Supporting Information

Amine-Catalyzed Copper-Mediated C–H Sulfonation of Benzaldehydes via a Transient Imine Directing Group

J. I. Higham, J. A. Bull*
# Table of Contents

General Experimental ........................................................................................................... S3
Comparison to Prior C(sp²)–H Sulfonylation Reports ............................................................ S4
Optimisation of Reaction Conditions for Copper Mediated C(sp²)–H Sulfonylation ........ S5
  Copper source ..................................................................................................................... S5
  Base ....................................................................................................................................... S6
  Solvent ................................................................................................................................... S7
  Transient directing group .................................................................................................... S8
  Ligand additive ..................................................................................................................... S9
  Interaction of copper and transient directing group loading .............................................. S10
  Effect of changing sulfinate salt loading ............................................................................ S11
  Attempts at achieving a protocol catalytic in copper ......................................................... S12
Optimisation using 2-methylbenzaldehyde as substrate ..................................................... S13
  Copper source ..................................................................................................................... S14
  Additional carboxylate additive .......................................................................................... S15
  Aldehyde in excess ............................................................................................................. S16
  Design of Experiment (DoE) Optimisation ....................................................................... S17
Mechanistic Investigation .................................................................................................... S23
  Kinetics ................................................................................................................................ S23
  Same Excess .......................................................................................................................... S24
  Different Excess .................................................................................................................... S27
  Imine formation in proteo HFIP ........................................................................................ S34
  Competition experiment ..................................................................................................... S37
Synthesis of Sulfinate Salts ................................................................................................ S43
  General Procedure A: Synthesis of Sulfinate Salts ............................................................. S43
Copper Mediated C(sp²)–H Sulfonylation .......................................................................... S44
  General Procedure B: Lab humidity<75% ....................................................................... S44
  General Procedure C: Lab humidity>75% ....................................................................... S44
  Reaction Scope Varying the Sulfinate Salt ......................................................................... S45
  Reaction Scope Varying the Aldehyde .............................................................................. S49
  Estrone Derived .................................................................................................................. S61
Procedure for Multi Gram Scale Synthesis of Sulfonyl Aldehyde 3a ................................. S68
  Unsuccessful Substrates ....................................................................................................... S69
  ¹H and ¹³C Spectra of Selected Compounds ....................................................................... S70
General Experimental

All reactions were run under an inert atmosphere (argon) with flame-dried glassware using standard techniques unless otherwise stated. Anhydrous solvents were obtained by filtration through drying columns (THF, diethyl ether, CH₂Cl₂, DMF). Cu(OAc)₂ (98%, product code: B23615) and anhydrous CuF₂ (99.5%, product code: 11489) were obtained from Alfa Aesar and used as provided. β-Alanine (99%, product code: 146064) was obtained from Sigma–Aldrich and used as provided. Potassium carbonate (99.5%, product code: 024862) was obtained from Fluorochem and used as provided. Liquid commercial aldehydes were distilled prior to use. Solid aldehydes with boiling points >300 °C were dissolved in CH₂Cl₂, washed with 1 M NaOH, dried over Na₂SO₄, filtered, then concentrated in vacuo. All other commercial reagents were used as supplied or purified by standard techniques where necessary. All C–H activation reactions were performed in microwave vials sealed with Fisherbrand™ 20 mm aluminium, plain, centre hole, molded septa butyl, dark grey, 55° shore A, 3.0 mm caps if using high boiling solvents (>100 °C). Fisherbrand™ 20mm Crimp Seal, Gold, Magnetic Cap, 8mm Center hole, assembled septum, molded septa butyl, dark grey, 55° shore A, 3.0 mm caps were used with lower boiling solvents (<100 °C) if heating significantly above their boiling point.

Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate, p-anisaldehyde, phosphomolybdic acid or vanillin stains. Infrared spectra (vₘₐₓ, FTIR ATR) were recorded in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz spectrometers. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ = 7.27 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet and b = broad), coupling constant in Hz, integration, assignment]. ¹³C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ = 77.00 ppm). J values are reported in Hz. Assignments of ¹H/¹³C spectra were made by the analysis of δ/J values, and COSY, HSQC, and HMBC experiments as appropriate. ¹⁹F NMR spectra were recorded without complete proton decoupling unless otherwise stated. ¹⁹F NMR spectra are indirectly referenced to CFCl₃ automatically via direct measurement of the absolute frequency of the deuterium lock signal by the spectrometer hardware. Melting points are uncorrected. Due to the PTFE lining in the NMR probe, there can be artifacts observed in the baseline of ¹⁹F NMR.

The high-resolution mass spectrometry (HRMS) analyses were performed using electrospray ion source (ESI) or pneumatically assisted atmospheric pressure chemical ionization (APCI) using an atmospheric solids analysis probe (ASAP). ESI was performed using a Waters LCT Premier equipped with an ESI source operated in positive or negative ion mode. The software used was MassLynx 4.1. This software does not account for the electron and all the calibrations/references are calculated accordingly, i.e. [M+H]+ is detected and the mass is calibrated to output [M+H]. APCI was performed using an Orbitrap XL or Xevo G2S using an ASAP to insert samples into the APCI source. The sample was introduced at ambient temperature and the temperature increased until the sample vaporised.

All Data for this manuscript can be found at the Imperial College London Research Data Repository: DOI:10.14469/hpc/8810 (https://doi.org/10.14469/hpc/8810)
Comparison to Prior C(sp²)–H Sulfonation Reports

Representative prior examples of cross-coupling and amide directed C(sp²)–H sulfonation strategies for the synthesis of sulfones are summarised below (Scheme S1). Cross-coupling strategies rely on pre-functionalised starting materials in the form of aryl iodides and boronic acids, detailed are two methods, one demonstrating the three component coupling of aryl iodides and boronic acids, and the other achieving the oxidative coupling of boronic acids and sulfinate salts (Scheme S1a). Previous amide directed C(sp²)–H sulfonation methods predominantly use stoichiometric copper salts as both metal salt and oxidant (Scheme S1b). It is possible to instead use superstoichiometric silver salts to render the reaction catalytic in copper, this is non ideal as copper is cheaper and more abundant than silver. This transient C(sp²)–H sulfonation method offers greater step efficiency (1 step vs 3 steps), is amenable to late stage functionalisation and by transforming the aldehyde moiety, complex derivatives are easily accessible (Scheme S1c).

Scheme S1 – Comparison of prior methods of sulfone synthesis to this report of transient C(sp²)–H Sulfonation.

a) Prior methods of copper catalysed sulfone synthesis by sulfinate cross coupling - Prefunctionalised starting material required

b) Prior C(sp²)–H Sulfonation methods - 3 steps required from feedstock to sulfonlated acid

Step 1 Amide coupling

Step 2 C–H Sulfonation

Step 3 DG removal

Stoichiometric copper used in most cases
Expensive superstoichiometric silver salts allows catalytic copper

Good yields for directing group removal, however overall yield suffers due to multiple steps required

Single step transformation from inexpensive aldehydes
No need for directing group removal
Aldehyde functionality intact and ready for diversification applicable for late stage sulfonation
Optimisation of Reaction Conditions for Copper Mediated C(sp²)–H Sulfonylation

**Copper source**

Initial studies were conducted using benzaldehyde as the substrate with reactions run under air (*Table S1*). Initial optimisation found copper acetate was the most effective and economical copper source.

![Reaction scheme](image)

| Entry | [Cu]         | Sulfonylated Aldehyde (%)<sup>a</sup> |
|-------|--------------|---------------------------------------|
| 1     | Cu(OAc)<sub>2</sub> | 11                                    |
| 2     | Cu(OTf)<sub>2</sub> | 11                                    |
| 3     | CuBr<sub>2</sub>   | 0                                     |
| 4     | CuSO<sub>4</sub>  | 0                                     |
| 5     | Cu(MeCN)<sub>4</sub>PF<sub>6</sub> | 7                                     |

*Table S1* – Effect of copper source. <sup>a</sup>Yields determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Base
Several bases were screened, many appeared to be effective however none more so than $\text{K}_2\text{CO}_3$ thus this base was retained as the optimal base (Table S2). The reduced efficacy of $\text{Cs}_2\text{CO}_3$ could due to the more hygroscopic carbonate drawing water into the reaction. We have observed this reaction is sensitive to water, thus this could be the reason for reduced reactivity with $\text{Cs}_2\text{CO}_3$ (Page S20, Table S16, Entry 4).

| Entry | Base          | Sulfonlated Aldehyde (%)$^a$ |
|-------|---------------|------------------------------|
| 1     | $\text{K}_3\text{PO}_4$ | 9                            |
| 2     | $\text{K}_2\text{CO}_3$ | 16                           |
| 3     | $\text{KOAc}$    | 9                            |
| 4     | $\text{KTFA}$    | 0                            |
| 5     | $\text{DBU}$     | 9                            |
| 6     | $\text{NEt}_3$   | 7                            |
| 7     | Pyridine        | 9                            |
| 8     | $\text{KF}$      | 12                           |
| 9     | $\text{Cs}_2\text{CO}_3$ | trace                        |

Table S2 – Effect of changing base. $^a$Yields determined by $^1\text{H}$ NMR using 1,3,5-trimethoxybenzene as an internal standard.
Solvent

Other solvents and mixed solvent systems were trialled; however only HFIP was effective in promoting the reaction (Table S3).

![Chemical structure](image)

| Entry | Solvent                  | Sulfonylated Aldehyde (%)<sup>a</sup> |
|-------|--------------------------|---------------------------------------|
| 1     | DMSO                     | 0                                     |
| 2     | TFE                      | trace                                 |
| 3     | MeCN                     | 0                                     |
| 4     | AcOH                     | 0                                     |
| 5     | CH₂Cl₂                   | 0                                     |
| 6     | MeOH                     | 0                                     |
| 7     | HFIP                     | 15                                    |
| 8     | HFIP:MeOH (1:1)          | 8                                     |
| 9     | HFIP:EtOH (1:1)          | Trace                                 |
| 10    | HFIP:H₂O (1:1)           | 0                                     |
| 11    | HFIP:MeCN (1:1)          | 0                                     |
| 12    | HFIP:DMSO (1:1)          | 0                                     |

Table S3 – Effect of changing solvent. <sup>a</sup>Yields determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Transient directing group

Initial investigation into TDG found b-alanine was effective. On testing more [5,6] chelating TDGs, β-alanine remained the most effective (Scheme S2).

Scheme S2 – Effect of changing transient directing group. Yields determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Further investigation into 5,6 chelating directing groups confirmed that β-alanine was the most effective. Additionally, a raised temperature led to a slight increase in yield (Scheme S3).

Scheme S3 – Further TDG investigation. Yields determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Ligand additive

Additional additives were tested as possible ligands for copper, however we found additional ligand additives did not improve the reaction (Scheme S4).

Scheme S4 – Effect of ligand additive. Yields shown are combined yield of Mono+Di. \(^a\)Yields determined by \(^1\)H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Interaction of copper and transient directing group loading
We found that when investigating the loading of TDG and copper, highest yield was observed at 25 mol% TDG and with increased Cu loading (2 equiv) (Scheme S5).

Scheme S5 – Effect of changing both TDG and copper loading. Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Effect of changing sulfinate salt loading

The sulfinate salt loading was found to be important, with a lower loading of 1 equiv promoting the reaction (Table S4).

| Entry | Equivalent of sulfinate salt | Yield sulfone (Mono+Di) (%) |
|-------|-----------------------------|-----------------------------|
| 1     | 2                           | 22                          |
| 2     | 3                           | 23                          |
| 3     | 4                           | 22                          |
| 4     | 1                           | 30                          |

Table S4 – Effect of sulfinate salt loading. *Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Attempts at achieving a protocol catalytic in copper

Attempts to achieve a protocol using catalytic copper were unsuccessful. The inclusion of additional oxidants was investigated, but these generally suppressed the reaction (Table S5).

![Reaction Scheme]

Table S5 – Attempt at protocol catalytic in copper. *Yields determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

| Entry | [O]                                  | Yield aldehyde (%) | RSM (%) |
|-------|--------------------------------------|--------------------|---------|
| 1     | none                                 | 5                  | 83      |
| 2     | 1-fluoro-2,4,6-trimethylpyridinium triflate | 0                  | 31      |
| 3     | potassium persulfate                 | 9                  | 71      |
| 4     | iodine                               | 0                  | 81      |
| 5     | diacetoxyiodobenzene                 | 0                  | 64      |
| 6     | MnO$_2$ + 2 equiv AcOH               | 0                  | 81      |
| 7     | O$_2$ atmosphere                     | 0                  | -       |
Optimisation using 2-methylbenzaldehyde as substrate

Further optimisation was conducted on 2-methylbenzaldehyde in order to simplify the product distribution to gain an easier understanding of the system reactivity.

Sulfinate Equivalents

The equivalent of sulfinate salt was re-investigated and a minor increase in yield was observed at 1.25 equiv of sulfinate salt (Table S6).

![Chemical Reaction Diagram]

**Table S6** – Re-investigation of sulfinate loading. Yields determined by \(^1\text{H} \) NMR using 1,3,5-trimethoxybenzene as an internal standard.

| Entry | Equivalent of sulfinate | Yield aldehyde 3a (%) | RSM (%) |
|-------|-------------------------|------------------------|---------|
| 1     | 1.00                    | 33                     | 45      |
| 2     | 1.25                    | 38                     | 46      |
| 3     | 1.50                    | 37                     | 44      |
Copper source
Further investigation into copper sources led to CuF₂ being identified as more effective (Table S7). The higher hygroscopicity of this copper source, and variable lab humidity, led to a variation in yield correlating with varying humidity. We found that the reaction was more reliable when an argon atmosphere was used, and when the base and copper source were flame dried in the vial prior to other components being added. This copper source was used in further optimisation.

| Entry | Cu             | Yield aldehyde 3a (%) | RSM (%) |
|-------|----------------|-----------------------|---------|
| 1     | Cu(OAc)₂       | 37                    | 60      |
| 2     | Cu₂CO₃(OH)₂    | trace                 | 92      |
| 3     | Cu(acac)₂      | 0                     | 100     |
| 4     | Cu₃(PO₄)₂      | 0                     | 90      |
| 5     | CuO            | Trace                 | 67      |
| 6     | CuSO₄•5H₂O     | 12                    | 86      |
| 7     | CuF₂           | 35–50                 | 46–55   |
| 8ᵃ    | CuF₂           | 51                    | 41      |
| 9     | CuCl₂          | 18                    | 43      |
| 10    | Cu(OPiv)₂      | 29                    | 65      |
| 11    | Cu(OBz)₂       | 18                    | 74      |

Table S7 – Further of Copper source investigation. Yields determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ᵃ Reaction run under argon atmosphere, flame drying base and copper source.
Additional carboxylate additive
When using CuF$_2$, additional carboxylate ligand additives led to increased yield. This effect could be exploited by adding Cu(OAc)$_2$ to lower the loading of CuF$_2$ while maintaining the higher yield (Table S8).

![Chemical structure and reaction scheme]

| Entry | MCO$_2$R | Yield aldehyde (%) | RSM (%) |
|-------|----------|--------------------|--------|
| 1     | none     | 53                 | 36     |
| 2     | TBAOAc   | 63                 | 41     |
| 3     | KOAc     | 63                 | 37     |
| 4     | KOPiv    | 57                 | 41     |
| 5     | KTFA     | 62                 | 24     |
| 6     | CuF$_2$ (1.5 equiv), Cu(OAc)$_2$ (50 mol%) | 64 | 33 |

Table S8 – Effect of Carboxylate additives. *Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Aldehyde in excess
It was possible to further increase the yield by using the aldehyde in excess, with 78% yield accessible when using the aldehyde in 2 equiv (Table S9).

| Entry | Equiv of aldehyde | Yield aldehyde (%) | RSM (%) |
|-------|-------------------|--------------------|--------|
| 1     | 1 (1.25 equiv Sulfinate salt) | 64 | 33 |
| 2     | 1.25              | 62 | 42 |
| 3     | 1.5               | 63 | 59 |
| 4     | 1.75              | 73 | 90 |
| 5     | 2                 | 78 | 116 |

Table S9 – Aldehyde in excess. \(^a\)Yields determined by \(^1\)H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Design of Experiment (DoE) Optimisation

We used a design of experiment (DoE) approach in order to evaluate the interactions and main factors influencing the yield. JMP pro 14 DoE software was used using a ‘custom design’, focusing on the following variables: aldehyde loading, CuF$_2$ loading and reaction concentration, in the constraints shown. All other variables were fixed. The DoE data is shown (Table S10).

![Chemical Reaction](image)

| Entry | CHO Loading (equiv) | CuF$_2$ Loading (equiv) | Conc. (M) | Yield (%)$^a$ |
|-------|--------------------|-------------------------|-----------|---------------|
| 1     | 2.5                | 1.5                     | 0.2       | 83            |
| 2     | 2                  | 1                       | 0.2       | 61            |
| 3     | 2                  | 1.5                     | 0.25      | 72            |
| 4     | 1.5                | 1                       | 0.15      | 54            |
| 5     | 2.5                | 2                       | 0.25      | 87            |
| 6     | 1.5                | 1                       | 0.25      | 62            |
| 7     | 1.5                | 1.5                     | 0.15      | 69            |
| 8     | 1.5                | 2                       | 0.25      | 66            |
| 9     | 2.5                | 1                       | 0.25      | 61            |
| 10    | 1.5                | 2                       | 0.2       | 73            |
| 11    | 2.5                | 1                       | 0.15      | 54            |
| 12    | 2                  | 1.5                     | 0.2       | 77            |
| 13    | 2                  | 1.5                     | 0.2       | 77            |
| 14    | 2                  | 2                       | 0.15      | 82            |
| 15    | 2.5                | 2                       | 0.15      | 87            |
| 16    | 2                  | 1                       | 0.2       | 63            |
| 17    | 2                  | 1.5                     | 0.25      | 73            |

Table S10 – DoE data. $^a$Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard.
From these results, the JMP software generated a model to predict the changes in yield with changes in the above variables (and their interactions). The actual by predicted plot show the data matches well with the model generated, without any major outliers (Figure S1). Additionally, the effect summary highlights CuF₂ loading, CHO loading, and their interaction and the interaction between CuF₂ loading and concentration as most significant (Figure S1).

Figure S1 – Actual by predicted plot and effect summary.

The interactions shown in figure S2 can be summarised as the following:

B1: Improved reactivity at high CuF₂ and CHO loading
C1: No strong interaction
A2: Increased reactivity when raising CHO loading only when CuF₂ loading is high
C2: Slight interaction, lower yield at lower loading of CuF₂
A3: No strong interaction
B3:Slight interaction, higher reactivity using more CuF₂ at lower conc.
Overall, the most interesting interaction is that of the CHO loading and CuF₂ loading, as higher yields are only observed when both are increased (Figure S2, A2). If the CuF₂ loading is 1 equiv, the yield is independent of the aldehyde loading.

In addition, the DoE model prediction could be plotted to give the following surface with CuF₂ loading and CHO loading as the X and Y axis respectively as the most important variables (Conc is set to 0.2 M). Clearly there is a maximum at 2 equiv CuF₂ and 2.5 equiv aldehyde, and this is further backed up by the best conditions predicted by the model shown (Figure S3, S4), which predict 92% if using those conditions.
The model was validated experimentally by running these ‘best conditions’ and pleasingly, the model correctly predicted a hotspot, and using the conditions suggested by the DoE gave 93% yield (Table S11). It was also possible to obtain 75% yield using the less expensive copper acetate as the sole copper source in 2.5 equiv, which could be used as a more economical alternative to the standard conditions on a large scale.

![Diagram of the reaction](image)

**Figure S4** – Best conditions predicted by the DoE model.

| Entry | Change to Conditions | Yield Sulfone (%) | RSM (%) |
|-------|----------------------|-------------------|---------|
| 1     | None                 | 93                | 151     |
| 2     | None                 | 93                | 153     |
| 3     | Cu(OAc)₂ (2.5 equiv) instead of CuF₂ | 75 | 150 |

**Table S11** – Model validation experiments. Yields determined *in situ* by ¹H NMR using 1,3,5-trimethoxybenzene and an internal standard.
Sensitivity Screen

The sensitivity of the reaction under the optimised conditions was evaluated using a method developed by Glorius. We found a particular sensitivity to the presence of water and when the reaction was run under air (Table S12).

![Reaction scheme]

Table S12 – Reaction sensitivity screen. *Average of 5 reactions. Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses. $^b$11% of HFIP adduct 4 was observed.
HFIP Adduct Formation

In the absence of the sulfinate salt, under otherwise identical reaction conditions the solvent was observed to couple and form HFIP adduct (4) in 33% yield \textit{in situ} (Scheme S6a). Due to the change in limiting reagent in the absence of the sulfinate salt, the equivalents of reagents and loading of catalyst are by definition different, despite the same number mmol of each component being employed. When reducing the amount of aldehyde to 0.2 mmol while keeping the amount of the other components the same (so effectively raising the equivalents of other components), a higher yield of 55% of the HFIP adduct was observed.

![Scheme S6](image-url)

\textbf{Scheme S6} – Investigation of HFIP adduct formation a) HFIP adduct formation under standard conditions in the absence of sulfinate salt. b) HFIP adduct formation lowering the amount of aldehyde while keeping amounts of other components identical. Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard.
Mechanistic Investigation

Kinetics

Procedures for same excess and different excess experiments

Visual comparison methods developed by Blackmond,4 and Burés,5 were used to elucidate key mechanistic information from kinetics experiments. Same excess experiments were conducted to determine if catalyst deactivation or product inhibition were occurring in the reaction, and different excess experiments were performed to estimate the orders of each component of the reaction. In all cases, reaction profiles were constructed from the sampling of two 0.5 mmol scale reactions (0.1 mL per aliquot) at the indicated time with a known quantity of internal standard (1,3,5-trimethoxybenzene) added to the reaction. 2–10 h and 24 h timepoints were collected from one reaction, and 12–18 h timepoints were collected from a second reaction. Control experiments showed that the addition of the internal standard had an insignificant effect on the final yield and sampling had no effect on the yield observed under these conditions. Additionally, changing from sampling one reaction to another had no effect and profiles remained smooth. We found the most reproducible set up was using a 25 mL microwave vial submerged in an oil bath just above the solvent line of the reaction in the centre of the hotplate. The stirring rate was set to 440 rpm.

