = 30.18 Hz), 92.68 (t, J = 2.48 Hz), 114.41 (t, J = 250.39 Hz), 116.07, 116.24, 131.69, 140.11, 183.39 (t, J = 30.43 Hz), 184.15; ^{19}F NMR ($CDCl_3$) δ –107.10 (t, J = 13.45 Hz, 2F), –104.12 (d, J = 8.65 Hz, 1F); IR (KBr) 3124, 3041, 2984, 1918, 1600, 1507, 1418, 1219, 1090, 1049, 809, 570; HRMS (FAB) m/z (M+H) Calcd for $C_{11}H_9BrF_3O_3$ 308.9745, found 308.9739.

5-Bromo-4,4-difluoro-1-hydroxy-1-(2-furyl)-pent-1-en-3-one (15f)

^{1}H NMR ($CDCl_3$) δ 3.78 (t, J = 13.38 Hz, 2H), 6.55 (s, 1H), 6.62–6.63 (m, 1H) 7.32 (d, J = 3.61 Hz, 2H), 7.67 (s, 1H), 14.88 (s, 1H).; ^{13}C NMR ($CDCl_3$) δ 28.54 (t, J = 30.69 Hz), 93.26 (t, J = 2.70 Hz), 112.36, 113.14, 114.37, 118.11, 147.57 (t, J = 219.95 Hz), 176.50, 179.25 (t, J = 31.44 Hz).; ^{19}F NMR ($CDCl_3$) δ –107.32 (t, J = 13.38 Hz, 2F); IR (neat) 3174, 1604, 1543, 1466, 1272, 1269, 1092, 1040, 1015, 931, 884, 806, 761; HRMS (FAB) Found: m/z (M+H) Calcd for $C_9H_8BrF_2O_3$ 280.9628, found 280.9626.

5-Bromo-4,4-difluoro-1-hydroxy-1-(2-thionyl)-pent-1-en-3-one (15g)

^{1}H NMR ($CDCl_3$) δ 3.79 (t, J = 13.36 Hz, 2H), 6.51 (s, 1H), 7.19 (t, J = 4.36 Hz, 1H), 7.73 (d, J = 4.36 Hz, 2H), 7.83 (d, J = 4.36 Hz, 2H), 15.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.60 (t, J = 30.95 Hz), 93.91 (t, J = 3.42 Hz), 114.52 (t, J = 248.38 Hz), 128.71, 133.05, 134.68, 139.95, 176.71 (t, J = 30.95 Hz), 182.52; ^{19}F NMR ($CDCl_3$) δ –107.23 (t, J = 13.36 Hz, 2F); IR (neat) 3109, 3040, 2961, 1775, 1584, 1414, 1255, 1046, 860, 801, 727; HRMS (FAB) m/z (M+H) Calcd for $C_9H_8BrF_2O_2S$ 296.9395, found 296.9397.

Typical procedure for the preparation of 4,4-bis(ethoxycarbonyl)-2,2-difluorobutanamide (16a)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with a suspension of 3.3 equiv of NaH in THF. To this suspension, 0.529 g (3.3 mmol) of diethyl malonate was added dropwise *via* a syringe at 0 °C and then stirred for 30 min. at 0 °C. To the resulting solution 0.130 g (1.0 mmol) of 2,2,3,3-tetrafluorooxetane (**2**) in THF (2 mL) was slowly added *via* a syringe at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (30 mL). The resultant mixture was extracted with ethyl

acetate (50 mL, 3 times) and the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography of residue using ethyl acetate gave pure product **16a**.

4,4-Bis(ethoxycarbonyl)-2,2-difluorobutanamide (16a)

M.P. 65–66 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.12 Hz, 6H), 2.70 (t, J = 17.32 Hz, 2H), 3.63 (t, J = 7.12 Hz, 1H), 4.11–4.17 (m, 4H), 6.69 (s, 1H), 6.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.68, 32.65 (t, J = 23.72 Hz), 45.62 (t, J = 2.68 Hz), 61.94, 116.10 (t, J = 253.15 Hz), 165.92 (t, J = 23.72 Hz), 167.94; ^{19}F NMR ($CDCl_3$) δ −105.20 (t, J = 14.12 Hz, 2F); IR (KBr) 3427, 3185, 2991, 1716, 1471, 1339, 1228, 1007, 974, 861, 663; HRMS (EI) m/z (M+H) Calcd for $C_{10}H_{16}F_2NO_5$ 268.0995, found 268.0997.

