

## Supporting information

Development and pilot scale implementation of safe aerobic Cu/TEMPO oxidation in batch reactor.

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## 1. General Remarks

All reagents and solvents were purchased from commercial suppliers and used without further purification. Reactions were monitored for completion by removing a small sample from the reaction mixture and analysing by UPLC (Waters ACQUITY). Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) were reported at ambient temperature on a Bruker 400 MHz spectrometer. J-modulated spin-echo (JMOD) were recorded at ambient temperature on a Bruker 101 MHz spectrometer. Chemical shifts are reported relative to the residual protons in DMSO ( $\delta\text{H}$  2.50 ppm) and coupling constants (J) are given in Hertz. Chemical shifts of JMOD were measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in DMSO ( $\delta\text{C}$  39.50 ppm). Data are reported as follows: Chemical shift (multiplicity, number of protons, coupling constants). Chemical shift was measured in ppm and quoted to the nearest 0.01 ppm. Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported.

DSC measurements were performed using a SETARAM DSC 121 calorimeter in stainless steel pans and were hermetically sealed. The sample (10 mg) were heated from 20 °C to a temperature in the range of 400 °C at a rate of 5 °C min<sup>-1</sup>. Onset temperatures were calculated by the instrument software.

## 2. Analytical method for UPLC analysis

Column	<b>Acquity UPLC BEH C18 – 50 mm x 2.1 mm – 1.7 <math>\mu\text{m}</math></b>
Eluent A	Water/CH <sub>3</sub> CN/ methane sulfonic acid (1000/25/1)
Eluent B	CH <sub>3</sub> CN/water/methane sulfonic acid (1000/25/1)
Flow	0.8 ml/min
Oven	40°C

Detection $\lambda$ (nm)	210 nm
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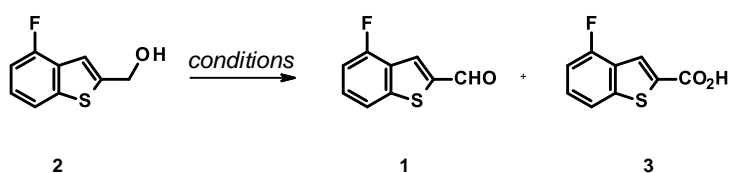
**Table S1:** UPLC analytical method used in this report.

The following gradient was used:

Time (min)	Solvent A %	Solvent B %
0	95	5
1	95	5
4.5	5	95
5.5	5	95
5.6	95	5
7.6	95	5

**Table S2:** Elution system used in UPLC analytical method.

### 3. Screening of conditions



Entry	Conditions	Alcohol 2 (%) <sup>a</sup>	Aldehyde 1 (%) <sup>a</sup>	Carboxylic Acid 3 (%) <sup>a</sup>	By Products <sup>a</sup>
1	TEMPO/ KBr/NaOCl (NaHCO <sub>3</sub> , PH = 9.5), DCM, 7h, 0°C.	0	85	0	15
2	TEMPO/NaOCl (NaHCO <sub>3</sub> , pH = 9.5), 0°C, 7h.	68	19	0	13
3	TCCA, TEMPO, MeOH, 20°C.	0	1		99
4	<i>t</i> -BuONa PhCOPh, 100°C, 18h.	37	1		62
5	SO <sub>3</sub> -Pyridine, Et <sub>3</sub> N, 12°C, 7h.	98	0		2
6	DMSO-TFAA, Et <sub>3</sub> N, -15°C, 7h.	13	66		21
7	DMSO, Ac <sub>2</sub> O, 80°C.	0	36		64

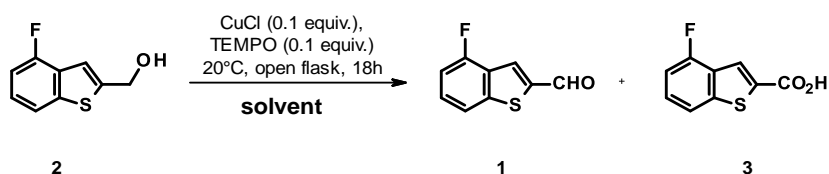
<b>8</b>	TEMPO (0.05 equiv.), Na <sub>2</sub> CO <sub>3</sub> (1 equiv.), CuI (0.05 equiv.), L-proline (0.05 equiv.), MeOH, r.t., 60h, air.	1	52	30	18
<b>9</b>	TEMPO (0.05 equiv.), Na <sub>2</sub> CO <sub>3</sub> (1 equiv.), CuI (0.05 equiv.), N-Ph-glycine (0.05 equiv.), water, reflux, 39h, air.	50	33	8	N.D
<b>10</b>	TEMPO (0.05 equiv.), Na <sub>2</sub> CO <sub>3</sub> (1 equiv.), CuBr (0.05 equiv.), proline (0.05 equiv.), MeOH, r.t., 20h, air.	31	45	19	N.D
<b>11</b>	TEMPO (0.05 equiv.), HCl (0.1 equiv.), NaNO <sub>2</sub> (0.05 equiv.), DCM, r.t., air.	90	2	0	N.D
<b>12</b>	ABNO (0.05 equiv.), HNO <sub>3</sub> (0.2 equiv.), NaNO <sub>2</sub> (0.1 equiv.), MeCN, r.t., air.	42	55	0	N.D
<b>13</b>	ABNO (0.05 equiv.), NaNO <sub>2</sub> (0.1 equiv.), CH <sub>3</sub> CO <sub>2</sub> H, r.t., 77h, air.	16	81	0	N.D
<b>14</b>	HNO <sub>3</sub> (1 equiv.), TFE, r.t., 20h, air.	28	0	72	N.D
<b>15</b>	V <sub>2</sub> O <sub>5</sub> (0.05 equiv.), K <sub>2</sub> CO <sub>3</sub> (0.5 equiv.), toluene, reflux, 20h, air.	95	0	0	N.D
<b>16</b>	Pt/C (0.1 equiv.), Bi/C (0.1 equiv.), KOH, MeCN, 40°C, 2h30.	61	6	32	N.D
<b>17</b>	Pd(OAc) <sub>2</sub> (0.15 equiv.), pyridine (0.2 equiv.), toluene, 80°C, 22h, air.	22	69	0	N.D
<b>18</b>	Pd(OAc) <sub>2</sub> (0.15 equiv.), NaHCO <sub>3</sub> (2 equiv.), DMSO, 80°C, 21h, air.	63	23	0	N.D
<b>19</b>	PdCl <sub>2</sub> (0.01 equiv.), NaOAc (0.5 equiv.), P.C, 100°C, 4h, air.	88	8	0	N.D
<b>20</b>	Pd(OAc) <sub>2</sub> (0.15 equiv.), pyridine (0.2 equiv.), DMSO, 80°C, 72h, air.	79	15	0	N.D
<b>21</b>	Pt/C (0.1 equiv.), Bi <sub>2</sub> O <sub>3</sub> (0.1 equiv.), NaOH, H <sub>2</sub> O, 45°C, 24h, air.	88	8	0	N.D
<b>22</b>	Pt/C (0.1 equiv.), Bi <sub>2</sub> O <sub>3</sub> (0.1 equiv.), Pd/C (0.1 equiv.), picolinic acid, AcOH, pyridine, 100°C, 24h.	76	13	0	N.D

<b>23</b>	Na <sub>2</sub> WO <sub>4</sub> ·2H <sub>2</sub> O (0.005 equiv.), (n-oct) <sub>3</sub> MeNHSO <sub>4</sub> (0.005 equiv.), H <sub>2</sub> O <sub>2</sub> (1.1 equiv.), 70°C, 16h.	31	0	0	N.D
<b>24</b>	TEMPO (0.1 equiv.), CuCl (0.1 equiv.), DMSO, r.t., air (open flask).	0	92	4	N.D

**Table S3:** Screening of oxidation methods for conversion of alcohol **1** into aldehyde **2**; a. Conversion was determined by Liquid Chromatography (relative % area).

## 4. Development of aerobic copper oxidation

### 4.1 Screening of solvents



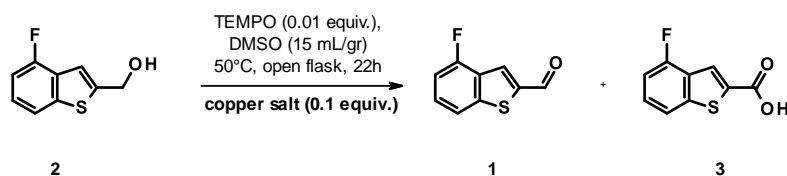
#### Procedure:

Alcohol **2** (200 mg, 1.1 mmol, 1 equiv.), CuCl (11 mg, 0.11 mmol, 0.1 equiv.), TEMPO (18 mg, 0.11 mmol, 0.1 equiv.) and solvent (4 mL) were charged in 10 ml three necks round bottom flask. Reaction mixture was stirred open flask at 20°C during 18h and was analysed to give the conversion.

<b>Solvent</b>	<b>Alcohol 2 (%)<sup>a</sup></b>	<b>Aldehyde 1 (%)<sup>a</sup></b>	<b>Carboxylic acid 3 (%)<sup>a</sup></b>
DMF	5	92	0.5
NBP	1	92.2	2.9
DMSO	1	91.2	5.4
EQUAMIDE M 100	1.4	93.8	1.8
PROPYLENE CARBONATE	9.4	85.6	2.3
ACETIC ACID	98	2	0
ETHYL ACETATE	96	4	0
M-THP	94	3	0
DIMETHOXYETHANE	96	3	0
ACETONITRILE	95	3	0
H <sub>2</sub> O	95	5	0
DMSO/H <sub>2</sub> O (40/60 v/v)	89	10	0

**Table S4:** Screening of solvents; a. Conversion was determined by Liquid Chromatography (relative % area).

### 4.2 Screening of Copper catalyst



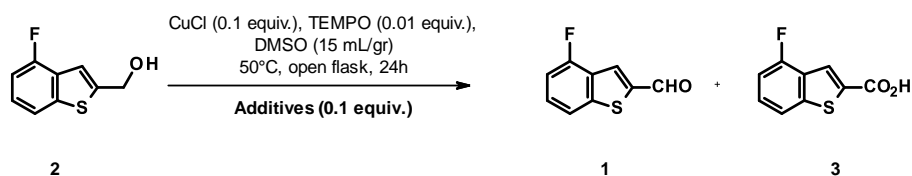
**Procedure:**

Alcohol **2** (1 g, 5.5 mmol, 1 equiv.), copper salt (0.11 mmol, 0.1 equiv.), TEMPO (8.6 mg, 0.055 mmol, 0.01 equiv.) and DMSO (15 mL) were charged in 50 mL three necks round bottom flask. Reaction mixture were purged for 2 minutes with air and stirred open flask, at 50°C, for 22h under magnetic stirring before to be analysed to give the conversion.

Copper salt	Alcohol <b>2</b> (%) <sup>a</sup>	Aldehyde <b>1</b> (%) <sup>a</sup>	Carboxylic acid <b>3</b> (%) <sup>a</sup>
CuCl	3.3	90.9	3.8
CuBr	100	0	0
CuBr.DMS <sup>b</sup>	Not detected	>95	Not quantify
CuI	3.5	90.4	4
CuOTf.toluene	3.3	87	5
CuBr <sub>2</sub>	95	0	1.8
CuCl <sub>2</sub>	95	0	1.8
CuOTf <sub>2</sub>	92.7	1.3	2
CuBr <sub>2</sub> , proline (0.1 equiv.), Na <sub>2</sub> CO <sub>3</sub> (1 equiv.) H <sub>2</sub> O, 100°C	0	0	95

**Table S5:** Screening of copper salts; a. Conversion was determined by Liquid Chromatography (relative % area); b. Determined by TLC monitoring.

**4.3 Screening of additives**



**Procedure:**

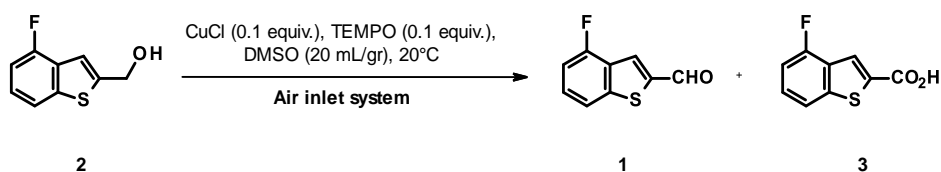
Alcohol **1** (1 g, 5.5 mmol, 1 equiv.), CuCl (54 mg, 0.55 mmol, 0.1 equiv.), TEMPO (8.6 mg, 0.055 mmol, 0.01 equiv.) and DMSO (15 mL) were charged in 50 ml three necks round bottom flask. Reaction mixture were purged for 2 minutes with air and stirred open flask, at 50°C, for 24h under magnetic stirring before to be analysed to give the conversion.

Ligand/base	Alcohol <b>2</b> (%) <sup>a</sup>	Aldehyde <b>1</b> (%) <sup>a</sup>	Carboxylic acid <b>3</b> (%) <sup>a</sup>
NMI	3	88	5
DBU	26	67	4.1
BiPyridine	2.6	89	6
MeO <sub>2</sub> BiPy	1.7	76	5.6

Phenanthroline	5.8	86.9	5.8
Proline	94.6	0	1.7
Cs <sub>2</sub> CO <sub>3</sub>	77.9	16.8	2.4
K <sub>3</sub> PO <sub>4</sub>	65	29.8	2.5
<i>t</i> -BuOK	57.7	36.7	3.2
K <sub>2</sub> CO <sub>3</sub>	0	95	2
DMAP	0	94	4

**Table S6:** Screening of additives; a. Conversion was determined by Liquid Chromatography (relative % area).

#### 4.4 Air inlet system impact



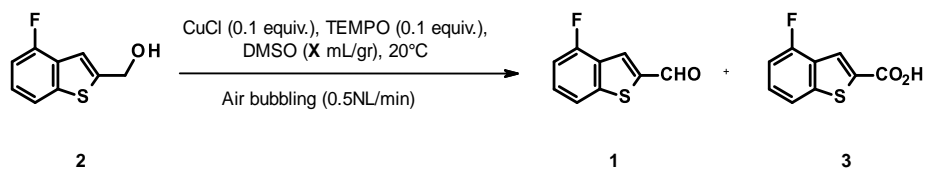
#### Procedure:

Alcohol **1** (1 g, 5.5 mmol, 1 equiv.), CuCl (54 mg, 0.55 mmol, 0.1 equiv.), TEMPO (86 mg, 0.55 mmol, 0.1 equiv.) and DMSO (20 mL) were charged in 50 mL three necks round bottom flask. Reaction mixture was stirred (magnetic stirring, 1400 rpm) in presence of air (see table S7 for detail) and at 20°C until maximum of conversion which was determined by UPLC analysis.

