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Defluorination of *gem*-difluoromethyl(ene) compounds with calcium salts

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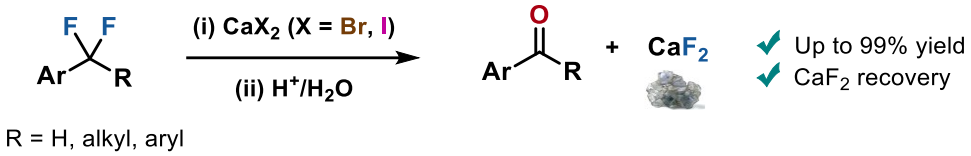
Abstract

We report a mild and efficient Ca^{2+}-mediated defluorination method that converts *gem*-difluoromethyl(ene) groups into aldehydes or ketones. This two-step operationally simple protocol allows for the recovery of CaF_2 as a by-product in the spirit of a circular fluorine economy.

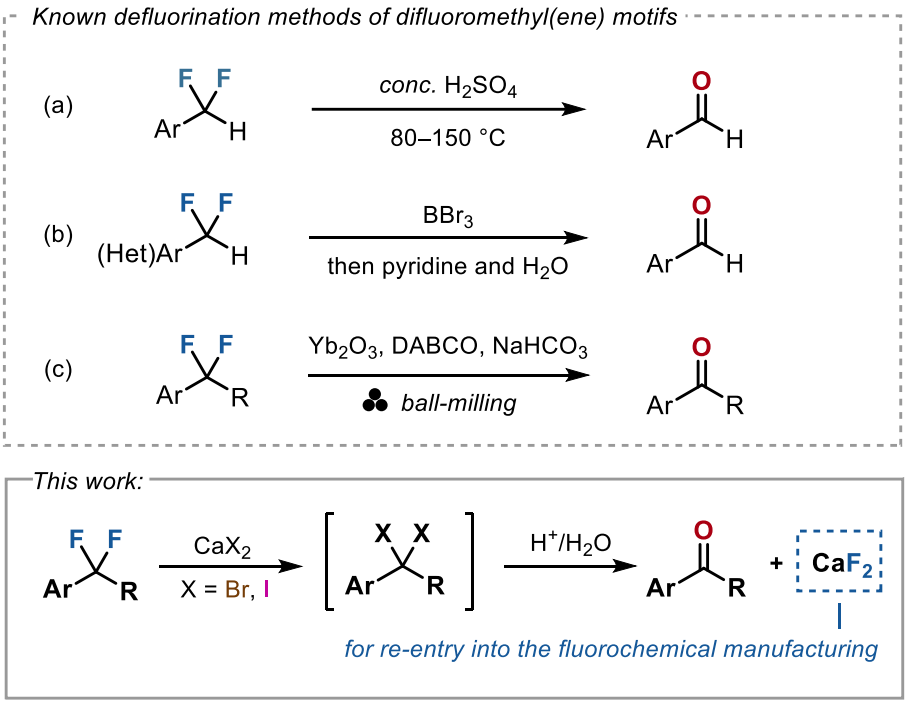


R = H, alkyl, aryl

Keywords: Defluorination; functional group interconversion; *gem*-difluoromethyl(ene); aldehyde; ketone

Introduction

Studies on the conversion of CF_2 and CF_2H groups to ketones and aldehydes are sparsely documented. Current technologies include the use of strong acids such as concentrated H_2SO_4, treatment with BBr_3 followed by debromination with pyridine and water, and more recently, mechanochemical defluorination using Yb_2O_3 in the presence of DABCO and $NaHCO_3$.[1–3] As part of our program on sustainable and circular fluorine chemistry, our objective was to develop a novel defluorination protocol of *gem*-difluoromethyl(ene) molecules enabling recovery of fluorine as calcium fluoride.[4–7] For implementation, inspiration stemmed from various reports on the defluorination of monofluorinated chemicals using inorganic salts such as $CaCl_2$,[8] TiX_4 (X = Cl, Br or I),[9] MgI_2,[10] YbI_3,[11] AlI_3[12] and LiI[13,14] and defluorination of difluoromethylpyridine derivatives using $AlCl_3$.[15] Herein, we report the facile and efficient defluorination of difluoromethyl(ene)-containing substrates into the corresponding aldehydes (or ketones) upon treatment with $CaBr_2$ or CaI_2, a process affording CaF_2 for re-entry in the fluorochemical industry.