Typical procedure for the preparation of methyl 2,2-difluoro-5-oxo-5-phenylpentanoate (20a)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with 0.67 g (3.3 mmol) of $Na_2S_2O_4$ and 0.28 g (3.3 mmol) of $NaHCO_3$ in DMF/H_2O (1 mL). To this solution 0.190 g (0.99 mmol) of 1-(trimethylsilyloxy)styrene in DMF/H_2O (2 mL) and 0.075 g (0.3 mmol) of methyl 2,2-difluoro-3-iodopropanoate (**18**) in DMF/H_2O (2 mL) was added slowly *via* a syringe at room temperature. After being stirred for 20 h at room temperature, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (40 mL). The resultant mixture was extracted with ether (50 mL, 3 times) and the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography of the residue using hexane/ethyl acetate (11 : 1) gave pure product **20a**.

Methyl 2,2-difluoro-5-oxo-5-phenylpentanoate (20a)

M.P. 48–50 °C; ^{1}H NMR ($CDCl_3$) δ 2.50–2.62 (m, 2H), 3.20–3.26 (m, 2H), 3.87 (s, 3H), 7.44–7.49 (m, 2H), 7.54–7.60 (m, 1H), 7.92–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.88 (t, J = 23.78 Hz), 30.61 (t, J = 3.69 Hz), 53.37, 115.83 (t, J = 249.86 Hz), 127.96, 128.65, 133.42, 136.17, 164.38 (t, J = 32.94 Hz), 196.98; ^{19}F NMR ($CDCl_3$) δ −106.53 (t, J = 16.94 Hz, 2F); IR (KBr) 3352, 2968, 1770, 1686, 1448, 1431, 1334, 1294, 1199, 1045, 970; HRMS (FAB) m/z (M+H) Calcd for $C_{12}H_{18}F_2O_3$ 243.0840, found 243.0834.

Methyl 2,2-difluoro-5-(4-methoxyphenyl)-5-oxopentanoate (20b)

M.P. 54–56 °C; ^{1}H NMR ($CDCl_3$) δ 2.49–2.61 (m, 2H), 3.18 (t, J = 7.40 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 6.94 (ABq, J = 8.81 Hz, 2H), 7.95 (ABq, J = 8.81 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.05 (t, J = 23.51 Hz), 30.24 (t, J = 3.48 Hz), 53.39, 55.47, 113.81, 115.94 (t, J = 250.05 Hz), 129.32, 130.29, 163.73, 164.46 (t, J = 33.07 Hz), 195.48; ^{19}F NMR ($CDCl_3$) δ −106.56 (t, J = 16.94 Hz, 2F); IR (KBr) 2945, 2847, 1774, 1674, 1577, 1421, 1336, 1255, 1186, 1074, 1024; HRMS (FAB) m/z (M+H) Calcd for $C_{13}H_{15}F_2O_4$ 273.0933, found 273.0939.

Methyl 2,2-difluoro-5-(4-methylphenyl)-5-oxopentanoate (20c)

M.P. 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.55 (tt, J = 16.94, 7.85 Hz, 2H), 3.20 (t, J = 7.85 Hz, 2H), 7.27 (ABq, J = 7.88 Hz, 2H), 7.86 (ABq, J = 7.88 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.60, 28.95 (t, J = 23.66 Hz), 30.48 (t, J = 3.61 Hz), 53.37, 115.90 (t, J = 249.92 Hz), 128.09, 129.34, 133.76, 144.30, 164.42 (t, J = 32.88 Hz), 196.58; ^{19}F NMR ($CDCl_3$) δ −106.53 (t, J = 16.94 Hz, 2F); IR (KBr) 2962, 1770, 1679, 1606, 1441, 1334, 1296, 1211, 1197, 1097, 1045, 974; HRMS (FAB) m/z (M+H) Calcd for $C_{13}H_{15}F_2O_3$ 257.0990, found 257.0988.