The reaction was less efficient on larger scale, and this was observed when comparing profiles from sampling vs profiles derived from individual experiments (0.2 mmol scale, 500 rpm stirring). However, the difference in yield was minimal, and the added convenience, reliability and reproducibility of the sampling method meant it was chosen for all following kinetics experiments. It was not possible to get reliable data from recovered starting material, as the starting material was found to be volatile enough to be removed when concentrating in vacuo so only product formation data was used in the analysis.

A general procedure used for same excess and different excess experiments are outlined below.

Potassium carbonate and copper(II) fluoride were added sequentially to a 25 mL microwave vial which was flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate, β-alanine, p-tolylsulfinic acid sodium salt, accurately weighed 1,3,5-trimethoxybenzene (0.3 equiv) and the aldehyde were added to a microwave vial sequentially under argon. The vial was sealed and HFIP (0.2 M) was added and the vial was submerged in an oil bath preheated to 100 °C [Stirring rate set to 440 rpm]. To take an aliquot: at the allotted time the vial was removed from the oil bath and 0.1 mL of solvent was removed by syringe while the reaction mixture was hot. [Caution: As the reaction is above the boiling point of the solvent, there is a small degree of back pressure. This was easily managed by holding the syringe plunger down gently while collecting the sample, and ensuring the liquid was taken up carefully and adequate inert atmosphere was taken up with the sample.] The aliquot was added to a small vial containing a mixture of saturated aqueous ammonium chloride and EtOAc (approx. 1:1). The vial was sealed and shaken until the aliquot was observed to change from brown to blue/green. The organic and aqueous layers were allowed to separate, and the organic layer was carefully removed by pipette then filtered through a small pad of Na2SO4 to remove any residual water, then the sample was concentrated in vacuo. The entire residue was dissolved CDCl3 (<1 mL) and the yield of sulfonylated material was determined by 1H NMR by comparison with the internal standard.
Timepoints for 2, 4, 6, 8, 10 and 24 h were collected from one reaction and 12, 15, and 18 h were collected from a second reaction. Concentrations were calculated from the total volumes of the parent liquids (aldehyde+HFIP): 2.5 equiv CHO – 2.6445 mL, 3 equiv CHO – 2.6734, 2 equiv CHO – 2.6156.

Control profile was constructed using the above method (Scheme S7), and was used as a comparison for subsequent kinetic experiments.

Same Excess
Same excess experiments were used to determine if catalyst deactivation or product inhibition were occurring in this reaction (Table S13). A 4 h timepoint was selected where the reaction had reached around 35% yield. Another experiment (Entry B) was performed in which each component was decreased by the amount that would have been consumed in the reaction until this point, assuming a 1:1 reaction stoichiometry in all cases except the CuF₂, where a 1:2 stoichiometry of sulfinate:CuF₂ is
assumed. Therefore, Experiments B was set up with the following quantities: aldehyde (125 μL, 1.08 mmol), sulfinate salt (59 mg, 0.33 mmol), CuF\(_2\) (67 mg, 0.66 mmol) and K\(_2\)CO\(_3\) (115 mg, 0.83 mmol). All catalytic components (TDG and Cu(OAc)\(_2\)) were assumed not to change in concentration.

To detect product inhibition, two further same experiments were conducted but with either the addition of all the assumed byproducts of the reaction + the sulfone product (Entry C) or the addition of only the aldehyde product (Entry D). [note: it was not possible to add copper(I) fluoride in experiment C as this has never been isolated and is not possible to make.]

| Entry | Experiment | [CHO] (M) | [Sulfinate] (M) | [CuF\(_2\)] (M) | [K\(_2\)CO\(_3\)] (M) | [P] added (M) | [KHCO\(_3\)] added (M) | [KF] added (M) |
|-------|------------|----------|-----------------|-----------------|---------------------|----------------|----------------------|----------------|
| A     | Control    | 0.473    | 0.189           | 0.378           | 0.378               | 0              | 0                    | 0              |
| B     | Same excess t = 4 h | 0.411 | 0.126          | 0.264          | 0.251               | 0              | 0                    | 0              |
| C     | Same excess t = 4 h + product + KHCO\(_3\) + 2KF | 0.411 | 0.126          | 0.264          | 0.251               | 0.065          | 0.065                | 0.130          |
| D     | Same excess t = 4 h + product | 0.411 | 0.126          | 0.264          | 0.251               | 0.065          | 0                    | 0              |

**Table S13** – Same excess experiments.

| Time (h) | Adjusted time (h) | Experiment B [P] Same excess t = 4 h [M] | Experiment C [P] Same excess t = 4 h + KHCO\(_3\) + KF [M] | Experiment D [P] Same excess t = 4 h + Product 3a only |
|----------|-------------------|-----------------------------------------|--------------------------------------------------|--------------------------------------------------|
| 0.00     | 4.00              | 0                                       | 0.065                                            | 0.065                                            |
| 2.00     | 6.00              | 0.032                                   | 0.097                                            | 0.088                                            | 0.080                                            |
| 4.00     | 8.00              | 0.055                                   | 0.120                                            | 0.105                                            | 0.099                                            |
| 6.00     | 10.00             | 0.070                                   | 0.135                                            | 0.118                                            | 0.112                                            |
| 8.00     | 12.00             | 0.082                                   | 0.147                                            | 0.130                                            | 0.124                                            |
| 10.00    | 14.00             | 0.095                                   | 0.160                                            | 0.141                                            | 0.135                                            |
| 12.00    | 16.00             | -                                       | -                                                | -                                                | 0.143                                            |
| 12.17    | 16.17             | 0.101                                   | 0.166                                            | -                                                | -                                                |
| 12.50    | 16.50             | -                                       | -                                                | 0.141                                            | -                                                |
| 15.00    | 19.00             | 0.097                                   | 0.162                                            | 0.154                                            | 0.154                                            |
| 18.00    | 22.00             | 0.099                                   | 0.163                                            | 0.154                                            | 0.158                                            |
| 21.50    | 25.50             | 0.103                                   | 0.168                                            | 0.156                                            | -                                                |

**Table S14** – Data for same excess experiments B, C and D.
Graph S1 – Product concentration against time for experiments A to D before normalisation for time and product concentration.

Graph S2 – Time and product normalised graph of product concentration against time for same excess experiments.

The data was normalised by the addition of 4 h to each point of the same excess experiments such that the profiles arising from B, C and D are all time shifted by 4 h. In addition to the + 4h timeshift, the profile arising from experiment B is adjusted to account for the expected [P] under standard conditions such that all points are shifted vertically (+ 0.065 M to each point of experiment B) (Graph S1 and S2).

The normalised same excess trace (green squares) shows a faster rate than the control (dark blue circles). This implies either catalyst deactivation or product inhibition occurs in the reaction. Comparison of the same excess trace with additional product, KHCO₃ and KF (light blue circles) shows a better overlap with the control profile than the same excess profile, indicating that product inhibition is occurring in the reaction. Additionally, another same excess experiment in which only the sulfone product was added (dark red circles) showed excellent overlap with the control profile, indicating that product inhibition arises from the sulfone formed and not one of the other potential by-products (Graph S2).
Different Excess
Visual comparisons were used to estimate the reaction order in each component using different excess experiments (Table S15) according to variable time normalisation analysis (VTNA) methods developed by Burés.5

| Experiment Profile | [CHO] (M) | [Sulfinate] (M) | [TDG] (M) | [CuF₂] (M) | [Cu(OAc)₂] (M) | [K₂CO₃] (M) |
|--------------------|-----------|----------------|-----------|-------------|---------------|------------|
| A                  | 0.473     | 0.189          | 0.0472    | 0.378       | 0.0945        | 0.378      |
| B                  | 0.567     | 0.189          | 0.0472    | 0.378       | 0.0945        | 0.378      |
| B2                 | 0.374     | 0.189          | 0.0472    | 0.378       | 0.0945        | 0.378      |
| C                  | 0.473     | 0.227          | 0.0472    | 0.378       | 0.0945        | 0.378      |
| C2                 | 0.473     | 0.151          | 0.0472    | 0.378       | 0.0945        | 0.378      |
| D                  | 0.473     | 0.189          | 0.0567    | 0.378       | 0.0945        | 0.378      |
| D2                 | 0.473     | 0.189          | 0.0756    | 0.378       | 0.0945        | 0.378      |
| D3                 | 0.473     | 0.189          | 0.0189    | 0.378       | 0.0945        | 0.378      |
| E                  | 0.473     | 0.189          | 0.0472    | 0.473       | 0.0945        | 0.378      |
| E2                 | 0.473     | 0.189          | 0.0472    | 0.284       | 0.0945        | 0.378      |
| F                  | 0.473     | 0.189          | 0.0472    | 0.378       | 0.142         | 0.378      |
| G                  | 0.473     | 0.189          | 0.0472    | 0.378       | 0.0945        | 0.473      |
| G2                 | 0.473     | 0.189          | 0.0472    | 0.378       | 0.0945        | 0.284      |

Table S15 – Different Excess experiments investigating 6 different components.
Order in Aldehyde (Expt A, B and B2)

| Time (h) | 3 equiv | 2.5 equiv | 2 equiv |
|----------|---------|-----------|--------|
| 0.00     | 0.000   | 0.000     | 0.000  |
| 2.00     | 0.051   | 0.039     | 0.034  |
| 4.00     | 0.084   | 0.062     | 0.057  |
| 6.00     | 0.105   | 0.085     | 0.075  |
| 8.00     | 0.122   | 0.102     | 0.092  |
| 10.00    | 0.131   | 0.113     | 0.103  |
| 12.00    | 0.129   | -         | 0.113  |
| 12.21    | -       | 0.122     | -      |
| 15.00    | 0.133   | 0.136     | 0.120  |
| 18.00    | 0.142   | 0.146     | 0.124  |
| 22.00    | -       | 0.159     | -      |
| 23.50    | 0.153   | -         | -      |
| 24.00    | -       | 0.161     | 0.1    |

**Figure S5** – a) Data for different CHO loadings. b) Normalised time data for different CHO loadings according to order x. Time normalised plots for CHO orders of c) x=0, d) x=1 and e) x=2.
Order in Sulfinate Salt (Expt A, C and C2)

| Time (h) | 1.2 equiv | 1 equiv | 0.8 equiv |
|----------|-----------|---------|-----------|
| 0.00     | 0.000     | 0.000   | 0.000     |
| 2.00     | 0.041     | 0.039   | 0.032     |
| 4.00     | 0.068     | 0.062   | 0.051     |
| 6.00     | 0.091     | 0.085   | 0.073     |
| 8.00     | 0.109     | 0.102   | 0.085     |
| 8.17     | -         | 0.109   | -         |
| 10.00    | 0.125     | 0.113   | 0.102     |
| 12.00    | -         | -       | 0.104     |
| 12.21    | -         | -       | 0.122     |
| 12.50    | 0.136     | -       | -         |
| 15.00    | 0.159     | 0.136   | 0.119     |
| 18.00    | 0.163     | 0.146   | 0.121     |
| 22.00    | -         | 0.159   | -         |
| 24.00    | 0.166     | 0.161   | -         |

| Time (h) | 1.2 equiv | 1 equiv | 0.8 equiv |
|----------|-----------|---------|-----------|
| 0.00     | 0.000     | 0.000   | 0.000     |
| 2.00     | 0.615     | 0.53    | 0.45      |
| 4.00     | 1.15      | 0.98    | 0.83      |
| 6.00     | 1.62      | 1.38    | 1.15      |
| 8.00     | 2.12      | 1.72    | 1.43      |
| 10.00    | 2.64      | 2.43    | 2.13      |
| 12.00    | 3.16      | 3.06    | 2.74      |
| 12.21    | 3.68      | 3.57    | 3.25      |
| 12.50    | 4.20      | 4.09    | 3.78      |
| 15.00    | 4.72      | 4.61    | 4.30      |
| 18.00    | 5.24      | 5.13    | 4.82      |
| 22.00    | 5.76      | 5.65    | 5.34      |
| 24.00    | 6.28      | 6.17    | 5.86      |

**Figure S6** – a) Data for different RSO₂Na loadings. b) Normalised time data for different RSO₂Na loadings according to order x. Time normalised plots for RSO₂Na orders of c) x=0, d) x=0.75 and e) x=1.
Order in Transient Directing Group (Expt A, D, D2 and D3)

a) Data for different TDG loadings. b) Normalised time data for different TDG loadings according to order x.

Figure S7 – a) Data for different TDG loadings. b) Normalised time data for different TDG loadings according to order x. Time normalised plots for TDG orders of c) x=0, d) x=1 and e) x=2.
Order in CuF\(_2\) (Expt A, E and E2)

| Time (h) | [P] for CuF\(_2\) loading (M) | \(\Sigma\)CuF\(_2\)\(\Delta t\) |
|----------|-------------------------------|-----------------------------|
| \(x = 0.0\) \(x = 0\) \(x = 0.5\) \(x = 1\) |
| Time (h) | 2.5 equiv | 2 equiv | 1.5 equiv | 2.5 equiv | 2 equiv | 1.5 equiv | 2.5 equiv | 2 equiv | 1.5 equiv |
| 0.00 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 2.00 | 0.055 | 0.040 | 0.034 | 0.129 | 0.116 | 0.100 | 0.84 | 0.68 | 0.50 |
| 4.00 | 0.081 | 0.062 | 0.064 | 2.45 | 2.21 | 1.86 | 1.51 | 1.23 | 0.87 |
| 6.00 | 0.104 | 0.085 | 0.087 | 3.59 | 3.17 | 2.59 | 2.08 | 1.69 | 1.13 |
| 8.00 | 0.115 | 0.102 | 0.098 | 4.65 | 4.05 | 3.21 | 2.59 | 2.07 | 1.33 |
| 10.00 | 0.121 | 0.113 | 0.106 | 5.50 | 4.86 | 3.78 | 3.06 | 2.40 | 1.49 |
| 12.00 | 0.130 | - | 0.115 | 6.44 | - | 4.28 | 3.51 | - | 1.61 |
| 12.21 | - | 0.123 | - | - | - | 5.69 | - | - | 2.71 |
| 15.00 | 0.142 | 0.136 | 0.129 | 7.79 | 6.65 | 4.88 | 4.11 | 3.04 | 1.73 |
| 18.00 | 0.157 | 0.146 | 0.129 | 9.04 | 7.58 | 5.36 | 4.63 | 3.33 | 1.81 |
| 22.00 | - | 0.159 | - | - | - | 8.67 | - | - | 3.63 |
| 24.00 | 0.164 | 0.160 | 0.140 | 11.3 | 9.15 | 6.10 | 5.54 | 3.74 | 1.90 |

**Figure S8** — a) Data for different CuF\(_2\) loadings. b) Normalised time data for different CuF\(_2\) loadings according to order x. Time normalised plots for CuF\(_2\) orders of c) x=0, d) x=0.5 and e) x=1.
Order in Cu(OAc)$_2$

| Time (h) | 75 mol%    | 50 mol%    | 75 mol%    | 50 mol%    |
|----------|------------|------------|------------|------------|
| 0.00     | 0.000      | 0.000      | 0.000      | 0.000      |
| 2.00     | 0.032      | 0.040      | 2.00       | 2.00       |
| 4.00     | 0.062      | 0.062      | 4.00       | 4.00       |
| 6.00     | 0.085      | 0.085      | 6.00       | 6.00       |
| 8.00     | 0.093      | 0.102      | 8.00       | 8.00       |
| 10.00    | 0.117      | 0.113      | 10.00      | 10.00      |
| 12.21    | -          | 0.123      | -          | 12.21      |
| 12.33    | 0.127      | -          | 12.33      | -          |
| 15.00    | 0.144      | 0.136      | 15.00      | 15.00      |
| 18.00    | 0.149      | 0.146      | 18.00      | 18.00      |
| 22.00    | -          | 0.159      | -          | 22.00      |
| 24.00    | 0.163      | 0.161      | 24.00      | 24.00      |

Figure S9  – a) Data for different Cu(OAc)$_2$ loadings. b) Normalised time data for different Cu(OAc)$_2$ loadings according to order $x$. Time normalised plots for CuF$_2$ orders of c) $x=0$, d) $x=1$. 
Order in K$_2$CO$_3$

| Time (h) | [P] for K$_2$CO$_3$ loading (M) | Time (h) | $\sum$[K$_2$CO$_3$]$^\Delta t$
|-----------------|---------------------------------|-----------------|------------------|
|                | 2.5 equiv | 2 equiv | 1.5 equiv | 2.5 equiv | 2 equiv | 1.5 equiv | 2.5 equiv | 2 equiv | 1.5 equiv |
| 0.00           | 0.000     | 0.000   | 0.000     | 0.000     | 0.000   | 0.000     | 0.000     | 0.000   | 0.000     |
| 2.00           | 0.047     | 0.040   | 0.021     | 0.000     | 0.000   | 0.000     | 0.000     | 0.000   | 0.000     |
| 4.00           | 0.070     | 0.062   | 0.047     | 0.000     | 0.000   | 0.000     | 0.000     | 0.000   | 0.000     |
| 6.00           | 0.096     | 0.085   | 0.064     | 2.000     | 2.000   | 2.000     | 1.730     | 1.370   | 1.050     |
| 8.00           | 0.121     | 0.102   | 0.079     | 6.000     | 6.000   | 6.000     | 2.510     | 1.980   | 1.500     |
| 10.00          | 0.132     | 0.113   | 0.098     | 8.000     | 8.000   | 8.000     | 3.230     | 2.550   | 1.920     |
| 12.00          | 0.149     | -       | 0.113     | 10.000    | 10.000  | 10.000    | 3.930     | 3.090   | 2.310     |
| 12.21          | -         | 0.123   | -         | 12.000    | 12.000  | -         | 4.590     | -       | 2.670     |
| 15.00          | 0.159     | 0.136   | 0.122     | 12.21     | -       | 12.21     | -         | 3.660   | -         |
| 18.00          | 0.166     | 0.146   | 0.132     | 15.000    | 15.000  | 15.000    | 5.540     | 4.360   | 3.170     |
| 22.00          | -         | 0.159   | -         | 18.000    | 18.000  | 18.000    | 6.470     | 5.070   | 3.630     |
| 24.00          | 0.174     | 0.160   | 0.146     | 22.00     | -       | 22.00     | -         | 5.970   | -         |

$\Delta t = \frac{T_{\text{time}}}{x}$

Figure S10 – a) Data for different K$_2$CO$_3$ loadings. b) Normalised time data for different K$_2$CO$_3$ loadings according to order $x$. Time normalised plots for K$_2$CO$_3$ orders of c) $x=0$, d) $x=1$ and e) $x=2$. 
Imine formation in proteo HFIP

2-Methylbenzaldehyde 1 (23 µL, 0.2 mmol) and/or sulfonylated aldehyde 3a (54.9 mg, 0.2 mmol), β-alanine (17.8 mg, 0.2 mmol) and accurately weighed 1,3,5-trimethoxybenzene (~7 mg, 0.3 equiv) were heated to 100 °C in HFIP until dissolution of the amine. Each solution was added to separate NMR tubes with glass inserts containing CDCl₃. We observed an almost 1:1 ratio of SM(CHO):SM(imine) (Table S16, Entry 1), whereas in we see only a small proportion of the product imine formed (Table S16, Entry 2 or 3). This indicates product inhibition is unlike to result from only imine formation and instead could be due to the product imine being a better ligand for copper.

**Table S16** – Imine formation NMR experiments. Yields determined *in situ* by ¹H NMR by comparison with 1,3,5-trimethoxybenzene as an internal standard.
Deuteration Labelling Experiments

Reaction in HFIP-d$_2$

Scheme S8 – Deuteration experiment using HFIP-d$_2$ with regions of relevant protons shown. $^1$H NMR was acquired with 30 s delay
KIE Experiments

Both parallel and competition experiments were carried out using benzaldehyde-d$_5$ as a substrate (Scheme S9 and Scheme S10).

A procedure used for parallel KIE experiments comparing initial rates is outlined below.

Potassium carbonate (110 mg, 0.8 mmol) and copper(II) fluoride (81 mg, 0.8 mmol) were added sequentially to a 5 mL microwave vial which was flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (36 mg, 0.2 mmol), β-alanine (8.9 mg, 0.1 mmol), p-tolylsulfinic acid sodium salt (71.2 mg, 0.4 mmol), accurately weighed 1,3,5-trimethoxybenzene (0.3 equiv) and the aldehyde were added to a microwave vial sequentially under argon. The vial was sealed and HFIP (0.2 M) was added and the vial was submerged in an oil bath preheated to 100 °C [Stirring rate set to 1000 rpm]. To take an aliquot: at the allotted time the vial was removed from the oil bath and 0.1 mL of solvent was removed by syringe while the reaction mixture is hot. [Caution: As the reaction is above the boiling point of the solvent, there is a small degree of back pressure. This was easily managed by holding the syringe plunger down gently while collecting the sample, and ensuring the liquid was taken up carefully and adequate inert atmosphere was taken up with the sample.] The aliquot was added to a vial containing a mixture of saturated aqueous ammonium chloride and EtOAc (approx. 1:1). This vial was sealed and shaken until the aliquot was observed to change from brown to blue/green. The organic and aqueous layers were allowed to separate, and the organic layer was carefully removed by pipette then filtered through a small pad of Na$_2$SO$_4$ and concentrated in vacuo. The entire residue was dissolved in CDCl$_3$ (<1 mL) and the yield of sulfonylated material was determined by $^1$H NMR by comparison with the internal standard.

