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Radical conjugate addition of ambiphilic fluorinated free radicals

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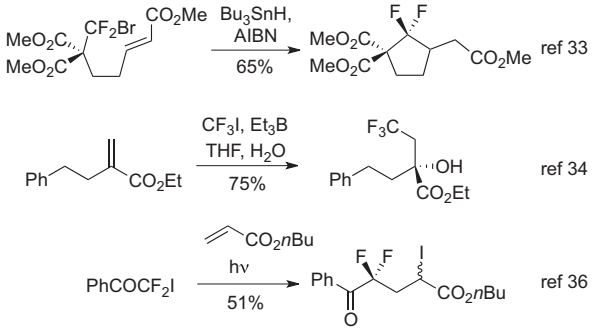
ABSTRACT

The ambiphilic character of fluorinated radicals was noticed during their radical conjugate addition onto electron-deficient alkenes. Free radicals were trapped with enones when the reaction was conducted from iododifluoro-acetate and -phosphonate derivatives in the presence of Et_3B. Competitive addition reaction onto electron-rich or -deficient alkenes was observed depending on the free radical initiator.

1. Introduction

The introduction of a fluoroalkyl chain onto organic compounds is an attractive strategy for the preparation of biomolecules or materials.[1–5] The main strategies to synthesize these compounds involved the addition of fluorinated carbanion onto a large variety of electrophiles and the reaction of electrophilic fluoroalkylating reagents with carbon nucleophiles.[6,7] The radical addition reaction of fluoroalkyl radicals has been mainly studied with electron-rich alkenes or alkynes as radical traps.[8] For example, trifluoromethyl radical was added onto enolates,[9–11] aromatic derivatives,[12,13] and alkoxycarbonyl-, phosphonyl- or phenylsulfonyl-difluoromethyl radicals onto electron-rich alkenes and alkynes.[14–23] Indeed, it has already been demonstrated that the electrophilic character of perfluoroalkyl radical $R_f^{\bullet}$ predominates and its addition onto electron-rich alkenes is efficient due to a favorable SOMO–HOMO interaction.[24–28] The addition of fluorinated radicals onto electron-deficient alkenes is rare, but would be an attractive alternative to the limited conjugate addition reaction of fluorinated carbanion.[29–32] Few works have been done in this field, and it has been shown that only the addition of $CF_3^{\bullet}$, $RCF_2^{\bullet}$, $RCOCF_2^{\bullet}$ radicals onto electron-deficient alkenes was possible (Scheme 1).[33–39] With these radicals, additional SOMO–LUMO interaction is expected, which confers them an ambiphilic character.[40]



Scheme 1. Addition of $CF_3^{\bullet}$, $RCF_2^{\bullet}$, $RCOCF_2^{\bullet}$.

We presume that the ambiphilic character of $CF_3^{\bullet}$ and $RCF_2^{\bullet}$ carbon centered radicals is due to the σ attracting effect of one fluorine atom and the π donating effect of the second fluorine atom (Fig. 1).

R = alkyl, F, COR

Fig. 1. Ambiphilic radical.

For $RCOCF_2^{\bullet}$ carbon centered radical, already substituted by one electron-withdrawing group and considered as ambiphilic,[41–44] the additional effect of the two fluorine atoms reinforces this character.

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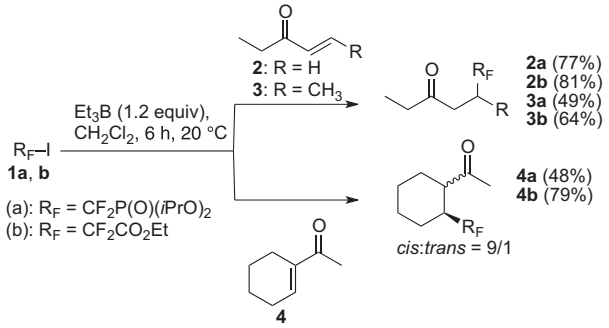
Previously, we reported our preliminary results focused on the radical conjugate addition (RCA) of the $(i-PrO)_2(O)PCF_2^{\bullet}$ radical onto enones **2**, which also confirmed an ambiphilic character (Scheme 2).[45]



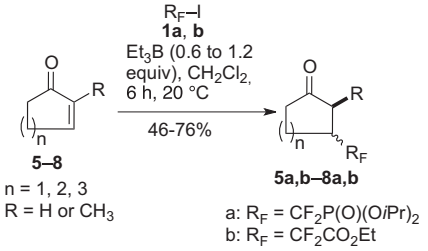
Scheme 2. RCA with unsaturated ketones.

2. Results and discussion

We report the scope and limitations of this RCA with the $(i-PrO)_2(O)PCF_2^{\bullet}$ radical and our preliminary results obtained with the $EtO_2CCF_2^{\bullet}$ radical. The liberation of the phosphonodifluoromethyl radical was conducted with iodophosphonate **1a** (1 equiv) and triethylborane (0.6–1.2 equiv, 1 M solution in *n*-hexane) in the presence of enones (1.2 equiv). This reaction did not proceed in the presence of sodium hydrosulfite ($Na_2S_2O_4$), or dilauroyl peroxide as initiators, but good results were obtained in the presence of triethylborane. Encouraged by the result obtained with **2** the reaction was extended to β- and α,β-substituted enones (Scheme 2). The introduction of a methyl group onto the β carbon atom was tolerated, and the radical trapped with β-substituted linear enone **3** afforded ketone **3a** in 49% yield (Scheme 2). The addition onto α,β-disubstituted enone **4** was also possible and product **4a** was isolated in similar yield as a mixture of diastereomers (Scheme 2).

