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Mechanochemical electrophilic fluorination of liquid beta-ketoesters

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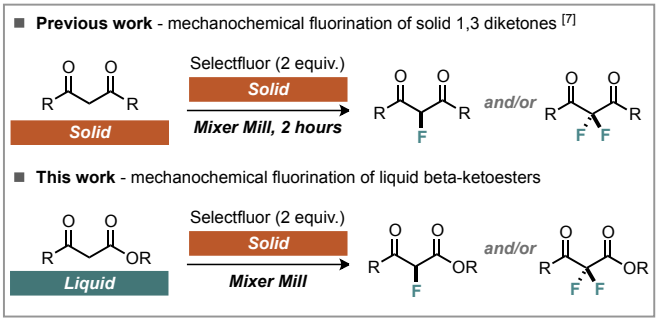
ABSTRACT

An improved substrate scope for the mechanochemical electrophilic fluorination of dicarbonyls is reported. The applicable substrates have now been broadened to include liquid β-ketoesters. Key to this capability is the inclusion of a grinding auxiliary (NaCl) to improve mass transfer and prevent pasting or gumming of the reaction mixture. Notably, the use of a small amount of acetonitrile is critical to increasing the rate of reaction, ensuring complete consumption of starting materials during the short reaction times as well as improving the selectivity for the monofluorinated product in the mill.

1. Introduction

Mechanochemistry is an emerging tool for organic synthesis, with a variety of synthetically important transformations now reported as possible under milling conditions in the absence of solvent.[1] From a sustainability perspective, it is highly desirable to operate under neat conditions, producing little or no solvent waste for the reaction part of a chemical synthesis process.[2] However, mechanochemical milling methods can also complement traditional solution-based synthetic methods. There are several examples of reactions that can be performed mechanochemically in shorter times, with different selectivities or that yield reaction products different from those afforded by solution based reaction.[3] With regards to scaling up reactions, it has been demonstrated that mechanochemical processes can be performed on scales useful for the manufacture of MOFs by making use of twin-screw extrusion or larger-mills.[4] However, the differences in reactivity observed under mechanochemical conditions are not well understood and are often not expected or predicted. There are many parameters involved in mechanochemical processes, finding optimal conditions can be challenging.[5] One such phenomenon is liquid assisted grinding (LAG), whereby the addition of a small quantity of liquid can lead to significant changes in the outcome of a mechanochemical reaction.[6] Our recent work, in which we reported the first mechanochemical fluorination, is one such example.[7] It was found that under LAG conditions, the selectivity of fluorination was significantly improved compared to neat reaction conditions. There are also several examples in which LAG enhances the rate of reaction, and it has also been demonstrated that both the quantity and identity of the added liquid can be used to switch between polymorphic forms.[8] A further consideration is in the physical state of the reagents, where liquid and solids behave differently, which is not normally an important factor in solution-based reactions. Under mechanochemical milling, this can have a significant effect on the performance of the reaction, possibly due to changes in the mixing or energy transfer through the reaction mixture. For example, when one or more reagents are liquid, the reaction



Scheme 1. Extending the scope of mechanochemical fluorination.

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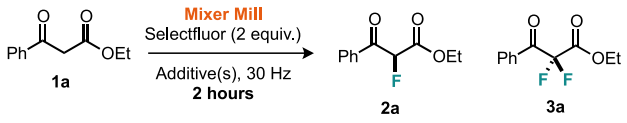
mixture can become a gum or paste that does not mix efficiently and can lead to poor conversions. Such mechanical effects have been shown to cause dramatic changes in a reaction's kinetic profile.[9] This can often be overcome by adding an inert solid as a grinding auxiliary, which can improve the texture of the reaction mixture and aid mass and energy transfer.[10] Such considerations are particularly important when considering one-pot, multistep mechanochemical processes.[11]

Having recently developed the mechanochemical fluorination of solid 1,3-diketones, we were interested to extend this to the fluorination of other nucleophilic carbon centers (Scheme 1). The controlled and selective fluorination of carbon atoms has been shown to dramatically alter the properties of materials, including for example, metabolic stability, solubility, bioavailability, structural rigidity and a molecules overall dipole moment.[12] In this work, we report the modification of our reaction conditions to allow the fluorination of less reactive, liquid substrates, thus improving the overall scope of the solventless process.[13]

Table 1
Optimization of mechanochemical fluorination of liquid β-ketoesters.