Timepoints at 0.25, 0.5, 0.75, 1 and 1.5 h were collected from one reaction and 2, 2.5 and 3 h were collected from a second reaction. Concentrations were calculated from the total volumes of the parent liquids (aldehyde+HFIP): 2.1015 mL.
A procedure used for competition KIE experiments comparing initial rates is outlined below.

Potassium carbonate (27.5 mg, 0.2 mmol) and copper(II) fluoride (20 mg, 0.2 mmol) were added sequentially to a 5 mL microwave vial which was flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (9 mg, 0.05 mmol), β-alanine (2.3 mg, 0.025 mmol), p-tolylsulfinic acid sodium salt (17.8 mg, 0.1 mmol), accurately weighed 1,3,5-trimethoxybenzene (4.5 mg, approx. 0.3 equiv) and benzaldehyde (25.4 μL, 0.25 mmol) were added to a microwave vial sequentially under argon. The vial was sealed and a solution of Benzaldehyde-d₅ in HFIP (25.4 μL in 0.5 mL HFIP) was added and the vial was submerged in an oil bath preheated to 100 °C for 3 h [stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous solution of ammonium chloride (5 mL). The product was extracted from the aqueous phase with EtOAc (2 × 5 mL) and the combined organic extracts were dried over Na₂SO₄, filtered, then concentrated in vacuo and analysed by ¹H NMR (with 30 s delay).

Due to volatility of starting material, accurate RSM values of proteo and deutero benzaldehydes were not possible to obtain, thus only product was considered. While it was not possible to directly analyse the quantity of the deutero benzaldehyde due to overlap of signals, it was possible to determine indirectly via comparison of the aldehyde signal at δ 10.86 ppm (which originates from both proteo and deutero product) and the signal at δ 8.03 ppm.
ppm (which can only originate from the proteo product) Analysis by $^1$H NMR (with 30 s delay) with comparison to an internal standard (1,3,5-trimethoxybenzene) allowed determination of the relative amounts of proteo and deuto products (13% and 4% respectively) which allowed a KIE of 3.25 to be determined. This is in agreement with the value derived from the parallel reactions, indicating a primary KIE and so a turnover limiting C–H activation.

Scheme S10 – Competition K.I.E. experiment
Hammett Analysis

Standard procedure for Hammett analysis: Potassium carbonate (110 mg, 0.8 mmol) and copper(II) fluoride (81 mg, 0.8 mmol) were added sequentially to a 5 mL microwave vial which was flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (36 mg, 0.2 mmol), β-alanine (8.9 mg, 0.1 mmol), p-tolylsulfonic acid sodium salt (71.2 mg, 0.4 mmol), accurately weighed 1,3,5-trimethoxybenzene (approx. 0.3 equiv) and the aldehyde (1 mmol) were added sequentially under argon. The vial was sealed and HFIP (0.2 M) was added, and the vial was submerged in an oil bath preheated to 100 °C [Stirring rate set to 1000 rpm]. To take an aliquot: at the allotted time the vial was removed from the oil bath and 0.2 mL of solvent was removed by syringe while the reaction mixture is hot. [Caution: As the reaction is above the boiling point of the solvent, there is a small degree of back pressure. This was easily managed by holding the syringe plunger down gently while collecting the sample, and ensuring the liquid is taken up carefully and adequate inert atmosphere was taken up with the sample.] The aliquot was added to a small vial containing a mixture of saturated aqueous ammonium chloride and EtOAc (approx. 1:1). The vial was sealed and shaken until the aliquot was observed to change from brown to blue/green. The organic layer was carefully removed by pipette then filtered through a small pad of Na₂SO₄ to remove any residual water, then the sample was concentrated in vacuo. The entire residue was dissolved in CDCl₃ (<1 mL) and the yield of sulfonlated material was determined by ¹H NMR by comparison with the internal standard. Concentrations were calculated from the total volumes of the parent liquids (aldehyde+HFIP): R = H (2.1015 mL), R = 2-Me (2.1156 mL), R = 2-OMe (2.1208 mL), R = 3-Me (2.1180 mL), R = 3-CF₃ (2.1340 mL), R = 3-Cl (2.1130 mL), 4-CF₃ (2.1370 mL), 4-Me (2.1180 mL), 4-OMe (2.1180 mL), 3-OMe (2.1220 mL).
### Table S17—Hammett analysis Data

| R  | Time (h) | Yield (%) | [Sulfone] (mM) | R = 2-Me | Time (h) | Yield (%) | [Sulfone] (mM) | R = 2-OMe | Time (h) | Yield (%) | [Sulfone] (mM) | R = 3-Me | Time (h) | Yield (%) | [Sulfone] (mM) | R = 3-CF₃ | Time (h) | Yield (%) | [Sulfone] (mM) |
|----|----------|-----------|----------------|----------|----------|-----------|----------------|----------|----------|-----------|----------------|----------|----------|-----------|----------------|----------|----------|-----------|----------------|
| H  | 0        | 0         | 0              | 0        | 0.25     | 2         | 3.81           | 0        | 0.5      | 3         | 5.67           | 1        | 6        | 15.13      | 1.5         | 9        | 16.97     | 1.5         | 11       | 20.80     |
|    | 0.5      | 3         | 5.71           |          | 1        | 8         | 15.13         |          | 1        | 6         | 11.32         | 1        | 8        | 15.11      |              |          | 20.77     | 1.5         | 11       | 20.77     |
|    | 0.75     | 4         | 7.61           |          | 1.5      | 10        | 20.80         |          | 1.5      | 9         | 16.97         | 1.5      | 11       | 20.77     |              |          | 20.77     | 1.5         | 11       | 20.77     |
|    | 1        | 6         | 11.42          |          | 2        | 16        | 30.25         |          | 2        | 12        | 22.63         | 2        | 15       | 28.33      |              |          | 28.33     | 2.5         | 11       | 20.94     |
|    | 2        | 10        | 19.03          |          | 3        | 15        | 28.29         |          | 3        | 22        | 41.55         | 3        | 6        | 11.25      |              |          | 11.25     | 3           | 6        | 11.25     |

| R  | Time (h) | Yield (%) | [Sulfone] (mM) | R = 3-Cl | Time (h) | Yield (%) | [Sulfone] (mM) | R = 4-CF₃ | Time (h) | Yield (%) | [Sulfone] (mM) | R = 4-Me | Time (h) | Yield (%) | [Sulfone] (mM) | R = 4-OMe | Time (h) | Yield (%) | [Sulfone] (mM) |
|----|----------|-----------|----------------|----------|----------|-----------|----------------|----------|----------|-----------|----------------|----------|----------|-----------|----------------|----------|----------|-----------|----------------|
| Cl | 0        | 0         | 0              | 0        | 0.5      | 1         | 1.89           |          | 0.5      | 2         | 3.74           | 1        | 4        | 7.55       |              |          | 7.54       | 0.5         | 4        | 7.54       |
|    | 1        | 3         | 5.68           |          | 1        | 5         | 9.36           |          | 1        | 4         | 7.55           | 1        | 7        | 13.02      |              |          | 13.02      | 1         | 7        | 13.20      |
|    | 1.5      | 5         | 9.47           |          | 1.5      | 7         | 13.10          |          | 1.5      | 12        | 22.66          | 1.5      | 11       | 20.74      |              |          | 20.74      | 1.5         | 11       | 20.74      |
|    | 2        | 6         | 11.36          |          | 2        | 9         | 16.85          |          | 2        | 15        | 28.33          | 2        | 15       | 28.28      |              |          | 28.28      | 2         | 15       | 28.28      |
|    | 3        | 9         | 17.04          |          | 3        | 14        | 26.20          |          | 3        | 22        | 41.55          | 3        | 6        | 11.25      |              |          | 11.25      | 3         | 6        | 11.25      |

| R  | Time (h) | Mono (%) | [mono] (mM) | Mono' (%) | [Mono'] (mM) | [Total] (mM) |
|----|----------|----------|-------------|-----------|--------------|-------------|
| Cl | 0        | 0        | 0           | 0         | 0            | 0           |
|    | 0.5      | 5        | 9.425071    | 3         | 5.655042     | 15.08011    |
|    | 1        | 9        | 16.96513    | 4         | 7.540057     | 24.50518    |
|    | 1.5      | 13       | 24.50518    | 5         | 9.425071     | 33.93025    |
|    | 2        | 17       | 32.04524    | 7         | 13.1951      | 45.24034    |

**Diagram:**
- Reaction scheme showing β-alanine (25 mol%), CuF₂ (2 equiv), Cu(OAc)₂ (50 mol%), K₂CO₃ (2 equiv), HFIP (0.2 M) at 100 °C, Ar.
A negative correlation was observed when constructing the Hammett plot from the perspective of the C–H position highlighted. A poorer correlation was observed when instead using Hammett parameters from the ipso position. This indicates the change in electronics with varying substituents is more significant at the ortho C–H position rather than the ipso position, and so indicating a mechanism of C–H activation in which there is build up of positive charge which is stabilised by electron donating substituents.

| Substituent | $k_{obs}$ (mM/h) | Log($k_{obs}/k_H$) | Substituent | $k_{obs}$ (mM/h) | Log($k_{obs}/k_H$) |
|-------------|------------------|---------------------|-------------|------------------|---------------------|
| H           | 8.04             | 0.00                | 3-Cl        | 5.84             | -0.139              |
| 2-Me        | 15.13            | 0.274               | 3-CF$_3$    | 3.75             | -0.331              |
| 2-OMe       | 9.43             | 0.069               | 4-Me        | 14.35            | 0.252               |
| 3-Me        | 13.76            | 0.233               | 4-OMe       | 13.95            | 0.239               |
| 3-OMe       | 21.87            | 0.435               | 4-CF$_3$    | 8.72             | 0.035               |

**Figure S11** – a) Hammett analysis table. b) Hammett plot varying substitution on the aldehyde from the perspective of the C–H bond. c) Hammett plot varying substitution on the aldehyde from the perspective of the ipso position.
Scheme S11 – Competition experiments.
Synthesis of Sulfinate Salts

General Procedure A: Synthesis of Sulfinate Salts

Thiol (1 equiv) was added to a stirring solution of methyl acrylate (1 equiv) in THF:H₂O (1:1, 0.3 M). Sodium acetate (0.15 equiv) was added, and the reaction stirred for 18 h. The reaction was concentrated in vacuo, then the product was extracted from the aqueous phase with ethyl acetate, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (0.05 M) and mCPBA (3 equiv) was added at rt. The reaction was stirred until completion, as determined by TLC. The reaction was quenched by the addition of 1 M NaOH (aq) then the product was extracted with CH₂Cl₂, dried over Na₂SO₄, filtered and concentrated in vacuo to afford the sulfone intermediate. The sulfone intermediate was then dissolved in CH₂Cl₂ and sodium hydroxide as a solution in MeOH (1.05 equiv, 5 M) was added to a stirring solution of sulfone in CH₂Cl₂ (0.17 M) at 0 °C. The precipitate was filtered off and washed with hexane to afford the sulfinate salt. Sulfinate salts were prepared as previously reported.

Sodium bicyclo[1.1.1]pentane-1-sulfinate (S1)

Using procedure modified from Bär et al.⁷ PhLi (1.79 M in Bu₂O, 5.59 mL, 10 mmol) was added dropwise to a stirring solution of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (1.484 g, 5 mmol) in Et₂O (7.2 mL) at -40 °C. After addition, the reaction was warmed to 0 °C then stirred for 2 h at 0 °C. Flame dried distillation apparatus purged with argon was attached to the reaction flask and the receiving flask was cooled to -78 °C. The reaction was placed in a water bath and warmed to 20 °C and the intermediary propellane was co distilled with Et₂O under reduced pressure (slowly from 500 to 20 mbar). Methyl 3-mercaptopropionate (719 μL, 6.5 mmol) was added to the solution of propellane in Et₂O at rt and the reaction was stirred for 30 min at this temperature. The reaction mixture was washed with 1 M NaOH (aq) (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude sulfide was dissolved in CH₂Cl₂ (100 mL) and mCPBA (2.9 g, 12.5 mmol) was added at rt and the solution was stirred for 1 h. 1 M NaOH (100 mL) was added and the product extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude sulfone was dissolved in CH₂Cl₂ (45 mL) and sodium hydroxide as a solution in MeOH (948 μL, 5 M) was added. The precipitate was filtered off and washed with hexane to
afford sodium bicyclo[1.1.1]pentane-1-sulfinate S1 as a white powder (355.3 mg, 46% over 4 steps). m.p. = >300 °C. IR (film)/cm⁻¹ 2974, 2955, 2900, 2869, 1553, 1449, 1203, 1015, 990, 931, 897, 858, 661, 607, 582, 542, 475. ¹H NMR (400 MHz, D₂O) δ 2.67 (s, 1H, CH), 1.87 (s, 6H, (CH₂)₃). ¹³C NMR (101 MHz, D₂O) δ 57.2 (Cq), 47.2 ((CH₂)₃), 25.8 (CH). Analytical data (¹H, ¹³C NMR) are in agreement with the reported literature.

Copper Mediated C(sp²)–H Sulfonylation

General Procedure B: Lab humidity<75%

Potassium carbonate (55 mg, 0.4 mmol) and copper(II) fluoride (40 mg, 0.4 mmol) were added sequentially to a microwave vial which was then flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (18 mg, 0.1 mmol), β-alanine (4.5 mg, 0.05 mmol), sulfinic acid sodium salt (0.2 mmol) and the aldehyde (0.5 mmol) were added to a microwave vial sequentially under argon, sealed and HFIP (1 mL, 0.2 M) was added and the vial was submerged in a preheated oil bath to 100 °C for 18 h [Stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous solution of ammonium chloride (10 mL). [Note: The crude should be shaken until a change from orange/brown to blue/green is observed. Should the resulting solution emulsify brine can be added. Occasionally a brown precipitate can remain which obscures the phase boundary, this is collected with the aqueous phase for the first two extractions then with the organic phase on the final extraction]. The product was extracted from the aqueous phase with EtOAc (2 × 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo.

[Note: We found that the presence of water (from lab humidity) can negatively impact the yield and reproducibility, therefore if lab humidity is >75% following general procedure C can be used to mitigate this effect.]

General Procedure C: Lab humidity>75%

Potassium carbonate (55 mg, 0.4 mmol) and copper(II) fluoride (40 mg, 0.4 mmol) were added sequentially to a microwave vial which was then flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (18 mg, 0.1 mmol), β-alanine (4.5 mg, 0.05 mmol), acid sodium salt (0.2 mmol) were added sequentially. The vial was sealed then purged and then backfilled with argon (3 times, purge for 30 s each time). To a separate flame dried vial under argon, aldehyde (0.5 mmol) was added then diluted with HFIP (1 mL, 0.2 M). The solution of aldehyde in HFIP was transferred to the reaction vial then submerged in a oil bath preheated to 100 °C for 18 h [Stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous solution of ammonium chloride (10 mL). [Note: The crude should be shaken until a change from orange/brown to blue/green is observed, should the resulting solution emulsify brine can be
added. Occasionally a brown precipitate can remain which obscures the phase boundary, this was collected with the aqueous phase for the first two extractions then with the organic phase on the final extraction] The product was extracted from the aqueous phase with EtOAc (2 × 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo.

**General Note on Purification**

Unless otherwise stated, sulfonylated aldehydes were purified by flash column chromatography using a short silica column (approx. 4 cm height in 2.5 cm diameter column). If the reaction gave 1 product: 10% Et₂O:pentane was used until the starting material came off the column, then 20% Et₂O:pentane was used until the product came off the column. If the reaction gave >1 products: 10% Et₂O:pentane was used until the starting material came off the column, then 20% Et₂O:pentane was used until the first product came off. At this point the solvent system was changed to 20% EtOAc:pentane for the remaining products.

**Reaction Scope Varying the Sulfinate Salt**

**2-(Phenylsulfonyl)-6-methylbenzaldehyde (3b)**

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and benzenesulfinic acid sodium salt (33.1 mg, 0.2 mmol). Purification by flash column chromatography (20% Et₂O:pentane) afforded sulfonyl aldehyde 3b as a white solid (34.0 mg, 65%). m.p. = 105–107 °C. Rf 0.26 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3064, 2863, 2930, 2967, 1703 (C=O), 1588, 1446, 1387, 1312, 1163, 1141, 1085, 1025, 880, 790, 753, 723, 686. ¹H NMR (400 MHz, CDCl₃) δ 10.80 (s, 1H, CHO), 8.00 (d, J = 7.7 Hz, 1H, Ar–CH), 7.90–7.87 (m, 2H, 2 × Ar–CH), 7.63–7.49 (m, 5H, 5 × Ar–CH), 2.45 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.3 (CHO), 141.54 (Ar–Cₖ), 141.46 (Ar–Cₜ), 139.7 (Ar–Cₖ), 136.9 (Ar–CH), 134.7 (Ar–Cₜ), 133.6 (Ar–CH), 131.3 (Ar–CH), 129.4 (2 × Ar–CH), 127.5 (2 × Ar–CH), 127.4 (Ar–CH), 20.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₅O₃S [M+H]: 261.0585; found: 261.0593.

**2-((4-Methoxyphenyl)sulfonyl)-6-methylbenzaldehyde (3c)**

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and 4-methoxybenzenesulfinic acid sodium salt (39.0 mg, 0.2 mmol). Purification by flash column chromatography (20% Et₂O:pentane) afforded sulfonyl aldehyde 3c as a white solid (40.1 mg, 69%). m.p. = 129–131 °C. Rf 0.06 (20% Et₂O:pentane). IR (film)/cm⁻¹ 2930, 2952, 2848, 2728, 1703 (C=O), 1595, 1498, 1498, 1446, 1379, 1308, 1267, 1155, 1084, 857, 835, 787. ¹H NMR (400 MHz, CDCl₃) δ 10.83 (s, 1H, CHO), 7.95 (dd, J = 7.7, 0.7 Hz, 1H, Ar–CH), 7.83–7.79 (m, 2H, 2 × Ar–CH), 7.52 (dd, J = 7.7, 7.7 Hz, 1H, Ar–CH), 7.47 (dt, J = 7.7, 0.7 Hz, 1H, Ar–CH), 7.01–6.97 (m, 2H, 2 × Ar–CH), 3.86 (s, 3H, OCH₃), 2.45 (s, 3H, ArCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.7 (CHO), 163.7 (Ar–Cₖ), 142.4 (Ar–Cₜ), 139.5 (Ar–Cₖ), 136.5 (Ar–CH), 134.6 (Ar–Cₜ), 132.8 (Ar–Cₖ), 131.2 (Ar–CH), 129.9 (2 × Ar–CH), 127.0 (Ar–CH), 114.6 (2 × Ar–CH), 55.7 (OCH₃), 20.6 (ArCH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₅O₃S [M+H]: 291.0691; found: 291.0686.
2-((4-tert-Butylphenyl)sulfonyl)-6-methylbenzaldehyde (3d)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and 4-(tert-butyl)benzenesulfonic acid sodium salt (44.1 mg, 0.2 mmol). Purification by flash column chromatography (10% EtOAc:pentane) afforded sulfonyl aldehyde 3d as a white solid (36.8 mg, 58%). m.p. = 126–127 °C. Rf = 0.33 (20% EtOAc:pentane). IR (film)/cm⁻¹ 2963, 2870, 1703 (C=O), 1591, 1562, 1454, 1398, 1316, 1141, 1107, 1014, 913, 880, 839, 753, 675. ¹H NMR (400 MHz, CDCl₃) δ 10.82 (s, 1H, CHO), 8.00 (dd, J = 7.7, 1.3, 0.6 Hz, 1H, Ar–CH), 7.82–7.78 (m, 2H, 2 × Ar–CH), 7.57–7.48 (m, 4H, 4 × Ar–CH), 2.46 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.4 (CHO), 157.6 (Ar–C₆), 142.0 (Ar–C₆), 139.6 (Ar–C₆), 138.4 (Ar–C₆), 136.8 (Ar–CH), 134.6 (Ar–C₆), 131.2 (Ar–CH), 127.4 (2 × Ar–CH), 127.3 (Ar–CH), 126.5 (2 × Ar–CH), 35.2 (C₆(CH₃)₃), 31.0 (C(CH₃)₃), 20.7 (Ar–CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₈H₂₁O₃S [M+H]: 317.1211; found: 317.1208.

2-((4-Trifluoromethylphenyl)sulfonyl)-6-methylbenzaldehyde (3e)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and 4-trifluorobenzenesulfonic acid sodium salt (46.4 mg, 0.2 mmol). Purification by flash column chromatography (10% EtOAc:pentane) afforded sulfonyl aldehyde 3e as a white solid (41.5 mg, 63%). m.p. = 93–94 °C. Rf = 0.16 (20% EtOAc:pentane). IR (film)/cm⁻¹ 2920, 2854, 1704 (C=O), 1586, 1558, 1401, 1320, 1165, 1334, 1134, 1060, 1014, 878, 842, 787, 739, 617, 556, 423. ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H, CHO), 8.04–8.00 (m, 3H, 3 × Ar–CH), 7.80 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.59 (dd, J = 7.7, 7.7 Hz, 1H, Ar–CH), 7.54 (d, J = 7.4 Hz, 1H, 1 × Ar–CH), 2.46 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.5 (CHO), 145.1 (Ar–C₆), 140.1 (Ar–C₆), 139.6 (Ar–C₆), 137.3 (Ar–CH), 135.7 (Ar–C₆), 135.2 (q, ²J_C_F = 38.0 Hz, Ar–C₆), 131.4 (Ar–CH), 128.2 (2 × Ar–CH), 127.7 (Ar–CH), 126.5 (q, ²J_C_F = 3.7 Hz, 2 × Ar–CH), 122.9 (q, ²J_C_F = 274.2 Hz, C₆(CH₃)₃), 20.3 (CH₃). ¹⁹F(¹H) NMR (377 MHz, CDCl₃) δ -63.24. HRMS (TOF–ESI⁺) m/z calcd. For C₁₈H₁₆F₃O₃S [M+H]: 329.0459; found: 329.0466.