The alkoxycarbonyldifluoromethyl radical $EtO_2CCF_2^{\bullet}$ described as rather electrophilic radical than nucleophilic,[22,23,28] was then involved in the RCA. When the experimental procedure used for **1a** was applied to ethyl iododifluoroacetate **1b** and enone **2** (Scheme 2), the expected RCA product **2b** was produced and isolated in 81% yield after 6 h at 20 °C (Scheme 2). As expected, this result supports that the carboxydifluoromethyl radical presents also an ambiphilic character. Indeed, it has been shown recently that photochemical activation promoted the formation and the addition of this radical onto acrylate derivatives.[38] Addition onto acyclic enones such as ketones **3**, **4** afforded the corresponding ketoesters **3b**[32,46] and **4b** in 64 and 79% yields, respectively (Scheme 2). The epimerization of **4b** was observed in the medium, leading to a mixture of both cis/trans isomers.

This reaction was then extended to cyclic enones **5**–**8** (Scheme 3). The radical generated from **1a** can be added onto five- and six-membered cyclic enones **5**, **6** and also onto larger cyclic enone, such as cycloheptenone **7** to afford the formal conjugate addition products **5a**–**7a** in 58–69% yield (Table 1, Scheme 3). The scope and limitations of the RCA were explored using substituted cyclic enones (Table 1, Scheme 3). The enone **8** reacted smoothly to produce the cycloalkanone **8a** in 69% yield (Table 1, Scheme 3). The product **8a** was not stable in the medium and fast epimerization occurred over the reaction or during the work-up affording a single isomer.[47] However, the reaction failed when β-substituted cyclic enone was involved. The carboxydifluoromethyl radical formed from **1b** was trapped with cyclic enones **5**–**7**, and corresponding difluoroester derivatives **5b**–**7b**[32,46] were obtained in 46–70% yield. In contrast to the result observed from **1a** and enone **8**, a mixture of diastereoisomers **8b** was obtained in 76% yield. HOESY experiment confirmed the trans isomer was the major product. However, product **8b** epimerized slowly in the reaction mixture.



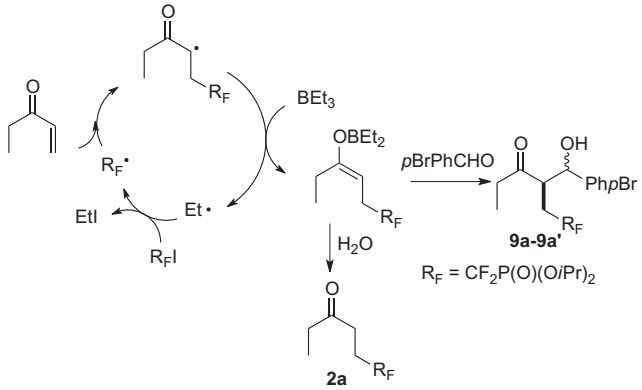
Scheme 3. Radical addition onto cyclic ketones and lactones.

Table 1
Radical conjugate addition

Radical acceptor	R	*n*	Product (yield, %)[a]	
5	H	1	**5a** (62)	**5b** (46)
6	H	2	**6a** (69)	**6b** (70)
7	H	3	**7a** (58)	**7b** (67)
8	CH_3	1	**8a** (69) trans[b]	**8b** (76) cis/trans=4:6[b]

[a] Isolated yields.
[b] Determined by ^{19}F and HOESY.

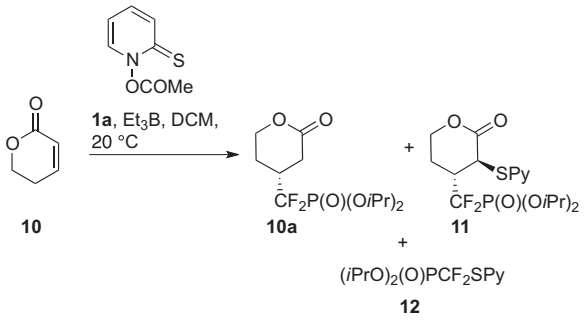
In agreement with literature precedents, the formal conjugate addition products, obtained in this reaction, were produced through the formation of the corresponding boron enolate formed via radical-polar crossover process (Scheme 4).[48,49] In order to trap this boron enolate, a three-component reaction was carried out by addition of Et_3B (1.2 equiv) to a solution of **1a**, *p*-bromobenzaldehyde (1.3 equiv), and enone **2** (1.3 equiv) in CH_2Cl_2.[50] After 4 h of stirring at 20 °C, the ^{19}F NMR analysis of the crude showed the formation of product **2a**, in combination with additional products, appearing as a second order pattern. Due to the complexity of the pattern, the ratio **9a**/**9a'**/**2a** was estimated to 2:2:1. After purification one isomer was obtained in the presence of compound **2a**, and the other was isolated as a pure compound in 69% yield.



Scheme 4. Mechanism for the addition to enones.

To extend this reaction to lactones, the intermediate radical was trapped with Barton carbonate instead of Et_3B. Indeed, it is known that the use of Et_3B as free radical initiator allowed the formation of boron enolates only from ketones and aldehydes.[51,52] Of note, the reaction did not reach completion when the experiment was conducted from lactone **10** and **1a** only in the presence of Et_3B (Scheme

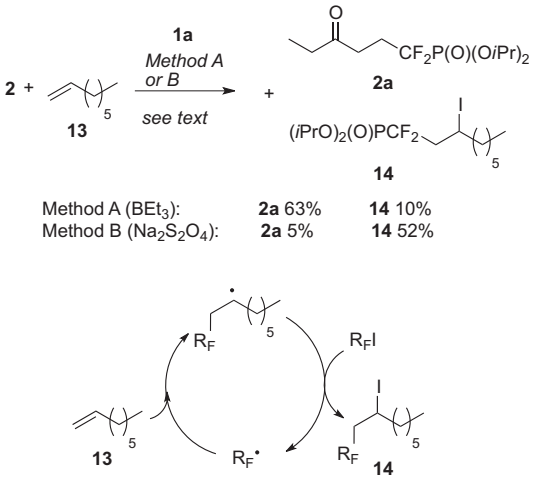
5). To drive the formation of carbon centered radicals from lactones, the Barton carbonate (pyridine-2-thione-*N*-oxycarbonyl, PTOC–OMe) was used as radical trap. The radical addition reaction was conducted by adding slowly a solution of PTOC–OMe (1.5 equiv), and simultaneously a Et_3B solution (1.2 equiv, 1 M in *n*-hexane) to a mixture of lactone **10** and **1a** (Scheme 5). After 5 h of stirring at room temperature, compound **10a** was formed in the presence of additional two pyridine-sulfanyl derivatives **11** and **12** in a 1:1:3 ratio.