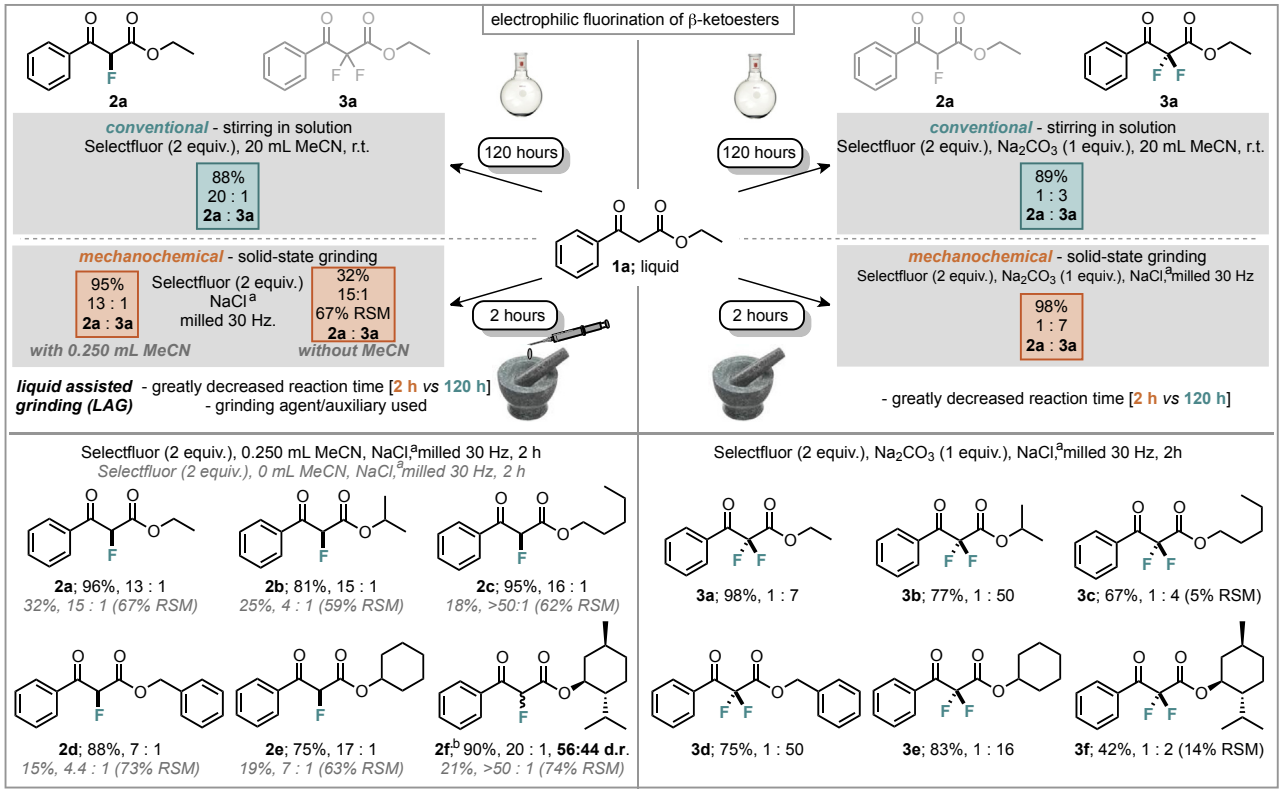


Entry	Additive	Yield[a]	Ratio (**2a:3a**)
1	–	70%	2.7:1
2	NaCl[b]	32%	15:1
3	MeCN (0.125 mL)	69%	7.6:1
4	NaCl[b], MeCN (0.125 mL)	83%	11:1
5	**NaCl[b], MeCN (0.250 mL)**	**96%**	**13:1**
6	**NaCl[b], Na_2CO_3**	**98%**	**1:7**

Bold signifies the conditions for entry 5 are optimal for monofluorination and conditions 6 are optimal for difluorination.
[a] Total yield of **2a** and **3a** determined by ^{19}F NMR compared to trifluorotoluene as an internal standard.
[b] Twice the total mass of reagents.