2-((4-Fluorophenyl)sulfonyl)-6-methylbenzaldehyde (3f)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and 4-fluorobenzenesulfonic acid sodium salt (34.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:pentane) afforded sulfonyl aldehyde 3f as a white solid (40.0 mg, 72%). m.p. = 97–100 °C. Rf = 0.17 (20% EtOAc:pentane). IR (film)/cm⁻¹ 3105, 3075, 2982, 2930, 2863, 1707 (C=O), 1592, 1491, 1454, 1405, 1320, 1293, 1238, 1137, 880, 839, 790, 746, 686, 593, 563, 500. ¹H NMR (400 MHz, CDCl₃) δ 10.80 (s, 1H, CHO), 7.98–7.96 (m, 1H, Ar–CH), 7.93–7.88 (m, 2H, 2 × Ar–CH), 7.56 (t, J = 7.7 Hz, 1H, Ar–CH), 7.54–7.50 (m, 1H, Ar–CH), 7.24–7.18 (m, 2H, 2 × Ar–CH), 2.45 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.7 (CHO), 165.6 (d, ³J_C_F = 257.0 Hz, Ar–C₆), 141.2 (Ar–C₆), 139.4 (Ar–C₆), 137.5 (d, ⁴J_C_F = 3.0 Hz, Ar–C₆), 136.9 (Ar–C₆), 135.1 (Ar–C₆), 131.2 (Ar–C₆), 130.6 (d, ³J_C_F = 9.6 Hz, Ar–C₆), 127.2 (Ar–C₆), 116.8 (d, ²J_C_F = 22.9 Hz, 2 × Ar–CH), 20.4 (CH₃). ¹⁹F(¹H) NMR (377 MHz, CDCl₃) δ -103.16. HRMS (TOF–ESI⁺) m/z calcd. For C₁₄H₁₂O₃SF [M+H]: 279.0491; found: 279.0492.
2-((4-Chlorophenyl)sulfonyl)-6-methylbenzaldehyde (3g)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 μL, 0.5 mmol) and 4-chlorobenzenesulfonic acid sodium salt (39.7 mg, 0.2 mmol). Purification by flash column chromatography (20% EtOAc:pentane) afforded sulfonyl aldehyde 3g as a white solid (43.7 mg, 74%). m.p. = 95–98 °C. Rf 0.19 (20% EtOAc:pentane). IR (film/cm⁻¹) 3090, 2960, 2862, 2930, 1707 (C=O), 1540, 1476, 1394, 1320, 1282, 1163, 1088, 1014, 880, 828, 794, 757, 708, 678. ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H, CHO), 7.99–7.97 (m, 1H, Ar–CH), 7.83–7.80 (m, 2H, 2 × Ar–CH), 7.56 (t, J = 7.7 Hz, 1H, Ar–CH), 7.54–7.49 (m, 3H, 3 × Ar–CH), 2.45 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 193.6 (CHO), 140.9 (Ar–C₆), 140.4 (Ar–C₆), 140.0 (Ar–C₆), 139.5 (Ar–C₆), 137.0 (Ar–C₆), 135.2 (Ar–C₆), 131.3 (Ar–C₆), 129.8 (2 × Ar–CH), 129.1 (2 × Ar–CH), 127.4 (Ar–CH), 20.4 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₁₄H₁₂O₃S³⁵Cl [M+H]: 295.0190; found: 295.0183.

2-((4-Bromophenyl)sulfonyl)-6-methylbenzaldehyde (3h)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 μL, 0.5 mmol) and 4-bromobenzenesulfonic acid sodium salt (48.6 mg, 0.2 mmol). Purification by flash column chromatography (20% EtOAc:pentane) afforded sulfonyl aldehyde 3h as a white solid (48.6 mg, 72%). m.p. = 97–98 °C. Rf 0.17 (20% EtOAc:pentane). IR (film/cm⁻¹) 3086, 2930, 2863, 1703 (C=O), 1573, 1472, 1386, 1230, 1163, 1164, 1070, 1010, 880, 824, 794, 742, 701, 675. ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H, CHO), 7.98 (d, J = 7.7 Hz, 1H, Ar–CH), 7.74 (d, J = 8.9 Hz, 2H, 2 × Ar–CH), 7.67 (d, J = 8.9 Hz, 2H, 2 × Ar–CH), 7.56 (dd, J = 7.7, 7.7 Hz, 1H, Ar–CH), 7.51 (d, J = 7.7 Hz, 1H, Ar–CH), 2.45 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.5 (CHO), 140.8 (Ar–C₆), 140.5 (Ar–C₆), 139.5 (Ar–C₆), 139.5 (Ar–C₆), 137.0 (Ar–C₆), 135.1 (Ar–C₆), 132.7 (2 × Ar–CH), 131.3 (Ar–C₆), 129.1 (2 × Ar–CH), 129.0 (Ar–C₆), 127.4 (Ar–CH), 20.4 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₄H₁₂O₃S₇Br [M+H]: 338.9691; found: 338.9678.

2-((2-Methylphenyl)sulfonyl)-6-methylbenzaldehyde (3i)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 μL, 0.5 mmol) and 2-methylbenzenesulfonic acid sodium salt (35.7 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:hexane) afforded sulfonyl aldehyde 3i as a yellow oil (23.0 mg, 42%). Rf 0.20 (20% EtOAc:hexane). IR (film/cm⁻¹) 3059, 2921, 2854, 1701 (C=O), 1587, 1454, 1382, 1308, 1183, 1144, 1123, 1059, 1038, 878, 794, 762, 698, 609, 588, 565. ¹H NMR (400 MHz, CDCl₃) δ 10.73 (s, 1H, CHO), 8.12 (dd, J = 7.7, 1.8 Hz, 1H, Ar–CH), 7.98 (dd, J = 7.7, 1.8 Hz, 1H, Ar–CH), 7.59–7.51 (m, 3H, 3 × Ar–CH), 7.43 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H, Ar–CH), 7.27–7.25 (m, 1H, Ar–CH), 2.50 (s, 3H, CH₃), 2.39 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.4 (CHO), 142.0 (Ar–C₆), 140.5 (Ar–C₆), 139.4 (Ar–C₆), 138.0 (Ar–C₆), 137.0 (Ar–C₆), 134.1 (Ar–C₆), 133.8 (Ar–C₆), 132.9 (Ar–C₆), 131.1 (Ar–C₆), 128.9 (Ar–C₆), 127.4 (Ar–C₆), 126.7 (Ar–C₆), 21.0 (CH₃), 20.1 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₃O₃S [M+H]: 275.0742; found: 275.0735. ¹³C signal overlaps with CDCl₃ signal, partly obscuring signal.

2-(Naphthalen-1-ylsulfonyl)-6-methylbenzaldehyde (3j)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 μL, 0.5 mmol) and naphthalene-1-sulfonic acid sodium salt (42.4 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:hexane) afforded sulfonyl aldehyde 3j as an white solid (30.7 mg, 50%). m.p. = 136–137 °C. Rf 0.19 (20% EtOAc:hexane). IR (film/cm⁻¹) 3059,
2-Methyl-6-(methylsulfonyl)benzaldehyde (3k)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and methylsulfinic acid sodium salt (20.1 mg, 0.20 mmol). Purification by flash column chromatography (30% EtO:pentane) afforded sulfonyl aldehyde 3k as a white solid (34.1 mg, 76%). m.p. = 98 °C. IR (film)/cm⁻¹ 3071, 3012, 2930, 1696 (C=O), 1587, 1561, 1439, 1402, 1290, 1182, 1118, 1014, 928, 876, 787, 753, 731, 675.¹H NMR (400 MHz, CDCl₃) δ 7.83 (dd, J = 7.1, 2.0 Hz, 1H, Ar–CH), 7.57–7.51 (m, 2H, 2 × Ar–CH), 2.70 (tt, J = 8.0, 4.8 Hz, 1H, SO₂CH₂), 2.51 (s, 3H, CH₃), 1.37–1.32 (m, 2H, CH₂(CH₃)₂). ¹³C NMR (101 MHz, CDCl₃) δ 194.4 (CHO), 140.1 (Ar–C₆), 139.1 (Ar–C₆), 136.7 (Ar–CH), 136.0 (Ar–C₆), 131.2 (Ar–CH), 127.5 (Ar–CH), 46.3 (CH₃), 19.7 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₉H₁₃O₂S [M+H]: 199.0423; found: 199.0421.

2-Methyl-6-(cyclopropylsulfonyl)benzaldehyde (3l)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and cyclopropylsulfinic acid sodium salt (25.5 mg, 0.20 mmol). Purification by flash column chromatography (20% EtO:pentane) afforded sulfonyl aldehyde 3l as a white solid (34.1 mg, 76%). m.p. = 98–99 °C. IR (film)/cm⁻¹ 3071, 3012, 2930, 1696 (C=O), 1587, 1561, 1439, 1402, 1290, 1182, 1118, 1014, 928, 876, 787, 753, 731, 675.¹H NMR (400 MHz, CDCl₃) δ 7.83 (dd, J = 7.1, 2.0 Hz, 1H, Ar–CH), 7.57–7.51 (m, 2H, 2 × Ar–CH), 2.70 (tt, J = 8.0, 4.8 Hz, 1H, SO₂CH₂), 2.51 (s, 3H, CH₃), 1.37–1.32 (m, 2H, CH₂(CH₃)₂). ¹³C NMR (101 MHz, CDCl₃) δ 194.6 (CHO), 140.4 (Ar–C₆), 139.1 (Ar–C₆), 136.4 (Ar–CH), 135.8 (Ar–C₆), 131.1 (Ar–CH), 127.2 (Ar–CH), 34.2 (SO₂CH₂), 20.1 (CH₃), 6.4 (SO₂CH₂CH₂). HRMS (TOF–ESI⁺) m/z calcd. For C₉H₁₃O₂S [M+H]: 199.0423; found: 199.0421.

2-(Bicyclo[1.1.1]pentan-1-ylsulfonyl)-6-methylbenzaldehyde (3m)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and bicyclo[1.1.1]pentan-1-ylsulfinic acid sodium salt (30.8 mg, 0.20 mmol). Purification by flash column chromatography (10% EtOAc:pentane) afforded sulfonyl aldehyde 3m as a white solid (13.5 mg, 27%). m.p. = 100–103 °C. IR (film)/cm⁻¹ 2969, 2918, 2882, 1703 (C=O), 1451, 1424, 1381, 1306, 1206, 1183, 1104, 876, 794, 681, 629, 560, 535.¹H NMR (400 MHz, CDCl₃) δ 7.87–7.84 (m, 1H, Ar–CH), 7.60–7.55 (m, 2H, 2 × Ar–CH), 2.77 (s, 1H, SO₂C(CH₂)₂CH₂), 2.53 (s, 3H, CH₃), 2.12 (s, 6H,SO₂C(CH₂)₂CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 193.9 (CHO), 139.5 (Ar–C₆), 137.6 (Ar–C₆), 137.2 (Ar–C₆), 136.2 (Ar–C₆), 131.2 (Ar–CH), 128.6 (Ar–CH), 55.9 (SO₂CH₂), 50.6 (3 × CH₂), 26.6 (CH), 20.8 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₁₃H₁₅O₃S [M+H]: 251.0736; found: 251.0742.
Reaction Scope Varying the Aldehyde

2-Methoxy-6-(4-methylbenzenesulfonyl)benzaldehyde (5a)

Synthesised according to general procedure B using 2-methoxybenzaldehyde (60 µL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (20% EtOAc:pentane) afforded sulfonyl aldehyde 5a as a white solid (30.5 mg, 53%). m.p. = 116–119 °C. Rf 0.1 (20% EtOAc:pentane). IR (film)/cm⁻¹ 3086, 2945, 2848, 2736, 1707 (C=O), 1588, 1461, 1491, 1461, 1435, 1402, 1297, 1267, 1163, 1141, 1088, 1036, 969, 813, 790, 738. ¹H NMR (400 MHz, CDCl₃) δ 10.59 (s, 1H, CHO), 7.80–7.77 (m, 2H, 2 × Ar–CH), 7.71 (dd, J = 8.0, 0.9 Hz, 1H, Ar–CH), 7.58 (dd, J = 8.3, 8.3 Hz, 1H, Ar–CH), 7.31 (d, J = 7.7 Hz, 2H, 2 × Ar–CH), 7.19 (d, J = 8.3 Hz, 1H, Ar–CH), 3.86 (s, 3H, OCH₃), 2.40 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 191.8 (CHO), 158.8 (Ar–Cₖ), 144.5 (Ar–Cₖ), 141.6 (Ar–Cₖ), 138.4 (Ar–Cₖ), 132.5 (Ar–CH), 129.8 (2 × Ar–CH), 127.9 (2 × Ar–CH), 126.2 (Ar–Cₖ), 121.3 (Ar–CH), 116.5 (Ar–CH), 56.4 (OCH₃), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₅O₄S [M+H]: 291.0691; found: 291.0692.

Also prepared on 10 mmol scale
Also prepared on 2 mmol scale

2-Methyl-6-(4-methylbenzenesulfonyl)benzaldehyde (3a)

Synthesised according to general procedure B using 2-methylbenzaldehyde (58 µL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:pentane) afforded sulfonyl aldehyde 3a as an off white solid (47.1 mg, 86%). m.p. = 112–114 °C. Rf 0.21 (20% EtOAc:pentane). IR (film)/cm⁻¹ 3064, 2967, 1703 (C=O), 1595, 1453, 1382, 1301, 1136, 1081, 1040, 880, 816. ¹H NMR (400 MHz, CDCl₃) δ 10.81 (s, 1H, CHO), 7.98 (d, J = 7.7 Hz, 1H, Ar–CH), 7.76 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.54 (t, J = 7.7, 7.7 Hz, 1H, Ar–CH), 7.48 (d, J = 7.7 Hz, 1H, Ar–CH), 7.32 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 2.45 (s, 3H, CH₃), 2.41 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.5 (CHO), 144.7 (Ar–Cₖ), 142.0 (Ar–Cₖ), 139.6 (Ar–Cₖ), 138.5 (Ar–Cₖ), 136.7 (Ar–CH), 134.6 (Ar–Cₖ), 131.2 (Ar–CH), 130.1 (2 × Ar–CH), 127.6 (2 × Ar–CH), 127.2 (Ar–CH), 21.6 (CH₃), 20.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₅O₄S [M+H]: 275.0742; found: 275.0739.

Also prepared on 0.4 mmol scale which afforded sulfonyl aldehyde 3a (89.1 mg, 81%) [note: on larger scale, a higher stirring rate (750 rpm) was necessary.]
Also prepared on 2 mmol scale which afforded sulfonyl aldehyde 3a (356 mg, 65%)
Also prepared on 10 mmol scale which afforded sulfonyl aldehyde 3a (2.07 g, 75%) For details of multigram scale synthesis, see page S68.

2-Trifluoromethyl-6-(4-methylbenzenesulfonyl)benzaldehyde (6a)

Synthesised according to general procedure B using 2-trifluoromethylbenzaldehyde (66 µL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonyl aldehyde 6a as a white solid (35.5 mg, 54%). m.p. = 138–139 °C. Rf 0.09 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3075, 2924, 1710 (C=O), 1592, 1567, 1315, 1210, 1159, 1138, 1117, 1093, 1069, 1043, 1017, 846, 808, 754, 710, 664, 644, 579, 542. ¹H NMR (400 MHz, CDCl₃) δ 10.77 (q, δJCF = 2.9 Hz, 1H, CHO), 8.25 (d, J = 8.0 Hz, 1H, Ar–CH), 7.92 (d, J = 7.8 Hz, 1H, Ar–CH), 7.78–7.72 (m, 3H, 3 × Ar–CH), 7.35 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 2.42 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 191.9 (CHO), 145.4 (Ar–Cₖ), 142.2 (Ar–Cₖ),
137.5 (Ar–C₆), 137.4 (Ar–C₆), 132.9 (Ar–CH), 131.0 (q, J_C–F = 4.8 Hz, Ar–CH), 130.9 (Ar–CH), 130.2 (2 × Ar–CH), 129.3 (q, J_C–F = 31.0 Hz, Ar–C₆), 128.1 (2 × Ar–CH), 122.8 (q, J_C–F = 275.5 Hz, CₛF₃), 21.6 (CH₃). ¹³F{¹H} NMR (377 MHz, CDCl₃) δ –57.25. HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₂O₃SF₃ [M+H]: 329.0459; found: 329.0459.

5-Methoxy-2-(4-methylbenzenesulfonyl)benzaldehyde (7a mono), 3-methoxy-2-(4-methylbenzenesulfonyl)benzaldehyde (7a mono') and 3-methoxy-2,6-di(4-methylbenzenesulfonyl)benzaldehyde (7a di)

| mono | mono' | di |
|------|-------|----|

Synthesised according to general procedure B using 3-methoxybenzaldehyde (61 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane to 20% EtOAc:pentane) afforded sulfonyl aldehyde 7a mono as a white solid (19.5 mg, 34%), followed by sulfonyl aldehyde 7a mono’ as a white solid (4.9 mg, 8%), followed by 7a di as a white solid (9.6 mg, 22%).

7a mono: m.p. = 85–87 °C. R₆. 0.18 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3094, 2941, 1692 (C=O), 1588, 1480, 1394, 1323, 1286, 1156, 1129, 1088, 1058, 1025, 932, 816, 764, 682. ¹H NMR (400 MHz, CDCl₃) δ 10.81 (s, 1H, CHO), 8.14 (d, J = 8.5 Hz, 1H, Ar–CH), 7.75 (d, J = 8.5 Hz, 2H, 2 × Ar–CH), 7.55 (d, J = 8.5 Hz, 2H, 2 × Ar–CH), 7.21 (dd, J = 8.5, 2.8 Hz, 1H, Ar–CH), 3.91 (s, 3H, OCH₃), 2.41 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 189.4 (CHO), 163.5 (Ar–C₆), 144.5 (Ar–C₆), 139.3 (Ar–C₆), 135.7 (Ar–C₆), 134.4 (Ar–C₆), 131.9 (Ar–CH), 130.2 (2 × Ar–CH), 127.2 (2 × Ar–CH), 119.2 (Ar–CH), 113.5 (Ar–CH), 56.0 (OCH₃), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₅O₂S [M+H]: 291.0691; found: 291.0696.

7a mono’: m.p. = 156–158 °C. R₆. 0.06 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3086, 2930, 1670 (C=O), 1573, 1469, 1316, 1282, 1152, 1085, 910, 813, 775, 738. ¹H NMR (400 MHz, CDCl₃) δ 10.98 (d, J = 0.7 Hz, 1H, CHO), 7.87–7.85 (m, 2H, 2 × Ar–CH), 7.61 (ddd, J = 8.4, 7.6, 0.7 Hz, 1H, Ar–CH), 7.33–7.29 (m, 3H, 3 × Ar–CH), 7.09 (dd, J = 8.4, 1.2 Hz, 1H, Ar–CH), 3.77 (s, 3H, OCH₃), 2.44 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 191.7 (CHO), 157.2 (Ar–C₆), 144.4 (Ar–C₆), 139.8 (Ar–C₆), 138.8 (Ar–C₆), 135.2 (Ar–C₆), 129.2 (2 × Ar–CH + Ar–C₆), 128.3 (2 × Ar–CH), 120.8 (Ar–CH), 116.4 (Ar–CH), 56.4 (OCH₃), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₅O₂S [M+H]: 291.0691; found: 291.0702.

7a di: m.p. = 200–201 °C. R₆. 0.01 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3068, 3027, 2986, 2945, 1703 (C=O), 1595, 1494, 1319, 1185, 1156, 1107, 768, 921, 813, 679, 708. ¹H NMR (400 MHz, CDCl₃) δ 10.89 (s, 1H, CHO), 8.18 (d, J = 8.9 Hz, 1H, Ar–CH), 7.79 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 7.24 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 7.34–7.29 (m, 4H, 4 × Ar–CH), 7.04 (d, J = 8.9 Hz, 1H, Ar–CH), 3.87 (s, 3H, OCH₃), 2.41 (s, 6H, 2 × CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 191.6 (CHO), 160.7 (Ar–C₆), 145.0 (Ar–C₆), 144.8 (Ar–C₆), 142.1 (Ar–C₆), 138.3 (Ar–C₆), 136.9 (Ar–C₆), 136.8 (Ar–CH), 133.3 (Ar–C₆), 129.9 (2 × Ar–CH), 129.6 (Ar–C₆), 129.4 (2 × Ar–CH), 128.9 (2 × Ar–CH), 128.1 (2 × Ar–CH), 113.3 (Ar–CH), 56.8 (OCH₃), 21.7 (CH₃), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₂₂H₂₁O₆S₂ [M+H]: 445.0773; found: 445.0780.
5-Methyl-2-(4-methylbenzenesulfonyl)benzaldehyde (8a)

Synthesised according to general procedure B using 3-methylbenzaldehyde (59 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonyl aldehyde 8a as a colourless oil (37.3 mg, 68%).