Scheme 5. Reaction with PTOC–OMe.

The major compound **12** was formed by the free radical addition of the fluorinated radical onto PTOC–OMe and was isolated in 40% yield. The minor product **11** was formed by the addition of the intermediate radical onto PTOC–OMe. The two products **10a** and **11** were obtained as an inseparable mixture by flash chromatography. However, compound **12** was still the main product of the reaction even when slow additions of the PTOC–OMe reagent or the Et_3B solution were carried out.

Finally, selective radical addition from **1a** was attempted by mixing electron-rich and electron-poor alkenes, such as enone **2** and 1-octene **13** (Scheme 6). The two radical initiators tested were Et_3B (method A: Et_3B, CH_2Cl_2, 20 °C) and sodium hydrosulfite (method B: $Na_2S_2O_4$, $NaHCO_3$, CH_3CN/H_2O, 20 °C). To our surprise, depending on the initiator it was possible to control the addition reaction. In the presence of Et_3B, the RCA of the phosphonylated radical onto **2** was the main reaction observed. Products **2a** and **14** were formed in 4:1 ratio, and ketophosphonate **2a** was isolated in 63% yield. In contrast, in the presence of sodium hydrosulfite the opposite selectivity was observed (**2a**/**14**=1:9), and compound **14** resulting from the group transfer reaction of **1a** onto **13** was isolated in 52% yield. The polarity-matched and -mismatched reactions of perfluoroalkyl radicals were recently studied, suggesting



Scheme 6. Selective addition reaction, and mechanism for the group transfer reaction.

in the present case, that Et_3B may also play the role of Lewis acid.[53] These results confirmed that the group transfer reaction is possible rather with electron-rich alkenes in the presence of sodium hydrosulfite than with electron-deficient alkenes (Scheme 6). When electron-deficient alkenes, such as enones, were involved, the radical addition is possible only in the presence of Et_3B, which drives the reaction by forming the boron enolate as depicted in Scheme 4. This reaction was conducted with iodoester **1b** and similar product distribution was observed. In this case the main products were obtained in the presence of many unidentified fluorinated adducts, making impossible their purification.

3. Conclusion

In conclusion, triethyl borane promoted the addition of carbonyl- and phosphono-difluoromethyl radicals onto electron-deficient alkenes, such as enones. These *gem*-difluorinated radicals present an ambiphilic character, allowing their addition onto electron-rich and electron-poor alkenes. Depending on the free radical initiator, it was possible to control the addition reaction. While sodium hydrosulfite promoted their addition onto electron-rich alkenes to afford the expected iodoalkanes, triethyl borane promoted their addition onto electron-poor alkenes, leading to the corresponding fluorinated ketones. This approach is competitive with the rare formal anionic conjugate addition reaction of fluoroalkyl group onto enones, and opens new routes for the synthesis of fluorinated biological active compounds. Current works are under investigation to understand the mechanism involved in the selective free radical addition and to access to highly functionalized fluoroorganic compounds by cascade reactions.

4. Experimental section

4.1. General information

All commercially available reagents were bought from Aldrich and used as received. For anhydrous conditions, the glassware was dried in the oven at 120 °C and cooled to room temperature under a continuous nitrogen flow. THF, CH_2Cl_2, Et_2O, and CH_3CN were dried at a solvent generator from 'Innovative Technologies Inc.', which uses an activated alumina column to remove water. DMF and NEt_3 were distilled under CaH_2 or 4 Å molecular sieves. Flash column chromatography was realized on silica gel 60 (40–63 μm) with air pressure and were detected by thin layer chromatography, on which the spots were visualized by UV-irradiation and/or $KMnO_4$ solution. NMR spectra were recorded on a 250 MHz or 400 MHz apparatus in deuterated solvent at 25 °C. ^{31}P and ^{19}F NMR spectral lines are with respect to the internal references H_3PO_4 (capillary) and $CFCl_3$. All chemical shifts are reported in δ parts per million (ppm) and coupling constants are in hertz (Hz). High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or ESI mode. High-resolution mass data were recorded on a Micromass Q-TOF (Quadrupole Time-of-Flight) instrument with an electrospray source in the EI or ESI mode.

4.2. Diisopropyl 1,1-difluoro-4-oxohexylphosphonate (2a)[45]

General procedure for the radical conjugated addition. To a stirred solution of iododifluoromethylphosphonate **1a** (100.0 mg, 0.29 mmol) and ethylvinylketone (0.04 mL, 0.40 mmol) in CH_2Cl_2 (2 mL) was added Et_3B (0.36 mL, 1 M in hexane, 1.2 equiv) over 4 h by portion of 0.1 equiv every 20 min at 20 °C. The mixture was then concentrated under reduced pressure. Compound **2a** was isolated after flash chromatography (EtOAc/pentane 4:6) as a colourless oil (69.8 mg, 79%). ^1H NMR ($CDCl_3$, 400 MHz) δ 4.80 (dsept, *J* 6.4, 6.4 Hz, 2H), 2.69 (t, *J* 7.3 Hz, 2H), 2.44 (q, *J* 7.3 Hz, 2H), 2.41–2.35 (m, 2H),

1.34 (d, *J* 6.4 Hz, 6H), 1.33 (d, *J* 6.4 Hz, 6H), 1.04 (t, *J* 7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −112.84 (dt, *J* 108.2 Hz, 19.6 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 4.9 (t, *J* 108.2 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 208.9, 120.3 (td, *J* 259.1, 217.9 Hz), 73.7 (d, *J* 7.1 Hz), 36.1, 33.7 (td, *J* 9.0, 4.6 Hz), 28.1 (td, *J* 21.5, 15.7 Hz), 24.2 (d, *J* 3.3 Hz), 23.8 (d, *J* 4.8 Hz), 7.9. MS-ESI (*m*/*z*) $[M+Na]^+$ 323 (54), 281 (50), 239 (100), 221 (8). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{12}H_{23}O_4PF_2Na$ 323.1194, found 323.1200.