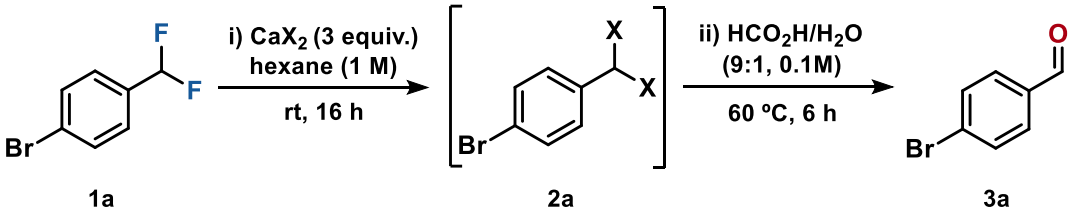


Scheme 1. Strategies for complete defluorination of *gem*-difluoromethyl(ene) to carbonyls.

Results and Discussion

Preliminary investigations were carried out on the model substrate **1a**, a precursor of 4-bromobenzaldehyde upon defluorination. To establish the optimal conditions, we evaluated various calcium salts in hexane (1 M) at room temperature, followed by hydrolysis under acidic conditions (formic acid/water) (Table 1). CaI_2 proved to be the most effective defluorinating reagent, affording the desired product in 82% yield (Entry 1). $CaBr_2$ was also competent (79%, Entry 2), whereas $CaCl_2$, $Ca(OH)_2$, and CaO led to the recovery of starting material (Entries 3–5). Alternatives to aqueous formic acid were considered, for example aqueous NaOH, HCl or $AgNO_3$, but these modifications were less effective (see details in Supplementary Material). In this chemistry, the

corresponding *gem*-diiodo and *gem*-dibromomethyl(ene) were unambiguously identified by NMR as intermediates upon defluorination with CaI_2 or $CaBr_2$, respectively (see details in the Experimental Section).



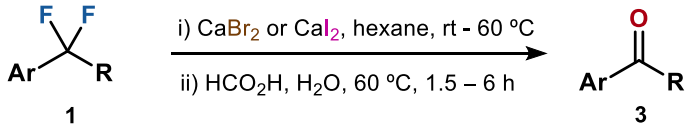
1a **2a** **3a**

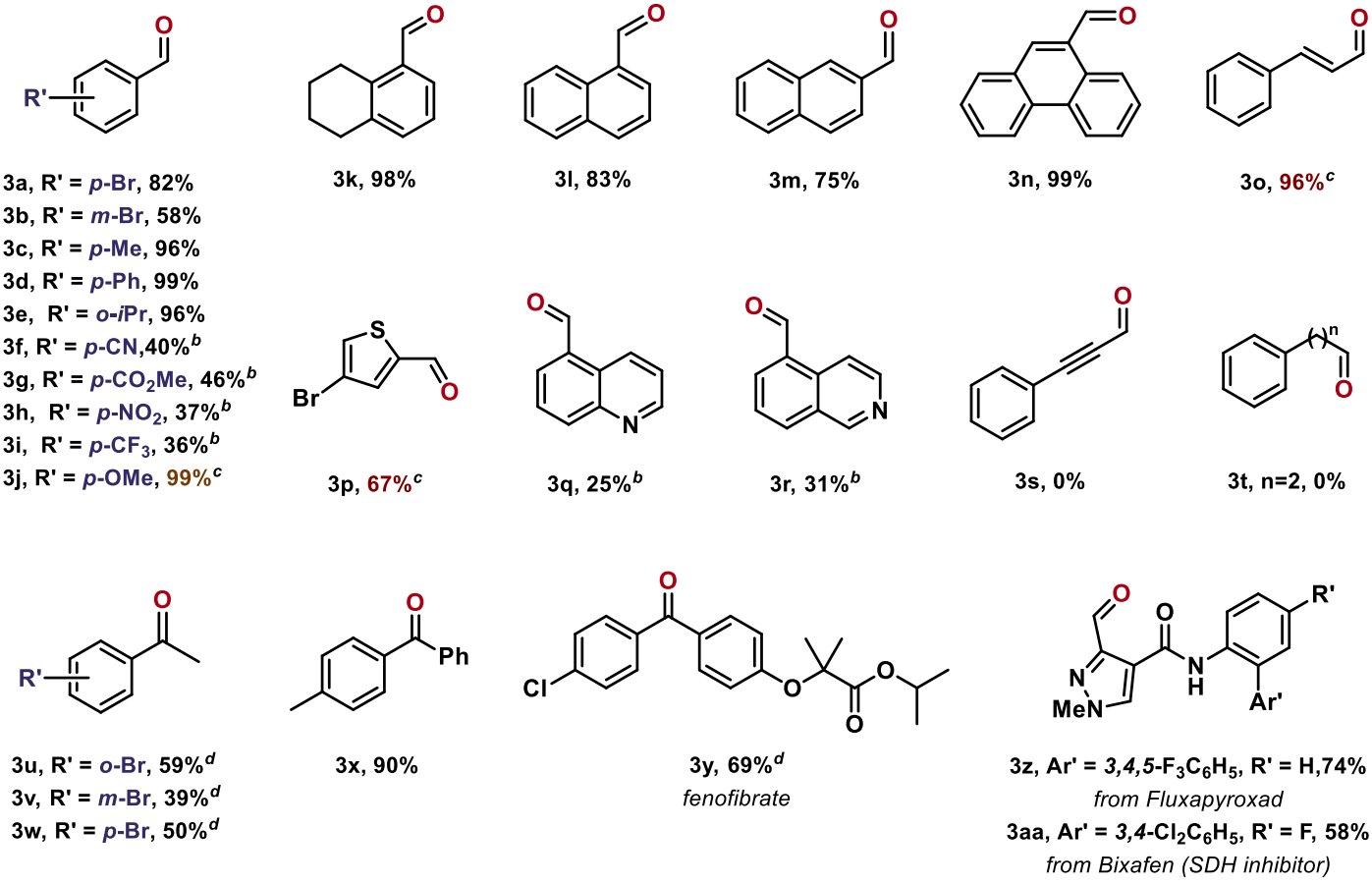
Entry	CaX_2	Yield[a]
1	**CaI_2**	**82%**
2	**$CaBr_2$**	**79%**
3	$CaCl_2$	0%[b]
4	$Ca(OH)_2$	0%[b]
5	CaO	0%[b]