2. Results and discussion

The previous conditions demonstrated the successful mechanochemical fluorination of solid 1,3-diketones, initial investigations here focused on the less reactive, liquid β-ketoesters. These can react with an electrophilic source of fluorine to afford the monofluorinated product (**2a**) or the difluorinated product (**3a**). On treating ethylbenzoylacetate (**1a**) with Selectfluor under the mechanochemical conditions previously established for solid 1,3-diketones, a total yield of 70% was obtained (Table 1, Entry 1), with a selectivity of 2.7:1. The addition of sodium chloride as a grinding auxiliary was investigated (Table 1, entry 2). This had a detrimental effect on the total yield, although an improvement in selectivity was observed. The addition of acetonitrile was investigated in order to test the effect of LAG conditions on the system (Table 1, Entry 3). Intriguingly this improved the selectivity, but had a detrimental effect on the yield likely because the reaction mixture in this case was the consistency of a paste, suggesting poor mass transfer within the reaction system. Pleasingly, the addition of acetonitrile and sodium chloride enhanced both the yield and selectivity (Table 1, entry 4). Increasing the amount of acetonitrile improved the yield further (Table 1, entry 5). Finally, in order to secure the difluorinated



a) NaCl used as a grinding agent/auxiliary/adsorbent for liquid reactants, the amount used is equal to twice that of the total of all other reactants. b) Starting material is a low melting point solid. RSM = Recovered Starting Material.

Scheme 2. Top: Comparison of mechanochemical conditions to reaction in solution. Bottom: Substrate scope of mechanochemical β-ketoester fluorination.

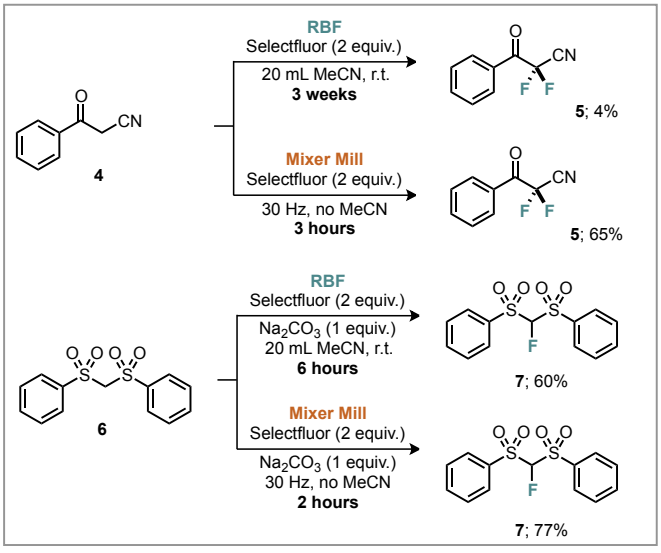
product, the addition of a sodium carbonate as base was used with good effect. Notably, this reaction under solution based conditions requires five days to go to completion.

Indeed, this observation is more generally applicable. The relatively poor nucleophilicity of β-ketoesters is exemplified in the reaction times required in solution for the fluorination to be complete (Scheme 2, top). Without a base, the monofluorinated β-ketoester **2a** was obtained in 88% yield after stirring at room temperature for 120 h. On the addition of Na_2CO_3, the difluorinated β-ketoester **3a** was obtained, also requiring 120 h for the reaction to be complete, with 88% yield. This is in comparison to the 2 h required to complete this reaction in the ball mill, a sixty-fold reduction in the reaction time.

Having demonstrated that the fluorination of the liquid ethylbenzoylacetate **1a** was possible under mechanochemical conditions, the application of this methodology to other substrates was tested (Scheme 2, bottom left). Of those β-ketoesters explored, all were successfully fluorinated when exposed to two hours of grinding in a ball mill in the presence of Selectfluor, sodium chloride and acetonitrile LAG. The addition of the LAG is paramount to the enhanced reaction rate of this reaction. Each process was repeated in duplicate but leaving out the added acetonitrile, as can be seen, significant recovery of starting materials (~50–75%) are evident under these altered conditions. This reaction rate enhancement is in complete contrast to our previous observations with solid diketones![7a] Good conversion to the difluorinated products was also achievable across the same substrate set resulting in good yields by switching the sodium chloride and acetonitrile LAG for sodium carbonate base. It is likely that the sodium carbonate in this instance is also having a grinding auxiliary effect to improve the reaction texture for the milling process (Scheme 2, bottom right).

The mechanochemical fluorination of other activated methylene groups was also investigated (Scheme 3). As with changing from 1,3-diketones to β-ketoesters, it was found that significantly different conditions were required to fluorinate these in the ball mill. For the β-ketonitrile, despite an extensive screening of reaction times, additives and different LAG agents, conditions for the selective monofluorination were not found. This suggests that the monofluorinated β-ketonitrile is more reactive than the starting material, this difficulty has also been observed by others.[14] However, the difluorination of β-ketonitrile **4** was successfully achieved by neat milling with 2 equivalents of Selectfluor to yield compound **5** in 65% yield. The comparable reaction in a solution of acetonitrile was very slow, with only 4% of **5** detected after stirring at room temperature for 3 weeks.