4.3. Diisopropyl 1,1-difluoro-2-methyl-4-oxohexylphosphonate (3a)

Following the general procedure used for **2a** from iododifluorophosphonate **1a** (100 mg, 0.29 mmol), *trans*-4-hexen-3-one (0.037 mL, 0.32 mmol), and Et_3B (0.36 mL) in CH_2Cl_2 (2 mL), compound **3a** was isolated after flash chromatography (EtOAc/pentane 2:8 to 3:7) as a colourless oil (45.2 mg, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.78 (dsept, *J* 6.9, 6.9 Hz, 2H), 3.03–2.36 (m, 2H), 2.95–2.79 (m, 1H), 2.53–2.36 (m, 2H), 1.38–1.36 (m, 12H), 1.09 (d, *J* 6.9 Hz, 3H), 1.06 (t, *J* 7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −114.88 (ddd, *J* 297.4, 110.5, 17.1 Hz, 1F), −116.47 (ddd, *J* 297.4, 110.5, 17.1 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 5.1 (t, *J* 110.5 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 208.8, 121.5 (td, *J* 262.8, 213.9 Hz), 73.8 (d, *J* 7.2 Hz), 73.7 (d, *J* 7.2 Hz), 42.2 (td, *J* 7.3, 4.0 Hz), 36.6, 33.8 (td, *J* 20.4, 15.5 Hz), 24.3, 23.9, 13.4, 7.8. MS-ESI (*m*/*z*) $[M+Na]^+$ 337 (19), 295 (43), 253 (100), 235 (19). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{13}H_{25}O_4PF_2Na$ 337.1356, found 337.1355.

4.4. Diisopropyl (2-acetylcyclohexyl)difluoromethylphosphonate (4a)

General procedure for the radical conjugate addition. To a stirred solution of iododifluoromethylphosphonate **1a** (50 mg, 0.15 mmol), and 1-acetylcyclohexene (0.023 mL, 0.18 mmol) in CH_2Cl_2 (1 mL) was added Et_3B (0.18 mL, 1 M in hexane, 1.2 equiv). After 1 h of stirring, Et_3B was added (0.18 mL, 1 M in hexane, 1.2 equiv) and the mixture was stirred additional 1 h. The mixture was then concentrated under reduced pressure. Compound **4a** was isolated after flash chromatography (EtOAc/pentane 2:8) as a colourless oil (23.9 mg, 48%) in a cis/trans mixture (92:8). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82 (dsept, *J* 6.3, 6.3 Hz, 2H), 3.16 (ddd, *J* 4.1, 4.1, 4.1 Hz, 1H), 2.43–2.23 (m, 1H), 2.19 (s, 3H), 1.90–1.24 (m, 8H), 1.36 (m, 12H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −103.08 (dd, *J* 298.5, 106.3 Hz, 1F, trans), −110.00 (dd, *J* 298.5, 107.9 Hz, 1F, cis), −112.77 (ddd, *J* 298.5, 107.9, 24.1 Hz, 1F, cis), −118.80 (ddd, *J* 298.5, 106.3, 23.9 Hz, 1F, trans); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 5.2 (t, *J* 107.9 Hz, 1P, cis), 4.6 (dd, *J* 110.5, 106.3 Hz, 1P, trans); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 210.2, 120.0 (td, *J* 263.0, 214.0 Hz), 73.9 (d, *J* 6.9 Hz), 73.7 (d, *J* 7.0 Hz), 44.3, 30.8, 27.5, 25.0, 24.3 (d, *J* 3.3 Hz), 24.1 (d, *J* 3.5 Hz), 23.9 (d, *J* 5.2 Hz), 23.7 (d, *J* 4.5 Hz), 21.2, 21.1. MS-ESI (*m*/*z*) $[M+H]^+$ 341 (8), 299 (32), 257 (100), 239 (15). HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{15}H_{28}O_4F_2P$ 341.1693, found 341.1690.

4.5. Diisopropyl difluoro(3-oxocyclopentyl)methylphosphonate (5a)[45]

Following the general procedure used for **2a** from iododifluorophosphonate **1a** (100.0 mg, 0.29 mmol), 2-cyclopentenone (0.049 mL, 0.58 mmol), and Et_3B (0.36 mL) in CH_2Cl_2 (2 mL), compound **5a** was isolated after flash chromatography (EtOAc/pentane 5:5) as a colourless oil (49.3 mg, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.85 (dsept, *J* 6.5, 6.5 Hz, 1H), 4.84 (dsept, *J* 6.5, 6.5 Hz, 1H), 3.02–2.85 (m, 1H), 2.49–2.06 (m, 6H), 1.39–1.37 (m, 12H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −117.13 (ddd, *J* 298.0, 108.5, 17.1 Hz, 1F), −118.83 (ddd, *J* 298.0, 108.5, 15.7 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 4.8 (t, *J* 108.5 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 216.1, 120.1 (td, *J* 261.3, 216.7 Hz), 74.1 (d, *J* 7.0 Hz), 74.0 (d, *J* 7.0 Hz), 40.7 (td, *J* 21.3, 15.1 Hz), 38.3, 37.7, 24.2, 23.9, 22.3 (td, *J* 5.5, 5.5 Hz). MS-ESI (*m*/*z*) $[M+Na]^+$ 321 (18), 279 (40), 237 (100). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{12}H_{21}O_4F_2PNa$ 321.1043, found 321.1039.