Air inlet	Time (minutes)	Aldehyde <b>1</b> (%) <sup>a</sup>	Alcohol <b>2</b> (%) <sup>a</sup>	Carboxylic Acid <b>3</b> (%) <sup>a</sup>
0.5N/L air Bubbling	0	0	100	0
	45	44	55.9	0.2
	100	95	4.5	0.8
Open flask	0	0	100	0
	25	6	94	0
	89	17.9	92	0.1
	162	36.2	63.6	0.2
	226	49.1	51.4	0.4
	360	86.1	12	0.9
	415	96.9	1.6	1.4
0,5NL/min air bubbling, 1,5NL/min N <sub>2</sub> sweep	0	0	100	0
	10	5	95	0
	22	10.6	89.4	0
	58	41.5	58.3	0.2
	98	80.7	18.7	0.5
	121	97.4	0.6	1

**Table S7:** Impact of air inlet system; a. Conversion was determined by Liquid Chromatography (relative % area).

#### 4.5 Impact of dilution



#### Procedure:

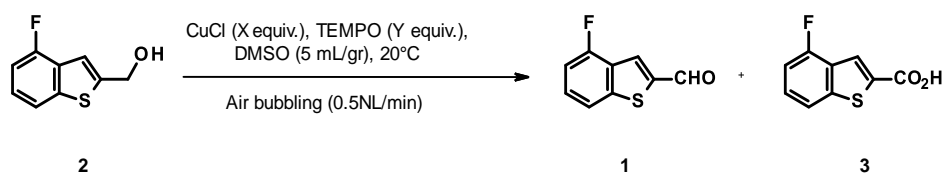
Alcohol **2** (1 g, 5.5 mmol, 1 equiv.), CuCl (54 mg, 0.55 mmol, 0.1 equiv.), TEMPO (86 mg, 0.55 mmol, 0.1 equiv.) and DMSO (X mL, see table S8) were charged in 50 mL three necks round bottom flask. Reaction mixture was stirred (magnetic stirring, 1400 rpm) in presence of air (air bubbling through reaction mixture, 0.5NL/min) and at 20°C until maximum of conversion.

Dilution	Time (minutes)	Aldehyde <b>1</b> (%) <sup>a</sup>	Alcohol <b>2</b> (%) <sup>a</sup>	Carboxylic Acid <b>3</b> (%) <sup>a</sup>
20 mL/gr	0	0	100	0
	20	14	86	0
	45	44	55.9	0.2
	70	59	40	0.3
	100	95	4.50	0.8
	120	98	1.2	1
15 mL/gr	0	0	100	0
	20	26.5	73.3	0.1
	50	79	20.6	0.7
	75	97.4	1.3	1.2
	180	97	1.4	1.95
10 mL/gr	0	0	100	0
	20	29.5	70.3	0
	40	69.5	30	0.5
	60	95.2	3.7	1.1
	80	97.3	1.3	1.4
5 mL/gr	0	0	100	0
	20	37.9	61.8	0.2
	40	72.7	26.6	0.7
	60	96.8	1.5	1.6
	80	96.4	1.3	2.2

**Table S8:** Impact of dilution; a. Conversion was determined by Liquid Chromatography (relative % area).



#### 4.6 Impact of catalyst loading



##### Procedure:

Alcohol **2** (1 g, 5.5 mmol, 1 equiv.), CuCl (X equiv., see table S9), TEMPO (Y equiv., see table S9) and DMSO (5 mL) was charged in 25 mL three necks round bottom flask. Reaction mixture was stirred (magnetic stirring, 1400 rpm) in presence of air (air bubbling through reaction mixture, 0.5NL/min) and at 20°C until maximum of conversion.

CuCl (equiv.)	Tempo (equiv.)	Time (minutes)	Aldehyde <b>1</b> (%) <sup>a</sup>	Alcohol <b>2</b> (%) <sup>a</sup>	Acide <b>3</b> (%) <sup>a</sup>
0.1	0.1	0	0	100	0
		20	37.9	61.8	0.2
		40	72.7	26.6	0.7
		60	96.8	1.5	1.6
		80	96.4	1.33	2.20
0.1	0.05	0	0	100	0
		10	16.3	83.6	0.08
		20	27.4	72.4	0.21
		40	56.1	42.7	0.6
		60	80.9	17.4	1.1
		80	96.7	0.9	1.8
		190	96.6	0.4	2.5
0.1	0.01	0	0	100	0
		20	20.1	79.8	0.1
		41	37.7	62	0.3
		60	53.1	46.3	0.6
		80	66.9	32.2	0.9
		102	80.6	18.1	1.3
		120	87.1	11.3	1.6
		141	90.2	8.1	1.7
		180	93	5.1	1.9
		240	94.9	3.10	2.0
		1140	97.0	0.4	2.6
		0	0	100	0
		10	13.7	86.3	0

0.2	0.01	20	24.7	75.2	0.1
		40	45.7	54.0	0.3
		60	65.6	33.9	0.5
		80	83.2	15.6	0.83
		100	94.4	4.3	1.2
		120	96.5	2.1	1.4
		180	98	0.7	1.6
		1440	95.6	0.3	4.2
0.05	0.1	0	0	100	0
		12	9.5	90.5	0.04
		30	21.8	78.0	0.2
		70	54.9	43.1	0.8
		125	88.2	8.1	2.8
		173	92.8	4.0	3.3
		255	95.7	1.2	2.3
0.01	0.1	0	0	100	0
		30	9.3	90.8	0
		79	19.8	79.9	0.3
		137	24.3	75.3	0.4
		225	27.6	71.9	0.54
		300	29.5	70.0	0.6
		480	33.3	65.9	0.8
0.05	0.05	0	0	100	0
		31	25.7	74.1	0.2
		52	43	56.5	0.5
		78	64.7	34.1	1.2
		99	82.3	15.3	2.0
		127	90.8	6.6	2.6
		156	93.4	3.7	2.8
		500	97.9	0.6	1.3

**Table S9:** Optimisation of catalyst loading; a. Conversion was determined by Liquid Chromatography (relative % area).

## 5. DDQ oxidation of (4-fluorobenzothiophen-2-yl) methanol 2

**Representative procedure:** In a pilot scale reactor were introduced alcohol **2** (12.5 Kg) and dichloromethane (120 Kg). DDQ (16 Kg) was added in one portion at 20-30°C and the reaction mixture could react under vigorous stirring for 16 hours at 20-30 °C (conversion controlled by TLC monitoring). The DDHQ was filtered off, re-slurred in dichloromethane (160 Kg) and filtered again. The combined filtrates were successively washed with saturated aqueous NaHCO<sub>3</sub> solution (4\*137.5 Kg) and with water (2\*80 Kg). Then, water (150 Kg) was added and the dichloromethane was evaporated in vacuum at 40°C. Another

charge of water (100 Kg) was added to the mixture and the resulting suspension was cooled to 20-25 °C, filtered off on pressure filter and dried in tray dryer in vacuum at 30-35°C for 8 hours (Drying endpoint was checked by determination of drying loss) to get aldehyde **1** with 80% yield (10 Kg).

**NB:** In some cases, reslurry was necessary to obtain targeted purity (ca >98%).

**Re-slurry procedure:**

Wet aldehyde **1** was suspended in di-isopropyl ether at 0-5°C (36 Kg), stirred and filtered off to give wet aldehyde **1** which was dried in tray dryer in vacuum at 30-35°C for 8 hours (Drying endpoint was checked by determination of drying loss) to get aldehyde **1** with required quality.

**Note:**

- This process was repeated 15 times with a range yield of 80-90% to manufacture around 150 Kg of aldehyde **2**.
- In some cases, reload of 1 Kg of DDQ was necessary to complete the reaction.
- Good stirring in the oxidation reaction is necessary.
- Re-slurry of the DDHQ is necessary to obtain good yield.

## 6. Pilot plant aerobic oxidation of (4-fluorobenzothiophen-2-yl) methanol **2**

### 6.1 Representative procedure

Reaction:

In a 80 L enamel reactor equipped with anchor, a multi-holes air inlet line dipping in reaction mixture and a "safety N<sub>2</sub> inlet" on the reactor dome were introduced alcohol **2** (7 Kg), CuCl (756 g), TEMPO (63 g) and DMSO (38.5 Kg). Reaction mixture was stirred at 20°C and air was introduced with a 60 NL/min flow rate through a multi-holes air inlet line. Reaction mixture was stirred under air bubbling until full conversion (determined by LC chromatography, < 0.5% of unreacted **2**) was observed. Then, air bubbling was stopped, nitrogen was introduced in the reactor and crude mixture was combined with two other batches for workup and isolation.

Workup and isolation:

In a 650 L enamel reactor equipped with an impeller were charged water (196 Kg) and ammonia (11N, 17.42 Kg) at 20°C. Then, DMSO solution of crude **1** (3 different batches coming from oxidation of 5.2 Kg, 7.29 Kg and 7.0 Kg of **2** were combined) was carefully added over 30 minutes to maintain internal reaction mixture below 22°C (exothermic addition). Then, reaction mixture was stirred at 20°C during 5h30 and the resulting blue suspension was filtered off. The crude cake was washed successively by water (2\*90 Kg) and HCl 1N (3\*95.6 Kg) and dried at 40°C under vacuum (4-40 mmbar) for 164 hours (KF<0.5%) to give 13.3 Kg of aldehyde **1** (68% yield, 97% LC purity) as yellow solid.

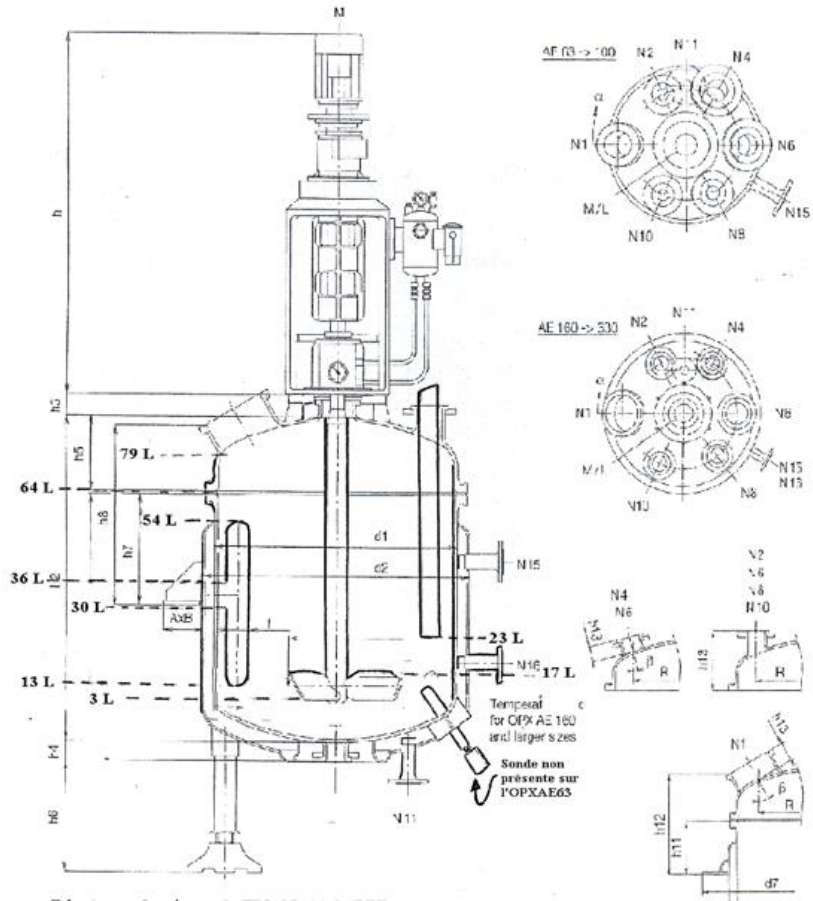
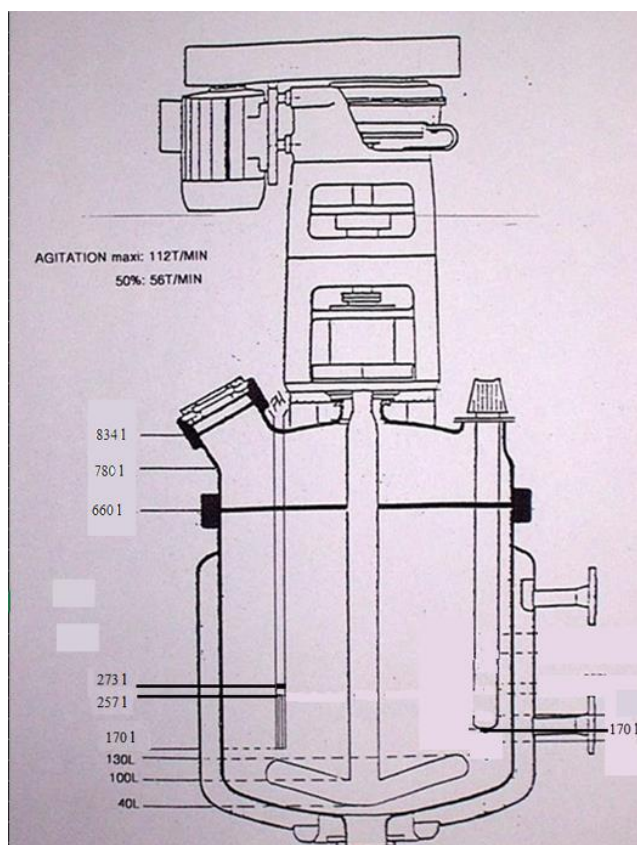


Fig. S1: Reactor used for the reaction



**Fig. S2:** Reactor used for workup and isolation.

## 6.2 Manufacturing campaign resume

Scale (Kg of 2)	IPC <sup>a</sup>				Yield <sup>b</sup>	Purity (LC) <sup>a</sup>
	Time (h)	2 (%)	1 (%)	3 (%)		
5.143	15h	0.3	90.1	9	69%	96.9%
7.371	13	0.7	90.7	7.3		
	17	0.3	90.9	7.5		
7	8	6.4	86.7	4.9		
	16	1.6	91.1	5.3		
	32	0.2	91.6	5.9		

**Table S10:** Resume of manufacturing campaign of aldehyde 1; a. Determined by liquid chromatography (method described in section 1); b. Isolation done by combining reaction mixture of those 3 batches.