IR (film)/cm⁻¹: 3034, 2922, 1684 (C=O), 1592, 1491, 1310, 1238, 1200, 1152, 1028, 880, 708.

HRMS (FTMS+pAPCI) m/z calcd. For C₁₅H₁₅O₃S [M+H]: 275.0736; found: 275.0733

5-Trifluoromethyl-2-(4-methylbenzenesulfonyl)benzaldehyde (9a)

Synthesised according to general procedure B using 3-trifluoromethylbenzaldehyde (67 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10% acetone:pentane) afforded sulfonyl aldehyde 9a as a colourless oil (32.1 mg, 49%) [note: a longer column (approx. 10 cm height, 2.5 cm width) was required]. Rf 0.19 (10% acetone:pentane). IR (film)/cm⁻¹: 2919, 1698 (C=O), 1598, 1403, 1326, 1255, 1175, 1156, 1134, 1077, 909, 848, 814, 718, 661, 588, 545, 415. ¹H NMR (400 MHz, CDCl₃) δ 10.90 (s, 1H, CHO), 8.30–8.27 (m, 2H, 2 × Ar–CH), 7.99 (dd, J = 8.2, 1.3 Hz, 1H, Ar–CH), 7.90 (dd, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.38 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.24 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 188.0 (CHO), 146.0 (Ar–C₉), 145.7 (Ar–C₈), 137.4 (Ar–C₇), 135.5 (q, ²Jₙ₉ = 33.9 Hz, Ar–C₈), 134.4 (Ar–C₇), 130.5 (2 × Ar–CH), 130.2* (m, Ar–CH), 130.1 (Ar–CH), 127.8 (2 × Ar–CH), 126.6 (q, ³Jₙ₈ = 3.6 Hz, Ar–CH), 21.7 (CH₃). ¹⁹F (¹H) NMR (377 MHz, CDCl₃) δ –63.42. HRMS (FTMS+pAPCI) m/z calcd. For C₁₅H₁₄F₃O₃S [M+H]: 329.0454; found: 329.0453. *peak is partially obscured by adjacent singlet at δ 130.1 ppm. It was not possible to observe the quaternary CF₃ due to C–F coupling.

4-Methoxy-2-(4-methylbenzenesulfonyl)benzaldehyde (10a mono) and 4-methoxy-2,6-di(4-methylbenzenesulfonyl)benzaldehyde (10a di)

Synthesised according to general procedure B using 4-methoxybenzaldehyde (61 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane to 20% EtOAc:pentane) afforded sulfonyl aldehyde 10a mono as a white solid (24.2 mg, 42%) followed by sulfonyl aldehyde 10a di as a white solid (20.2 mg, 45%).

10a mono: m.p. = 158–160 °C. Rf 0.14 (20% Et₂O:pentane). IR (film)/cm⁻¹: 3086, 2810, 2844, 1685 (C=O), 1592, 1491, 1310, 1238, 1200, 1152, 1028, 880, 708. ¹H NMR (400 MHz, CDCl₃) δ 10.71 (d, J = 0.8 Hz, 1H, CHO), 8.04 (d, J = 8.7 Hz, 1H, Ar–CH), 7.78 (d, J = 8.4 Hz, 2H, 2
× Ar–CH), 7.70 (d, J = 2.6 Hz, 1H, Ar–CH), 7.33 (dd, J = 8.7, 0.8 Hz, 2H, 2 × Ar–CH), 7.16 (ddd, J = 8.7, 2.6, 0.8 Hz, 1H, Ar–CH), 3.97 (s, 3H, OCH₃), 2.42 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 188.2 (CHO), 163.6 (Ar–C), 144.9 (Ar–Cₙ), 144.7 (Ar–Cₙ), 138.5 (Ar–Cₙ), 131.8 (Ar–CH), 130.2 (2 × Ar–CH), 127.4 (2 × Ar–CH), 126.5 (Ar–Cₙ), 118.5 (Ar–CH), 114.8 (Ar–CH), 56.2 (OCH₃), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₅O₅S [M+H]: 291.0691; found: 291.0698.

10a di: m.p. = 218–219 °C. Rᵣ 0.03 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3071, 2922, 2885, 1710 (C=O), 1595, 1323, 1163, 1115, 1081, 813, 779, 667. ¹H NMR (400 MHz, CDCl₃) δ 10.76 (s, 1H, CHO), 7.73 (d, J = 8.4 Hz, 4H, 4 × Ar–CH), 7.68 (s, 2H, 2 × Ar–CH), 7.32 (d, J = 8.1 Hz, 4H, 4 × Ar–CH), 3.93 (s, 3H, OCH₃), 2.41 (s, 6H, 2 × CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.3 (CHO), 160.6 (Ar–Cₙ), 145.3 (2 × Ar–Cₙ), 143.2 (2 × Ar–Cₙ), 137.3 (2 × Ar–Cₙ), 130.1 (4 × Ar–CH), 128.3 (2 × Ar–CH), 119.2 (2 × Ar–CH), 56.5 (OCH₃), 21.6 (2 × CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₂₃H₂₁NO₅S₂ [M+Na+MeCN]: 478.0759; found: 478.0777.

4-Methyl-2-(4-methylbenzenesulfonyl)benzaldehyde (11a mono) and 4-methyl-2,6-di(4-methylbenzenesulfonyl)benzaldehyde (11a di)

Synthesised according to general procedure B using 4-methylbenzaldehyde (59 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane then 20% EtOAc:pentane) afforded sulfonyl aldehyde 11a mono as a white solid (17.9 mg, 33%) followed by sulfonyl aldehyde 11a di as a white solid (11.4 mg, 27%)

11a mono: m.p. = 138–140 °C. Rᵣ 0.19 (20% Et₂O:pentane). IR (film)/cm⁻¹ 2951, 2919, 1691 (C=O), 1595, 1449, 1400, 1316, 1197, 1151, 1090, 1054, 882, 814, 707, 655, 578, 512. ¹H NMR (400 MHz, CDCl₃) δ 10.80 (d, J = 0.8 Hz, 1H, CHO), 8.02 (d, J = 0.8 Hz, 1H, Ar–CH), 7.94 (d, J = 7.8 Hz, 1H, Ar–CH), 7.79–7.76 (m, 2H, 2 × Ar–CH), 7.51 (ddd, J = 7.8, 0.8, 0.8 Hz, 1H, Ar–CH), 7.35–7.31 (m, 2H, 2 × Ar–CH), 2.53 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 189.2 (CHO), 145.3 (Ar–Cₙ), 144.8 (Ar–Cₙ), 142.5 (Ar–Cₙ), 138.7 (Ar–Cₙ), 134.3 (Ar–Cₙ), 131.4 (Ar–Cₙ), 130.2 (2 × Ar–CH), 129.9 (Ar–CH), 129.6 (Ar–CH), 127.4 (2 × Ar–CH), 21.8 (CH₃), 21.6 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₁₆H₁₅O₃S [M+H]: 275.0736; found: 275.0735.

11a di: m.p. = 233–234 °C. Rᵣ 0.04 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3059, 3087, 2952, 2920, 1706 (C=O), 1594, 1446, 1377, 1321, 1187, 1150, 1082, 912, 810, 664, 601, 579, 499. ¹H NMR (400 MHz, CDCl₃) δ 10.85 (s, 1H, CHO), 7.97 (s, 2H, 2 × Ar–CH), 7.74 (d, J = 8.2 Hz, 4H, 4 × Ar–CH), 7.32 (d, J = 8.2 Hz, 4H, 4 × Ar–CH), 2.48 (s, 3H, CH₃), 2.40 (s, 6H, 2 × CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.9 (CHO), 145.2 (2 × Ar–Cₙ), 142.1 (2 × Ar–Cₙ), 137.4 (2 × Ar–Cₙ), 138.0 (Ar–Cₙ), 134.4 (2 × Ar–CH), 130.1 (4 × Ar–CH + Ar–Cₙ), 128.3 (4 × Ar–CH), 21.6 (2 × CH₃), 21.3 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₂₃H₂₁O₅S₂ [M+H]: 429.0825; found: 429.0821.
4-(Trifluoromethyl)-2-(4-methylbenzenesulfonyl)benzaldehyde (12a mono) and 4-(trifluoromethyl)-2,6-di(4-methylbenzenesulfonyl)benzaldehyde (12a di)

Synthesised according to general procedure B using 4-(trifluoromethyl)benzaldehyde (68 µL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:pentane) afforded sulfonyl aldehyde 12a mono as a white solid (20.3 mg, 31%) followed by sulfonyl aldehyde 12a di as a white solid (2.8 mg, 6%) [note: a longer column (approx. 10 cm height, 2.5 cm width) was required].

12a mono: m.p. = 139–141 °C. Rf 0.44 (20% EtOAc:pentane). IR (film)/cm⁻¹ 2923, 1698 (C=O), 1594, 1384, 1322, 1180, 1155, 1134, 1079, 853, 814, 779, 721, 578, 545, 506. \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 10.89 (d, \(J = 0.9\) Hz, 1H, CHO), 8.43 (d, \(J = 0.9\) Hz, 1H, Ar–CH), 8.12 (d, \(J = 8.0\) Hz, 1H, Ar–CH), 7.97 (d, \(J = 8.0\) Hz, 1H, Ar–CH), 7.80 (d, \(J = 8.4\) Hz, 2H, 2 × Ar–CH), 7.38 (d, \(J = 8.4\) Hz, 2H, 2 × Ar–CH), 2.44 (s, 3H, CH₃). \(^1^3\)C NMR (101 MHz, CDCl₃) \(\delta\) 188.3 (CHO), 145.7 (Ar–C₉), 143.9 (Ar–C₉), 137.6 (Ar–C₀), 136.3 (Ar–C₀), 135.3 (q, \(\delta J_{C-F} = 34.1\) Hz, Ar–C₀), 130.5 (2 × Ar–CH), 130.4 (q, \(\delta J_{C-F} = 3.3\) Hz, Ar–CH), 130.3 (Ar–CH), 127.7 (2 × Ar–CH), 126.5 (q, \(\delta J_{C-F} = 3.3\) Hz, Ar–CH), 122.6 (q, \(\delta J_{C-F} = 273.5\) Hz, C₉F₃), 21.7 (CH₃). \(^1^9\)F\(^{[1]}\)H NMR (377 MHz, CDCl₃) \(\delta\) –63.16. HRMS (FTMS+pAPCI) m/z calcd. For C₁₃H₁₂F₃O₃S [M+H]: 329.0454; found: 329.0461.

12a di: m.p. = 210–212 °C. Rf 0.26 (20% EtOAc:pentane). IR (film)/cm⁻¹ 2923, 1699, 1707 (C=O), 1593, 1446, 1398, 1318, 1179, 1156, 1083, 910, 811, 729, 661, 574, 534. \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 10.85 (s, 1H, CHO), 8.40 (s, 2H, 2 × Ar–CH), 7.74 (d, \(J = 8.4\) Hz, 4H, 4 × Ar–CH), 7.35 (d, \(J = 8.4\) Hz, 4H, 4 × Ar–CH), 2.42 (s, 6H, 2 × CH₃). \(^1^3\)C NMR (377 MHz, CDCl₃) \(\delta\) –62.90. HRMS (FTMS+pAPCI) m/z calcd. For C₂₂H₁₆F₆O₅S₂ [M+H]: 483.0542; found: 483.0563. Due to small quantity of material, it was not possible to obtain a clear \(^1^3\)C NMR.

2-(4-Methylbenzenesulfonyl)benzaldehyde (13a mono) and 2,6-di(4-methylbenzenesulfonyl)benzaldehyde (13a di)

Synthesised according to general procedure B using benzaldehyde (51 µL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonyl aldehyde 13a mono as a white solid (21.3 mg, 41%) followed by sulfonyl aldehyde 13a di as a white solid (13.0 mg, 32%).

13a mono: m.p. = 75–76 °C [lit. m.p. = 72–73 °C]. Rf 0.18 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3090, 2922, 1696, 1595, 1320, 1193, 1156, 1088, 816, 768, 731. \(^1\)H NMR (400 MHz, CDCl₃)
δ 10.87 (d, J = 0.8 Hz, 1H, CHO), 8.18 (dd, J = 7.7, 1.5 Hz, 1H, Ar–CH), 8.02 (dd, J = 7.1, 2.0 Hz, 1H, Ar–CH), 7.80–7.70 (m, 4H, 4 × Ar–CH), 7.34 (d, J = 8.1 Hz, 2H, 2 × Ar–CH), 2.42 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 189.5 (CHO), 145.0 (Ar–C₆), 142.7 (Ar–C₆), 138.5 (Ar–C₆), 133.8 (Ar–C₆), 133.7 (2 × Ar–CH), 130.2 (2 × Ar–CH), 129.41 (Ar–CH), 129.37 (Ar–CH), 127.5 (2 × Ar–CH), 21.6 (CH₃). Analytical data (¹H, ¹³C, IR, m.p.) is in agreement with the reported literature. ¹³

13a di: m.p. = 184–186 °C. Rᵣ 0.04 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3071, 2960, 2922, 2885, 1710 (C=O), 1595, 1323, 1163, 1115, 1081, 779, 749, 105, 667. ¹H NMR (400 MHz, CDCl₃) δ 10.89 (s, 1H, CHO). 8.19 (d, J = 7.9 Hz, 2H, 2 × Ar–CH), 7.75–7.68 (m, 5H, 5 × Ar–CH), 7.32 (d, J = 7.7 Hz, 4H, 4 × Ar–CH), 2.40 (s, 6H, 2 × CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.7 (C=O), 145.3 (2 × Ar–C₆), 142.4 (2 × Ar–C₆), 138.6 (Ar–C₆), 137.3 (2 × Ar–C₆), 134.1 (2 × Ar–CH), 130.9 (Ar–CH), 130.1 (4 × Ar–CH), 128.4 (Ar–CH), 21.7 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₂H₁₀NO₃NaS⁺ [M+Na+MeCN]: 478.0759; found: 478.0777.

2,3-Dimethyl-6-(4-methylbenzenesulfonyl)benzaldehyde (14a)

Synthesised according to general procedure B using 2,3-dimethylbenzaldehyde (65.2 µL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonyl aldehyde 14a as a yellow solid (23.1 mg, 40%). m.p. = 126–127 °C. Rᵣ 0.10 (20% Et₂O:pentane). IR (film)/cm⁻¹ 3056, 2948, 2973, 2919, 1700 (C=O), 1593, 1573, 1449, 1391, 1311, 1289, 1203, 1156, 1134, 1081, 1017, 876, 814, 703, 686, 651, 596, 508, 477. ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H, CHO), 7.84 (d, J = 8.1 Hz, 1H, Ar–CH), 7.73 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 7.40 (d, J = 8.1 Hz, 1H, Ar–CH), 7.31–7.28 (m, 2H, 2 × Ar–CH), 2.39 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 2.26 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 195.3 (CHO), 144.6 (Ar–C₆), 144.5 (Ar–C₆), 138.8 (Ar–C₆), 138.7 (Ar–C₆), 136.7 (Ar–C₆), 136.3 (Ar–C₆), 132.1 (Ar–CH), 129.9 (2 × Ar–CH), 127.6 (2 × Ar–CH), 126.8 (Ar–CH), 21.6 (CH₃), 20.7 (CH₃), 16.2 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₆H₁₇O₂S [M+H⁺]: 289.0898; found: 289.0891.

2,4-Dimethyl-6-(4-methylbenzenesulfonyl)benzaldehyde (15a)

Synthesised according to general procedure B using 2,4-dimethylbenzaldehyde (65.2 µL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonyl aldehyde 15a as a yellow solid (35.7 mg, 62%). m.p. = 152–156 °C. Rᵣ 0.25 (20% Et₂O:pentane). IR (film)/cm⁻¹ 2960, 2922, 2857, 1698 (C=O), 1597, 1493, 1427, 1316, 1191, 1150, 1083, 1038, 1038, 855, 814, 792, 706, 664. ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H, CHO), 7.86 (s, 1H, Ar–CH), 7.75 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 7.33–7.29 (m, 3H, 3 × Ar–CH), 2.45 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 2.41 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.8 (CHO), 144.6 (Ar–C₆), 142.5 (Ar–C₆), 142.4 (Ar–C₆), 140.4 (Ar–C₆), 138.8 (Ar–C₆), 137.6 (Ar–CH), 131.4 (Ar–C₆), 130.0 (2 × Ar–CH), 127.8 (Ar–CH), 127.5 (2 × Ar–CH), 21.6 (CH₃), 21.5 (CH₃), 20.9 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₁₆H₁₇O₂S [M+H]: 289.0893; found: 289.0894.

4-(Benzyloxy)-3-methylbenzaldehyde (S2)

Synthesised using a modified procedure by Sparks et al.⁸ Benzyl bromide (262 µL, 2.2 mmol) was added to a stirring solution of 4-hydroxy-3-methylbenzaldehyde (272.3 mg, 2 mmol) and potassium carbonate (552 mg, 4 mmol) in DMF (2.7 mL), then the reaction was heated to 55 °C for 3
The reaction was diluted with H₂O (10 mL) and the product extracted with EtOAc (3 × 10 mL), the combined organic extracts were washed with 1 M NaOH (aq.) (30 mL) then the combined organic extracts were dried over Na₂SO₄, filtered then concentrated in vacuo. Azetropic removal of DMF with heptane (3 × 5 mL) afforded sulfonfyl aldehyde S2 as a white solid (406.2 mg, 90%). m.p. = 49–50 °C [lit. 51–53 °C]. IR (film/cm⁻¹) 3063, 3030, 2940, 2900, 2804, 2717, 1675 (C=O), 1593, 1495, 1418, 1384, 1326, 1260, 1229, 1160, 1117, 987, 903, 811, 732, 552, 503, 450, 425. ¹H NMR (400 MHz, CDCl₃) δ 9.87 (s, 1H, CHO), 7.73–7.69 (m, 2H, 2 × Ar–CH), 7.47–7.36 (m, 5H, 5 × Ar–CH), 7.00 (d, J = 8.3 Hz, 1H, Ar–CH), 5.19 (s, 2H, CH₂), 2.34 (s, 3H, CH₃) ¹³C NMR (101 MHz, CDCl₃) δ 191.1 (CHO), 161.9 (Ar–C₆), 136.3 (Ar–C₆), 131.6 (Ar–CH), 130.5 (Ar–CH), 129.6 (Ar–C₆), 128.6 (2 × Ar–CH), 128.1 (Ar–CH), 128.0 (Ar–C₆), 127.1 (2 × Ar–CH), 110.9 (Ar–CH), 70.0 (CH₂), 16.4 (CH₃). Analytical data (¹H, ¹³C, m.p.) are in agreement with the reported literature.

4-(Benzyloxy)-5-methyl-2-(4-methylbenzenesulfonfyl)benzaldehyde (16a)

Synthesised according to general procedure B using 4-(benzyloxy)-3-methylbenzaldehyde (113 mg, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonfyl aldehyde 16a as a yellow solid (48.5 mg, 64%). m.p. = 139–141 °C. Rᵣ 0.20 (20% Et₂O:pentane). IR (film/cm⁻¹) 3058, 3028, 2947, 2917, 1680 (C=O), 1585, 1487, 1452, 1405, 1383, 1310, 1264, 1161, 1137, 1017, 907, 813, 732, 677, 636, 559, 530, 474. ¹H NMR (400 MHz, CDCl₃) δ 10.70 (s, 1H, CHO), 7.87 (s, 1H, Ar–CH), 7.70 (s, 1H, Ar–CH), 7.64 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.27 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 5.31 (s, 2H, CH₂), 2.40 (s, 3H, CH₃), 2.34 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 188.6 (CHO), 160.5 (Ar–C₆), 144.6 (Ar–C₆), 142.0 (Ar–C₆), 139.0 (Ar–C₆), 135.5 (Ar–C₆), 133.4 (Ar–C₆), 131.8 (Ar–CH), 130.1 (2 × Ar–CH), 128.8 (2 × Ar–CH), 128.4 (Ar–CH), 127.3 (2 × Ar–CH), 127.2 (2 × Ar–CH), 126.2 (Ar–C₆), 111.8 (Ar–CH), 70.7 (CH₂), 21.6 (CH₃), 16.4 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₂₃H₂₁O₂S [M+H⁺]: 381.1161; found: 381.1154.