Methyl 2,2-difluoro-5-(4-fluorophenyl)-5-oxopentanoate (20e)

M.P. 42–44 °C; ^{1}H NMR ($CDCl_3$) δ 2.50–2.64 (m, 2H), 3.19–3.24 (m, 2H), 3.89 (s, 3H), 7.12–7.19 (m, 2H), 7.97–8.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.86 (t, J = 23.76 Hz), 30.56 (t, J = 3.69 Hz), 53.41, 115.77 (t, J = 250.17 Hz), 115.80 (d, J = 22.01 Hz), 130.65 (d, J = 9.18 Hz), 132.66 (d, J = 2.77 Hz), 164.35 (t, J = 32.88 Hz), 165.90 (d, J = 255.40 Hz), 195.36; ^{19}F NMR ($CDCl_3$) δ −104.50–−105.05 (m, 1F), −106.57 (t, J = 16.94 Hz, 2F); IR (neat) 2960, 2361, 1770, 1689, 1508, 1443, 1292, 1159, 1097; HRMS (FAB) m/z (M+H) Calcd for $C_{12}H_{12}F_3O_3$ 261.0739, found 261.0745.

Methyl 2,2-difluoro-5-(1-naphthyl)-5-oxopentanoate (20f)

^{1}H NMR ($CDCl_3$) δ 2.65 (tt, J = 17.08, 7.45 Hz, 2H), 3.33 (t, J = 7.45 Hz, 2H), 3.89 (s, 3H), 7.46–7.66 (m, 3H), 7.84–7.93 (m, 2H), 7.98–8.07 (m, 1H), 8.58–8.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.24 (t, J = 23.86 Hz), 33.77 (t, J = 2.55 Hz), 53.43, 115.85 (t, J = 250.24 Hz), 124.31, 125.61, 126.54, 127.88, 128.13, 128.45, 130.05, 133.16, 133.94, 134.81, 164.43 (t, J = 32.94 Hz), 200.76; ^{19}F NMR ($CDCl_3$) δ −106.59 (t, J = 17.08 Hz, 2F); IR (neat) 2959, 2924, 1770, 1689, 1591, 1574, 1442, 1290, 1176, 1093, 982; HRMS (FAB) m/z (M+H) Calcd for $C_{16}H_{15}F_2O_3$ 293.0997, found 293.0990.

Methyl 2,2-difluoro-5-(2-furyl)-5-oxopentanoate (20g)

^{1}H NMR ($CDCl_3$) δ 2.53 (tt, J = 17.02, 7.76 Hz, 2H), 3.10 (t, J = 7.76 Hz, 2H), 3.89 (s, 3H), 6.57 (dd, J = 3.57, 1.08 Hz, 1H), 7.24 (d, J = 3.57 Hz, 1H), 7.61 (d, J = 1.08 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.44 (t, J = 23.95 Hz), 30.35 (t, J = 3.97 Hz), 53.39, 112.35, 115.66 (t, J = 250.24 Hz), 117.29, 146.57, 152.06, 164.29 (t, J = 32.88 Hz), 186.10; ^{19}F NMR ($CDCl_3$) δ −106.66 (t, J = 17.02 Hz, 2F); IR (neat) 3138, 2960, 1770, 1682, 1572, 1470, 1308, 1211, 1084, 905, 766; HRMS (FAB) m/z (M+H) Calcd for $C_{10}H_{11}F_2O_4$ 233.0629, found 233.0626.

Methyl 2,2-difluoro-5-oxo-5-(2-thienyl)pentanoate (20h)

^{1}H NMR ($CDCl_3$) δ 2.55 (tt, J = 17.02, 7.81 Hz, 2H), 3.17 (t, J = 7.81 Hz, 2H), 3.88 (s, 3H), 7.14 (dd, J = 4.96, 3.78 Hz, 1H), 7.66 (d, J = 4.96 Hz, 1H), 7.75 (d, J = 3.78 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.92 (t, J = 23.85 Hz), 31.19 (t, J = 3.91 Hz), 53.44, 115.68 (t, J = 250.36 Hz), 120.20, 132.14, 134.02, 143.28, 164.31 (t, J = 32.95 Hz), 189.85; ^{19}F NMR ($CDCl_3$) δ −106.63 (t, J = 17.02 Hz, 2F); IR (neat) 2959, 1770, 1668, 1416, 1356, 1211, 1097, 1063, 966, 858, 729; HRMS (FAB) m/z (M+H) Calcd for $C_{10}H_{11}F_2O_3S$ 249.0389, found 249.0398.