## 7. NMR spectra

### 7.1 (4-fluorobenzothiophen-2-yl)methanol 2: match with reported literature data<sup>1</sup>

<sup>1</sup> (a) N. Matsunaga, T. Kaku, F. Itoh, T. Tanaka, T. Hara, H. Miki, M. Iwasaki, T. Aono, M. Yamaoka, M. Kusaka and A. Tasaka, *Bioorg. Med. Chem.*, 2004, **12**, 2251; (b) B. Petho, G. B. Szilágyi, B. Mengyel, T. Nagy, F. Farkas, K. Kátai-Fadgyas and B. Volk, *Org. Process Res. Dev.*, 2022, **26**, 1223.

44819 - AD2 - NP - fluorothinol - - NEO44819035 - NA - 1705A02005  
10 mg - DMSO - PEMN

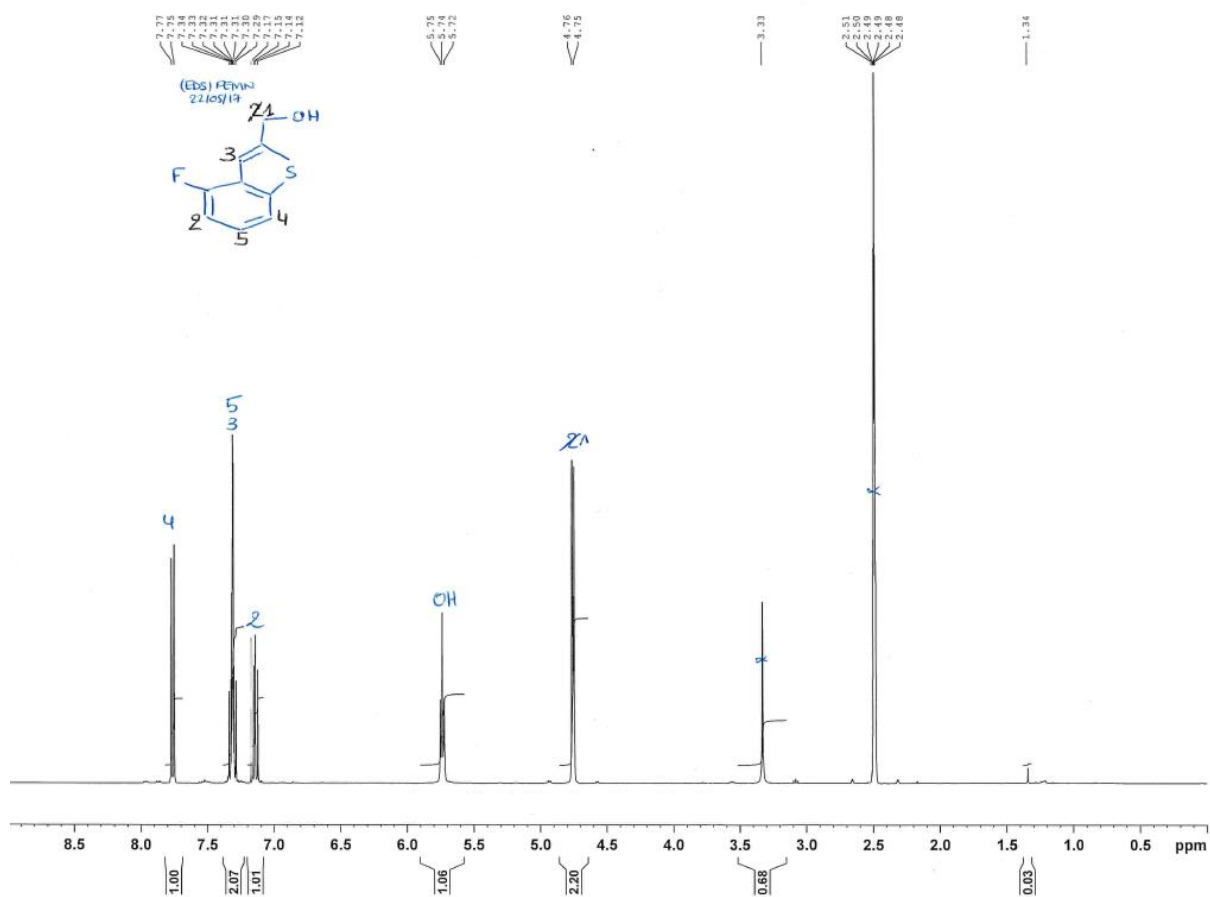


Fig. S3: Recorded  $^1\text{H}$  NMR spectra of alcohol 2.

44819 - AD2 - NP - fluorothinol - - NEO44819035 - NA - 1705A02005  
 10 mg - DMSO - PENN

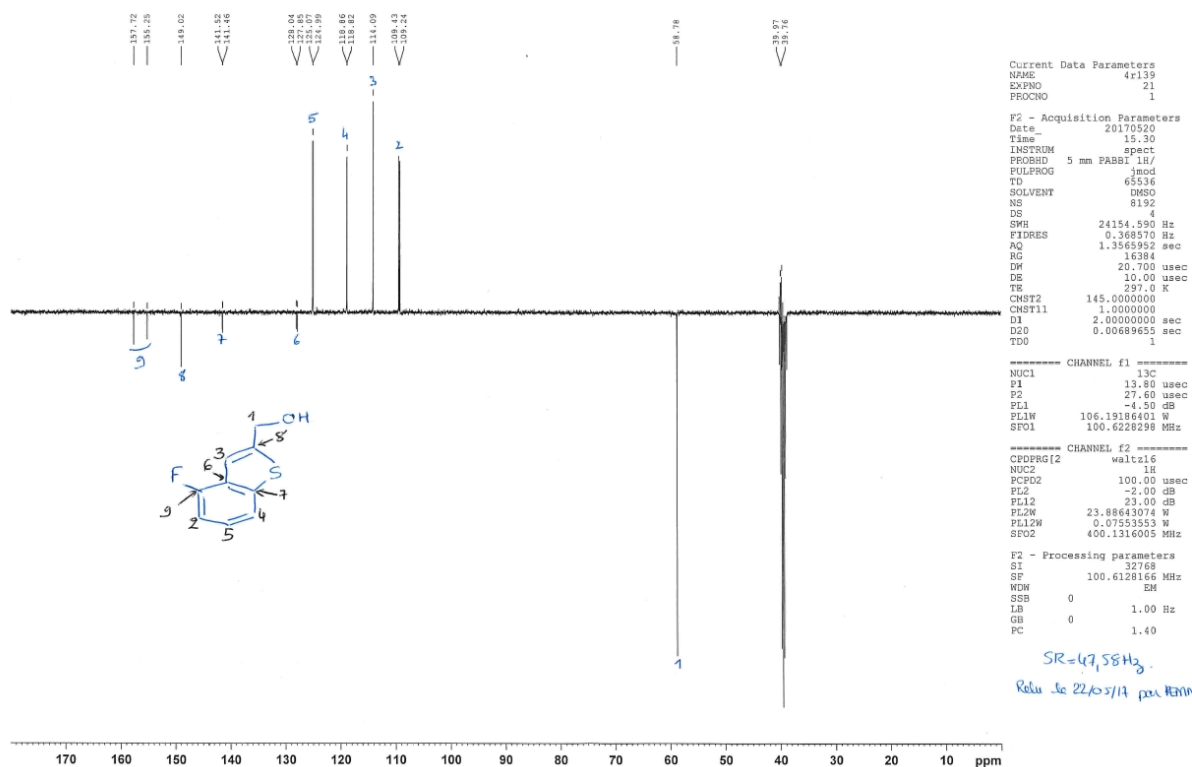


Fig. S4: Recorded JMOD spectra of alcohol 2.

7.2 4-fluorobenzothiophene-2-carbaldehyde 1: match with reported literature data<sup>1</sup>

44819 - 44819AD3 - NA - FLUOROTHIANAL - - 44819A16JFG012 PUR - NA - 1603A01647 -  
10 mg - DMSO - GECT/NJT

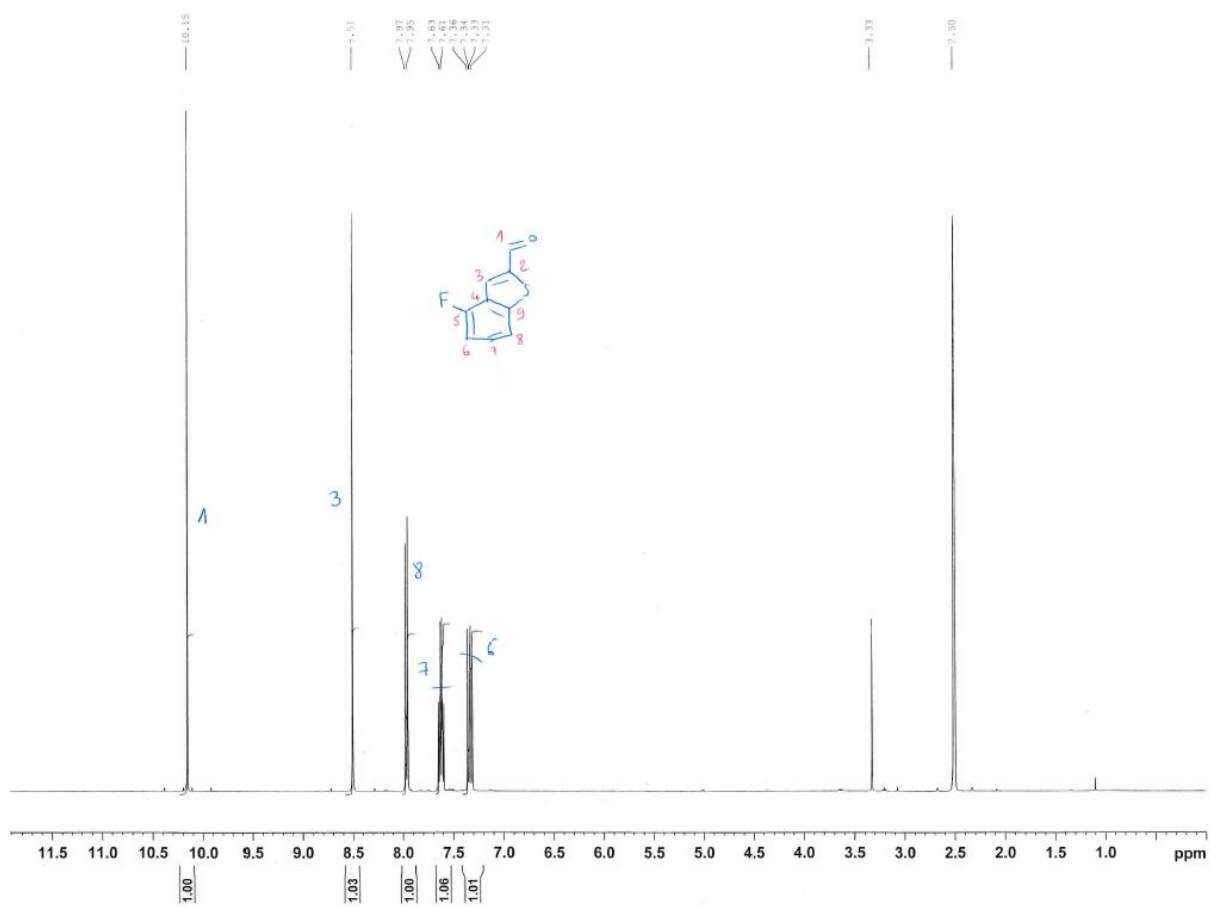


Fig. S5: Recorded <sup>1</sup>H spectra of aldehyde 1.