The fluorination of bis-sulfone **6** was also investigated (Scheme 3), and on being subjected to ball milling with Selectfluor this substrate produced the monofluorinated product **7** in 77% yield after milling for 2 h with Selectfluor and Na_2CO_3. Increasing the reaction time further led to slow formation of the difluorinated bis-sulfone. The comparable monofluorination reaction in solution was slightly slower than the mechanochemical reaction, leading to a 60% yield after 6 h.



Scheme 3. Exploration of electrophilic fluorination of further substrates.

3. Conclusion

The mechanochemical fluorination of liquid β-ketoesters has been achieved, making use of liquid assisted grinding and a grinding auxiliary. In this way, good yields of mono- and difluorinated β-ketoesters were obtained with good selectivities. The conditions were further modified to fluorinate a β-ketonitrile and bis-sulfone. It is noteworthy that the use of mechanochemical conditions enabled shorter reaction times to the corresponding solution based reactions.

4. Experimental section

4.1. General

^1H, ^{19}F and ^{13}C NMR spectra were obtained on Bruker 400 Ultrashield™ and Bruker 500 MHz spectrometers with chloroform-d as deuterated solvent. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal. Spin-spin coupling constants J are given in Hz. High resolution mass spectral (HRMS) data were obtained on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University or on a Waters MALDI-TOF mx in Cardiff University. Infrared spectra were recorded on a Shimadzu IR-Affinity-1S FTIR spectrometer. Melting points were measured using a Gallenkamp apparatus and are reported uncorrected. The ball mill used was a Retsch MM 400 mixer mill. Unless otherwise stated, mechanochemical reactions were performed in 10 mL stainless steel jars with one stainless steel ball of mass 4 g. All chemicals were obtained from commercial sources and used without further purification unless stated otherwise.

4.2. General procedure for the synthesis of β-ketoesters

Following a modified literature procedure[15]; an aqueous sodium hydroxide solution (1 M, 50 mL) was added to ethylbenzoylacetate (8.7 mL, 50 mmol). This mixture was stirred overnight at room temperature then transferred to a separating funnel. It was washed with dichloromethane (3 × 10 mL) and the aqueous layer acidified to pH 1 by the addition of aqueous HCl (3 M). The precipitate was collected by suction filtration and dried under vacuum to yield benzoylacetic acid (6.325 g, 39 mmol, 78%), which was used without further purification. A solution of this acid (1.640 g, 10 mmol) and the corresponding alcohol (10 mmol) in acetonitrile (20 mL) was prepared. To this solution was added a solution of dicyclohexylcarbodiimide (2.063 g, 10 mmol) and 4-dimethylaminopyridine (0.061 g, 0.5 mmol) in acetonitrile (10 mL) under rapid stirring. This mixture was stirred overnight at room temperature then directly dry loaded onto silica and purified by flash column chromatography eluting with 40–60 petroleum ether and ethyl acetate to yield the product.

4.2.1. Isopropyl 3-oxo-3-phenylpropanoate (**1b**)

1.820 g, 8.8 mmol, 88%, 3:1 keto:enol. yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, enol), 7.86 (t, J = 7.7 Hz, 2H), 7.67 (t, J = 11.0 Hz, enol), 7.57–7.44 (m, 1H), 7.43–7.28 (m, 2H), 5.55 (s, enol), 5.06 (sep, J = 6.2 Hz, enol), 4.99 (sep, J = 6.3 Hz, 1H), 3.87 (s, 2H), 1.22 (d, J = 6.3 Hz, enol), 1.14 (d, J = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 167.1, 133.7, 128.8, 128.5, 126.1, 69.1, 46.4, 22.0. IR: 1732, 1684, 1265, 1200, 1103, 689 cm^{-1}. HRMS (ES+) [$C_{12}H_{14}O_3$ + Na] calc. 229.0841, found 229.0849.