[a] ^{1}H NMR yield with 4-fluoroanisole used as an internal standard.
[b] No conversion of starting material.

Table 1. Reaction optimization.

With the optimized condition in hand, we investigated the scope of this defluorination protocol, with either CaI_2 or $CaBr_2$ (Scheme 2). Arenes bearing substituents at the ortho, meta, and para positions, as well as a representative tetrahydronaphthalene afforded the corresponding aldehydes (**3a**–**3e, 3k**) in yields ranging from 58% to 99%. Substrates featuring electron-withdrawing groups such as ester, nitro, and trifluoromethyl required higher temperature and delivered the corresponding aldehydes (**3f**–**3i**) in moderate yields (up to 46%). Notably, the trifluoromethyl group of substrate **1i** remained unreacted even at elevated temperatures, a result illustrating the selectivity of our defluorination protocol for difluoromethyl versus trifluoromethyl groups. *p*-Anisaldehyde (**3j**) was obtained in near-quantitative yield with $CaBr_2$ as the defluorinating reagent. The reaction proceeded well for polycyclic arenes (**3l**–**3n**) and styrene (**3o**), providing up to quantitative yields. Electron-rich bromothiophene (**3p)** performed well using $CaBr_2$ (67%), whereas quinoline (**3q**), and isoquinoline (**3r**) required elevated temperatures in octane and afforded the corresponding aldehydes in lower yields (25% and 31%). Propargylic (**1s**) and aliphatic (**1t**) substrates were found to be unreactive. The protocol was extended to ketones, with some substrates not requiring a mild acidic hydrolytic step (**1u**–**1w, 1y**). The method proved effective for more complex bioactive molecules, including fenofibrate (**3y**), Fluxapyroxad (**3z**) and Bixafen (**3aa**).

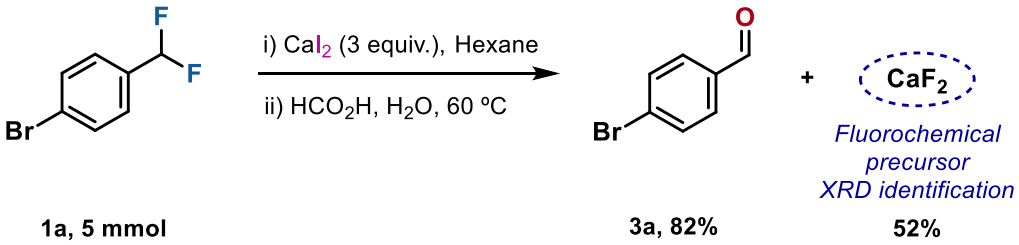




[a]Reaction conditions: Difluorinated compound **1** (0.1 mmol), CaI_2 (0.3 mmol), hexane (0.1 mL), HCO_2H (0.9 mL), H_2O (0.1 mL), [b]80 °C in octane (0.1 mL), [c]$CaBr_2$ (0.3 mmol), [d]hydrolysis (step ii) not needed.