4.6. Diisopropyl difluoro(3-oxocyclohexyl)methylphosphonate (6a)[45]

Following the general procedure used for **2a** from iododifluorophosphonate **1a** (50.0 mg, 0.15 mmol), 2-cyclohexenone (0.017 mL, 0.18 mmol), and Et_3B (0.18 mL) in CH_2Cl_2 (1 mL), compound **6a** was isolated after flash chromatography (EtOAc/pentane 5:5) as a colourless oil (28.4 mg, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.84 (dsept, *J* 6.2, 6.2 Hz, 1H), 4.83 (dsept, *J* 6.2, 6.2 Hz, 1H), 2.58–2.44 (m, 1H), 2.68–1.61 (m, 8H), 1.37 (d, *J* 6.2 Hz, 6H), 1.36 (d, *J* 6.2 Hz, 6H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −115.81 (ddd, *J* 299.1, 108.1, 13.5 Hz, 1F), −118.02 (ddd, *J* 299.1, 108.1, 15.9 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 4.6 (t, *J* 108.1 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 209.0, 120.0 (td, *J* 263.0, 214.2 Hz), 73.9 (d, *J* 5.5 Hz), 73.8 (d, *J* 5.7 Hz), 42.8 (td, *J* 20.6, 15.3 Hz), 41.1, 39.9 (td, *J* 7.9, 4.7 Hz), 24.3, 24.2, 23.8. MS-ESI (*m*/*z*) $[M+H]^+$ 313 (40), 271 (100), 229 (75). HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{13}H_{24}O_4F_2P$ 313.1380, found 313.1391.

4.7. Diisopropyl difluoro(3-oxocycloheptyl)methylphosphonate (7a)

Following the general procedure used for **2a** from iododifluorophosphonate **1a** (200.0 mg, 0.58 mmol), 2-cyclohepten-1-one (0.080 mL, 0.72 mmol), and Et_3B (0.72 mL) in CH_2Cl_2 (4 mL), compound **7a** was isolated after flash chromatography (EtOAc/pentane 4:6) as a colourless oil (83.0 mg, 57%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87–4.81 (m, 2H), 2.82 (dd, *J* 15.1, 2.4 Hz, 1H), 2.61 (dd, *J* 15.1, 11.6 Hz, 1H), 2.52–2.48 (m, 2H), 2.47–2.37 (m, 1H), 2.36–1.40 (m, 6H), 1.38 (d, *J* 6.0 Hz, 6H), 1.37 (d, *J* 6.0 Hz, 6H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −113.33 (ddd, *J* 298.6, 109.4, 15.6 Hz, 1F), −116.02 (ddd, *J* 298.6, 109.4, 17.3 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 5.0 (t, *J* 109.4 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 211.8, 120.9 (td, *J* 264.6, 213.9 Hz), 73.9 (d, *J* 7.3 Hz), 73.8 (d, *J* 7.3 Hz), 43.5, 42.5, 41.3 (td, *J* 19.9, 15.6 Hz), 29.0, 28.4, 24.4, 24.2, 23.7. MS-ESI (*m*/*z*) $[M+Na]^+$ 349 (5), 307 (19), 265 (100). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{14}H_{25}O_4F_2PNa$ 349.1356, found 349.1356.

4.8. Diisopropyl difluoro(2-methyl-3-oxocyclopentyl)methylphosphonate (8a)

General procedure for the radical conjugate addition. To a stirred solution of iododifluoromethylphosphonate **1a** (100 mg, 0.29 mmol) and 3-methyl-2-cyclopentenone (0.035 mL, 0.35 mmol) in CH_2Cl_2 (2 mL) was added Et_3B (0.35 mL, 1 M in hexane, 1.2 equiv). After 1 h of stirring, Et_3B was added (0.35 mL, 1 M in hexane, 1.2 equiv) and the mixture was stirred additional 1 h. The mixture was then concentrated under reduced pressure. Compound **8a** was isolated after flash chromatography (EtOAc/pentane 4:6 to 5:5) as a colourless oil (62.7 mg, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.86 (dsept, *J* 6.3, 6.3 Hz, 1H), 4.85 (dsept, *J* 6.3, 6.3 Hz, 1H), 2.59–1.92 (m, 6H), 1.38 (d, *J* 6.1 Hz, 6H), 1.36 (d, *J* 6.1 Hz, 6H), 1.23 (d, *J* 6.8 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.79 (ddd, *J* 300.0, 108.5, 9.3 Hz, 1F), −119.91 (ddd, *J* 300.0, 108.5, 21.8 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 4.6 (t, *J* 108.5 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.1, 120.9 (td, *J* 259.8, 215.1 Hz), 74.0 (d, *J* 7.2 Hz), 73.8 (d, *J* 7.2 Hz), 48.2 (td, *J* 20.0, 15.2 Hz), 43.5, 36.8, 24.2 (d, *J* 3.3 Hz), 24.1 (d, *J* 3.7 Hz), 23.8 (d, *J* 4.8 Hz), 23.7 (d, *J* 4.9 Hz), 21.1 (td, *J* 3.7, 3.7 Hz), 15.1 (d, *J* 2.3 Hz). MS-ESI (*m*/*z*) $[M+Na]^+$ 335 (22), 293 (44), 251 (100). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{13}H_{23}O_4F_2PNa$ 335.1200, found 335.1216.