44819 - NA - NA - FLUOROTHIOLIC - - NEO44819016 APTRAIT - NA - 1705A02093  
12 mg - DMSO - PEMN

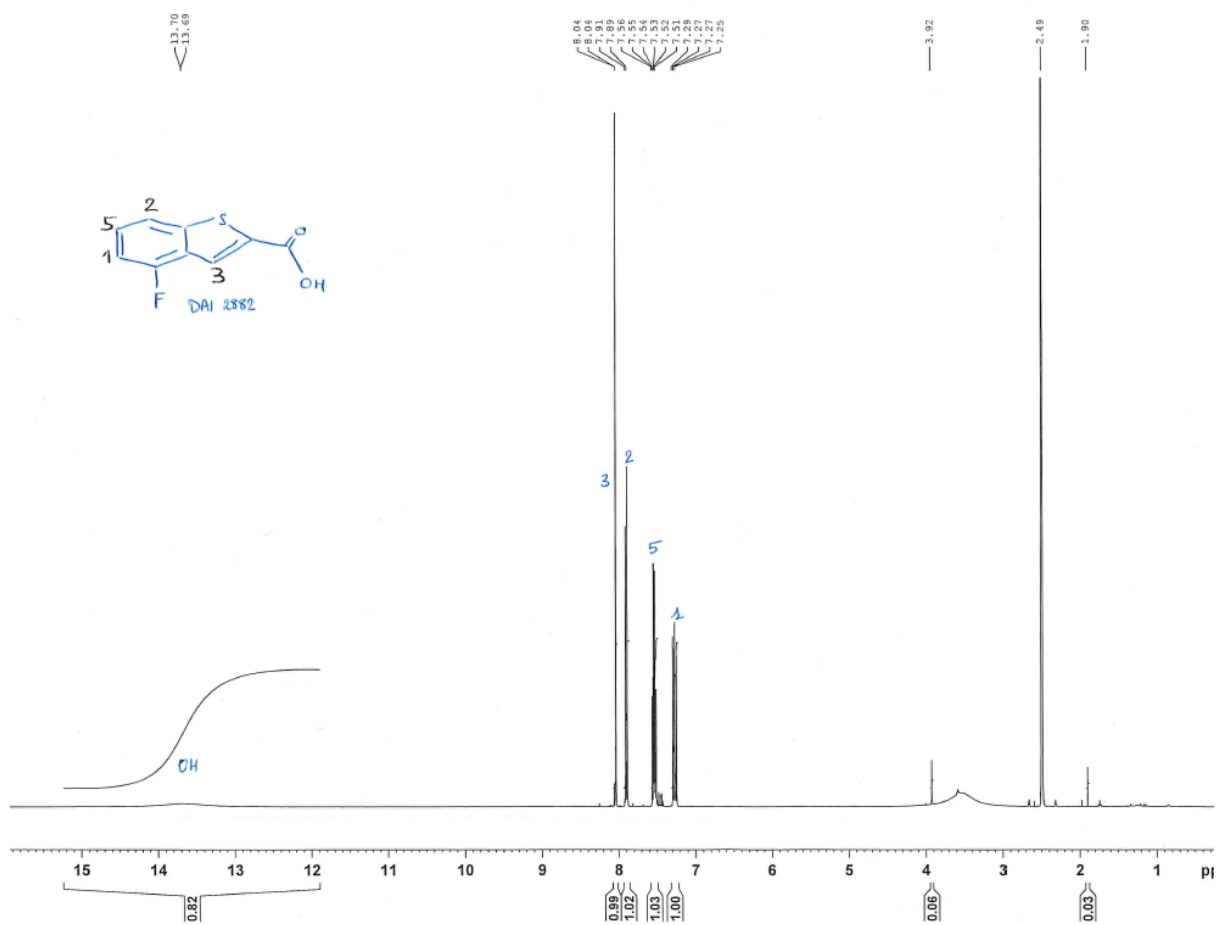


Fig. S7: Recorded  $^1\text{H}$  spectra of overoxidation by-product 3.

44819 - NA - NA - FLUOROTHIOIC - - NEO44819016 APTRAIT - NA - 1705A02093  
12 mg - DMSO - PEMN

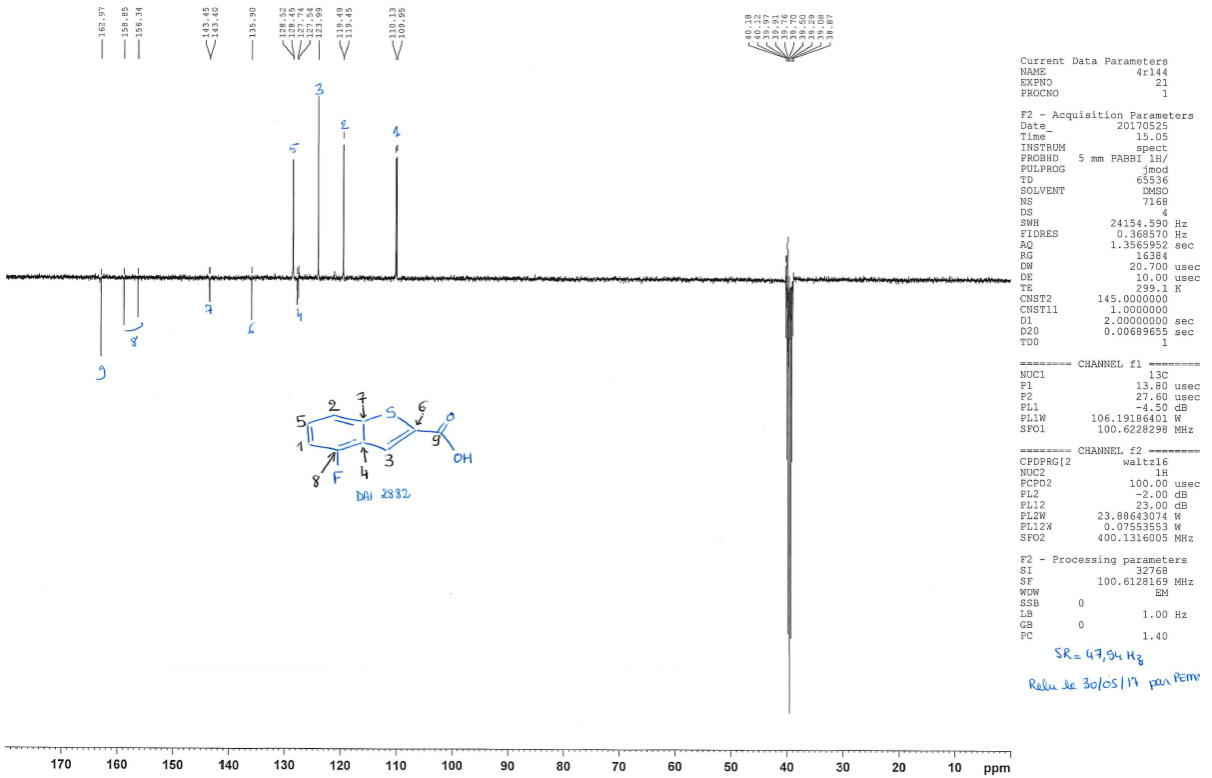


Fig. S8: Recorded JMOD spectra of overoxidation by-product 3.

## 8. Liquid chromatography spectra<sup>3</sup>

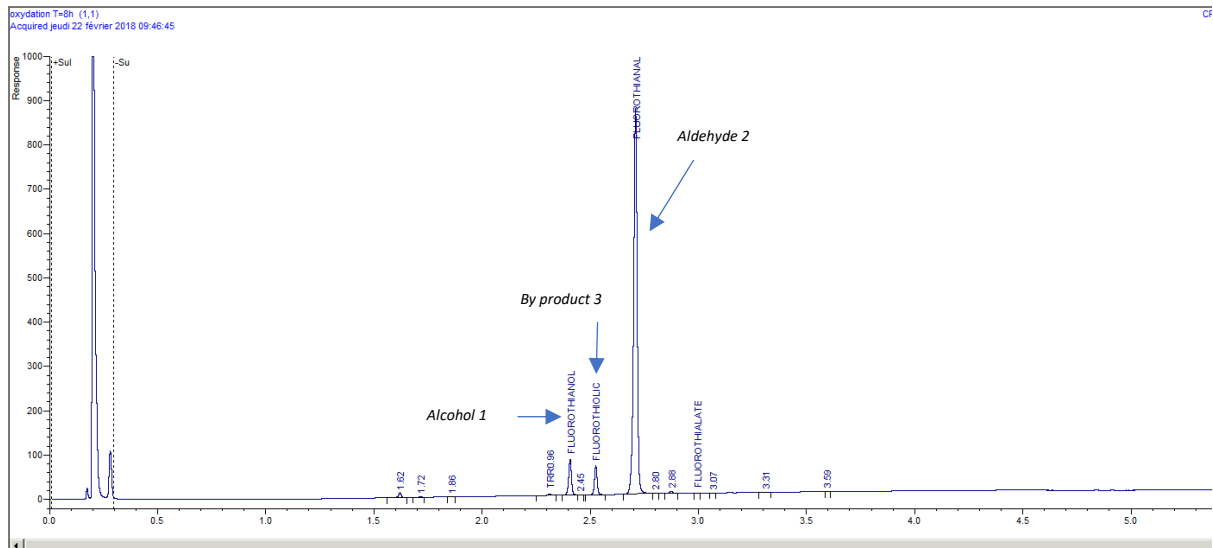
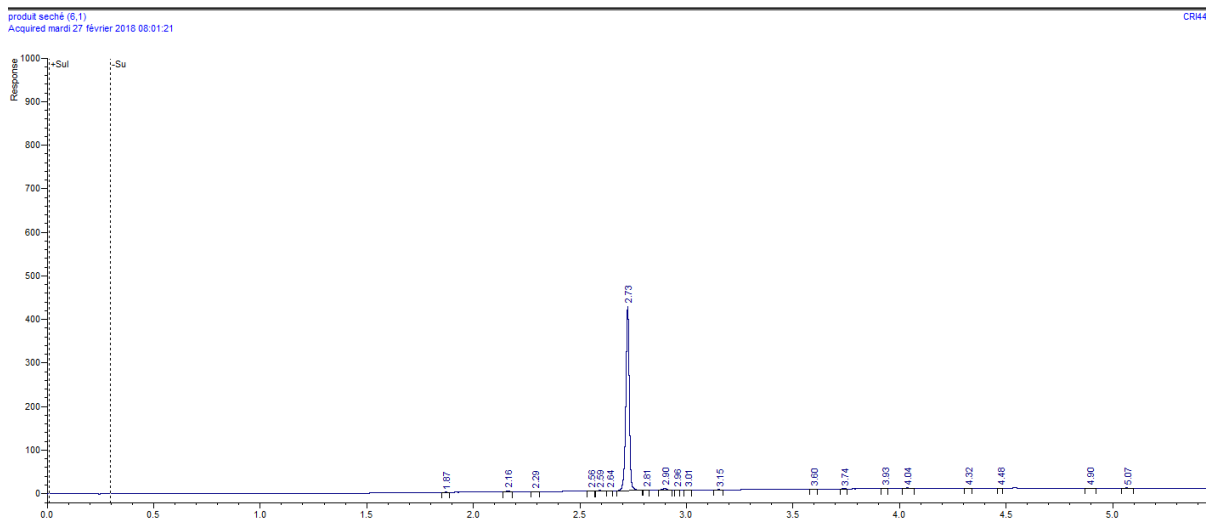


Fig. S9: Typical in Process Control (here after 8 hours) (7 Kg scale). Alcohol 2: 6.44 %; Aldehyde 1: 86.7 %; Carboxylic acid 3: 4.9 %.

<sup>3</sup> Analytical conditions reported in section 1.



**Fig. S10:** LC spectra of isolated 4-fluorobenzothiophene-2-carbaldehyde **1**, 96.9% purity.

## 9. DSC analysis

### 9.1 Calculation method for TMRad and TD24

Hypothesis: 0 order reaction kinetic.

Adiabatic Time to Maximum Raise is calculated according the following formula:

$$TMR_{ad}(T) = \frac{C_p \times R \times T^2}{E_a \times Q}$$

Where:

$$Q = Q_{ref} \times e^{\left(\frac{-E_a}{R} \left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right)}$$

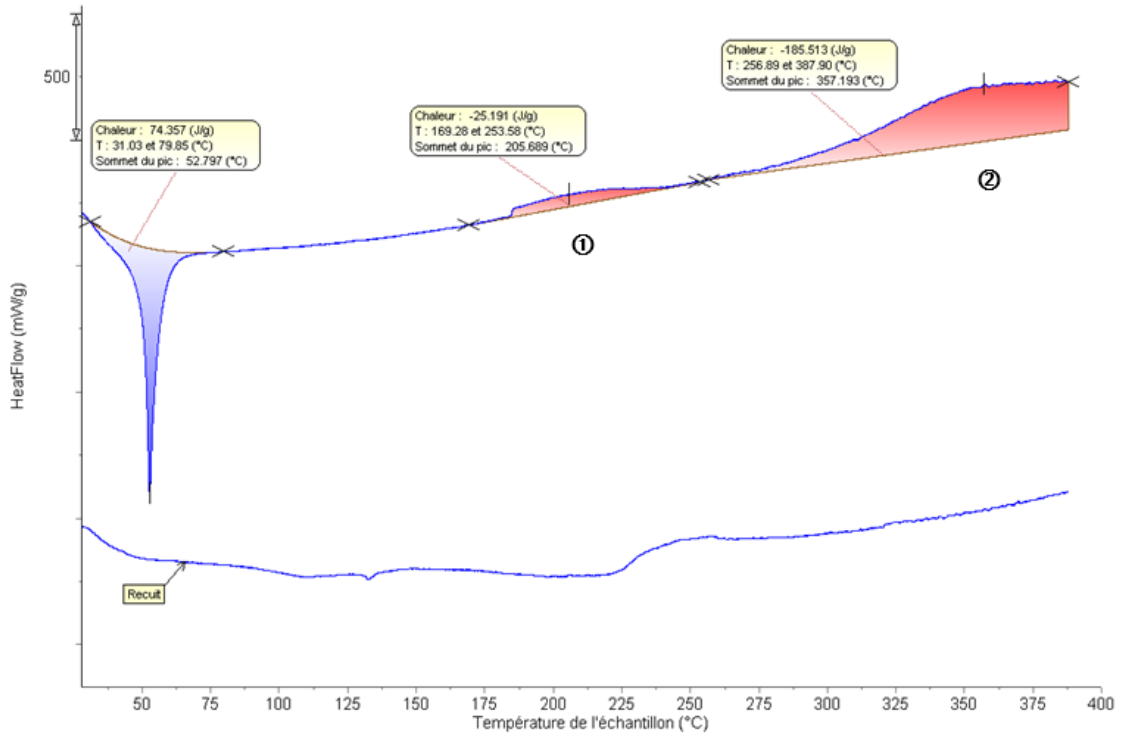
→ Q ref and Tref are extracted from the DSC thermogram.