Scheme 2. Scope of aldehydes and ketones from difluoromethyl(ene)[a].

To demonstrate the scalability of the method, defluorination of 1-bromo-4-(difluoromethyl)benzene **1a** was performed on a gram-scale (Scheme 3). The corresponding aldehyde **3a** was isolated in 82% yield. CaF_2 was recovered from the residue mixture and characterized unambiguously by X-ray Powder Diffraction (XRD), demonstrating the feasibility of fluoride recovery.



Scheme 3. Scale-up reaction and isolation of CaF_2.

Conclusions

In summary, we have developed a practical and efficient method for the defluorination of *gem*-difluoromethyl(ene) groups to carbonyl compounds using $CaBr_2$ or CaI_2. This transformation proceeds via halogen exchange followed by hydrolysis with aqueous formic acid, affording a range of aldehydes and ketones. The protocol is scalable and compatible with late-stage functionalization of complex molecules, including pharmaceutical and agrochemical scaffolds. Moreover, the recovery of CaF_2 as a by-product demonstrates the circularity of this approach with respect to fluorine, a closed-loop strategy for fluorine economy.

Experimental Section

General. All reagents were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, Fluorochem Apollo Scientific, Thermo Fisher or BLDphram) and used without further purification. Moisture sensitive reactions were carried out using solvents obtained from the MBRAUN-SPS solvent purification system (CH_2Cl_2, THF, toluene, Et_2O). All other solvents were used as received. Reactions were monitored by thin layer chromatography (TLC) on silica gel pre-coated aluminium sheets (Merck Kieselgel 60 F254 plates). Visualization was accomplished by irradiation with UV light at 254 nm, and/or permanganate stain. Flash column chromatography (FCC) was performed on Merck silica gel (60, particle size 0.040-0.063 mm). All NMR spectra were recorded on a Bruker AVIIIHD 400 spectrometer with standard pulse sequences operating at 400 MHz, using $CDCl_3$ as solvent. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Coupling constants (J) are measured in hertz (Hz). The following abbreviations are used to describe multiplicities s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, td=triplet of doublets, tt=triplet of triplets, b=broad. NMR spectra were processed with MestReNova 14.1.2. Quantitative NMR analysis was determined using 4-fluoroanisole as an internal standard. The standard was added to the crude reaction mixture after solvent evaporation, dilution in $CDCl_3$, and an aliquot was taken to be analyzed by ^{19}F NMR and ^{1}H NMR. High resolution mass spectra (HRMS, m/z) were recorded on a Thermo Exactive High Resolution Orbitrap FTMS instrument equipped with Waters Acquity liquid chromatography system using either the heated electrospray (HESI-II) probe for positive electrospray ionization (ESI^+). Agilent 5977B was used for GC-MS (EI^+). Infrared spectra were recorded as the neat compound or in solution using a Bruker tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumber (cm^{-1}). CaF_2 structural characterization was performed using X-ray powder diffraction (PXRD) data collected using a Bruker D8 Advance X-ray diffractometer (Bragg−Brentano geometry). Melting points of solids were measured on a Griffin apparatus and are uncorrected IUPAC names were obtained using the ChemDraw service. Weighing was performed with a 4 decimal place balance.

Identification of dihalide intermediates.

To a 1.75 ml vial, CaI_2 (88 mg, 0.3 mmol.) or $CaBr_2$ (60 mg, 0.3 mmol) was charged, followed by addition of 1-bromo-4-(difluoromethyl)benzene **1a** (21 mg, 0.1 mmol) and hexane (0.1 mL, 1 M). The vial was covered with a cap, sealed with Parafilm, and stirred overnight at room temperature. The suspension was concentrated and $CDCl_3$ (0.3 mL) was added. The mixture was filtered through a short pad of Celite and washed with $CDCl_3$ (0.2 mL).