4.2.2. Pentyl 3-oxo-3-phenylpropanoate (**1c**)

0.760 g, 4.9 mmol, 49%, 2.5:1 keto:enol. yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, enol), 7.93 (d, J = 7.9 Hz, 2H), 7.77 (d, J = 7.8 Hz, enol), 7.57 (t, J = 7.4 Hz, 1H), 7.52–7.35 (m, 2H), 5.66 (s, enol), 4.19 (t, J = 6.7 Hz, enol), 4.13 (t, J = 6.7 Hz, 2H), 3.98 (s, 2H), 1.690–1.70 (m, enol), 1.64–1.52 (m, 2H), 1.36 (dd, J = 8.5, 5.3 Hz, enol), 1.31–1.16 (m, 4H), 0.91 (t, J = 6.6 Hz, enol), 0.85 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 173.4, 171.5, 167.6, 136.1, 133.8, 133.5, 131.3, 128.8, 128.6, 128.6, 126.1, 87.4, 65.7, 64.6, 46.1, 28.5, 28.2, 28.1, 27.9, 22.4, 22.3, 14.0, 14.0. IR: 1738, 1686, 1450, 1411, 1263, 1190, 1144, 978, 775, 754, 687 cm^{-1}. HRMS (ES+) [$C_{14}H_{18}O_3$ + Na] calc. 257.1154, found 257.1144.

4.2.3. Benzyl 3-oxo-3-phenylpropanoate[16] (**1d**)

2.176 g, 8.6 mmol, 86%, 10:3 keto:enol. yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.48 (s, enol), 7.90 (d, J = 8.0 Hz, enol), 7.86 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 7.9 Hz, enol), 7.51 (t, J = 7.5 Hz, 1H), 7.44–7.24 (m, 7H), 5.68 (s, enol), 5.19 (s, enol), 5.13 (s, 2H), 3.98 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 167.4, 135.4, 133.8, 128.8, 128.6, 128.6, 128.5, 128.4, 128.3, 67.1, 45.9. IR: 1738, 1682, 1263, 1182, 1140, 752, 689 cm^{-1}. HRMS (ES+) [$C_{16}H_{14}O_3$ + Na] calc. 277.0841, found 277.0842.

4.2.4. Cyclohexyl 3-oxo-3-phenylpropanoate (**1e**)

2.135 g, 8.7 mmol, 87%, 2.5:1 keto:enol. yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (s, enol), 7.94 (d, J = 7.9 Hz, 2H), 7.77 (d, J = 7.8 Hz, enol), 7.57 (t, J = 7.4 Hz, enol), 7.52–7.37 (m, 3H), 5.66 (s, enol), 4.95–4.88 (m, enol), 4.88–4.79 (m, 1H), 3.97 (s, 2H), 2.09–1.10 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 166.9, 133.6, 128.7, 128.5, 126.0, 87.9, 73.8, 46.4, 31.3, 25.3, 23.5. IR: 2936, 2859, 1732, 1684, 1449, 1263, 1194, 1013, 756, 689 cm^{-1}. HRMS (ES+) [$C_{15}H_{18}O_3$ + Na] calc. 269.1154, found 269.1154.

4.2.5. (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 3-oxo-3-phenylpropanoate (**1f**)

1.697 g, 5.6 mmol, 56%, 2.5:1 keto:enol. yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.62 (s, enol), 7.85 (t, J = 11.1 Hz, 2H), 7.68 (d, J = 7.5 Hz, enol), 7.47 (t, J = 7.4 Hz, 1H), 7.40–7.25 (m, 4H), 5.56 (s, enol), 4.74 (td, J = 10.8, 4.3 Hz, enol), 4.63 (td, J = 10.9, 4.3 Hz, 1H), 3.86 (q, J = 15.4 Hz, 2H), 2.03–1.75 (m, 1H), 1.71–1.48 (m, 3H), 1.45–1.14 (m, 2H), 1.0–0.65 (m, 10H), 0.59 (d, J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 167.1, 133.6, 128.7, 128.5, 126.0, 87.7, 75.5, 74.1, 47.1, 34.1, 31.3, 26.3, 25.9, 23.6, 23.2, 22.0. IR: 2957, 2932, 2866, 1630, 1576, 1406, 1223, 1182, 1080, 810, 772, 689 cm^{-1}. HRMS (ES+) [$C_{19}H_{26}O_3$ + Na] calc. 325.1780, found 325.1776. mp 40 °C (dichloromethane).

4.3. General procedure for monofluorination of β-ketoesters

To a 10 mL stainless steel milling jar was added the β-ketoester (1 mmol), selectfluor (0.708 g, 2 mmol), sodium chloride (twice the total mass of substrate and selectfluor) and acetonitrile (0.25 mL). The ball was added and the mixture milled at 30 Hz for 2 h. The resulting powder was transferred into a flask, washing the residue with chloroform (about 40 mL). The insoluble material was removed by gravity filtration. The solvent was removed under reduced pressure to yield the product. The selectivity ratio was determined by fluorine NMR. The yield was determined from the mass of material recovered.