4-(Allyloxy)-3-methylbenzaldehyde (S3)

Synthesised according to a modified procedure from Sarkar et. al. Allyl bromide (208 µL, 2.4 mmol) was added to a stirring solution of 4-hydroxy-3-methylbenzaldehyde (272 mg, 2 mmol) and potassium carbonate (386 mg, 2.8 mmol) in acetone (4 mL) at rt. The reaction mixture was heated to reflux for 4 h. The reaction mixture was diluted with water (5 mL) and the product extracted from the aqueous layer with EtOAc (3 × 10 mL). The combine organic extracts were washed with 1 M NaOH (aq.) (30 mL), dried over Na₂SO₄, filtered then concentrated in vacuo to afford aldehyde S3 as a yellow oil (310 mg, 88%). IR (film)/cm⁻¹ 2919, 2718, 1679 (C=O), 1596, 1495, 1450, 1421, 1378, 1318, 1252, 1230, 1163, 1117, 991, 924, 808, 774, 654, 557, 500, 480, 443. ¹H NMR (400 MHz, CDCl₃) δ 9.86 (s, 1H, CHO), 7.71–7.68 (m, 2H, 2 × Ar–CH), 6.93–6.90 (m, 1H, Ar–CH), 6.08 (ddt, J = 17.3, 10.5, 5.0 Hz, 1H, CH₂CH), 5.46 (dd, J = 17.3, 1.7 Hz, 1H, CH₂CH=CHH), 5.33 (dd, J = 10.5, 1.7 Hz, 1H, CH₂CH=CHH), 4.66–4.64 (m, 2H, CH₂), 2.30 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 191.1 (CHO), 161.8 (Ar–C₆), 132.5 (Ar–CH), 131.6 (Ar–CH), 130.5 (Ar–CH), 129.5 (Ar–C₆), 127.8 (Ar–C₆), 117.7 (CH₂CH=CHH), 110.7 (CH₂CH=CHH), 68.8 (CH₂), 16.3 (CH₃). Analytical data (¹H, ¹³C) is in agreement with the reported literature.
4-(Allyloxy)-5-methyl-2-(4-methylbenzenesulfonyl)benzaldehyde (17a)

Potassium carbonate (55 mg, 0.4 mmol) and copper(II) fluoride (40 mg, 0.4 mmol) were added sequentially to a microwave vial which was then flame dried under argon until a blue colour just appears (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (18 mg, 0.1 mmol), β-alanine (4.5 mg, 0.05 mmol), 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol) and a solution of aldehyde S3 in HFIP (88 mg, 0.5 mmol in 1 mL HFIP) were added sequentially under argon. The vial was sealed and submerged in an oil bath preheated to 100 °C for 18 h [Stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and washed with a saturated aqueous solution of ammonium chloride (10 mL). The product was extracted from the aqueous phase with EtOAc (2 × 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:pentane) afforded sulfonyl aldehyde 17a as a white solid (26.5 mg, 40%) [note: a longer column was required (approx. 10 cm height, 2.5 cm width)].

m.p. = 119–121°C. Rf: 0.22 (10% EtOAc:pentane). IR (film)/cm⁻¹: 3068, 2980, 2919, 1681 (C=O), 1588, 1487, 1453, 1408, 1312, 1267, 1164, 1140, 1086, 1021, 931, 814, 748, 681, 586, 557, 531. ¹H NMR (400 MHz, CDCl₃): δ 10.69 (s, 1H, CHO), 7.86 (s, 1H, Ar–CH), 7.74 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.63 (s, 1H, Ar–CH), 7.31 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 6.08 (ddd, J = 17.3, 10.6, 5.2 Hz, 1H, CH₂CH=CHH), 5.49 (dd, J = 17.3, 1.5 Hz, 1H, CH₂CH=CHH), 5.39 (dd, J = 10.6, 1.5 Hz, 1H, CH₂CH=CHH), 4.76 (m, 2H), 2.41 (s, 3H), 2.31 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 188.6 (CHO), 160.5 (Ar–C), 144.7 (Ar–C), 142.0 (Ar–C), 139.1 (Ar–C), 133.2 (Ar–C), 131.82 (Ar–C), 131.77 (Ar–C), 130.2 (2 × Ar–CH), 127.2 (2 × Ar–CH), 126.1 (Ar–C), 118.5 (CH₂CH=CHH), 111.4 (CH₂CH=CHH), 69.5 (CH₂), 21.6 (CH₃), 16.3 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₉O₂S [M+H⁺]: 331.1004; found: 331.1004.

3-(4-Methylbenzenesulfonyl)-[1,1'-biphenyl]-2-carboxaldehyde (18a)

Synthesised according to general procedure B using biphenyl-2-carboxaldehyde (80.6 µL, 0.5 mmol) and 4-methylbenzenesulfinic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:pentane) afforded sulfonyl aldehyde 18a as a colourless oil (58.4 mg, 87%). Rf: 0.19 (20% EtOAc:pentane). IR (film)/cm⁻¹: 3055, 3026, 2947, 2918, 2850, 2730, 1706 (C=O), 1592, 1492, 1445, 1381, 1315, 1202, 1182, 1167, 1158, 1084, 1019, 910, 811, 760, 732, 702, 680, 654, 578, 547. ¹H NMR (400 MHz, CDCl₃): δ 10.42 (s, 1H, CHO), 8.19 (dd, J = 7.9, 1.3 Hz, 1H, Ar–CH), 7.84 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 7.68 (dd, J = 7.8, 7.8 Hz, 1H, Ar–CH), 7.60 (dd, J = 7.7, 1.3 Hz, 1H, Ar–CH), 7.42–7.39 (m, 3H, 3 × Ar–CH), 7.35 (d, J = 8.6 Hz, 2H, 2 × Ar–CH), 7.25–7.23 (m, 2H, 2 × Ar–CH), 2.43 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃): δ 194.0 (CHO), 144.5 (Ar–C), 143.2 (Ar–C), 140.9 (Ar–C), 138.6 (Ar–C), 137.5 (Ar–C), 136.4 (Ar–C), 135.6 (Ar–C), 130.7 (Ar–C), 129.8 (2 × Ar–CH), 129.6 (2 × Ar–CH), 128.9 (Ar–CH), 128.6 (2 × Ar–CH), 128.4 (Ar–CH), 128.1 (2 × Ar–CH), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₂₀H₁₇O₃S [M+H⁺]: 337.0898; found: 337.0897.

3-(4-Methylbenzenesulfonyl)-2-naphthaldehyde (19a)

Synthesised according to general procedure B using 2-naphthaldehyde (78.1 mg, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:pentane) afforded sulfonyl aldehyde 19a as a white solid (59.8 mg, 96%). m.p. = 159–160 °C. Rf: 0.13 (20% EtOAc:pentane). IR (film)/cm⁻¹: 3054, 2946, 2916, 2950, 1689 (C=O), 1617, 1593, 1491, 1442, 1379, 1307, 1149, 1126,
6-Methoxy-3-(4-methylbenzenesulfonyl)-2-naphthaldehyde (20a)

Synthesised according to general procedure B using 6-methoxy-2-naphthaldehyde (93.0 mg, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol) [note: reaction time = 22 h.]. Purification by flash column chromatography (20% EtOAc:hexane) afforded sulfonyl aldehyde 20a as an off white solid (48.6 mg, 39%). m.p. = 91–92 °C. Rf: 0.23 (20% EtOAc:pentane). IR (film)/cm⁻¹ 3082, 2948, 2917, 2323, 1780, 1692, 1647, 1595, 1322. HRMS (TOF-ESI⁺) m/z calcd. For C₁₉H₁₇O₃S [M+H⁺]: 341.0848; found: 341.0848.

5-Chloro-2-(4-methylbenzenesulfonyl)benzaldehyde (21a)

Synthesised according to general procedure B using 3-chlorobenzaldehyde (57 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonyl aldehyde 21a as a colourless oil (23.2 mg, 40%). Rf: 0.23 (20% EtOAc:pentane). IR (film)/cm⁻¹ 3086, 2956, 2922, 1696 (C=O), 1595, 1322, 1185, 1156, 1129, 1084, 898, 746, 708. ¹H NMR (400 MHz, CDCl₃) δ 10.81 (s, 1H, CHO), 8.13 (d, J = 8.4 Hz, 1H, Ar–CHO), 8.13 (d, J = 8.4 Hz, 1H, Ar–CHO), 7.79 (s, 1H, Ar–CHO). ³¹C NMR (101 MHz, CDCl₃) δ 188.2 (CHO), 145.1 (Ar–C(q)), 130.5 (Ar=C(q)), 130.4 (Ar=CH), 130.4 (Ar=CH), 129.4 (Ar–C(q)), 127.5 (2 × Ar–CH), 127.5 (2 × Ar–CH), 127.5 (2 × Ar–CH), 127.5 (2 × Ar–CH), 21.6 (CH₃). HRMS (TOF-ESI⁺) m/z calcd. For C₁₉H₁₇O₃S³Cl [M+H⁺]: 295.0189; found: 295.0187.

5-Bromo-2-(4-methylbenzenesulfonyl)benzaldehyde (22a)

Synthesised according to general procedure B using 3-bromobenzaldehyde (58.0 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et₂O:pentane) afforded sulfonyl aldehyde 22a as a white solid (26.7 mg, 39%). m.p. = 91–92 °C. Rf: 0.30 (20% EtOAc:pentane). IR (film)/cm⁻¹ 3082, 2948, 2917, 1692 (C=O), 1593, 1570, 1552, 1454, 1398, 1320, 1288, 1182, 1155, 1080, 875, 813, 738, 656, 588, 553, 404. ¹H NMR (400 MHz, CDCl₃) δ 10.81 (s, 1H, CHO), 8.12 (d, J = 2.2 Hz, 1H, Ar–CHO), 8.04 (d, J = 8.4 Hz, 1H, Ar–CHO), 7.88 (dd, J = 8.4, 2.2 Hz, 1H, Ar–CHO), 7.77 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 7.35 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 2.43 (s, 3H, CH₃). ³¹C NMR (101 MHz, CDCl₃) δ 188.1 (CHO), 145.3 (Ar–C(q)), 141.6 (Ar–C(q)), 138.1 (Ar=C(q)), 130.4 (Ar=CH), 129.4 (Ar–C(q)), 127.5 (2 × Ar–CH), 127.5 (2 × Ar–CH), 21.6 (CH₃). HRMS (TOF-ESI⁺) m/z calcd. For C₁₉H₁₇O₃S³Cl [M+H⁺]: 295.0189; found: 295.0187.
127.5 (2 × Ar–CH), 21.6 (CH$_3$). HRMS (FTMS+pAPCI) m/z calcd. For C$_{14}$H$_{12}$O$_3$S$_{59}$Br [M+H]: 338.9865; found: 338.9692.

**Methyl 3-formyl-4-(4-methylbenzenesulfonyl)benzoate (23a)**

Synthesised according to general procedure B using Methyl 3-formylbenzoate (82.1 mg, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% Et$_2$O:pentane) afforded sulfonyl aldehyde 23a as a white solid (23.8 mg, 37%). m.p. = 124–126 °C. R$_t$ 0.13 (20% Et$_2$O:pentane). IR (film)/cm$^{-1}$ 2919, 2950, 1729 (C=O aldehyde), 1693 (C=O ester), 1594, 1436, 1322, 1291, 1243, 1196, 1177, 1155, 1129, 1086, 814, 737, 660, 590, 552, 530. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.88 (s, 1H, CHO), 8.62 (d, J = 1.8 Hz, 1H, Ar–CH), 8.37 (dd, J = 8.2, 1.8 Hz, 1H, Ar–CH), 8.23 (d, J = 8.2 Hz, 1H, Ar–CH), 7.79 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 7.36 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 3.97 (s, 3H, OCH$_3$), 2.43 (s, 3H, CH$_3$). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 188.6 (CHO), 164.7 (Ar–C$_{a}$), 146.1 (Ar–C$_{a}$), 145.5 (Ar–C$_{b}$), 137.7 (Ar–C$_{b}$), 135.0 (Ar–C$_{b}$), 134.2 (Ar–CH), 134.1 (Ar–C$_{a}$), 130.5 (Ar–CH), 130.4 Ar–C$_{a}$ (2 × Ar–CH), 129.6 (Ar–CH), 127.7 (2 × Ar–CH), 52.9 (OCH$_3$), 21.7 (CH$_3$). HRMS (TOF–ESI$^+$) m/z calcd. For C$_{18}$H$_{15}$O$_5$S [M+H]: 319.0640; found: 319.0637.

**N-(3′-Formyl-[1,1′-biphenyl]-4-yl)acetamide (S4)**

3-Formylphenylboronic acid (300 mg, 2 mmol), N-(4-iodophenyl)acetamide (553 mg, 2.12 mmol) and palladium acetate (22.4 mg, 0.1 mmol), Isopropanol (1.3 mL), water (1.3 mL), and potassium carbonate (552 mg, 4 mmol) were added sequentially to a round bottom flask and stirred at rt for 18 h. The reaction was concentrated in vacuo and purification by flash column chromatography (30% acetone:pentane) afforded alkyldyde S4 as a white solid (188.7 mg, 39%). m.p. = 164–165 °C. R$_t$ 0.25 (30% acetone:pentane). IR (film)/cm$^{-1}$ 3298 (N=H), 3186, 3112, 2360, 1694 (C=O aldehyde), 1670 (C=O amide), 1531, 1371, 1320, 1183, 794, 689. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.09 (s, 1H, CHO), 8.08 (dd, J = 1.9,1.9 Hz, 1H, Ar–CH), 7.84 (dd, J = 7.9, 1.9 Hz, 2H, 2 × Ar–CH), 7.68–7.52 (m, 5H, 5 × Ar–CH), 7.45 (s, 1H, N–H), 2.23 (s, 3H, CH$_3$). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 192.4 (CHO), 168.4 (C=O amide), 141.4 (Ar–C$_{a}$), 137.8 (Ar–C$_{b}$), 136.9 (Ar–C$_{b}$), 135.5 (Ar–C$_{b}$), 132.7 (Ar–CH), 129.5 (Ar–CH), 127.8 (Ar–CH), 127.7 (Ar–CH), 127.65 (2 × Ar–CH), 120.2 (2 × Ar–CH), 24.7 (CH$_3$). HRMS (TOF–ESI$^+$) m/z calcd. For C$_{20}$H$_{18}$O$_2$N$_2$ [M+H]: 440.1025; found: 440.1029.

**N-(3′-Formyl-4′-(4-methylbenzenesulfonyl)-[1,1′-biphenyl]-4-yl)acetamide (24a)**

Synthesised according to general procedure B using N-(3′-Formyl-[1,1′-biphenyl]-4-yl)acetamide S4 (119.6 mg, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (40% acetone:pentane) afforded sulfonyl aldehyde 24a as an off white solid (37.8 mg, 48%). R$_t$ 0.23 (40% acetone:pentane). IR (film)/cm$^{-1}$ 3369 (N=H), 3278, 3056, 2362, 2336, 1693 (C=O), 1594, 1525, 1372, 1320, 1300, 1156, 826, 752, 670, 659, 559, 539, 404. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.89 (s, 1H, CHO), 8.21 (d, J = 8.2 Hz, 1H, Ar–CH), 8.18 (d, J = 2.1 Hz, 1H, Ar–CH), 7.91 (dd, J = 8.2, 2.1 Hz, 1H, Ar–CH), 7.83–7.77 (m, 2H, 2 × Ar–CH), 7.67–7.61 (m, 2H, 2 × Ar–CH), 7.60–7.49 (m, 3H, 2 × Ar–CH + N–H), 7.35 (dd, J = 8.6, 0.7 Hz, 2H, 2 × Ar–CH), 2.42 (s, 3H, COCH$_3$), 2.22 (s, 3H, ArCH$_3$). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 189.6 (CHO), 168.5 (C=O amide), 145.8 (Ar–C$_{a}$), 144.9 (Ar–C$_{a}$), 140.6 (Ar–C$_{a}$), 139.0 (Ar–C$_{b}$), 138.6 (Ar–C$_{b}$), 134.2 (Ar–C$_{b}$), 133.4 (Ar–C$_{b}$), 131.2 (Ar–CH), 130.3 (2 × Ar–CH), 130.2 (Ar–CH), 127.9 (2 × Ar–CH), 127.5 (2 × Ar–CH),
127.3 (Ar–CH), 120.2 (2 × Ar–CH), 24.7 (COCH₃), 21.6 (ArCH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₂₃H₂₃N₂O₅S [M+H+MeCN]: 435.1397; found: 435.1397.

4'-{(Hydroxymethyl)-[1,1'-biphenyl]}-3-carbaldehyde (S5)

3-Formylphenylboronic acid (300 mg, 2 mmol), 4-iodobenzyl alcohol (496 mg, 2.12 mmol) and palladium acetate (22.4 mg, 0.1 mmol), Isopropanol (1.3 mL), water (1.3 mL), and potassium carbonate (552 mg, 4 mmol) were added sequentially to a round bottom flask and stirred at rt for 18 h. The reaction was concentrated in vacuo and purification by flash column chromatography (20% acetone;pentane) afforded aldehyde S5 as a white solid (212.8 mg, 50%). m.p. = 58–59 °C. Rf 0.17 (20% acetone;pentane). IR (film)/cm⁻¹ 3369 (O–H), 2825, 2742, 1692 (C=O), 1595, 1443, 1385, 1180, 1161, 993, 898, 788, 689, 648, 570, 500, 431. ¹H NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H, CHO), 8.11 (d, J = 1.8 Hz, 1H, Ar–CH), 7.88 (dd, J = 7.6, 1.8 Hz, 2H, 2 × Ar–CH), 7.74–7.58 (m, 3H, 3 × Ar–CH), 7.50 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 4.79 (d, J = 6.0 Hz, 2H, CH₂OH), 1.76 (t, J = 6.0 Hz, 1H, OH). ¹³C NMR (101 MHz, CDCl₃) δ 192.3 (CHO), 141.8 (Ar–C₆), 140.7 (Ar–C₆), 139.0 (Ar–C₆), 136.9 (Ar–C₆), 133.0 (Ar–CH), 129.5 (Ar–CH), 128.7 (Ar–CH), 128.0 (Ar–CH), 127.6 (2 × Ar–CH), 127.3 (2 × Ar–CH), 65.0 (CH₂). HRMS (EI⁺) m/z calcd. For C₁₄H₁₂O₂ [M]: 212.0832; found: 212.0839.

4'-{(Hydroxymethyl)-4-(4-methylbenzenesulfonyl)-[1,1'-biphenyl]}-3-carbaldehyde (25a)

Synthesised according to general procedure B using 4'-{(hydroxymethyl)-[1,1'-biphenyl]}-3-carbaldehyde S5 (106.1 mg, 0.5 mmol) and 4-methylbenzenesulfinic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (30% acetone;pentane) afforded sulfonyl aldehyde 25a as a white solid (37.5 mg, 51%). Rf 0.25 (30% acetone;pentane). IR (film)/cm⁻¹ 3521 (OH), 2919, 1692 (C=O), 1592, 1401, 1316, 1299, 1180, 1156, 1136, 1091, 747, 665, 582, 541. ¹H NMR (400 MHz, CDCl₃) δ 10.91 (s, 1H, CHO), 8.31–8.15 (m, 2H, 2 × Ar–CH), 7.95 (dd, J = 8.2, 2.1 Hz, 1H, Ar–CH), 7.85–7.78 (m, 2H, 2 × Ar–CH), 7.62 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 7.49 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 7.35 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 4.78 (d, J = 5.7 Hz, 2H, CH₂), 2.43 (s, 3H, CH₃), 1.84 (s, 1H, O–H). ¹³C NMR (101 MHz, CDCl₃) δ 189.6 (CHO), 146.3 (Ar–C₆), 145.0 (Ar–C₆), 142.0 (Ar–C₆), 141.0 (Ar–C₆), 138.7 (Ar–C₆), 137.2 (Ar–C₆), 134.3 (Ar–C₆), 131.6 (Ar–CH), 130.3 (Ar–CH), 130.3 (2 × Ar–CH), 127.73 (Ar–CH), 127.67 (2 × Ar–CH), 127.53 (2 × Ar–CH), 127.46 (2 × Ar–CH), 64.8 (CH₂), 21.7 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₄H₁₂O₂S [M]+: 367.1004; found: 367.1002.

N-(3-Formyl-2-(4-methylbenzenesulfonyl)phenyl)methanesulfonamide (26a)

Synthesised according to general procedure B using N-(3-formylphenyl)methanesulfonamide (99.6 mg, 0.5 mmol) and 4-methylbenzenesulfinic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (100% CH₂Cl₂) afforded sulfonyl aldehyde 26a as a yellow amorphous gum (21.2 mg, 30%). Rf 0.51 (100% CH₂Cl₂). IR (film)/cm⁻¹ 3253 (N–H), 2932, 1695 (C=O), 1580, 1457, 1374, 1331, 1306, 1269, 1149, 971, 857, 811, 727, 654, 554, 464. ¹H NMR (400 MHz, CDCl₃) δ 10.74 (s, 1H, CHO), 9.51 (s, 1H, NH), 7.93 (dd, J = 8.2, 1.3 Hz, 1H, Ar–CH), 7.80 (d, J = 8.6 Hz, 2H, 2 × Ar–CH), 7.68 (dd, J = 8.2, 8.2 Hz, 1H, Ar–CH), 7.50 (dd, J = 8.2, 1.3 Hz, 1H, Ar–CH). ³¹C NMR (101 MHz, CDCl₃) δ 190.3 (CHO), 146.0 (Ar–C₆), 138.6 (Ar–C₆), 137.8 (Ar–C₆), 137.5 (Ar–C₆), 135.2 (Ar–C₆), 130.5 (2 × Ar–CH), 127.2 (Ar–C₆), 126.8 (2 × Ar–CH), 124.6 (Ar–CH), 123.5 (Ar–CH),
Potassium carbonate (55 mg, 0.4 mmol) and copper(II) fluoride (40 mg, 0.4 mmol) were added sequentially to a microwave vial which was then flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (18 mg, 0.1 mmol), β-alanine (4.5 mg, 0.05 mmol), 4-methylbenzenesulfinic acid sodium salt (35.6 mg, 0.2 mmol), 4-pyridinecarboxaldehyde (58.0 μL, 0.5 mmol) and HFIP (1 mL) were added to a microwave vial sequentially under argon. The vial was sealed and submerged in an oil bath preheated to 100 °C for 18 h [Stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The product was extracted from the aqueous phase with EtOAc (2 × 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:hexane) afforded sulfonyl aldehyde 27a as a white solid (13.0 mg, 25%). m.p. = 125–127 °C. Rᵣ 0.37 (EtOAc). IR (film)/cm⁻¹ 3083, 2988, 2947, 2907, 1706 (C=O), 1591, 1542, 1473, 1369, 1323, 1284, 1161, 1142, 1094, 1019, 925, 814, 789, 575, 536. ¹H NMR (400 MHz, CHCl₃) δ 13.56 (s, 1H, CHO), 9.26 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 7.49 (m, 2H, 2 × Ar–CH), 2.39 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 188.7 (CHO), 155.3 (Ar–CH), 150.2 (Ar–CH), 145.8 (Ar–C₆H₅), 139.7 (Ar–C₆H₅), 137.5 (Ar–C₆H₅), 130.6 (2 × Ar–CH), 127.8 (2 × Ar–CH), 121.4 (Ar–CH), 21.7 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₁₅H₁₂NO₃S [M+H]⁺: 262.0532; found: 262.0539. [note significant broadening of pyridyl NMR signals was observed in CDCl₃, such broadening was not observed in DMSO-d₆.