Typical procedure for the preparation of methyl 2,2-difluoro-5-iodo-undecanoate (22a)

A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum and an inlet tube for argon was charged with 0.224 g (2.0 mmol) of 1-octene in hexane (1 mL). To this solution, 0.250 g (1.0 mmol) of methyl 2,2-difluoro-3-iodopropanoate (**18**) in hexane (1 mL) was added slowly *via* a syringe at room temperature and then 0.1 mL (0.1 mmol) of 1.01 M Et_3B in *n*-hexane was added slowly *via* a syringe at 0 °C. The whole was stirred for 1.5 h at 0 °C and then 0.1 mL (0.1 mmol) of 1.01 M Et_3B in *n*-hexane was added slowly *via* a syringe at 0 °C 2 times. After being stirred for 4.5 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (40 mL). The resultant mixture was extracted with ether (50 mL, 3 times) and the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography of the residue using hexane/benzene (5 : 1) gave pure product **22a**.

Methyl 2,2-difluoro-5-iodo-undecanoate (22a)

^{1}H NMR ($CDCl_3$) δ 1.20–1.41 (m, 10H), 1.41–1.53 (m, 1H), 1.65–1.72 (m, 1H), 1.85–2.02 (m, 3H), 2.09–2.23 (m, 1H), 2.31–2.44 (m, 1H), 3.87 (s, 3H), 4.04–4.10 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.02, 22.54, 28.39, 29.36, 29.36, 31.59, 32.17 (t, J = 3.92 Hz), 34.72 (t, J = 23.42 Hz), 36.79, 40.59, 53.41, 115.73 (t, J = 250.39 Hz), 164.48; ^{19}F NMR ($CDCl_3$) δ −107.00—105.50 (m, 2F); IR (neat) 2957, 2929, 2857, 1771, 1445, 1349, 1303, 1201, 1081, 948, 827.

Methyl 5-cyclohexyl-2,2-difluoro-5-iodo-pentanate (22b)

^{1}H NMR ($CDCl_3$) δ 1.04–1.35 (m, 7H), 1.62–1.81 (m, 5H), 1.90–1.92 (m, 1H), 2.04–2.13 (m, 2H), 2.38–2.45 (m, 1H), 3.89 (s, 3H), 4.03 (dt, J = 9.84 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.89, 25.95, 26.17, 29.66 (t, J = 3.97 Hz), 31.32, 32.39, 35.17 (t, J = 23.44 Hz), 45.10, 46.85, 53.41, 115.73 (t, J = 250.51 Hz), 164.50; ^{19}F NMR ($CDCl_3$) δ −105.00—107.10 (m, 2F); IR (neat) 2928, 2854, 1770, 1447, 1299, 1222, 1087, 952, 827, 659.

Methyl 2,2-difluoro-9-hydroxy-5-iodo-nonanate (22c)

^{1}H NMR ($CDCl_3$) δ 1.40–1.45 (m, 1H), 1.47–1.60 (m, 3H), 1.81–1.98 (m, 3H), 2.05–2.19 (m, 1H), 2.27–2.39 (m, 1H), 2.28 (s, 1H), 3.58 (t, J = 6.26 Hz, 2H), 3.84 (s, 3H), 4.00–4.06 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.65, 31.51, 32.02 (t, J = 3.85 Hz), 34.52 (t, J = 23.11 Hz), 36.42, 40.12, 53.35, 62.17, 115.56 (t, J = 250.77 Hz), 164.31 (t, J = 32.95 Hz); ^{19}F NMR ($CDCl_3$) δ −107.20—105.40 (m, 2F); IR (neat) 3368, 2938, 2863, 2354, 1766, 1445, 1309, 1201, 1076, 913, 828, 734; HRMS (FAB) m/z (M+H) Calcd for $C_{10}H_{18}F_2IO_3$ 351.0242, found 351.0269.

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