4.3.1. Ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**2a**)[17]

0.201 g, 0.96 mmol, 96%, 12.5:1 mono:di, dark red liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 5.86 (d, J = 48.9 Hz, 1H), 4.30 (q, J = 6.8 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7 (d, J = 20.2 Hz), 165.1 (d, J = 24.2 Hz), 134.7, 133.5, 129.7 (d, J = 3.4 Hz), 129.0, 90.2 (d, J = 197.7 Hz), 62.7, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −190.29 (d, J = 48.8 Hz). IR: 2983, 1759, 1693, 1597, 1448, 1371, 1242, 1095, 686 cm^{-1}. HRMS (ASAP+) [$C_{11}H_{11}O_3F$ + H] calc. 211.0770, found 211.0773.

4.3.2. Isopropyl 2-fluoro-3-oxo-3-phenylpropanoate (**2b**)

0.182 g, 0.81 mmol, 81%, 15:1 mono:di, light brown liquid. ^{1}H NMR (400 MHz) δ 8.03 (d, J = 7.8 Hz, 2H), 7.64 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 5.83 (d, J = 48.9 Hz, 1H), 5.20–5.10 (m, 1H), 1.28 (d, J = 6.2 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8 (d, J = 20.1 Hz), 164.6 (d, J = 24.1 Hz), 134.6, 129.6 (d, J = 3.3 Hz), 128.9, 128.6 (d, J = 26.3 Hz), 90.3 (d, J = 197.4 Hz), 71.1, 21.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −190.28 (d, J = 48.9 Hz). IR: 2984, 1755, 1692, 1597, 1449, 1098, 689 cm^{-1} HRMS (ASAP+) [$C_{12}H_{13}O_3F$ + H] calc. 225.0927, found 225.0922.

4.3.3. Pentyl 2-fluoro-3-oxo-3-phenylpropanoate (**2c**)

0.239 g, 0.95 mmol, 95%, 16:1 mono:di, pale red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 5.88 (d, J = 48.8 Hz, 1H), 4.22 (sep, J = 5.1 Hz, 2H), 1.64–1.54 (m, 2H), 1.30–1.14 (m, 4H), 0.82 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6 (d, J = 20.0 Hz), 165.0 (d, J = 24.2 Hz), 134.6, 133.5 (d, J = 1.9 Hz), 129.6 (d, J = 3.3 Hz), 128.9, 90.1 (d, J = 197.3 Hz), 66.8, 28.1, 27.8, 22.2, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −190.61 (d, J = 48.8 Hz). IR: 1759, 1694, 1597, 1449, 1240, 1099, 959, 880, 689 cm^{-1}.

4.3.4. Benzyl 2-fluoro-3-oxo-3-phenylpropanoate (**2d**)[16]

0.239 g, 0.88 mmol, 88%, 7:1 mono:di, dark yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.4 Hz, 3H), 7.31 (s, 4H), 5.92 (d, J = 48.7 Hz, 1H), 5.31–5.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5 (d, J = 20.2 Hz), 164.9 (d, J = 24.3 Hz), 134.7, 134.5, 129.7 (d, J = 3.4 Hz), 129.1 (d, J = 4.9 Hz), 129.0, 128.8, 128.8, 128.5, 90.1 (d, J = 198.1 Hz), 68.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −190.39 (d, J = 48.6 Hz). IR: 1761, 1688, 1597, 1449, 1101, 955, 743, 687, 586 cm^{-1}. HRMS (EI+): [$C_{16}H_{13}O_3F$] calc. 272.0849, found 272.0850.

4.3.5. Cyclohexyl 2-fluoro-3-oxo-3-phenylpropanoate (**2e**)

0.199 g, 0.75 mmol, 75%, 17:1 mono:di, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 5.85 (d, J = 48.9 Hz, 1H), 4.96–4.90 (m, 1H), 1.91–1.15 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8 (d, J = 20.0 Hz), 164.5 (d, J = 24.2 Hz), 134.6, 133.6 (d, J = 1.9 Hz), 129.6 (d, J = 3.3 Hz), 128.9, 90.2 (d, J = 197.1 Hz), 75.6, 31.3, 31.1, 23.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −190.44 (d, J = 49.0 Hz). IR: 2936, 2860, 1755, 1690, 1597, 1449, 1236, 1007, 689 cm^{-1} HRMS (EI+): [$C_{15}H_{17}O_3F$] calc. 264.1162, found 264.1161.