Potassium carbonate (55 mg, 0.4 mmol) and copper(II) fluoride (40 mg, 0.4 mmol) were added sequentially to a microwave vial which was then flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (18 mg, 0.1 mmol), β-alanine (4.5 mg, 0.05 mmol), 4-methylbenzenesulfinic acid sodium salt (35.6 mg, 0.2 mmol), 2-methoxy-4-pyridinecarboxaldehyde (69 mg, 0.5 mmol) and HFIP (1 mL) were added to a microwave vial sequentially under argon. The vial was sealed, submerged in an oil bath preheated to 100 °C for 18 h [Stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The product was extracted from the aqueous phase with EtOAc (2 × 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (10–50% EtOAc:hexane) afforded sulfonyl aldehyde 28a as a white solid (13.0 mg, 23%). m.p. = 145–148 °C. Rᵣ 0.30 (20% EtOAc:hexane). IR (film)/cm⁻¹ 3062, 2988, 2947, 2907, 1706 (C=O), 1591, 1542, 1473, 1369, 1323, 1284, 1161, 1142, 1094, 1019, 925, 814, 789, 575, 536. ¹H NMR (400 MHz, CDCl₃) δ 10.71 (s, 1H, CHO), 8.95 (s, 1H, Ar–CH), 7.80–7.77 (m, 2H, 2 × Ar–CH), 7.35 (dd, J = 8.5, 0.6 Hz, 2H, 2 × Ar–CH), 7.14 (d, J = 0.6 Hz, 1H, Ar–CH), 4.04 (s, 3H, OCH₃), 2.43 (s,
Estrone Derived

**(8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3-carbaldehyde (S6)**

Estrone (541 mg, 2 mmol) was dissolved in CH₂Cl₂ (10 mL), cooled to 0 °C, then pyridine (324 μL, 4 mmol) and Tf₂O (405 μL, 2.4 mmol) were added sequentially under argon. The reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched by the addition of water (10 mL) and the triflated intermediate was extracted from the aqueous phase with CH₂Cl₂ (3 × 10 mL), dried over Na₂SO₄, filtered, then concentrated *in vacuo*. In a separate flame dried microwave vial, palladium acetate (22.4 mg, 0.1 mmol), dpff (83 mg, 0.15 mmol) and N-formylsaccharin (633 mg, 3 mmol) were added sequentially followed by MeCN (10 mL). The vial was purged then backfilled with argon three times then estrone triflate, triethylsilane (479 μL, 3 mmol) and sodium carbonate (318 mg, 3 mmol) were added sequentially. The vial sealed and submerged in an oil bath preheated to 80 °C for 16 h. The reaction was then removed from the oil bath, allowed to cool to rt then pierced with a needle to release any internal pressure. The reaction was diluted with water (10 mL) and the product was extracted with CH₂Cl₂ (3 × 10 mL), dried over Na₂SO₄, filtered, then concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded aldehyde S6 as a white solid (162 mg, 29%). [α]₁⁰₊₁ +130 (c 0.81, CHCl₃ 0.6% EtOH as stabiliser). m.p. 190–191 °C. Rf 0.24 (20% EtOAc:hexane). IR (film)/cm⁻¹ 2927, 2858, 2723, 1736 (C=O), 1693 (C=O), 1602, 1567, 1226, 1083, 1007, 822. 

**Potassium carbonate (55 mg, 0.4 mmol) and copper(II) fluoride (40 mg, 0.4 mmol) were added sequentially to a microwave vial which was then flame dried under argon until a blue colour just appears (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (18 mg, 0.1 mmol), β-alanine (4.5 mg, 0.05 mmol), 4-methylbenzenesulfonic acid sodium salt (44.5 mg, 0.25 mmol), aldehyde S6 (79.9 mg, 0.201 mmol) and HFIP (1 mL) were added to a microwave vial sequentially under argon. The vial was sealed and submerged in an oil bath preheated to 100 °C for 18 h [Stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous solution of ammonium chloride (10 mL). The product was extracted from the aqueous phase with EtOAc (2 × 10 mL) and the combined
organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (20–40% EtOAc:pentane) afforded sulfonyl aldehyde 29a as a white solid (31.2 mg, 36%) [α]D₀ +72 (c 1.19, CHCl₃ (0.6% EtOH as stabiliser)). m.p. = 140–141 °C. Rᵣ 0.29 (40% EtOAc:hexane). IR (film)/cm⁻¹ 2926, 2859, 2249, 1732 (C=O), 1686 (C=O), 1590, 1451, 1377, 1317, 1298, 1161, 1137, 1084, 1010, 910, 810, 727, 662, 614, 486. ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H, CHO), 8.13 (s, 1H, Ar–CH), 7.77–7.74 (m, 3H, 3 × Ar–CH), 7.32 (dd, J = 8.3, 0.8 Hz, 2H, 2 × Ar–CH), 3.07–2.91 (m, 2H, C=OCH₂), 2.58–2.47 (m, 2H, 2 × CH), 2.41 (s, 3H, ArCH₃), 2.21–2.16 (m, 1H, CH), 2.12–2.04 (m, 3H, 3 × CH), 1.68–1.51 (m, 6H, 6 × CH), 0.94 (s, 3H, C₃H₃CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 220.0 (C=O ketone), 189.6 (CHO), 146.6 (Ar–C₀), 144.6 (Ar–C₀), 143.4 (Ar–C₀), 139.7 (Ar–C₀), 139.1 (Ar–C₀), 131.1 (Ar–C₀), 130.2 (2 × Ar–CH), 130.1 (Ar–CH), 127.3 (2 × Ar–CH), 126.9 (Ar–CH), 50.3 (C₃H₃CH₃), 44.7 (CH₃), 37.4 (CH₃), 35.7 (CH₂), 31.3 (CH₂), 29.3 (CH₂), 25.7 (CH₂), 25.5 (CH₂), 21.6 (CH₂), 21.5 (ArCH₃), 13.8 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₂₉H₂₅O₅S [M+H]: 437.1792; found: 437.1787. ₉¹% purity, contains an inseparable impurity which we believe to be another regioisomer, where the position alpha to the carbonyl was sulfonylated, however due to the low intrinsic amount of the alpha functionalised regioisomer it was not possible to fully characterise this impurity. ¹²⁶¹signal overlapping with H₂O in CDCl₃

8-(4-Methylbenzenesulfonyl)phenanthrene-9-carbaldehyde (30a)

Synthesised according to general procedure B using phenanthrene-9-carbaldehyde (103 mg, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (20% EtOAc:pentane) afforded sulfonyl aldehyde 30a as a white solid (46.4 mg, 64%). m.p. = 162–164 °C. Rᵣ 0.04 (20% EtOAc:pentane). IR (film)/cm⁻¹ 3056, 2948, 2919, 1851, 1690 (C=O), 1610, 1592, 1565, 1487, 1443, 1389, 1358, 1295, 1219, 1158, 1139, 1080, 1019, 910, 805, 759, 731, 664, 575, 528, 472. ¹H NMR (400 MHz, CDCl₃) δ 10.58 (s, 1H, CHO), 8.97 (d, J = 8.2 Hz, 1H, Ar–CH), 8.66 (d, J = 8.4 Hz, 1H, Ar–CH), 8.53 (s, 1H, Ar–CH), 8.12 (dd, J = 7.6, 1.2 Hz, 1H, Ar–CH), 8.08 (d, J = 7.9 Hz, 1H, Ar–CH), 7.85–7.71 (m, 5H, 5 × Ar–CH), 7.32 (d, J = 8.1 Hz, 2H, 2 × Ar–CH), 2.43 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 189.3 (CHO), 144.5 (Ar–C₀), 138.8 (Ar–C₀), 138.1 (Ar–C₀), 133.5 (Ar–CH), 132.5 (Ar–C₀), 132.2 (Ar–C₀), 131.7 (Ar–CH), 131.5 (Ar–CH), 130.8 (Ar–CH), 130.2 (Ar–C₀), 130.0 (Ar–CH), 129.9 (2 × Ar–CH), 128.4 (Ar–CH), 128.3 (Ar–CH), 128.2 (2 × Ar–CH), 125.9 (Ar–CH), 125.2 (Ar–C₀), 123.0 (Ar–CH), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₂₉H₂₅O₅S [M+H]: 361.0898; found: 361.0896.

2-(4-Methylbenzenesulfonyl)-1-naphthaldehyde (31a ortho) and 8-(4-methylbenzenesulfonyl)-1-naphthaldehyde (31a peri)

Synthesised according to general procedure B using 1-naphthaldehyde (67.9 μL, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (10–20% EtOAc:pentane) afforded sulfonyl aldehyde 31a ortho as a
white solid (14.2 mg, 23%) followed by sulfonyl aldehyde 31a peri as a white solid (29.5 mg, 48%).

31a ortho: m.p. = 130–135 °C. Rf 0.36 (20% EtOAc:pentane). IR (film)/cm⁻¹: 3058, 2919, 1699 (C=O), 1593, 1500, 1450, 1426, 1377, 1315, 1175, 1151, 1128, 1082, 1051, 892, 815, 706, 624, 683, 603, 542 493. ¹H NMR (400 MHz, CDCl₃) δ 11.16 (s, 1H, CHO), 8.27–8.24 (m, 1H, Ar–CH), 8.09 (d, J = 8.8 Hz, 1H, Ar–CH), 8.03 (d, J = 8.8 Hz, 1H, Ar–CH), 7.94–7.91 (m, 1H, Ar–CH), 7.83 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 7.70–7.63 (m, 2H, 2 × Ar–CH), 7.33 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 2.40 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 194.4 (CHO), 144.9 (Ar–C₉), 139.0 (Ar–C₈), 138.5 (Ar–C₇), 135.5 (Ar–C₆), 135.2 (Ar–C₅), 132.3 (Ar–CH), 130.1 (2 × Ar–CH), 129.3 (Ar–CH), 129.2 (Ar–C₄), 129.1 (Ar–CH), 128.5 (Ar–CH), 127.7 (2 × Ar–CH), 126.4 (Ar–CH), 126.2 (Ar–C₉), 125.3 (Ar–CH), 21.6 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₀H₇NO₃NaS [M+Na+MeCN]: 374.0827; found: 374.0833. *87% purity.

31a peri: m.p. = 179–182 °C. Rf 0.12 (20% EtOAc:pentane). IR (film)/cm⁻¹: 3062, 2922, 2878, 1690 (C=O), 1595, 1562, 1500, 1299, 1239, 1198, 1154, 1139, 1074, 803, 759, 714, 660. ¹H NMR (400 MHz, CDCl₃) δ 10.70 (s, 1H, CHO), 8.22 (dd, J = 7.2, 1.6 Hz, 1H, Ar–CH), 8.15 (d, J = 8.1 Hz, 1H, Ar–CH), 8.14–8.10 (m, 2H, 2 × Ar–CH), 7.81–7.79 (m, 2H, 2 × Ar–CH), 7.70 (dd, J = 7.6, 7.6 Hz, 1H, Ar–CH), 7.58 (dd, J = 7.8, 7.8 Hz, 1H, Ar–CH), 7.34 (d, J = 8.4 Hz, 2H, 2 × Ar–CH), 2.44 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 190.4 (CHO), 144.7 (Ar–C₉), 138.1 (Ar–C₈), 137.1 (Ar–C₇), 135.3 (Ar–C₆), 134.8 (Ar–C₅), 134.4 (Ar–C₄), 134.1 (Ar–CH), 132.8 (Ar–CH), 131.1 (Ar–CH), 130.0 (2 × Ar–CH), 127.6 (2 × Ar–CH), 126.6 (Ar–CH), 126.4 (Ar–C₉), 124.8 (Ar–CH), 21.6 (CH₃). HRMS (FTMS+pAPCI) m/z calcd. For C₁₅H₁₅O₃S [M+H]: 311.0736; found: 311.0735.

2-Methyl-8-(4-methylbenzenesulfonfonyl)-1-naphthaldehyde (32a)

Synthesised according to general procedure B using 2-methyl-1-naphthaldehyde (85 mg, 0.5 mmol) and 4-methylbenzenesulfonic acid sodium salt (35.6 mg, 0.2 mmol). Purification by flash column chromatography (20% EtOAc:pentane) afforded sulfonyl aldehyde 32a as a white solid (8.6 mg, 13%). m.p. = 138–140 °C. Rf 0.16 (20% EtOAc:pentane). IR (film)/cm⁻¹: 3056, 2922, 2363, 1700 (C=O), 1595, 1550, 1446, 1305, 1215, 1140, 1073, 924, 812, 731, 663, 589. ¹H NMR (400 MHz, CDCl₃) δ 10.63 (s, 1H, CHO), 8.24 (d, J = 7.9 Hz, 1H, Ar–CH), 8.07 (d, J = 7.9 Hz, 1H, Ar–CH), 7.92 (d, J = 8.3 Hz, 1H, Ar–CH), 7.77 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.55 (dd, J = 7.8, 7.8 Hz, 1H, Ar–CH), 7.45 (d, J = 8.3 Hz, 1H, Ar–CH), 7.32 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 2.73 (s, 3H, CH₃), 2.43 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.1 (CHO), 144.1 (Ar–C₉), 140.5 (Ar–C₈), 139.3 (Ar–C₇), 136.7 (Ar–C₆), 135.0 (Ar–CH), 133.8 (Ar–CH), 133.5 (Ar–C₄), 132.2 (Ar–CH), 131.8 (Ar–C₅), 131.1 (Ar–CH), 129.7 (2 × Ar–CH), 127.3 (Ar–C₉), 127.1 (2 × Ar–CH), 124.3 (Ar–CH), 21.6 (CH₃), 21.1 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₉H₁₇O₃S [M+H]: 325.0898; found: 325.0910.
Derivatisation

(2-Methyl-6-(4-methylbenzenesulfonyl)phenyl)methanol (33)

Lithium borohydride (22.8 mg, 1 mmol) was added to a stirring solution of sulfonyl aldehyde 3a (54.5 mg, 0.2 mmol) in THF (0.34 mL) which was sealed and heated to 65 °C for 15 min. The reaction was quenched by the addition of MeOH, allowed to cool to rt then concentrated in vacuo. Water (10 mL) was added, and the product was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered, then concentrated in vacuo to afford sulfonyl amine 33 as a pink solid (39.5 mg, 72%). IR (film)/cm⁻¹ 3532 (O–H), 2962, 2919, 1595, 1455, 1287, 1183, 1157, 1081, 1014, 814, 677, 582. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (dd, J = 7.9, 1.6 Hz, 1H, Ar–CH), 7.79 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 7.47 (dd, J = 7.8, 1.4 Hz, 1H, Ar–CH), 7.39 (dd, J = 7.8, 7.8 Hz, 1H, Ar–CH), 7.33 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 4.71 (d, J = 7.6 Hz, 2H, CH₂), 3.02 (t, J = 7.6 Hz, 2H, CH₂), 2.29 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 144.4 (Ar–C₆), 140.5 (Ar–C₆), 140.4 (Ar–C₆), 138.3 (Ar–C₆), 137.6 (Ar–C₆), 136.3 (Ar–CH), 129.9 (2 × Ar–CH), 128.1 (Ar–CH), 127.5 (Ar–CH), 127.4 (2 × Ar–CH), 57.8 (CH₂), 21.6 (CH₃), 19.3 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₅H₁₂O₃S [M⁺]: 277.0898; found: 277.0907.

4-(2-Methyl-6-(4-methylbenzenesulfonyl)benzyl)morpholine (34)

Sodium triacetoxyborohydride (51.0 mg, 0.24 mmol) was added to a solution of sulfonyl aldehyde 3a (55.1 mg, 0.2 mmol) and morpholine (21.0 μL, 0.24 mmol) in CH₂Cl₂ (0.67 mL) at rt and was stirred overnight at rt. The reaction was quenched by the addition of 1 M aqueous NaOH (10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was acidified by the addition of 1 M aqueous HCl (7 mL), and washed with Et₂O. The organic phase was discarded, and the aqueous phase was basified by the addition of 1 M aqueous NaOH (14 mL) and the product extracted from the aqueous phase with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, then concentrated in vacuo to afford sulfonylamine 34 as an amorphous white solid (31.7 mg, 46%). IR (film)/cm⁻¹ 2924, 2853, 2810, 1453, 1306, 1158, 1137, 1115, 1084, 10005, 664, 612, 680, 579. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 7.8 Hz, 1H, Ar–CH), 7.75 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 7.45–7.35 (m, 2H, 2 × Ar–CH), 7.31 (d, J = 8.2 Hz, 2H, 2 × Ar–CH), 3.87 (s, 2H, ArCH₂), 3.56–3.30 (brs, 4H, 2 × CH₂CH₂H), 2.49 (s, 3H, CH₃), 2.43 (s, 3H, CH₃), 2.29 (brs, 4H, 2 × CH₂CH₂H). ¹³C NMR (101 MHz, CDCl₃) δ 143.6 (Ar–C₆), 141.8 (Ar–C₆), 140.4 (Ar–C₆), 140.2 (Ar–C₆), 136.0 (Ar–C₆ + Ar–CH), 129.5 (2 × Ar–CH), 128.0 (Ar–CH), 127.2 (3 × Ar–CH), 66.9 (OCH₂), 54.9 (ArCH₂), 52.6 (NCH₂), 21.5 (CH₃), 20.7 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₁₉H₂₄NO₃S [M⁺]: 346.1477; found: 346.1473.

(2-Methyl-6-(4-methylbenzenesulfonyl)phenyl)methanol (35)

4-Methoxyphenylmagnesium bromide (0.23 mL, 0.5 M) was added to a stirring solution of sulfonyl aldehyde 3a (27.6 mg, 0.1 mmol) in THF (0.2 mL) at 0 °C then the reaction was allowed to warm to rt overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (1 mL), diluted with water (10 mL) and the product extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered then concentrated in vacuo to afford sulfonyl alcohol 35 as a pink solid (34.9 mg, 91%). m.p. = 149–150 °C. IR (film)/cm⁻¹ 3493 (O–H), 2997, 2956, 2836, 1609, 1511, 1457,
1297, 1246, 1156, 1130, 1035, 829, 814, 683, 658, 574, 455. 1H NMR (400 MHz, CDCl_3) δ 8.12 (dd, J = 7.3, 2.3 Hz, 1H, Ar–CH), 7.65 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 7.45–7.34 (m, 2H, 2 × Ar–CH), 7.21 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 6.86 (d, J = 8.8 Hz, 2H, 2 × Ar–CH), 6.80 (d, J = 4.6 Hz, 1H, ArCH(OH)), 6.68 (d, J = 8.8 Hz, 2H, 2 × Ar–CH), 3.76 (s, 3H, OCH_3), 2.88 (s, 1H, OH), 2.36 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). 13C NMR (101 MHz, CDCl_3) δ 158.2 (Ar–C_q), 144.0 (Ar–C_o), 141.5 (Ar–C_o), 140.5 (Ar–C_o), 140.4 (Ar–C_o), 138.8 (Ar–C_o), 137.7 (Ar–CH), 133.5 (Ar–C_q), 129.8 (2 × Ar–CH), 127.8 (Ar–CH), 127.3 (2 × Ar–CH), 127.0 (Ar–CH), 126.5 (2 × Ar–CH), 113.2 (2 × Ar–CH), 69.4 (CH), 55.1 (OCH_3), 21.5 (CH_3), 20.8 (CH_3). HRMS (TOF–ESI^+) m/z calcd. For C_{22}H_{22}O_4SNa [M+Na]: 405.1137; found: 405.1127.

1-(2-Methyl-6-(4-methylbenzenesulfonyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (36)

Sulfonyl aldehyde 3a (55.0 mg, 0.2 mmol) and tryptamine (32.0 mg, 0.2 mmol) were added to a microwave vial. The vial was sealed then HFIP (0.32 mL) was added and the reaction was submersed in a preheated oil bath at 60 °C for 48 h. The reaction was concentrated in vacuo which afforded cyclised product 36 as an amorphous brown solid (60.4 mg, 73%). IR (film)/cm⁻¹ 3401 (N–H), 3055, 2919, 2846, 1649, 1594, 1454, 1292, 1182, 1132, 1082, 908, 812, 730, 659, 582, 562, 499. 1H NMR (400 MHz, CDCl_3) δ 8.84 (s, 1H, NH), 8.07 (s, 1H, NH), 8.02 (dd, J = 7.2, 2.2 Hz, 1H, Ar–CH), 7.68–7.61 (m, 3H, 3 × Ar–CH), 7.47–7.34 (m, 3H, 3 × Ar–CH), 7.25–7.13 (m, 4H, 4 × Ar–CH), 7.09–7.03 (m, 1H, ArCH(NH)), 3.97 (t, J = 7.7, 1.5 Hz, 2H, CH_2), 3.14 (t, J = 7.7 Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). 13C NMR (101 MHz, CDCl_3) δ 160.2 (Ar–C_q), 144.1 (Ar–C_o), 139.9 (Ar–C_o), 138.9 (Ar–C_o), 138.8 (Ar–C_q), 136.3 (Ar–C_q), 136.0 (Ar–CH), 135.1 (Ar–C_q), 129.6 (2 × Ar–CH), 128.7 (Ar–CH), 127.6 (2 × Ar–CH), 127.4 (Ar–C_q), 126.8 (Ar–CH), 122.0 (Ar–CH), 121.8 (CH), 119.3 (Ar–CH), 118.8 (Ar–CH), 113.7 (Ar–C_q), 111.2 (Ar–CH), 62.3 (CH_2), 26.5 (CH_2), 21.5 (CH_3), 20.3 (CH_3). HRMS (TOF–ESI^+) m/z calcd. For C_{25}H_{25}N_2O_2S [M+H]: 417.1637; found: 417.1635.