4.9. Three-component reaction: diisopropyl 1,1-difluoro-3-(hydroxy-parabromobenzyl)-4-oxohexylphosphonate (9a)

To a solution of iodophosphonate **2a** (100 mg, 0.29 mmol), *para*-bromobenzaldehyde (70 mg, 0.37 mmol), and enone **2** (40 μL, 0.40 mmol) in CH_2Cl_2 (2 mL) was added Et_3B (360 μL, 1 M in hexane, 1.2 equiv) over 4 h by portion of 0.1 equiv every 20 min at 20 °C. The mixture was quenched by addition of saturated solution NH_4Cl (1 mL), extracted with CH_2Cl_2 (2×2 mL), then concentrated under reduced pressure. The isomer **9a** was isolated by flash chromatography (EtOAc/pentane 4:6) as a colourless oil (98 mg, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, *J* 8.9, 2H), 7.18 (d, *J* 8.9, 2H), 4.85–4.57 (m, 3H), 3.58 (d, *J* 2.5, 1H), 3.31–3.23 (m, 1H), 2.9–1.95 (m, 4H), 1.40–1.20 (m, 12H), 0.84 (t, *J* 6.9, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −107.8 (dddd, *J* 294.1, 104.3, 29.4, 8.3, 1F), −113.0 (dddd, 294.1, 109.3, 29.4, 14.8, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 4.2 (dd, *J* 109.4, 104.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 213.1, 140.4, 131.5, 127.9, 121.6, 120.1 (td, *J* 259.8, 217.3 Hz), 73.9 (d, *J* 7.5 Hz), 73.8 (d, *J* 7.8 Hz), 72.9, 51.4 (td, *J* 5.2, 2.5), 37.5, 32.0 (td, *J* 20.7, 16.0 Hz), 24.1 (d, *J* 3.3 Hz), 24.0 (d, *J* 3.4 Hz), 23.6 (d, *J* 5.2 Hz), 23.5 (d, *J* 5.1 Hz), 7.1. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{12}H_{28}O_5PBrF_2Na$ 507.0718, found 507.0724.

4.10. β-(Diisopropyl 1,1-difluoromethylphosphonate)-δ-valerolactone (10a)

Following the general procedure used for **2a** from iododifluorophosphonate **1a** (150 mg, 0.44 mmol), 5,6-dihydro-2*H*-pyran-2-one (0.096 mL, 1.11 mmol), and Et_3B (0.54 mL) in CH_2Cl_2 (2 mL), compound **10a** was isolated after flash chromatography (CH_2Cl_2 then EtOAc/pentane 5:5) as a colourless oil (43.9 mg, 32%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.86 (dsept, *J* 6.3, 6.3 Hz, 1H), 4.84 (dsept, *J* 6.3, 6.3 Hz, 1H), 4.40 (dt, *J* 11.5, 5.0 Hz, 1H), 4.25 (ddd, *J* 11.5, 9.3, 3.8 Hz, 1H), 2.83–2.66 (m, 3H), 2.15–2.10 (m, 1H), 2.08–2.04 (m, 1H), 1.39–1.36 (m, 12H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −118.20 (ddd, *J* 300.4, 105.6, 14.3 Hz, 1F), −119.31 (ddd, *J* 300.4, 105.6, 14.3 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 4.0 (t, *J* 105.6 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.7, 119.6 (td, *J* 263.4, 214.1 Hz), 74.4 (d, *J* 7.5 Hz), 74.3 (d, *J* 7.5 Hz), 67.4, 36.2 (td, *J* 21.4, 15.7 Hz), 28.8 (td, *J* 5.5, 5.5 Hz), 24.3 (d, *J* 3.6 Hz), 24.2 (d, *J* 3.9 Hz), 23.9 (d, *J* 4.8 Hz), 23.8 (d, *J* 4.8 Hz), 22.2 (td, *J* 5.5, 5.5 Hz). MS-ESI (*m*/*z*) $[M+Na]^+$ 337 (20), 295 (44), 253 (100). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{12}H_{21}O_5F_2PNa$ 337.0992, found 337.0982.

4.11. Diisopropyl difluoro-(3*S*,4*S*)-2-oxo-3-(pyridin-2-ylthio)(tetrahydro-2*H*-pyran-4-yl)-methylphosphonate (11)

General procedure for the Barton carbonate preparation. The sodium salt of *N*-hydroxypyridine-2-thione (55 mg, 0.36 mmol) and methyl chloroformate (33 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) were stirred for 1 h in the dark. To a solution of iododifluoromethylphosphonate **1a** (50 mg, 0.15 mmol) and 5,6-dihydro-2*H*-pyran-2-one (0.045 mL, 0.53 mmol) in CH_2Cl_2 (1.5 mL), PTOC–OMe (1.5 equiv), freshly prepared, was introduced dropwise over 4 h. Following general procedure used for **2a**, Et_3B (0.18 mL, 1 M in hexane) was added, at the same time, to the mixture and the reaction mixture was stirred at room temperature for 4 h. The mixture was quenched with H_2O, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography using CH_2Cl_2 then EtOAc/pentane 5:5 as eluent to give **11** in a mixture with the reduced product **10a** (1:1) as a colourless oil (11.7 mg, 10% **11**, 13% **10a**) and mostly pyridine-sulfanyl derivative **12** as a colourless oil (19.5 mg, 40%). Compound (**11**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (dd, *J* 4.9, 1.8 Hz, 1H), 7.52 (ddd, *J* 8.1, 8.1, 1.0 Hz, 1H), 7.23 (dd, *J* 8.1, 1.0 Hz, 1H), 7.02 (ddd, *J* 8.1, 4.9, 1.0 Hz, 1H), 4.91–4.80 (m, 2H), 4.75 (ddd, *J* 11.0, 11.0, 2.4 Hz, 1H), 4.53–4.47 (m, 1H), 4.37 (d, *J* 7.2 Hz, 1H), 3.25–3.11 (m, 1H), 2.42–2.32 (m, 1H), 2.23–2.13 (m, 1H), 1.36–1.31 (m, 12H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −111.83 (ddd, *J* 302.8, 104.2, 8.7 Hz, 1F), −118.08 (ddd, *J* 302.8, 104.2, 21.5 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 3.5 (t, *J* 104.2 Hz, 1P). MS-ESI (*m*/*z*) $[M+H]^+$ 424 (7), 382 (27), 340 (100), 322 (22). HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{17}H_{25}NO_5F_2PS$ 424.1159, found 424.1138. Compound (**12**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55–8.52 (m, 1H), 7.64–7.61 (m, 2H), 7.24–7.18 (m, 1H), 4.85 (dsept, *J* 6.2, 6.2 Hz, 2H), 1.33 (dd, *J* 6.2, 2.4 Hz, 12H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −84.33 (d, *J* 98.0 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 1.3 (t, *J* 98.0 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 150.6, 150.4, 137.3, 129.8, 126.8 (td, *J* 300.7, 219.6 Hz), 123.6, 75.1 (d, *J* 6.9 Hz), 24.3 (d, *J* 3.2 Hz), 23.8 (d, *J* 5.2 Hz). MS-ESI (*m*/*z*) $[M+H]^+$ 326 (10), 284 (33), 242 (100). HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{12}H_{19}NO_3F_2PS$ 326.0791, found 326.0801.