→ EA = activation energy

→ R = gaz constant

→ Cp = heat capacity of the mixture

### 9.2 DSC Spectra



Description des phénomènes exothermiques

	T(onset / max / final) [°C]	Enthalpie [J/g]	Commentaires
①	<u>169</u> / 206 / 254	(-) 25.2	Energie faible ( $\Delta T_{ad} \approx 25.2^\circ\text{C}$ )
②	<u>257</u> / 357 / 388	(-) > 185.5	Energie modérée ( $\Delta T_{ad} \approx 185.5^\circ\text{C}$ )

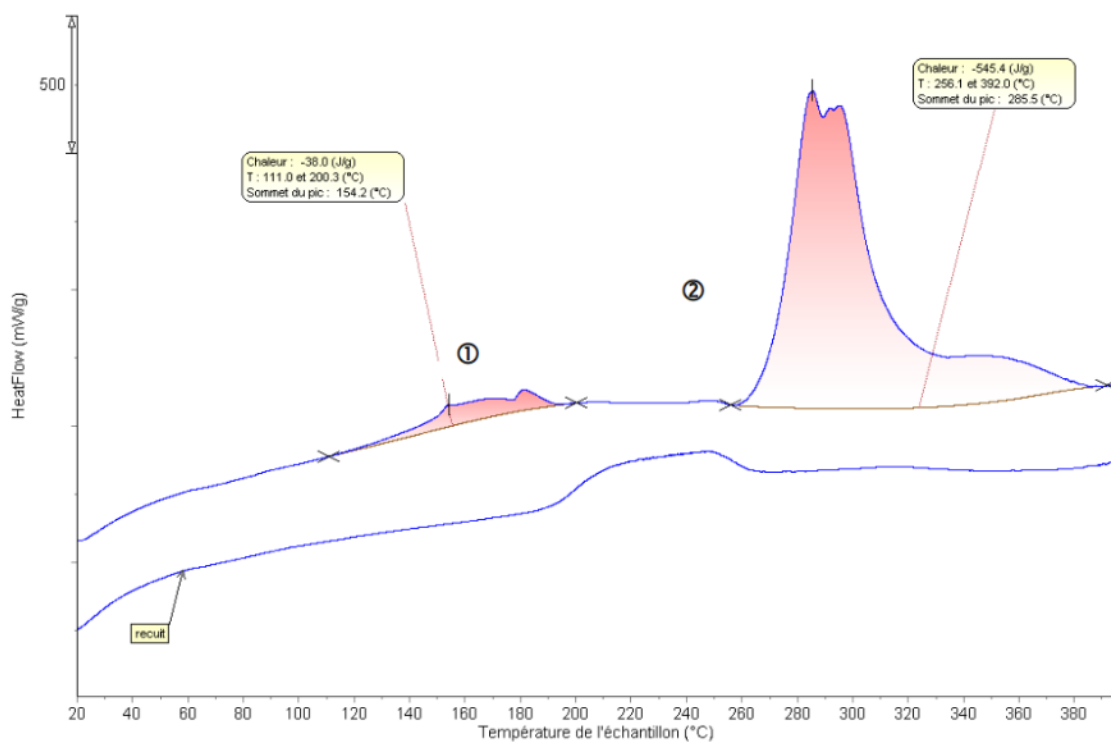
Fig. S11: DSC of alcohol 2; The  $\Delta T_{ad}$  was calculated with a value of  $C_p = 1.00 \text{ kJ} \cdot \text{kg}^{-1} \cdot \text{K}^{-1}$ .

### Annex 8 Thermal stability of organic phase in DMSO

Sample name: NEO\_44819\_373

Sample aspect: Solution

N° DSC : DSC823\_085/2017



#### Description of exothermic phenomenon

	T(onset / max / final) [°C]	Enthalpie [J/g]	Comments
①	111 / 154 / 200	(-) 38	Energie faible ( $\Delta T_{ad} \approx 19^\circ\text{C}$ )
②	256 / 285 / 392	(-) 545	Energie forte ( $\Delta T_{ad} \approx 278^\circ\text{C}$ )

#### Evaluation of $TMR_{ad}$

Quick TMR

AKTS

8h	12h	24h	47 h	Ea [kJ/mol]	Cp [kJ/kg.K]	T <sub>ref</sub> [°C]	q <sub>ref</sub> [W/kg]
85°C	79°C	68°C	T <sub>procédé</sub> 58°C	70	1.96	137	21

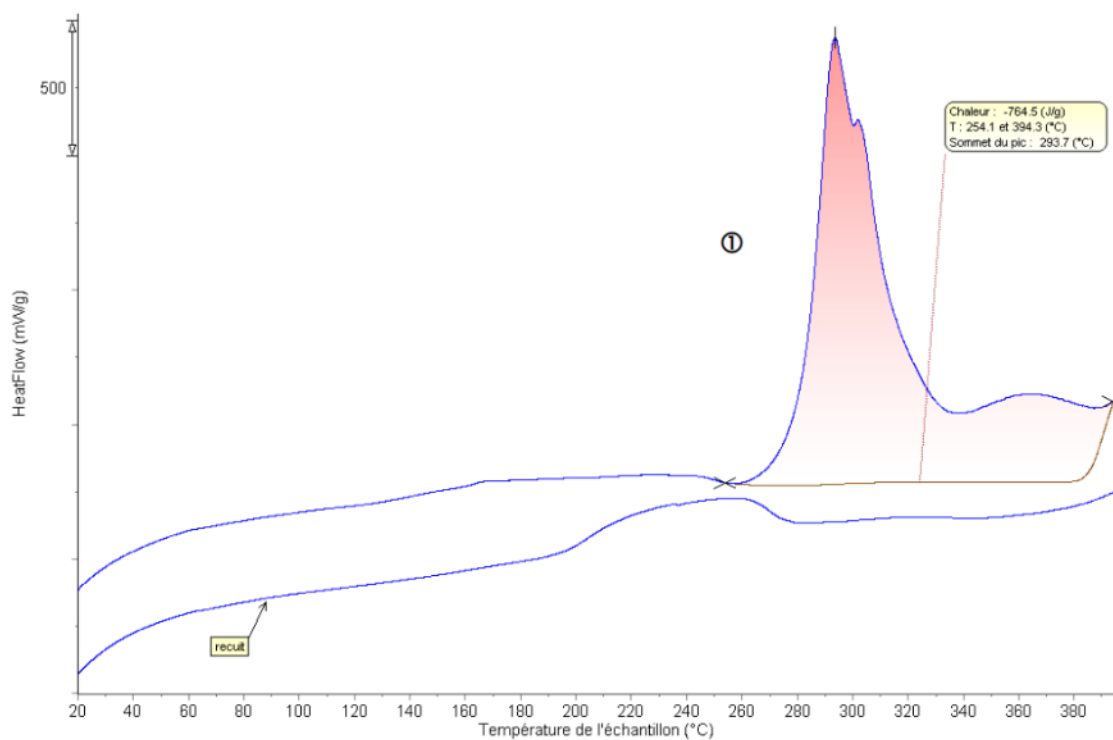
Fig. S12: Solution of alcohol 2 in DMSO; The  $\Delta T_{ad}$  was calculated with a value of  $C_p = 1.96 \text{ kJ.Kg}^{-1}.\text{K}^{-1}$ .

### Annex 9 Thermal stability at the end of TEMPO/CuCl addition

Sample name: NEO\_44819\_373

Sample aspect: solution

N° DSC : DSC823\_086/2017



#### Description of exothermic phenomenon

	T(onset / max / final) [°C]	Enthalpie [J/g]	Comments
①	254 / 294 / 394	(-) 764	Energie forte ( $\Delta T_{ad}^9 \approx 380^\circ\text{C}$ )

Fig. S13: DSC of reaction mixture before introduction of air; The  $\Delta T_{ad}$  was calculated with a value of  $C_p = 1.96 \text{ KJ.Kg}^{-1}.\text{K}^{-1}$ .

## Annex 10 Thermal stability at the end of reaction

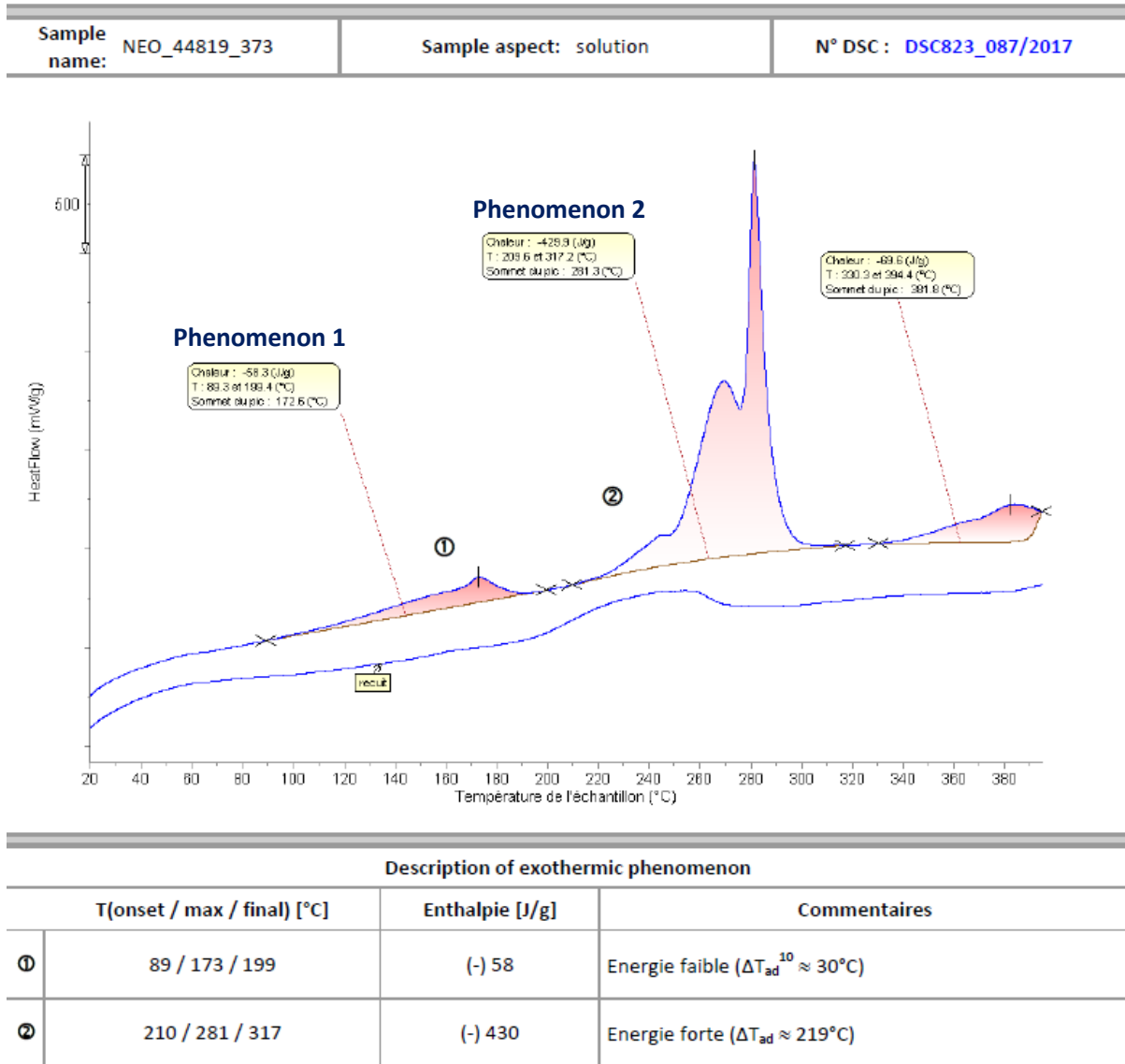


Fig. S14: DSC of reaction mixture at the end of reaction. The  $\Delta T_{ad}$  was calculated with a value of  $C_p = 1.96 \text{ kJ}\cdot\text{kg}^{-1}\cdot\text{K}^{-1}$ .

### Evaluation of TMRad of phenomenon 1 (from DSC in fig.S14):

- With an EA of  $50 \text{ kJmol}^{-1}$

Estimation du TMRad					Ea [kJ/mol]	Cp [kJ/kg.K]	Tref [°C]	Qref [W/kg]
8h	12h	24h	63h	3jours				
57,5°C	49,5°C	36,5°C	Tp = 20°C		50	1,957	117,8	21,1

Estimation du TMRad					Ea [kJ/mol]	Cp [kJ/kg.K]	Tref [°C]	Qref [W/kg]
8h	12h	24h	1h	0jours				
57,5°C	49,5°C	36,5°C	Tp = 119°C		50	1,957	117,8	21,1

- With an EA of  $70 \text{ kJmol}^{-1}$



Estimation du TMRad					Ea	Cp	Tref	Qref
8h	12h	24h	350h	15jours	[kJ/mol]	[kJ/kg.K]	[°C]	[W/kg]
69,0°C	63,0°C	53,0°C	Tp = 20°C		70	1,957	117,8	21,1

Estimation du TMRad					Ea	Cp	Tref	Qref
8h	12h	24h	0h	0jours	[kJ/mol]	[kJ/kg.K]	[°C]	[W/kg]
69,0°C	63,0°C	53,0°C	Tp = 119°C		70	1,957	117,8	21,1

### Evaluation of TMRad of phenomenon 2 (from DSC in fig. S14):

- With an EA of 50 KJmol<sup>-1</sup>

Estimation du TMRad					Ea	Cp	Tref	Qref
8h	12h	24h	15h	1jours	[kJ/mol]	[kJ/kg.K]	[°C]	[W/kg]
138,5°C	125,5°C	105,5°C	Tp = 119°C		50	1,957	225,4	25,0

Estimation du TMRad					Ea	Cp	Tref	Qref
8h	12h	24h	6h	0jours	[kJ/mol]	[kJ/kg.K]	[°C]	[W/kg]
138,5°C	125,5°C	105,5°C	Tp = 149°C		50	1,957	225,4	25,0

- With an EA of 70 KJmol<sup>-1</sup>

Estimation du TMRad					Ea	Cp	Tref	Qref
8h	12h	24h	39h	2jours	[kJ/mol]	[kJ/kg.K]	[°C]	[W/kg]
154,5°C	144,5°C	129,5°C	Tp = 119°C		70	1,957	225,4	25,0