4.3.6. (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-fluoro-3-oxo-3-phenylpropanoate (**2f**)

0.288 g, 0.90 mmol, 90%, 20:1 mono:di, isolated as a mixture of diastereomers. dr 56:44, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, J = 6.2 Hz, 2H), 7.61 (t, J = 6.8 Hz, 1H), 7.47 (t, J = 7.2 Hz,

2H), 5.83 (m, 1H), 4.94–4.55 (m, 1H), 1.87–0.36 (m, 18H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −189.94 (d, J = 48.8 Hz), −190.52 (d, J = 48.7 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6 (d, J = 21 Hz), 189.4 (d, J = 20 Hz), 164.5 (d, J = 23 Hz), 164.4 (d, J = 24 Hz), 134.5, 134.4, 133.4, 129.5, 129.47, 129.41, 129.38, 128.78, 90.3 (d, J = 198 Hz), 90.1 (d, J = 198 Hz), 46.7, 40.5, 33.9, 31.4, 25.6, 22.9, 21.9, 20.5, 16.1, 15.5. IR: 2955, 2870, 1755, 1694, 1449, 1238, 1096, 953, 910, 689 cm^{-1}. HRMS (ES+) [$C_{19}H_{25}O_3F$ + Na] calc. 343.1685, found 343.1683.

4.4. General procedure for difluorination of β-ketoesters

To a 10 mL stainless steel milling jar was added the β-ketoester (1 mmol), selectfluor (0.708 g, 2 mmol), sodium carbonate (0.106 g, 1 mmol) and sodium chloride (twice the total mass of substrate and selectfluor). The ball was added and the mixture milled at 30 Hz for 2 h. The resulting powder was transferred into a flask, washing the residue with chloroform (about 40 mL). The insoluble material was removed by gravity filtration. The solvent was removed under reduced pressure to yield the product. The selectivity ratio was determined by fluorine NMR. The yield was determined directly from the mass of material recovered, except for examples obtained impure (**3c** and **3f**), where the ratio **1**:**2**:**3** was determined by ^{1}H and ^{19}F NMR and used in comparison to the mass of material obtained to calculate the yield of the desired product.

4.4.1. Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**3a**)[18]

0.227 g, 1 mmol, 100%, 7:1 di:mono, yellow-green liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.9 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6 (t, J = 30.3 Hz), 162.0 (t, J = 30.6 Hz), 135.2, 131.2, 130.1 (t, J = 2.7 Hz), 129.1, 109.9 (t, J = 264.6 Hz), 63.9, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.61 (s). IR: 1770, 1697, 1597, 1450, 1371, 1307, 1255, 1155, 1097, 1001, 921, 684, 582 cm^{-1}. HRMS (ASAP+) [$C_{11}H_{10}O_3F_2$ + H] calc. 229.0676, found 229.0680.

4.4.2. Isopropyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**3b**)

0.187 g, 0.77 mmol, 77%, >50:1 di:mono, light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 5.29–5.14 (m, 1H), 1.29 (d, J = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.7 (t, J = 27.5 Hz), 161.5 (t, J = 30.3 Hz), 135.2, 131.3 (t, J = 1.9 Hz), 130.0 (t, J = 2.7 Hz), 129.1, 109.7 (t, J = 264.5 Hz), 72.5, 21.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.93 (s). IR: 2988, 1769, 1599, 1450, 1307, 1260, 1159, 1092, 922, 831, 685, 584 cm^{-1}. HRMS (EI+): [$C_{12}H_{12}O_3F_2$] calc. 242.0755, found 242.0753.

4.4.3. Pentyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**3c**)

0.239 g material, (75:20:5 **3c**:**2c**:**1c**) corresponding to 0.182 g **3c**, 0.67 mmol, 67%. 4:1 di:mono, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 4.34–4.19 (m, 2H), 1.73–1.52 (m, 2H), 1.45–1.12 (m, 4H), 0.85 (t, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.62 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.5 (t, J = 27.5 Hz), 162.0 (t, J = 30.6 Hz), 135.2, 134.6, 130.0 (t, J = 2.7 Hz), 129.1, 109.9 (t, J = 264.4 Hz), 67.9, 28.0, 27.7, 22.2, 13.9. IR: 2957, 2932, 2868, 1632, 1614, 1450, 1406, 1256, 1200, 1080, 959, 810, 773, 725, 689 cm^{-1}. HRMS (ASAP+) [$C_{13}H_{16}O_3F_2$ + H] calc. 271.1146, found 271.1144.