4.12. Selective radical addition with enone and octene: diisopropyl 1,1-difluoro-3-iodononylphosphonate (14)

General procedure for the selective radical addition with triethylborane. To a stirred solution of iododifluoromethylphosphonate **1a** (50 mg, 0.15 mmol), ethylvinylketone (0.017 mL, 0.18 mmol), and 1-octene (0.028 mL, 0.18 mmol) in CH_2Cl_2 (2 mL) was added Et_3B (0.18 mL, 1 M in hexane, 1.2 equiv) over 4 h by portion of 0.1 equiv every 20 min at 20 °C. The mixture was then concentrated under reduced pressure. The residue was purified by flash chromatography using EtOAc/pentane 3:7 as eluent to give compound **14** (6.7 mg, 10%) and compound **2a** (27.7 mg, 63%) as colourless oils.

4.13. General procedure for selective radical addition with sodium dithionite

To a solution of sodium dithionite (102 mg, 0.59 mmol), sodium carbonate (25 mg, 0.24 mmol), ethylvinylketone (0.017 mL, 0.18 mmol), and 1-octene (0.028 mL, 0.18 mmol) in a 5:3 mixture of CH_3CN/H_2O (0.5 mL), iododifluoromethylphosphonate **1a** (50 mg, 0.15 mmol) in CH_3CN/H_2O 5:3 was introduced. The mixture was stirred at room temperature for 15 h and then poured into Et_2O (5 mL) and H_2O (1 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography using EtOAc/pentane 3:7 as eluent to give compound **14** (34.5 mg, 52%) and compound **2a** (2.1 mg, 5%) as colourless oils. *Diisopropyl 1,1-difluoro-3-iodononylphosphonate (**14**)*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.84 (dsept, *J* 6.4, 6.4 Hz, 1H), 4.83 (dsept, *J* 6.4, 6.4 Hz, 1H), 4.46–4.38 (m, 1H), 3.00–2.70 (m, 2H), 1.80–1.71 (m, 2H), 1.55–1.23 (m, 8H), 1.37 (d, *J* 6.2 Hz, 6H), 1.36 (d, *J* 6.2 Hz, 6H), 0.87 (t, *J* 6.7 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.50 (dddd, *J* 296.7, 105.6, 30.5, 10.4 Hz, 1F), −113.91 (dddd, *J* 296.7, 105.6, 26.8, 10.7 Hz, 1F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 4.2 (t, *J* 105.6 Hz, 1P); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 120.0 (td, *J* 263.0, 214.6 Hz), 74.0 (d, *J* 6.2 Hz), 73.9 (d, *J* 6.2 Hz), 44.7 (td, *J* 19.8, 14.6 Hz), 40.6 (d, *J* 1.6 Hz), 31.6, 29.7, 28.3, 24.2 (d, *J* 3.3 Hz), 24.1 (d, *J* 3.3 Hz), 23.9, 23.8 (d, *J* 4.8 Hz), 22.6, 14.1. MS-ESI (*m*/*z*) $[M+Na]^+$ 477 (20), 435 (45), 393 (100), 349 (55), 307 (51), 287 (24), 265 (73), 243 (24). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{15}H_{30}O_3F_2PINa$ 477.0843, found 477.0864.

4.14. Ethyl 2,2-difluoro-5-oxoheptanoate (2b)

General procedure used for **2a** was followed with ethyl iododifluoroacetate (53 mg, 0.22 mmol), ethyl vinyl ketone (0.027 mL, 0.27 mmol), Et_3B (0.264 mL), and CH_2Cl_2 (1 mL). Purification by flash chromatography (EtOAc/pentane 5:5) afforded **2b** as a colourless oil (37.8 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (q, *J* 7.1 Hz, 2H), 2.62 (t, *J* 7.2 Hz, 2H), 2.42 (q, *J* 7.3 Hz, 2H), 2.40–2.35 (m,

2H), 1.32 (t, *J* 7.1 Hz, 3H), 1.00 (t, *J* 7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −106.50 (t, *J* 17.1 Hz, 2F); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 208.3, 164.0 (t, *J* 32.7 Hz), 115.7 (t, *J* 250.0 Hz), 63.0, 35.9, 34.0 (t, *J* 3.7 Hz), 28.5 (t, *J* 23.9 Hz), 13.9, 7.7. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_9H_{14}O_3F_2Na$ 231.0809, found 231.0804.