Estimation du TMRad					Ea	Cp	Tref	Qref
8h	12h	24h	10h	0jours	[kJ/mol]	[kJ/kg.K]	[°C]	[W/kg]
154,5°C	144,5°C	129,5°C	Tp = 149°C		70	1,957	225,4	25,0

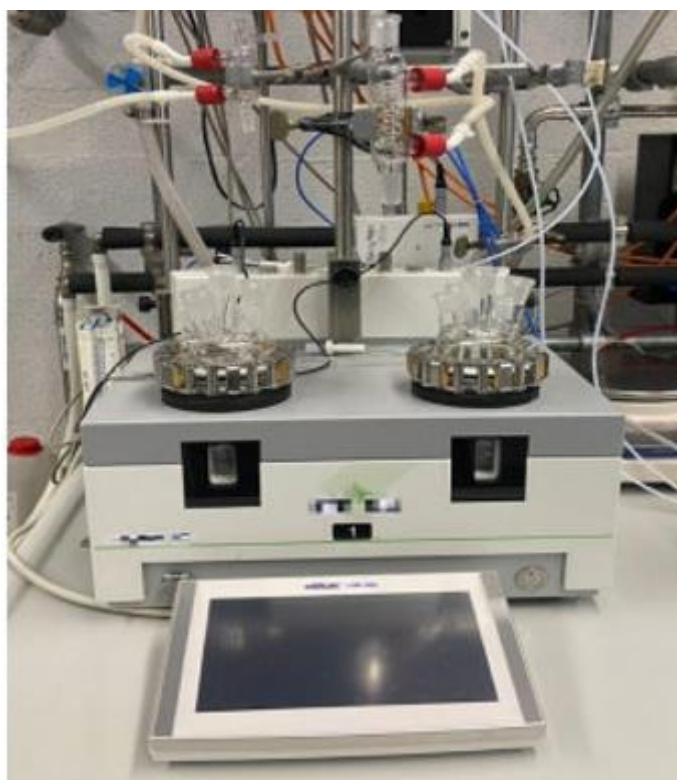
## 10. Calorimetric study

### 10.1 Apparatus

Experiment was recorded using METTLER-TOLEDO EasyMax 102 heat flow calorimeter on 15 gr scale.

EasyMax 102	Description
Device	EasyMax 102 (Serial #: B308064965 / Firmware: 5.2.2.0)
Reactor	100 ml
Stirrer	Overhead

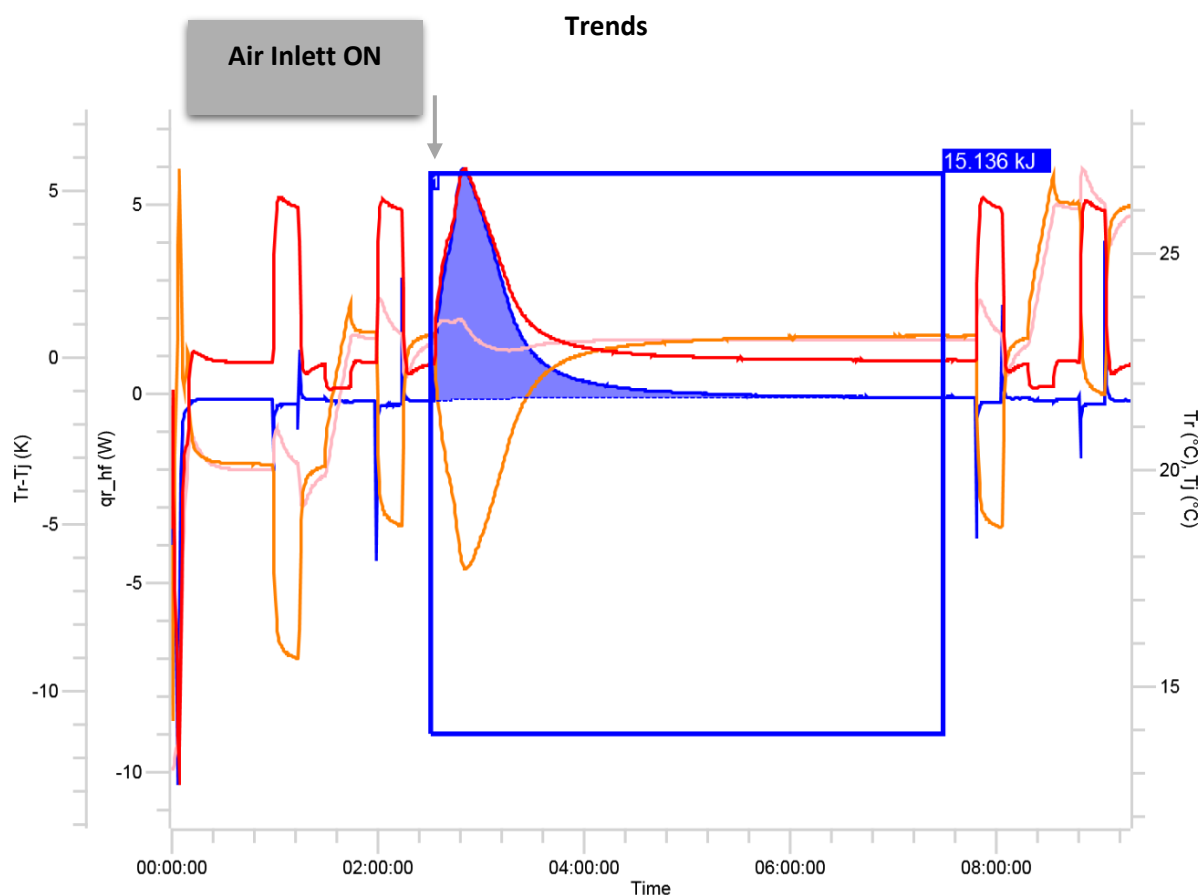
EasyMax 102	Description
Other	Tr Sensor HFCal (last adjusted on 07/03/2023) Calibration Heater



NB: This experiment was repeated 3 times with reproducible results.

## 10.2 EasyMax report

### 10.2.1 Calorimetric experiment



### Integral Results

Trend	Name	Start Time	End Time	Integral	Baseline Type	$\Delta T_{ad}$
qr_hf	1	02:30:32	07:28:46	15.136 kJ	Proportional To Conversion	98.783 K

### Virtual Volume (Vv)

Time	Vv (used)	Interpolation
00:00:06	89.06 ml	Proportional to Vr
00:44:08	90 ml	Constant offset

### Heat Transfer Coefficient (U)

Time	U (used)	Calculated by	Interpolation
01:06:40	125.56 W/K*m <sup>2</sup>	Standard method	Proportional to Vv_observed
02:06:44	127.31 W/K*m <sup>2</sup>	Standard method	Proportional to Vv_observed
07:55:28	127.46 W/K*m <sup>2</sup>	Standard method	Proportional to Vv_observed
08:55:32	128.55 W/K*m <sup>2</sup>	Standard method	Hold value

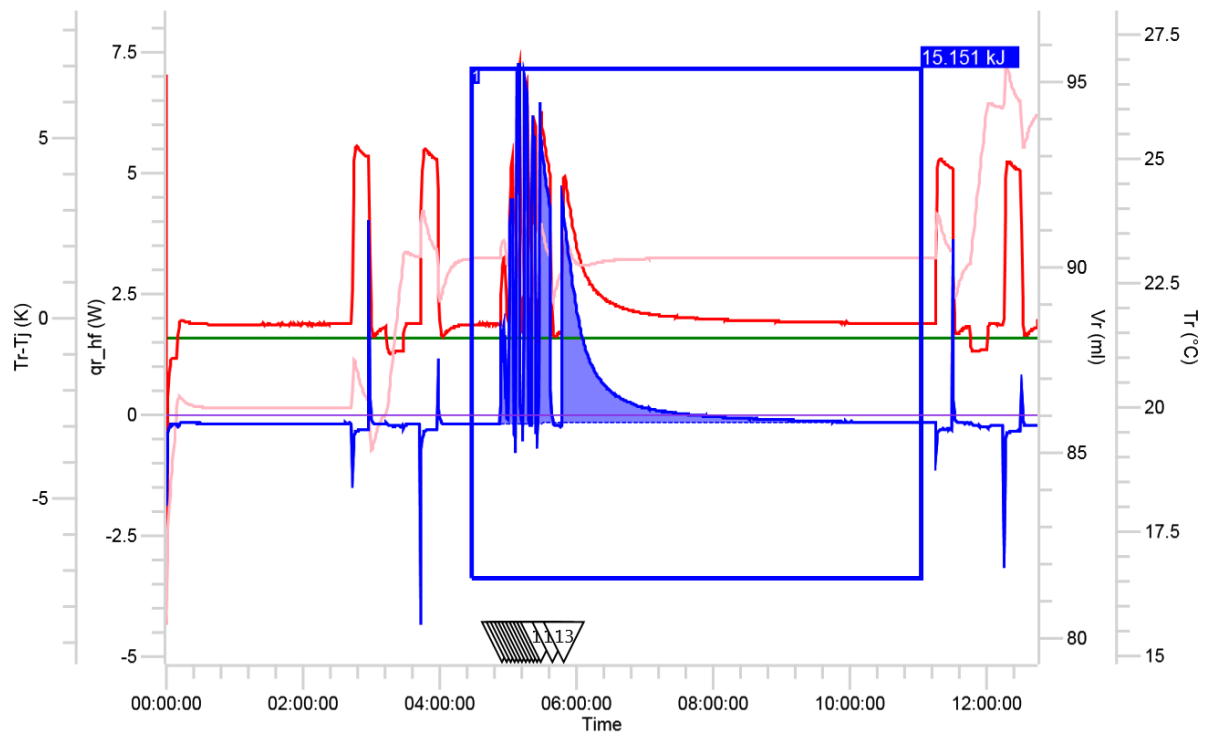
### Specific Heat (cpr)

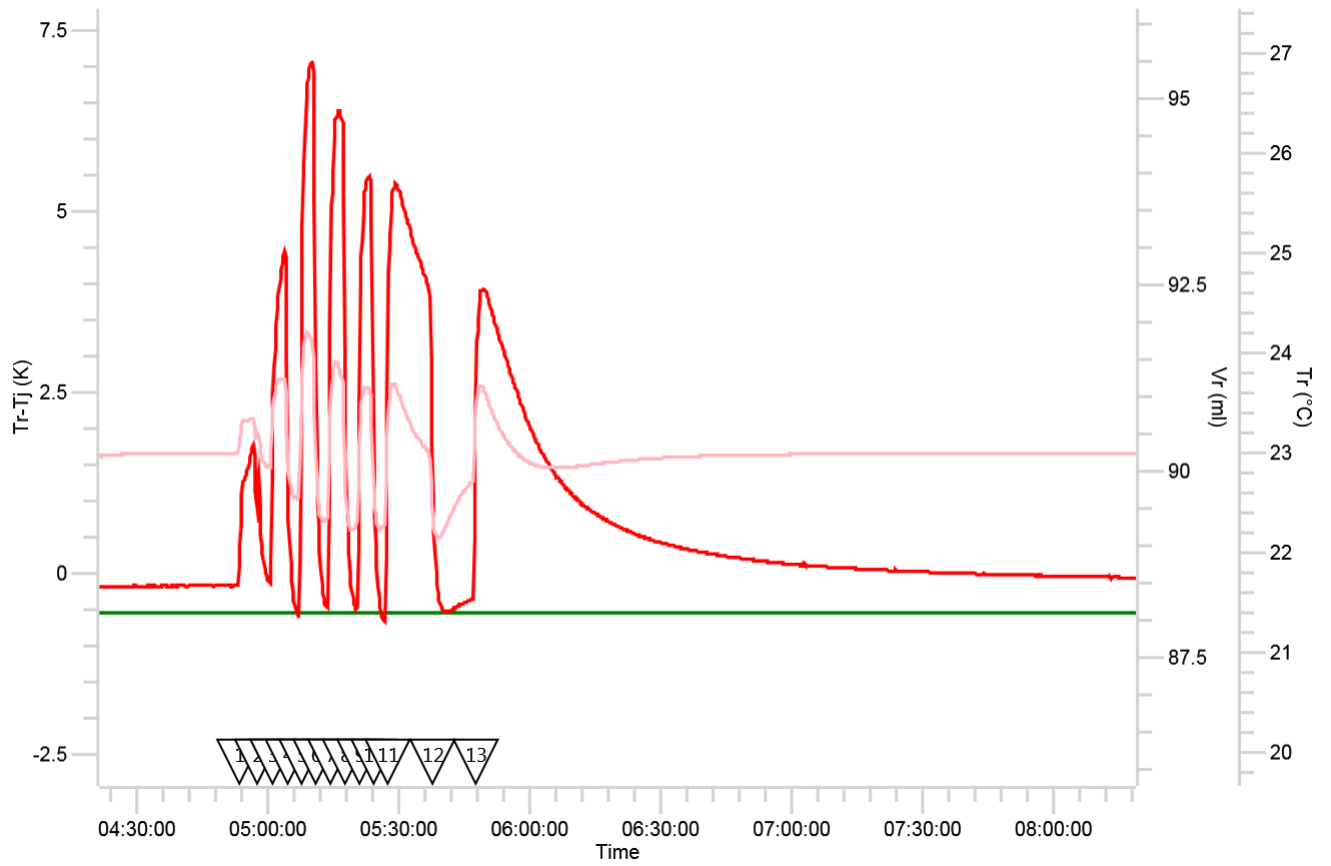
Time	cpr (used)	Calculated by	Interpolation
01:36:40	1.6002 J/g*K	Standard method	Proportional to Mr
08:25:28	1.5870 J/g*K	Standard method	Hold value

## Various Parameters

qr definition	$qr\_hf = qflow\_hf - qc + qaccu + qdos$
qdos averaged	yes
cpi at 50 ml	7.1 J/K
cpi at 100 ml	16.79 J/K
Reactor Time Constant	15 s
$\Delta T_{ad}$ calculation	Use mr and cpr at the end of the integral