1-bromo-4-(diiodomethyl)benzene (2a-I). 2a-I was identified according to the procedure using CaI_2. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 4H), 6.15 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 131.5, 128.0, 122.9, –38.9.

1-bromo-4-(dibromomethyl)benzene (2a-Br). **2a-Br** was identified according to the procedure using $CaBr_2$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 131.9, 128.2, 123.9, 39.6. Spectroscopic data are in accordance with those in literature.[16]

General procedures for defluorination (GP-A, B, C, and D). GP-A: 1.75 ml vial was charged with CaI_2 (88 mg, 3 equiv.), the corresponding fluorinated substrate (0.1 mmol) and hexane (0.1 mL, 1 M). The vial was covered with a cap, sealed with Parafilm, and stirred overnight at room temperature. The suspension was filtered through a short pad of Celite washing with small portions of CH_2Cl_2. The filtrate was transferred to another vial and concentrated, and water (0.1 ml) followed by formic acid (0.9 ml) were added. The vial was capped, and secured with parafilm, and then heated to 60 ^{o}C for 6 h (or until completion as observed by TLC). The reaction mixture was allowed to cool down to room temperature, and then transferred to a separatory funnel, where it was quenched with saturated $NaHCO_3$ aq. solution until pH 7. Both organic and aqueous layers were washed with sodium thiosulfate 5% aq. solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 6 ml), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired product. **GP-B**: 1.75 ml vial was charged with CaI_2 (88 mg, 3 equiv), the corresponding fluorinated substrate (0.1 mmol) and octane (0.1 mL, 1 M). The vial was covered with a cap, sealed with Parafilm, and stirred overnight at 80 °C. After cool at room temperature, the suspension was filtered through a short pad of Celite washing with small portions of CH_2Cl_2. The filtrate was transferred to another vial and concentrated, and water (0.1 ml) followed by formic acid (0.9 ml) were added. The vial was capped, and secured with parafilm, and then heated to 60 ^{o}C for 6 h (or until completion as observed by TLC). The reaction mixture was allowed to cool down to room temperature, and then transferred to a separatory funnel, where it was quenched with saturated $NaHCO_3$ aq. solution until pH 7. Both organic and aqueous layers were washed with sodium thiosulfate 5% aq. solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 6 ml), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired product if otherwise is not indicated. **GP-C**: 1.75 ml vial was charged with $CaBr_2$ (60 mg, 3 equiv), the corresponding fluorinated substrate (0.1 mmol) and hexane (0.1 mL, 1 M). The vial was covered with a cap, sealed with Parafilm, and stirred overnight at room temperature. The suspension was filtered through a short pad of Celite washing with small portions of CH_2Cl_2. The filtrate was transferred to another vial and concentrated, and water (0.1 ml) followed by formic acid (0.9 ml) were added. The vial was capped, and secured with parafilm, and then heated to 60 ^{o}C for 6 h (or until completion as observed by TLC). The reaction mixture was allowed to cool down to room temperature, and then transferred to a separatory funnel, where it was quenched with saturated $NaHCO_3$ aq. solution until pH 7. Both organic and aqueous layers were washed with sodium thiosulfate 5% aq. solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 6 ml), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired product. **GP-D**: 1.75 ml vial was charged with CaI_2 (88 mg, 3 equiv), the corresponding fluorinated substrate (0.1 mmol) and hexane (0.1 mL, 1 M). The vial was covered with a cap, sealed with Parafilm, and stirred overnight at 60 °C. After cool at room temperature, the suspension was filtered through a short pad of Celite washing with small portions of CH_2Cl_2. The filtrate was transferred to a separatory funnel, where it was quenched with saturated $NaHCO_3$ aq. solution until pH 7. Both organic and aqueous layers were washed with sodium thiosulfate 5% aq. solution. The

aqueous layer was extracted with CH_2Cl_2 (3 x 6 ml), and the combined organic layers were dried over $MgSO_4$ and filtered. Finally, solvents were removed and the crude mixture was purified by flash chromatography on silica gel using mixtures of eluents pentane: ethyl acetate.