4.15. Ethyl 2-(2-acetylcyclohexyl)-2,2-difluoroacetate (4b)

General procedure used for **4a** was followed with ethyl iododifluoroacetate **1b** (132 mg, 0.56 mmol), 1-acetylcyclohexene (0.065 mL, 0.51 mmol), Et_3B (1.340 mL), and CH_2Cl_2 (2 mL). Purification by flash chromatography (CH_2Cl_2/pentane 6:4) afforded **10b** as a colourless oil (99.1 mg, 79%) in a cis/trans mixture (97:3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35–4.20 (m, 2H), 3.00 (ddd, *J* 4.0, 4.0, 4.0 Hz, 1H), 2.35–2.18 (m, 1H), 2.18–1.17 (m, 8H), 2.13 (s, 3H), 1.32 (t, *J* 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −106.60 (dd, *J* 268.0, 17.2 Hz, 1F, cis), −107.89 (dd, *J* 268.0, *J* 18.4 Hz, 1F, cis), −109.69 (dd, *J* 257.5, 11.5 Hz, 1F, trans), −113.82 (dd, *J* 257.5, 16.1 Hz, 1F, trans); ^{13}C NMR ($CDCl_3$, 101 MHz) cis isomer: δ 209.7, 164.0 (t, *J* 33.0 Hz), 117.0 (t, *J* 251.0 Hz), 62.8, 45.0 (t, *J* 22.2 Hz), 44.4, 30.5, 27.6, 24.8, 21.1, 21.4 (t, *J* 3.5 Hz), 13.9. MS-ESI (*m*/*z*) $[M+Na]^+$ 271 (100), 251 (27), 231 (32). HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{12}H_{18}O_3F_2Na$ 271.1122, found 271.1113.

4.16. Ethyl 2,2-difluoro-2-(3-oxocyclopentyl)acetate (5b)

General procedure used for **2a** was followed with ethyl iododifluoroacetate **1b** (100 mg, 0.42 mmol), 2-cyclopentenone (0.042 mL, 0.5 mmol), Et_3B (0.500 mL), and CH_2Cl_2 (2 mL). The crude product was purified by flash chromatography (EtOAc/pentane 4:6) to afford **5b** as a colourless oil (40.1 mg, 46%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.34 (q, *J* 7.1 Hz, 2H), 3.06–2.90 (m, 1H), 2.44–1.95 (m, 6H), 1.35 (t, *J* 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −111.35 (dd, *J* 260.7, 14.9 Hz, 1F), −113.75 (dd, *J* 260.7, 14.9 Hz, 1F); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 215.3, 163.6 (t, *J* 32.8 Hz), 115.9 (t, *J* 252.3 Hz), 63.2, 40.5 (t, *J* 23.6 Hz), 37.7 (dd, *J* 4.5, 2.1 Hz), 37.4, 22.0 (dd, *J* 4.9, 3.4 Hz), 14.0. HRMS compound unstable.

4.17. Ethyl 2,2-difluoro-2-(3-oxocycloheptyl)acetate (7b)

General procedure used for **2a** was followed with ethyl iododifluoroacetate **1b** (200 mg, 0.84 mmol), 2-cyclohepten-1-one (0.112 mL, 1.0 mmol), Et_3B (1.0 mL), and CH_2Cl_2 (4 mL). Purification by flash chromatography (EtOAc/pentane 2:8) afforded **7b** as a colourless oil (131 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.32 (q, *J* 7.5 Hz, 2H), 2.61–2.41 (m, 5H), 2.07–1.35 (m, 6H), 1.33 (t, *J* 7.5 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.57 (dd, *J* 257.0, 13.9 Hz, 1F), −113.39 (dd, *J* 257.0, 13.9 Hz, 1F); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 211.0, 163.6 (t, *J* 32.5 Hz), 116.7 (t, *J* 254.6 Hz), 63.1, 43.5, 42.1, 40.5 (t, *J* 22.4 Hz), 29.0 (t, *J* 3.4 Hz), 28.2, 24.2, 14.0. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{11}H_{16}O_3F_2Na$ 257.0965, found 257.0965.

4.18. Ethyl 2,2-difluoro-2-(2-methyl-3-oxocyclopentyl)acetate (8b)

General procedure used for **4a** was followed with ethyl iododifluoroacetate **1b** (100 mg, 0.42 mmol), 2-methyl-2-cyclopentenone (0.083 mL, 0.85 mmol), Et_3B (1.0 mL), and CH_2Cl_2 (2 mL). Purification by flash chromatography (CH_2Cl_2/pentane 6:4) afforded **8b** as a colourless oil (70.2 mg, 76%) in a trans/cis mixture (57:43). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35–4.28 (m, 2H, trans and cis), 3.13–2.99 (m, 1H, cis), 2.60–2.47 (m, 1H, trans), 2.47–1.77 (m, 5H, trans and cis), 1.36–1.31 (m, 3H, trans and cis), 1.14 (d, *J* 7.0 Hz, 3H, trans), 1.11 (dt, *J* 7.5, 1.8 Hz, 3H, cis); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −106.58 (dd, *J* 268.3, 17.1 Hz, 1F, cis), −107.87 (dd, *J* 268.3, 17.1 Hz, 1F, cis), −109.71 (dd, *J* 257.9, 15.6 Hz, 1F, trans), −113.78 (dd, *J* 257.9, 15.6 Hz, 1F, trans); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.4 (cis), 217.2 (trans), 163.9 (t, *J* 32.7 Hz, cis), 163.7 (t, *J* 32.7 Hz, trans), 117.0 (t, *J* 252.4 Hz, cis), 116.4 (t, *J* 252.4 Hz, trans), 63.2 (cis), 63.2 (trans), 47.9 (t, *J* 22.9 Hz, trans), 44.7 (d, *J* 5.0 Hz, cis), 43.7 (d, *J* 2.9 Hz, trans), 43.4 (t, *J* 22.2 Hz, cis), 36.3 (cis), 35.2 (trans), 20.3 (trans and cis), 14.3 (trans), 14.0 (trans), 13.9 (cis), 10.6 (cis). HRMS compound unstable.

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Supplementary data

NMR spectra for all new compounds and HOESY experiment for compounds **8b**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.006.

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