2-Methyl-6-(4-methylbenzenesulfonyl)benzoic acid (37)

Hydrogen peroxide (30% in H_2O, 41 μL, 0.4 mmol) was added to a solution of sodium phosphate monobasic (105 mg, 0.88 mmol) and sulfonyl aldehyde 3a in acetonitrile (1.6 mL). The reaction was cooled to 0 °C then a solution of sodium chloride (72 mg, 0.8 mmol) in H_2O (0.64 mL) was added and the reaction was allowed to warm to rt. [NOTE: on addition of sodium chloride, the reaction turned yellow and decolourised as the reaction progressed.] After 3 h, the reaction was quenched by the addition of sodium thiosulfate, acidified by the addition of 1 M aqueous HCl (5 mL) and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, then concentrated in vacuo to afford sulfonic acid 37 as a white solid (55.5 mg, 96%). m.p. = 173–176 °C. IR (film)/cm⁻¹ 3200 (O–H), 2924, 1738, 1712 (C=O), 1595, 1450, 1320, 1290, 1188, 1143, 1081, 876, 814, 708, 690, 657, 586. 1H NMR (400 MHz, MeOD) δ 7.88–7.84 (m, 3H, 3 × Ar–CH), 7.50–7.43 (m, 2H, 2 × Ar–CH), 7.31 (d, J = 8.3 Hz, 2H, 2 × Ar–CH), 2.35 (s, 6H, 2 × CH_3). 13C NMR (101 MHz, MeOD) δ 171.0 (C=O acid), 146.0 (Ar–C_q), 140.0 (Ar–C_q), 139.2 (Ar–C_q), 137.2 (Ar–C_q), 136.4 (Ar–CH), 135.7 (Ar–C_q), 130.7 (2 × Ar–CH), 130.6 (Ar–CH), 129.1 (2 × Ar–CH), 128.1 (Ar–CH), 21.5 (CH_3), 19.2 (CH_3). HRMS (TOF–ESI^+) m/z calcd. For C_{13}H_{15}O_3S [M+H]: 291.0691; found: 291.0701.
2-(2-Methyl-6-(4-methylbenzenesulfonyl)phenyl)-1H-benzo[d]imidazole (38)

Sulfonyl aldehyde 3a (55.1 mg, 0.2 mmol), o-phenylenediamine (21.6 mg, 0.2 mmol) and ceric ammonium nitrate (11 mg, 0.02 mmol) were added sequentially to microwave vial. The vial was sealed and acetonitrile (2 mL) and hydrogen peroxide (30 % in water, 0.2 mL) were added then the vial was submerged in an oil bath preheated to 50 °C overnight. The reaction was diluted with water (5 mL) and the product was extracted with CH₂Cl₂ (3 x 10 mL) The combined organic phases were dried over Na₂SO₄, filtered, then concentrated *in vacuo*. Purification by flash column chromatography (20% acetone:pentane) afforded sulfonyl benzimidazole 38 as a orange solid (48.3 mg, 66%). m.p. = 272–273 °C. IR (film)/cm⁻¹ 3295 (NH), 3103, 2363, 1668, 1639, 1594, 1432, 1321, 1205, 1162, 1141, 1083, 829, 531, 494m 457. 'H NMR (400 MHz, CDCl₃) δ 9.83 (s, 1H, N=CH), 8.26 (d, J = 7.5 Hz, 1H, Ar=CH), 7.70–7.49 (m, 4H, 4 × Ar=CH), 7.38–7.23 (m, 2H, 2 × Ar=CH), 7.15 (d, J = 8.2 Hz, 2H, 2 × Ar=CH), 6.84 (d, J = 8.1 Hz, 2H, 2 × Ar=CH), 6.24 (s, 3H, CH₃), 2.17 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 146.4 (Ar–C), 144.1 (Ar–C), 143.2 (Ar–C), 141.9 (Ar–C), 141.7 (Ar–C), 136.2 (Ar–C), 135.4 (Ar–CH), 133.3 (Ar–C), 129.7 (Ar–CH), 129.6 (Ar–C), 129.2 (2 × Ar–CH), 127.2 (2 × Ar–CH), 126.1 (Ar–CH), 123.5 (Ar–CH), 122.3 (Ar–CH), 119.5 (Ar–CH), 111.3 (Ar–CH), 21.5 (CH₃), 20.1 (CH₃). HRMS (TOF–ESI⁺) m/z calcd. For C₂₁H₁₉N₂O₂S: [M+H⁺]: 363.1167; found: 363.1155.

Other Starting Material and Product

Benzaldehyde-2,3,4,5,6-d₅ (13-d₅)

Dess Martin periodinane (937 mg, 2.21 mmol) was added to a stirring solution of Benzyld-2,3,4,5,6-d₅ alcohol (228.5 mL, 2.21 mmol) in CH₂Cl₂ (44 mL) at 0 °C which was allowed to warm to rt and stirred for 4 h. The reaction was quenched by the addition of saturated aqueous NaHCO₃ (40 mL) and the product extracted with CH₂Cl₂ (2 × 40 mL). The combined organic phases were dried over Na₂SO₄, filtered then concentrated *in vacuo*. Purification by flash column chromatography (20% Et₂O:pentane) afforded deuterobenzaldehyde 13-d₅ as a colourless oil (157.2 mg, 64%). CAS no.: 14132-51-5. R₆ 0.6 (20% Et₂O:pentane). 'H NMR (400 MHz, CDCl₃) δ 10.0 (s, 1H). analytical data ('H NMR) is in agreement with the reported literature.¹²

2-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)-6-methylbenzaldehyde (4)

Potassium carbonate (138.2 mg, 1 mmol) and copper(II) fluoride (101.5 mg, 1 mmol) were added sequentially to a microwave vial which was then flame dried under argon until a blue colour just appeared (ca. 2–5 seconds). The microwave vial was allowed to cool to room temperature and copper(II) acetate (45 mg, 0.25 mmol), β-alanine (11.1 mg, 0.125 mmol), 2-methylbenzaldehyde (57.8 μL, 0.5 mmol) and HFIP (2.5 mL) were added to a microwave vial sequentially under argon. The vial was sealed and submerged in an oil bath preheated to 100 °C for 18 h (Stirring rate set to 500 rpm). The reaction was allowed to cool to room temperature, diluted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous solution of ammonium chloride (10 mL). The product was extracted from the aqueous phase with EtOAc (2 × 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* [note: rotary evaporator bath set to 40 °C] to remove any remaining starting material afforded HFIP adduct 4 as a clear and colourless crystalline solid (26.7 mg, 19%). m.p. = 52–53 °C. R₆ 0.29 (2.5% EtOAc:hexane). IR (film)/cm⁻¹ 2967, 2892, 1692 (C=O), 1573, 1469, 1372, 1252, 1200, 1111, 902, 828, 738. 'H NMR (400 MHz, CDCl₃) δ 10.63 (s, 1H, CHO), 7.27 (dd, J = 8.3, 8.3 Hz, 1H, Ar–CH), 7.07–7.05 (m, 1H, Ar–CH), 6.95 (d, J = 8.3 Hz,
$^1$H, Ar–CH), 5.02 (hept, $J = 5.7$ Hz, 1H, CH(CF$_3$)$_2$), 2.62 (s, 3H, CH$_3$). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 190.7 (CHO), 160.5 (Ar–C$_q$), 143.0 (Ar–C$_q$), 134.4 (Ar–CH), 128.0 (Ar–CH), 125.1 (Ar–C$_q$), 123.2–115.4$^b$ (m), 112.0 (Ar–CH), 76.6–75.3$^b$ (m, CH(CF$_3$)$_2$), 21.4 (CH$_3$). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ –73.25 (d, $J = 6.9$ Hz, CH(CF$_3$)$_2$). HRMS (EI$^+$) m/z calcld. For C$_{11}$H$_8$F$_6$O$_2$ [M+H]: 286.0423; found: 286.0431. $^a$93% purity, contains EtOAc. [Note: This material readily sublimes under reduced pressure at rt, so it was not possible to fully remove the EtOAc without evaporation of the product. Attempts to remove trace solvent under vacuum led to complete loss of product.] $^b$Signal partly obscured. Analytical data ($^1$H, $^{13}$C, $^{19}$F NMR are in agreement with the reported literature.$^{13}$
Procedure for Multi Gram Scale Synthesis of Sulfonyl Aldehyde 3a

Potassium carbonate (2.75 g, 20 mmol) and copper(II) fluoride (2.00 g, 20 mmol) were added sequentially to a schlenk tube which was then flame dried under argon until a blue colour just appeared (ca. 5–10 seconds). The Schlenk tube was allowed to cool to room temperature and copper(II) acetate (900 mg, 5 mmol), β-alanine (225 mg, 2.5 mmol), p-toluene sulfinic acid sodium salt (1.78 g, 10 mmol) and 2-methylbenzaldehyde (2.90 mL, 25 mmol) were added sequentially under argon, HFIP (50 mL, 0.2 M) was added then the tube sealed with a young’s tap and was submerged in a preheated oil bath to 100 °C for 24 h [Stirring rate set to 500 rpm]. The reaction was allowed to cool to room temperature, diluted with EtOAc (50 mL) and the organic phase was washed with a saturated aqueous solution of ammonium chloride (150 mL) and brine (50 mL), [Note: The crude should be shaken until a change from orange/brown to blue/green is observed. Should the resulting solution emulsify brine can be added. Occasionally a brown precipitate can remain which obscures the phase boundary, this is collected with the aqueous phase for the first two extractions then with the organic phase on the final extraction]. The product was extracted from the aqueous phase with EtOAc (2 × 50 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (10–20% EtOAc:hexane) afforded sulfonyl aldehyde 3a as an off white solid (2.07 g, 75%).
**Unsuccessful Substrates**

\[
\text{O} \quad \text{R} \\
2.5 \quad \text{equiv}
\]

\[
\text{NaOS} \quad \text{SO}_2 \quad \text{R}
\]

\[
\text{CuF}_2 (2 \text{ equiv}) \\
\text{Cu(OAc)}_2 (50 \text{ mol}%) \\
\beta\text{-alanine} (25 \text{ mol}%) \\
\text{K}_2\text{CO}_3 (2 \text{ equiv})
\]

HFIP (0.2 M) 
100 °C, 18 h

![Chemical Reaction](image)

**Aldehydes (using 4-methylbenzenesulfinic acid sodium salt)**

- Complex Mixture (Evidence of products of S_NAr)
- X = CN or SF_5
- <10% yield
- Unable to adopt reactive conformer due to steric clash

**Sulfinate salts (using 2-methylbenzaldehyde)**

- 0%, gave exclusive formation of HFIP adduct insufficient nucleophilicity
- <10%, <5%, NR
- Sulfinates possessing β-hydrogens were not tolerated in the reaction
$^1$H and $^{13}$C Spectra of Selected Compounds
$S_1$

$^1$H NMR
(400 MHz, D$_2$O)

$S_1$

$^{13}$C NMR
(101 MHz, D$_2$O)
$3b$

$^1$H NMR
(400 MHz, CDCl$_3$)

$^13$C NMR
(101 MHz, CDCl$_3$)
$3c$

$\textsuperscript{1}H$ NMR

(400 MHz, CDCl$_3$)

$3c$

$\textsuperscript{13}C$ NMR

(101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{19}$F NMR
$(377$ MHz,$CDCl_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)
3f

$^{19}F$ NMR

(400 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR
(400 MHz, CDCl$_3$)

$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR
(400 MHz, CDCl$_3$)

$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
3m
$^1$H NMR
(400 MHz, CDCl$_3$)

3m
$^{13}$C NMR
(101 MHz, CDCl$_3$)
J. I. Higham and J. A. Bull

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
6a

$^1$H NMR

(400 MHz, CDCl$_3$)

$^{13}$C NMR

(101 MHz, CDCl$_3$)
6a
$^{19}$F NMR
(377 MHz, CDCl$_3$)
7a mono
$^1$H NMR
(400 MHz, CDCl$_3$)

$^1$H NMR
(400 MHz, CDCl$_3$)

7a mono
$^{13}$C NMR
(101 MHz, CDCl$_3$)

$^{13}$C NMR
(101 MHz, CDCl$_3$)
$7a$ mono$'$

$^1$H NMR
(400 MHz, CDCl$_3$)

$7a$ mono$'$

$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR
$(400 \text{ MHz, CDCl}_3)$

$^{13}C$ NMR
$(101 \text{ MHz, CDCl}_3)$
$^1$H NMR
(400 MHz, CDCl$_3$)

$^13$C NMR
(101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
9a

$^{19}$F NMR
(377 MHz, CDCl$_3$)
J. I. Higham and J. A. Bull

10a mono
$^1$H NMR
(400 MHz, CDCl$_3$)

10a mono
$^{13}$C NMR
(101 MHz, CDCl$_3$)
10a di
$^1$H NMR
(400 MHz, CDCl$_3$)

10a di
$^{13}$C NMR
(101 MHz, CDCl$_3$)
11a mono
$^1$H NMR
(400 MHz, CDCl$_3$)

11a mono
$^{13}$C NMR
(101 MHz, CDCl$_3$)
11a di
$^1$H NMR
(400 MHz, CDCl$_3$)

11a di
$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR
$(400 \text{ MHz, CDCl}_3)$

$^{13}C$ NMR
$(101 \text{ MHz, CDCl}_3)$
12a mono
$^{19}$F NMR
(377 MHz, CDCl$_3$)
$^{12}$a di
$^1$H NMR
($400$ MHz, CDCl$_3$)

$^{12}$a di
$^{19}$F NMR
($377$ MHz, CDCl$_3$)
13a mono

$^1$H NMR

(400 MHz, CDCl$_3$)

13a mono

$^{13}$C NMR

(101 MHz, CDCl$_3$)
$^{13}$a di
$^1$H NMR
(400 MHz, CDCl$_3$)

$^{13}$a di
$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)
$^{15}$a

$^{1}$H NMR
(400 MHz, CDCl$_3$)

$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^13$C NMR (101 MHz, CDCl$_3$)
16a
$^1$H NMR
(400 MHz, CDCl$_3$)

16a
$^{13}$C NMR
(101 MHz, CDCl$_3$)
S3
$^1$H NMR
(400 MHz, CDCl$_3$)

S3
$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
\[ \text{J. I. Higham and J. A. Bull} \]

\[ 18a \]

\[^1\text{H NMR} \]

(400 MHz, CDCl\(_3\))

\[ \begin{align*} 
\text{13C NMR} & \quad (101 \text{MHz, CDCl}_3) \\
\end{align*} \]
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR
(400 MHz, CDCl$_3$)

$^{13}C$ NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR
(400 MHz, CDCl$_3$)

$^{13}C$ NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR
(400 MHz, CDCl$_3$)

$^1$C NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$27a$

$^1$H NMR
(400 MHz, DMSO-$d_6$)

$13^C$ NMR
(101 MHz, DMSO-$d_6$)
27a
COSY (CDCl₃)

27a
HSQC (CDCl₃)
27a
HMBC
(DMSO-d$_6$)
$^{13}$H NMR
(400 MHz, CDCl$_3$)

$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR
(400 MHz, CDCl$_3$)

$^{13}$C NMR
(101 MHz, CDCl$_3$)
DEPT-135 NMR (101 MHz, CDCl₃)

- 189.61
- 130.16
- 130.07
- 127.27
- 126.88
- 50.30
- 44.88
- 37.39
- 29.24
- 21.59
- 13.77
$^{1}H$ NMR $(400 \text{ MHz, CDCl}_3)$

$^{13}C$ NMR $(101 \text{ MHz, CDCl}_3)$
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
31a peri
$^1$H NMR
(400 MHz, CDCl$_3$)

31a peri
$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^13$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR 
(400 MHz, CDCl₃)

$^{13}$C NMR 
(101 MHz, CDCl₃)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^{13}$C NMR
(400 MHz, CDCl$_3$)

$^{1}$H NMR
(400 MHz, CDCl$_3$)

35
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR
(400 MHz, CDCl$_3$)

$^{13}$C NMR
(101 MHz, CDCl$_3$)
$^1{\text{H}}$ NMR (400 MHz, CDCl$_3$) 

$^{13}{\text{C}}$ NMR (101 MHz, CDCl$_3$)
$^{13}$-d$_5$

$^1$H NMR (400 MHz, CDCl$_3$)
1H NMR (400 MHz, CDCl$_3$)

13C NMR (101 MHz, CDCl$_3$)
$^{19}$F NMR (377 MHz, CDCl$_3$)

P P P P P P P P P P P P P P P P P P P P P P P P P P P P P

-90 -70 -50 -30 -10 10 30 50 70 90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290 ppm
References

1. a) Y. Chen, M. C. Willis, *Chem. Sci.* 2017, 8, 3249–3253. b) Nandi, G. C. An Efficient Cu-Catalyzed Microwave-Assisted Synthesis of Diaryl Sulfones. *Synth. Commun.* 2017, 47, 319–323.

2. (a) Liu, J.; Yu, L.; Zhuang, S.; Gui, Q.; Chen, X.; Wang, W.; Tan, Z. Copper-Mediated Ortho C-H Sulfonylation of Benzoic Acid Derivatives with Sodium Sulfinates. *Chem. Commun.* 2015, 51, 6418–6421. (b) Rao, W. H.; Shi, B. F. Copper(II)-Catalyzed Direct Sulfonylation of C(sp2)-H Bonds with Sodium Sulfinates. *Org. Lett.* 2015, 17, 2784–2787. (c) Liang, S.; Liu, N. W.; Manolikakes, G. Copper-Mediated Sulfonylation of Aryl C(sp2)-H Bonds with Sodium and Lithium Sulfinates. *Adv. Synth. Catal.* 2016, 358, 159–163.

3. Pitzer, L.; Schäfers, F.; Glorius, F. Rapid Assessment of the Reaction-Condition-Based Sensitivity of Chemical Transformations. *Angew. Chem. Int. Ed.* 2019, 58, 8572–8576.

4. (a) Blackmond, D. G. Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions. *Angew. Chem. Int. Ed.* 2005, 44, 4302–4320. (b) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J. Q.; Blackmond, D. G. Mechanistic Rationalization of Unusual Kinetics in Pd-Catalyzed C-H Olefination. *J. Am. Chem. Soc.* 2012, 134, 4600–4606.

5. (a) Burés, J. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem. Int. Ed.* 2016, 55, 2028–2031. (b) Burés, J. Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles. *Angew. Chem. Int. Ed.* 2016, 55, 16084–16087. c) Nielsen, C. D. T.; Burés, J. Visual Kinetic Analysis. *Chem. Sci.* 2019, 10, 348–353.

6. Higham, J. I.; Bull, J. A. Copper Catalysed Oxidative α-Sulfonylation of Branched Aldehydes Using the Acid Enhanced Reactivity of Manganese(IV) Oxide. *Chem. Commun.* 2020, 56, 4587–4590.

7. Bär, R. M.; Gross, P. J.; Niegé, M.; Bráse, S. Sodium Bicyclo[1.1.1]Pentanesulfinate: A Bench-Stable Precursor for Bicyclo[1.1.1]Pentylsulfones and Bicyclo- [1.1.1]Pentanesulfonamides. *Chem. Eur. J.* 2020, 26, 4242–4245.

8. Sparks, S. M.; Aquino, C.; Banker, P.; Collins, J. L.; Cowan, D.; Diaz, C.; Dock, S. T.; Hertzog, D. L.; Liang, X.; Swiger, E. D.; et al. Exploration of Phenylpropanoic Acids as Agonists of the Free Fatty Acid Receptor 4 (FFA4): Identification of an Orally Efficacious FFA4 Agonist. *Bioorganic Med. Chem. Lett.* 2017, 27, 1278–1283.

9. Cheng, X. Q.; Chen, X.; Hughes, R. A.; Williams, S. J.; Woodman, O. L. Understanding the Cardioprotective Effects of Flavonols: Discovery of Relaxant Flavonols without Antioxidant Activity. *J. Med. Chem.* 2008, 51, 1874–1884.

10. Sarkar, D.; Ghosh, M. K.; Rout, N. Phenyl Trimethyl Ammonium Tribromide Mediated Robust One-Pot Synthesis of Spiro-Oxacycles-an Economic Route-Stereoselective Synthesis of Oxaspirohexacyclodieneones. *Org. Biomol. Chem.* 2016, 14, 7883–7898.

11. Zhang, M.; Li, N.; Tao, X.; Ruzi, R.; Yu, S.; Zhu, C. Selective Reduction of Carboxylic Acids to Aldehydes with Hydrosilane: Via Photoredox Catalysis. *Chem. Commun.* 2017, 53, 10228–10231.

12. Mohr, L. M.; Bauer, A.; Jandl, C.; Bach, T. Visible Light-Mediated Intermolecular [2 + 2] Photocycloaddition of 1-Aryl-2-Nitroethenes and Olefins. *Org. Biomol. Chem.* 2019, 17, 7192–7203.

13. Zhou, J.; Liu, D.; Bai, C.; Bao, A.; Musch, T.; Baiyin, M.; Bao, Y.-S. Transient Directing Groups Controlled Regiodivergent C(Sp2)-H and C(Sp3)-H Polyfluoroalkoxylation of Aromatic Aldehydes. *Org. Chem. Front.* 2021, 8, 5975–5981.