4-bromobenzaldehyde (3a). Prepared following **GP-A**, **3a** (15.4 mg, 82% yield) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.76 – 7.73 (m, 2H), 7.70 – 7.67 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.2, 135.2, 132.6, 131.1, 129.9. Spectroscopic data are in accordance with those in literature.[17]

3-bromobenzaldehyde (3b). Prepared following **GP-A**, **3b** (10.9 mg, 58% yield) was obtained as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.01 (m, 1H), 7.81 (ddd, *J* = 7.7, 1.4, 1.2 Hz, 1H), 7.76 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.42 (dd, *J* = 8.0, 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.9, 138.1, 137.5, 132.5, 130.8, 128.5, 123.5. Spectroscopic data are in accordance with those in literature.[17]

4-methylbenzaldehyde (3c). Prepared following **GP-A**, **3c** (11.4 mg, 96% yield) was obtained as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.2, 145.7, 134.4, 130.0, 129.9, 22.0. Spectroscopic data are in accordance with those in literature.[18]

[1,1'-biphenyl]-4-carbaldehyde (3d). Prepared following **GP-A**, **3d** (18.5 mg, 99% yield) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.65 – 7.63 (m, 2H), 7.51 – 7.46 (m, 2H), 7.44 – 7.40 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.0, 147.3, 139.8, 135.3, 130.4, 129.1, 128.6, 127.8, 127.5. Spectroscopic data are in accordance with those in literature.[18]

2-isopropylbenzaldehyde (3e). Prepared following **GP-A**, **3e** (14.2 mg, 96% yield) was obtained as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.82 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.55 (ddd, *J* = 7.8, 7.3, 1.5 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.35 (ddd, *J* = 7.7, 7.3, 1.1 Hz, 1H), 3.98 (hept, *J* = 6.9 Hz, 1H), 1.31 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.5, 151.6, 134.2, 133.1, 131.6, 126.28, 126.25, 27.8, 24.0. Spectroscopic data are in accordance with those in literature.[19]

4-formylbenzonitrile (3f). Prepared following **GP-B**, **3f** (5.5 mg, 40% yield) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.7, 138.9, 133.1, 130.0, 117.8, 117.8. Spectroscopic data are in accordance with those in literature.[20]

methyl 4-formylbenzoate (3g). Prepared following **GP-B**, **3g** (7.9 mg, 47% yield) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 1H), 3.96 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.8, 166.2, 139.3, 135.2, 130.3, 129.7, 52.7. Spectroscopic data are in accordance with those in literature.[21]

4-nitrobenzaldehyde (3h). Prepared following **GP-B**, **3h** (5.8 mg, 37% yield) was obtained as a white solid after flash chromatography with 10:1 pentane: ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.40 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.4, 151.2, 140.2, 130.6, 124.5. Spectroscopic data are in accordance with those in literature.[18]

4-(trifluoromethyl)benzaldehyde (3i). Prepared following **GP-B**, **3i** (6.4 mg, 36% yield) was obtained as a colourless oil after flash chromatography with 20:1 pentane: ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.21. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.2, 138.8, 135.8 (q, *J* = 32.9 Hz), 130.1, 126.3 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.8 Hz). Spectroscopic data are in accordance with those in literature.[18]

4-methoxybenzaldehyde (3j). Prepared following **GP-C**, **3j** (13.7 mg, 99% yield) was obtained as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 4.14 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.9, 164.7, 132.1, 130.1, 114.4, 55.7. Spectroscopic data are in accordance with those in literature.[18]

5,6,7,8-tetrahydronaphthalene-1-carbaldehyde (3k). Prepared following **GP-A**, **3k** (16.5 mg, 99% yield) was obtained as a colourless oil**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.63 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.32 – 7.24 (m, 2H), 3.21 (t, *J* = 6.1 Hz, 2H), 2.83 (t, *J* = 6.0 Hz, 2H), 1.89 – 1.76 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.4, 139.8, 138.8, 135.2, 134.1, 130.8, 125.7, 30.1, 26.44, 22.9, 22.3. Spectroscopic data are in accordance with those in literature.[22]

1-naphthaldehyde (3l). Prepared following **GP-A**, **3l** (13.1 mg, 83% yield) was obtained as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 9.26 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.00 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.93 (m, 1H), 7.70 (ddd, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.66 – 7.58 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.7, 136.8, 135.4, 133.9, 131.6, 130.7, 129.2, 128.6, 127.1, 125.04, 125.02. Spectroscopic data are in accordance with those in literature.[23]