### 10.2.2 Air supply impact evaluation





Trend	Color	Units
Tr		°C
Vr		ml
Tr-Tj		K

#	Action / Annotation
1	AD CATA AIR
2	NITROGENE
3	AIR
4	NITROGENE
5	AIR
6	NITROGENE
7	AIR
8	NITROGENE
9	AIR
10	NITROGENE
11	AIR
12	NITROGENE

#	Action / Annotation
13 v	AIR

### Integral Results

Trend	Name	Start Time	End Time	Integral	Baseline Type	$\Delta T_{ad}$
qr_hf	1	04:45:28	10:56:28	15.304 kJ	Proportional To Conversion	96.634 K

### Virtual Volume (Vv)

Time	Vv (used)	Interpolation
00:00:06	88.12 ml	Proportional to Vr
02:28:20	90 ml	Constant offset

### Heat Transfer Coefficient (U)

Time	U (used)	Calculated by	Interpolation
02:50:52	125.76 W/K*m <sup>2</sup>	Standard method	Proportional to Vv_observed
03:50:56	127.48 W/K*m <sup>2</sup>	Standard method	Proportional to Vv_observed
11:22:04	135.05 W/K*m <sup>2</sup>	Standard method	Proportional to Vv_observed
12:22:08	136.52 W/K*m <sup>2</sup>	Standard method	Hold value

### Specific Heat (cpr)

Time	cpr (used)	Calculated by	Interpolation
03:20:52	1.6248 J/g*K	Standard method	Proportional to Mr
11:52:08	1.6625 J/g*K	Standard method	Hold value

### Various Parameters

qr definition	$qr\_hf = qflow\_hf - qc + qaccu + qdos$
qdos averaged	yes
cpi at 50 ml	7.1 J/K
cpi at 100 ml	16.79 J/K
Reactor Time Constant	15 s
$\Delta T_{ad}$ calculation	Use mr and cpr at the end of the integral

## 11. Green metrics calculation

### 11.1 DDQ process

Materials	Input (Kg)	Output (Kg)	Hazardous
Alcohol 2	12.5		Yes <sup>a</sup>
CH <sub>2</sub> Cl <sub>2</sub>	120		yes
DDQ	16		yes
CH <sub>2</sub> Cl <sub>2</sub>	160		yes
Aq NaHCO <sub>3</sub>	137.5		
Aq NaHCO <sub>3</sub>	137.5		
Aq NaHCO <sub>3</sub>	137.5		
Aq NaHCO <sub>3</sub>	137.5		
water	80		

water	80		
water	150		
water	100		
di-isopropylether	36		
Aldehyde 1		10	
total	1304.5	10	

**Table S11:** Materials charges used for the DDQ process; a. In order to compare DDQ and Cu/air process, and in absence of any data, alcohol 1 is considered as non-hazardous material.

$$\text{PMI} = \frac{\Sigma m (\text{Input materials incl water})}{m (\text{Product})} = \frac{1304.5}{10} = \mathbf{130 \text{ Kg/Kg of 1}}$$

$$\text{RME} = \frac{m \text{ Product} * 100}{\Sigma m (\text{Raw materials})} = \frac{10 * 100}{12.5 + 16} = \mathbf{35\%}$$

$$\text{EMY} = \frac{m \text{ Product} * 100}{\Sigma m (\text{Hazardous reactants/reagents})} = \frac{10}{16} = \mathbf{63\%}$$

$$\text{Reagents cost}^a = \frac{\Sigma (\text{reagent's price})}{m \text{ Product}} = \frac{16 * 1510.4}{10} = \mathbf{2416 \text{ euros/Kg 1}}$$

**Fig. S15:** selected metrics calculation for DDQ oxidation process; a. Price (from ABCR) of = 1510.4 euros/Kg.

## 11.2 Aerobic copper oxidation process

Material <sup>a</sup>	Input (Kg)	Output (Kg)	Hazardous
Alcohol 2	19.51		yes <sup>b</sup>
CuCl	2.107		yes <sup>c</sup>
TEMPO	0.176		yes <sup>d</sup>
DMSO	107.3		
WATER	196		
AMMONIA (11 N)	17.4		
water	90		
water	90		
HCl 1N	95.6		
HCl 1N	95.6		
HCl 1N	95.6		
Aldehyde 1		13.3	
total	809.3	13.3	

**Table S12:** Materials charges used for the Cu/Tempo/Air process; a. Charge of Input material is an average of the 3 batches of the campaign; b. In order to compare DDQ and Cu/air process, and in absence of any data, alcohol 2 is considered as non-hazardous material. c. CuCl is considered as hazardous for environment; d. TEMPO is considered as hazardous material.

$$\text{PMI} = \frac{\Sigma m (\text{Input materials incl water})}{m (\text{Product})} = \frac{809.3}{13.3} = \mathbf{60.8 \text{ Kg/Kg of 1}}$$

$$\text{RME} = \frac{m \text{ Product} * 100}{\Sigma m (\text{Raw materials})} = \frac{13.3}{19.51} = \mathbf{68\%}$$

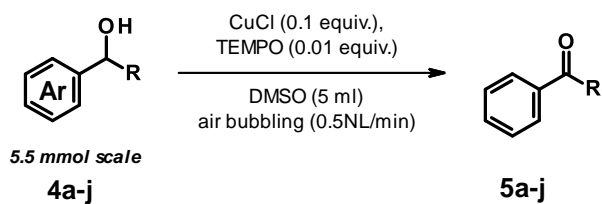
$$\text{EMY} = \frac{m \text{ Product} * 100}{\Sigma m (\text{Hazardous reactants/reagents})} = \frac{13.3}{2.107 + 0.176} = \mathbf{583\%}$$

$$\text{Reagents cost}^a = \frac{\Sigma (\text{reagent's price})}{m \text{ Product}} = \frac{(2.107 * 94.5) + (1076.8 * 0.176)}{13.3} = \mathbf{29.2 \text{ euros/Kg 1}}$$

**Fig. S16:** Selected metrics calculation for Cu/TEMPO/air oxidation process; a. Price (from ABCR): CuCl = 94.5 euros/Kg, TEMPO = 1076.8 euros/Kg.

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## 12. Scope of the method

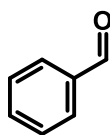


### Standard procedure:

Alcohol **4a-j** (5.5 mmol, 1 equiv.), CuCl (54 mg, 0.55 mmol, 0.1 equiv.), TEMPO (8.6 mg, 0.55 mmol, 0.01 equiv.) and DMSO (5 mL) were charged in 10 mL three necks round bottom flask. Reaction mixture was stirred (magnetic stirring, 1400 rpm) in presence of air (air bubbling through reaction mixture, 0.5NL/min) and at 20°C until maximum of conversion. Reaction mixture was quenched by addition of NH<sub>4</sub>OH solution (10% w.w, 10ml), turning the color from green to deep blue and extracted by MTBE (2\*15 ml). Organic layers were combined, washed by brine (2\*10 ml) and concentrated to dryness to give title compound **4a-j**.



## Benzaldehyde 5a: match with reported data<sup>4</sup>



5a

Obtained using standard procedure with 96% content in reaction mixture (determined by LC chromatography, reaction performed from 595 mg of **4a**). Partial decomposition of product was observed during isolation.

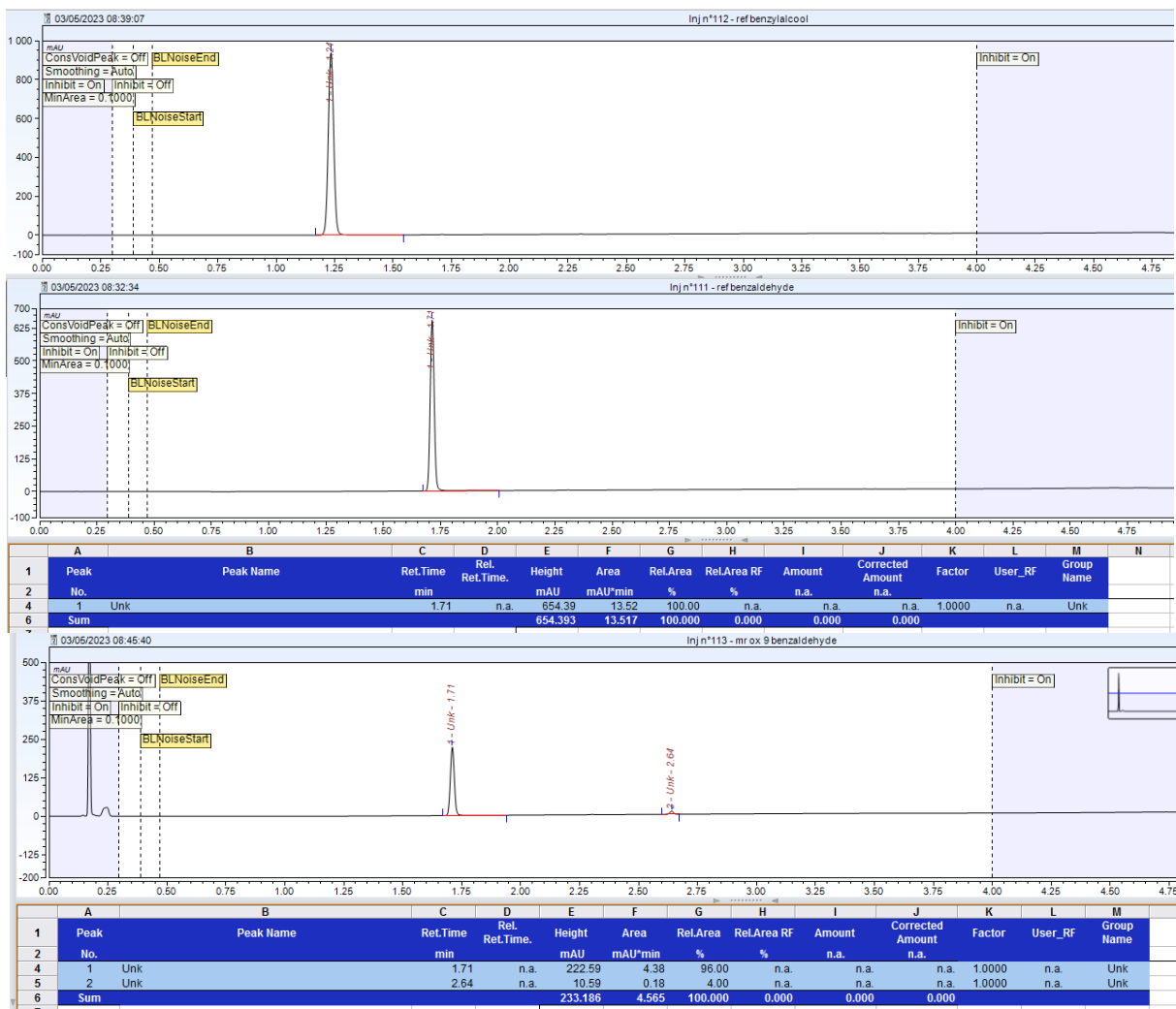
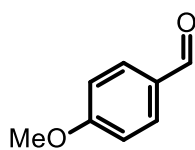


Fig S17. top: LC spectra of **4a**; middle = LC spectra of commercial benzaldehyde; bottom = ICP (In Process Control) at the end of oxidation of **4a**

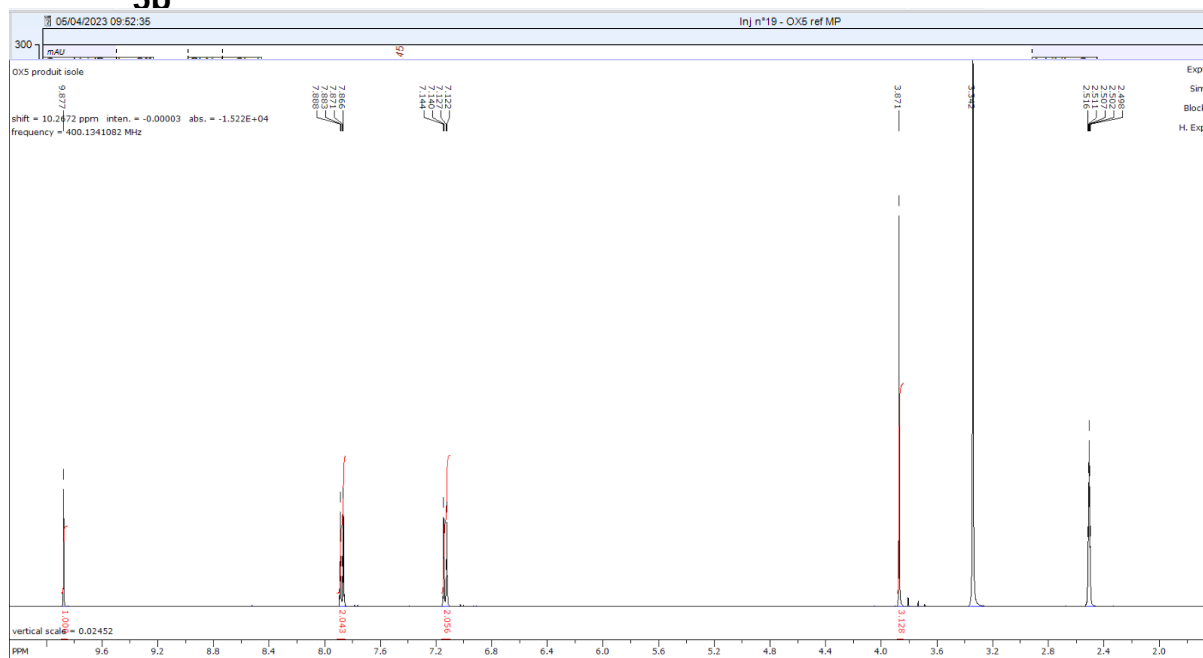
<sup>4</sup> S. Velusamy and T. Punniyamurthy, *Org. Lett.* 2004, 6, 2, 217.

4-methoxybenzaldehyde **5b**: match with reported data<sup>5</sup>



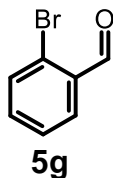
Obtained using standard procedure with 80% yield (600 mg isolated from 760 mg of **4b**) as yellow liquid. No purification was required.