4.4.4. Benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**3d**)[16]

0.218 g, 0.75 mmol, 75%, >50:1 di:mono, light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.9 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.36–7.28 (m, J = 5.7 Hz, 5H), 5.34 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (t, J = 27.4 Hz), 161.8 (t, J = 30.7 Hz), 135.2, 133.9, 131.1 (t, J = 1.9 Hz), 130.0 (t, J = 2.7 Hz), 129.1, 129.1, 128.8, 128.6, 109.9 (t, J = 265.1 Hz), 69.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.40 (s, J = 9.2 Hz). IR: 1773, 1697, 1597, 1450, 1304, 1263, 1155, 1099, 920, 793, 745, 685 cm^{-1}. HRMS (EI+): [$C_{16}H_{12}O_3F_2$] calc. 290.0755, found 290.0752.

4.4.5. Cyclohexyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**3e**)

0.234 g, 0.83 mmol, 83%, 16:1 di:mono, light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 5.04–4.95 (m, 1H), 1.90–1.18 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6 (t, J = 27.4 Hz), 161.4 (t, J = 30.4 Hz), 135.1, 131.3 (t, J = 1.7 Hz), 130.0 (t, J = 2.7 Hz), 129.1, 109.7 (t, J = 264.2 Hz), 77.0, 31.0, 25.2, 23.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.90 (s). IR: 2940, 2862, 1769, 1697, 1597, 1450, 1306, 1258, 1161, 1101, 1003, 930, 826, 685, 407 cm^{-1}. HRMS (EI+): [$C_{15}H_{16}O_3F_2$] calc. 282.1068, found 282.1067.

4.4.6. (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**3f**)

0.263 g material, (52:31:17 **3f**:**2f**:**1f**) corresponding to 0.141 g **3c**, 0.42 mmol, 42%. 2:1 di:mono, orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–7.90 (m, 2H), 7.72–7.55 (m, 1H), 7.55–7.37 (m, 2H), 4.91–4.65 (m, 1H), 2.10–0.38 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3 (t, J = 27.3 Hz), 161.5 (t, J = 30.0 Hz), 135.0, 129.8 (t, J = 2.6 Hz), 129.5 (t, J = 8.9 Hz), 129.0, 90.3 (t, J = 197.4 Hz), 78.7, 46.6, 40.0, 33.9, 31.4, 25.9, 23.1, 21.9, 20.6, 15.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.37 (d, J = 284.5 Hz), −108.58 (d, J = 284.5 Hz). IR: 2957, 1765, 1695, 1599, 1450, 1369, 1308, 908, 687 cm^{-1}. HRMS (EI+): [$C_{19}H_{24}O_3F_2$] calc. 338.1694, found 338.1696.

4.4.7. Preparation of 2,2-difluoro-3-oxo-3-phenylpropanenitrile (**5**)

To a 10 mL stainless steel milling jar was added a benzoylacetonitrile (0.145 g, 1 mmol) and Selectfluor (0.708 g, 2 mmol). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 3 h. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. The solvent was removed under reduced pressure to give 2,2-difluoro-3-oxo-3-phenylpropanenitrile **5** (0.118 g, 0.65 mmol, 65%, 50:1 di:mono) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 2H), 7.76 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.0 (t, J = 27.6 Hz), 136.3, 130.4 (t, J = 2.5 Hz), 129.5, 129.2 (t, J = 2.6 Hz), 110.3 (t, J = 42.4 Hz), 106.1 (t, J = 260.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.02 (s). IR: 2345, 2261,1701, 1597, 1450, 1292, 1175, 1094, 887, 716 cm^{-1}. HRMS (ASAP+) [$C_9H_5NF_2O$ + H] calc. 182.0417, found 182.0415.

4.4.8. Preparation of α-fluorobis(phenylsulfonyl)methane (**7**)

To a 10 mL stainless steel milling jar was added bis(phenylsulfonyl)methane (0.296 g, 1 mmol), Selectfluor (0.708 g, 2 mmol) and sodium carbonate (0.106 g, 1 mmol). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 h. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. The solvent was removed under reduced pressure to give α-fluorobis(phenylsulfonyl)methane **7** (0.267 g, 0.85 mmol, 85%, 9.5:1 mono:di) as a colourless powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–7.93 (m, 4H), 7.86–7.74 (m, 2H), 7.69–7.58 (m, 4H), 5.71 (d, J = 45.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 135.5, 130.3, 129.6, 105.9 (d, J = 266.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −168.21 (d, J = 45.8 Hz). IR: 2365, 1582, 1449, 1356, 1167, 1096, 1076, 791, 681, 550, 517 cm^{-1}. HRMS (ES+): [$C_{13}H_{11}O_4F$ + H] calc. 315.0161, found 315.0172. mp 104–106 °C (chloroform).

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Further reading

19. Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2017.0043204405.