2-naphthaldehyde (3m). Prepared following **GP-A**, **3m** (11.8 mg, 75% yield) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.34 (s, 1H), 8.02 – 7.90 (m, 4H), 7.67 – 7.57 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.4, 136.6, 134.7, 134.3, 132.8, 129.7, 129.3, 129.2, 128.2, 127.2, 122.9. Spectroscopic data are in accordance with those in literature.[23]

phenanthrene-9-carbaldehyde (3n). Prepared following **GP-A**, **3o** (20.4 mg, 98% yield) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 9.38 – 9.35 (m, 1H), 8.73 – 8.67 (m, 2H), 8.25 (s, 1H), 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.81 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.67 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.7, 141.4, 133.1, 130.8, 130.6, 130.5, 130.4, 130.3, 128.40, 128.37, 127.8, 127.4, 126.1, 123.1, 122.9. Spectroscopic data are in accordance with those in literature.[24]

cinnamaldehyde (3o). Prepared following **GP-C**, **3n** (13.2 mg, 96% yield) was obtained as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 7.7 Hz, 1H), 7.59 – 7.56 (m, 2H), 7.51 – 7.43 (m, 4H), 6.73 (dd, *J* = 16.0, 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.9, 153.0, 134.1, 131.4, 129.3, 128.7, 128.6. Spectroscopic data are in accordance with those in literature.[25]

4-bromothiophene-2-carbaldehyde (3p). Prepared following **GP-B**, **3p** (13.2 mg, 67% yield) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.87 (d, *J* = 1.3 Hz, 1H), 7.68 (d, *J* = 1.4 Hz, 1H), 7.64 (dd, *J* = 1.4, 1.3

Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.9, 144.11, 138.0, 132.3, 111.6. Spectroscopic data are in accordance with those in literature.[26]

quinoline-5-carbaldehyde (3q). Prepared following **GP-B**, **3q** (4 mg, 25% yield) was obtained as a pale yellow solid after flash chromatography with ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 9.61 (m, 1H), 9.01 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.37 (m, 1H), 8.06 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.88 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.59 (dd, *J* = 8.6, 4.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.2, 151.5, 148.4, 137.2, 136.7, 133.7, 131.9, 128.5, 126.1, 123.8. Spectroscopic data are in accordance with those in literature.[27]

isoquinoline-5-carbaldehyde (3r). Prepared following **GP-B**, **3r** (4.9 mg, 31% yield) was obtained as a pale-yellow solid after flash chromatography with ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.34 (d, *J* = 1.0 Hz, 1H), 8.99 (m, 1H), 8.72 (d, *J* = 6.0 Hz, 1H), 8.25 – 8.20 (m, 2H), 7.78 (dd, *J* = 8.2, 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.7, 153.0, 146.5, 139.9, 134.8, 133.4, 130.7, 128.8, 126.6, 117.8. Spectroscopic data are in accordance with those in literature.[28]

1-(2-bromophenyl)ethan-1-one (3u). Prepared following **GP-D**, **3u** (11.9 mg, 59% yield) was obtained as a colourless oil after flash chromatography with 30:1 pentane:ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.36 (ddd, *J* = 7.6, 7.5, 1.1 Hz, 1H), 7.29 (ddd, *J* = 7.9, 7.5, 1.8 Hz, 1H), 2.63 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.5, 141.6, 134.0, 131.9, 129.0, 127.6, 119.0, 30.4. Spectroscopic data are in accordance with those in literature.[29]

1-(3-bromophenyl)ethan-1-one (3v). Prepared following **GP-D**, **3v** (7.9 mg, 39% yield) was obtained as a colourless oil after flash chromatography with 30:1 pentane:ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 2.0, 1.7 Hz, 1H), 7.87 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.68 (d, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.34 (dd, *J* = 7.9, 7.8 Hz, 1H), 2.59 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.8, 138.9, 136.1, 131.5, 130.3, 127.0, 123.1, 26.7. Spectroscopic data are in accordance with those in literature.[29]

1-(4-bromophenyl)ethan-1-one (3w). Prepared following **GP-D**, **3w** (10.1 mg, 50% yield) was obtained as a white solid after flash chromatography with 30:1 pentane:ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 2.58 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.2, 136.0, 132.0, 130.0, 128.4, 26.7. Spectroscopic data are in accordance with those in literature.[29]

phenyl(p-tolyl)methanone (3x). Prepared following **GP-A**, **3x** (17.8 mg, 90% yield) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 2.44 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.6, 143.3, 138.0, 135.0, 132.2, 130.4, 130.0, 129.1, 128.3, 21.7. Spectroscopic data are in accordance with those in literature.[30]

isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (3y). Prepared following **GP-D**, **3y** (25.3 mg, 69% yield) was obtained as a white solid after flash chromatography with 9:1 pentane:ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 5.08 (hept, *J* = 6.3 Hz, 1H), 1.66 (s, 6H), 1.20 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.4, 173.2, 159.9, 138.5, 136.6, 132.1, 131.3, 130.4, 128.7, 117.4, 79.6, 69.5, 25.5, 21.7. Spectroscopic data are in accordance with those in literature.[31]

3-formyl-1-methyl-*N*-(3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide (3z). Prepared following **GP-A**, **3z** (27.2 mg, 74% yield) was obtained as a white solid after flash chromatography with 1:1 pentane: ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.58 (bs, 1H), 9.66 (d, *J* = 0.8 Hz, 1H), 8.09 (d, *J* = 0.8 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.21 – 7.18 (m, 2H), 7.01 – 6.95 (m, 2H), 3.97 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.36 – -134.54 (m), -162.22 (tt, *J* = 20.8, 6.5 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.7, 159.2, 151.3 (ddd, *J* = 250.0, 9.8, 4.4 Hz), 145.9, 139.4 (dt, *J* = 251.5, 14.5 Hz), 138.2, 135.1 (td, *J* = 8.0, 4.7 Hz), 134.8, 132.7, 130.2, 129.1, 125.7, 125.1, 120.8, 113.8 (dd, *J* = 14.6, 6.8 Hz), 40.4. Spectroscopic data are in accordance with those in literature.[32]

***N*-(3',4'-dichloro-5-fluoro-[1,1'-biphenyl]-2-yl)-3-formyl-1-methyl-1H-pyrazole-4-carboxamide (3aa).** Prepared following **GP-A**, **3aa** (23 mg, 74% yield) was obtained as a white solid X after flash chromatography with 1:1 pentane: ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 9.72 (d, *J* = 0.8 Hz, 1H), 8.14 (s, 1H), 7.90 (dd, *J* = 9.0, 5.3 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.12 (ddd, *J* = 9.0, 8.3, 3.0 Hz, 1H), 7.02 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.04 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.5, 160.1 (d, *J* = 246.0 Hz), 159.3, 145.9, 138.1, 137.9 (d, *J* = 1.8 Hz), 135.4 (d, *J* = 8.0 Hz), 132.6, 132.2, 131.2, 130.6, 130.6, 128.6, 127.4 (d, *J* = 8.4 Hz), 120.5, 116.8 (d, *J* = 23.3 Hz), 115.5 (d, *J* = 22.2 Hz), 40.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.23 (ddd, *J* = 8.8, 8.3, 5.3 Hz). **IR** (neat, cm^{-1}), ν = 1658, 1427, 1221, 1121,1100, 1015, 805, 784. **HRMS** (ESI) m/z calculated for $C_{18}H_{12}Cl_2FN_3O_2$ $[M+H]^+$ 392.0363, found 392.0366.

Procedures for scale-up defluorination of 4-bromobenzaldehyde (3a) and CaF_2 isolation. A round bottom flask equipped with a stirrer bar was charged with 1-bromo-4-(difluoromethyl)benzene (1.035 g, 5.0 mmol, 1 equiv.), followed by calcium iodide (4.408 g, 15 mmol, 3 equiv.) and hexane (5 ml, 1 M). The resulting mixture was stirred at room temperature for 16 h. After that, the suspension was filtered through filter paper in a Buchner funnel washing with small portions of CH_2Cl_2 and the products were purified in different ways:
The filtrate was transferred to another round bottom flask and concentrated, and water (5 ml) followed by formic acid (45 ml) were added. The reaction mixture was heated to 60 ^{o}C for 6 h. After cool at room temperature, it was transferred to a separatory funnel, where it was quenched carefully with saturated $NaHCO_3$ aq. solution until pH 7. Both organic and aqueous layers were washed with sodium thiosulfate 5% aq. solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 60 ml), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to afford 4-bromobenzaldehyde X (759.9 mg, 82% yield) as a pale-yellow solid. The residue from the initial filtration was washed with large amounts of water using a centrifuge to be able to decant the liquid easily. When the yellow colour disappeared, it was dried to afford CaF_2 (201.3 mg, 52% yield) as a white solid which was analysed by powder XRD and compared with commercial CaF_2.

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Supplementary Material

Reaction optimization tables; procedures for synthesis of starting materials; characterizations of starting materials; copy of powder XRD spectrum; copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra.

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