**5b**



**Fig S18**: At the top = alcohol **4b**; middle: reaction mixture at 100% conversion. bottom. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) of isolated product **5b**.

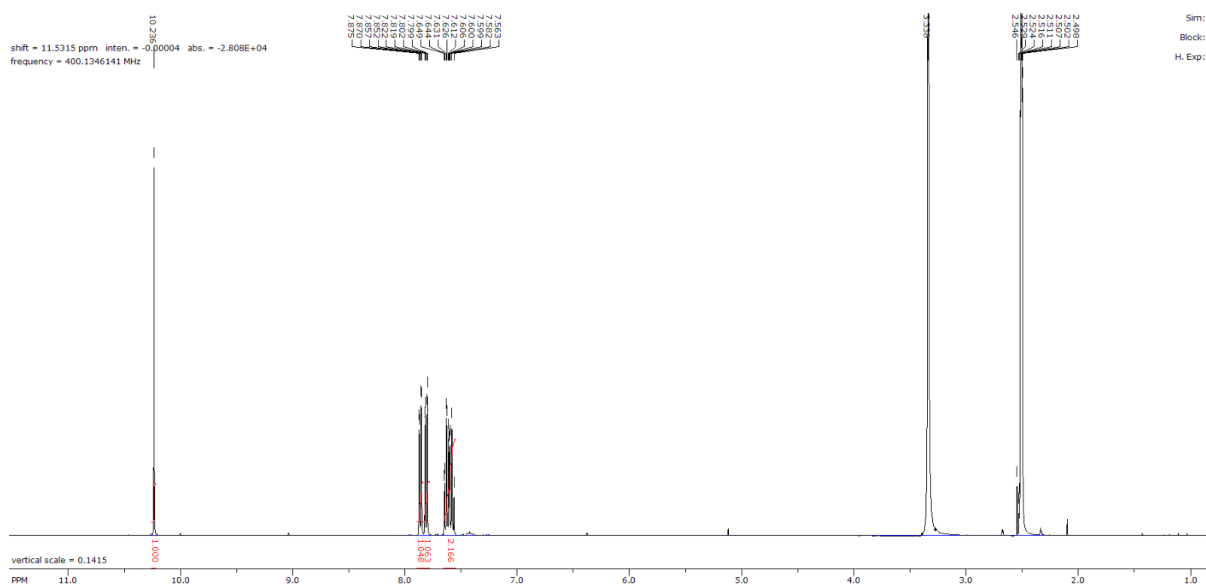
2-bromobenzaldehyde **5g**: match with reported data<sup>6</sup>



Obtained using standard procedure with 85% yield (850 mg isolated from 1.02 g of **4g**) of alcohol Y as slightly orange liquid. No purification was required.

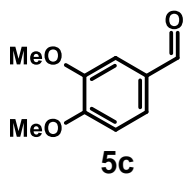
<sup>5</sup> J. Zhang, J. Du, C. Zhang, K. Liu, F. Yu, Y. Yuan, B. Duan and R. Liu, *Org. Lett.*, 2022, **24**, 1152.

<sup>6</sup> G. Zhang, X. Wen, Y. Wang, X. Han, Y. Luan, L. Zheng, C. Ding, and X. Cao, *RSC Adv.*, 2013, **45**, 22918.

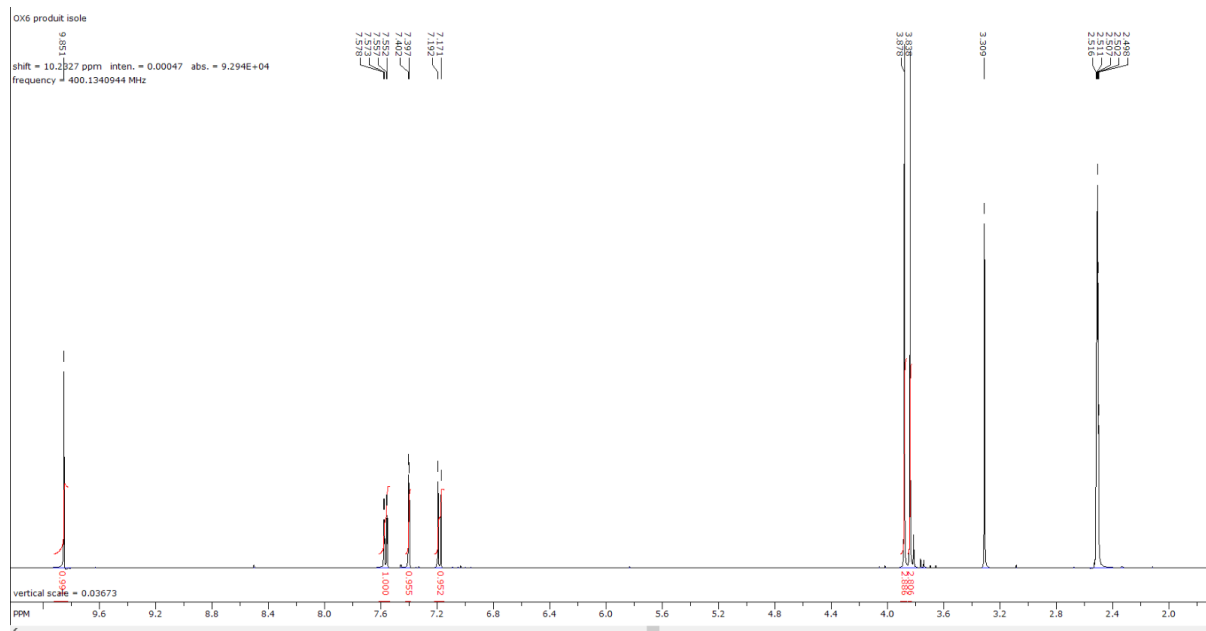


**Fig S19.**  $^1\text{H}$  NMR (d6-DMSO) of isolated product **5g**.

### 3,4-dimethoxybenzaldehyde **5c**: match with reported data<sup>7</sup>



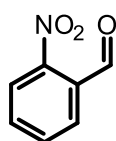
Obtained using standard procedure with 87.5% yield (800 mg isolated from 925 mg of **4c**) as white off solid. No purification was required.



**Fig S20:**  $^1\text{H}$  NMR (d6-DMSO) of isolated product **5c**.

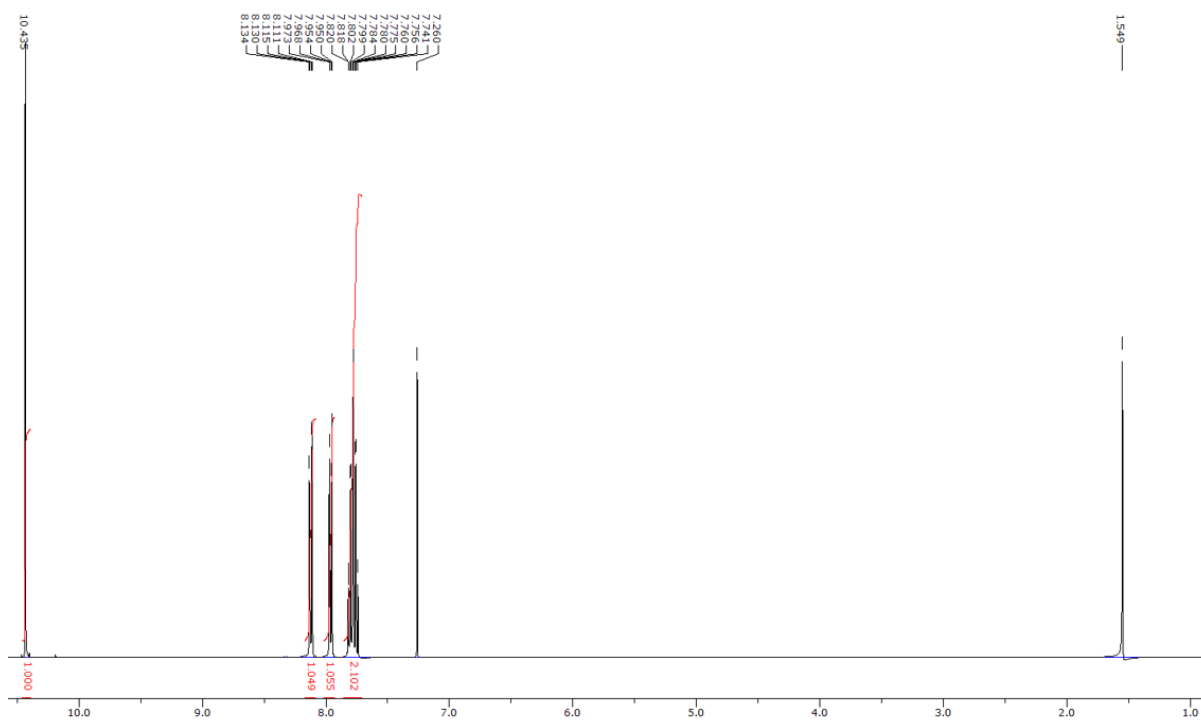
<sup>7</sup> R. Iioka, K. Yorozu, Y. Sakai, R. Kawai, N. Hatae, K. Takashima, G. Tanabe, H. Wasada and M. Yoshimatsu, *Eur. J. Org. Chem.*, 2021, **10**, 1553.

### 2-nitrobenzaldehyde **5e**: match with reported data<sup>7</sup>



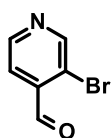
**5e**

Obtained using standard procedure with 73.4% yield (610 mg isolated from 832 mg of alcohol **4e**) as pale-yellow solid. The reaction was monitored by TLC. Purification was performed by flash chromatography on silica with CH<sub>2</sub>Cl<sub>2</sub>/MethylCyclohexane (50/50).



**Fig S21:** <sup>1</sup>H NMR (CDCl<sub>3</sub>) of isolated product **5e**.

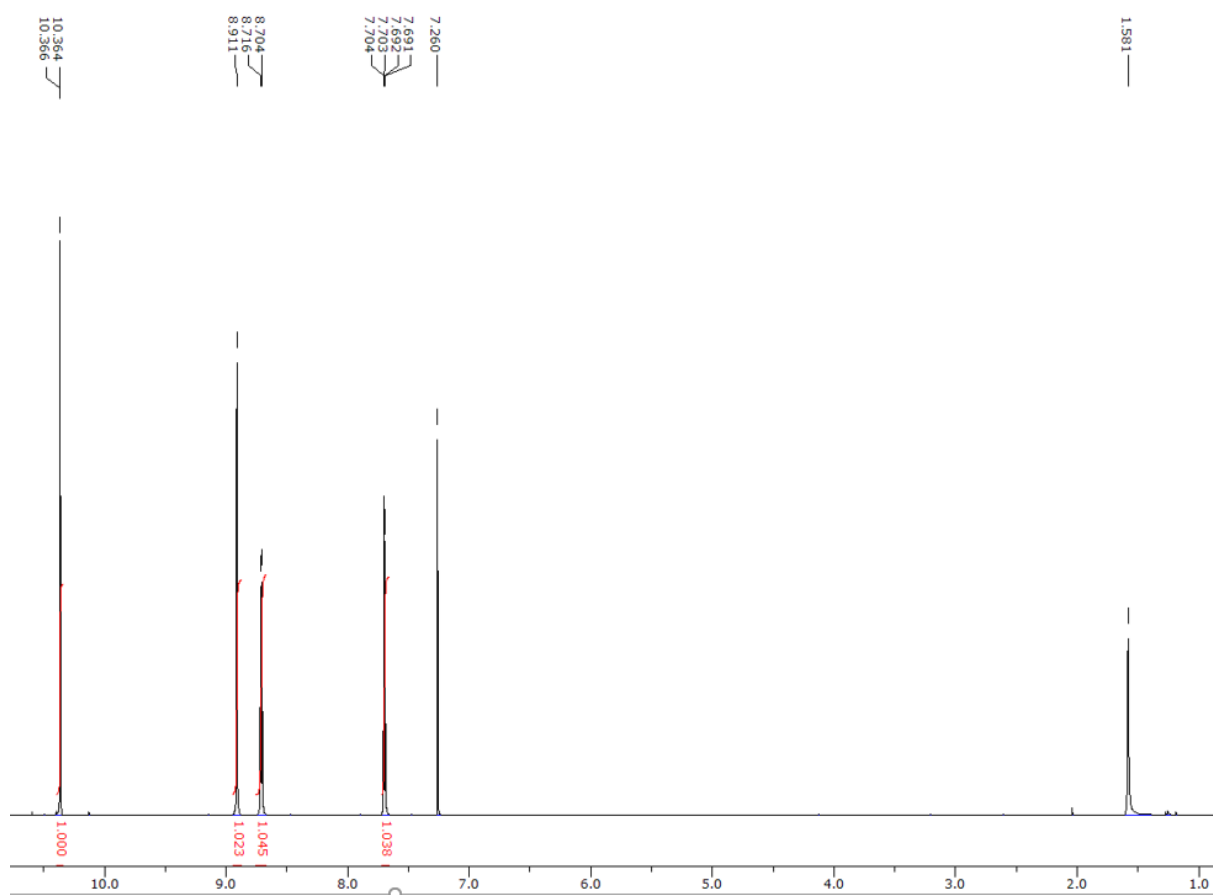
### Pyridine-2-carbaldehyde **5g**: match with reported data<sup>8</sup>



**5g**

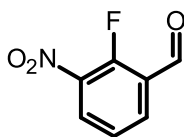
Obtained using standard procedure with 50% yield (520 mg isolated from 1.03 gr of alcohol **4g**) as white powder. Reaction was monitoring by TLC (DCM/OAcEt 80/20). Purification was performed by filtration on silica pad with Dichloromethane/OEtAc (80/20).

<sup>8</sup> X. Gao, S. Han, M. Zheng, A. Liang, J. Li, D. Zou, Y. Wu and Y. Wu, *J. Org. Chem.*, 2019, **84**, 4040.



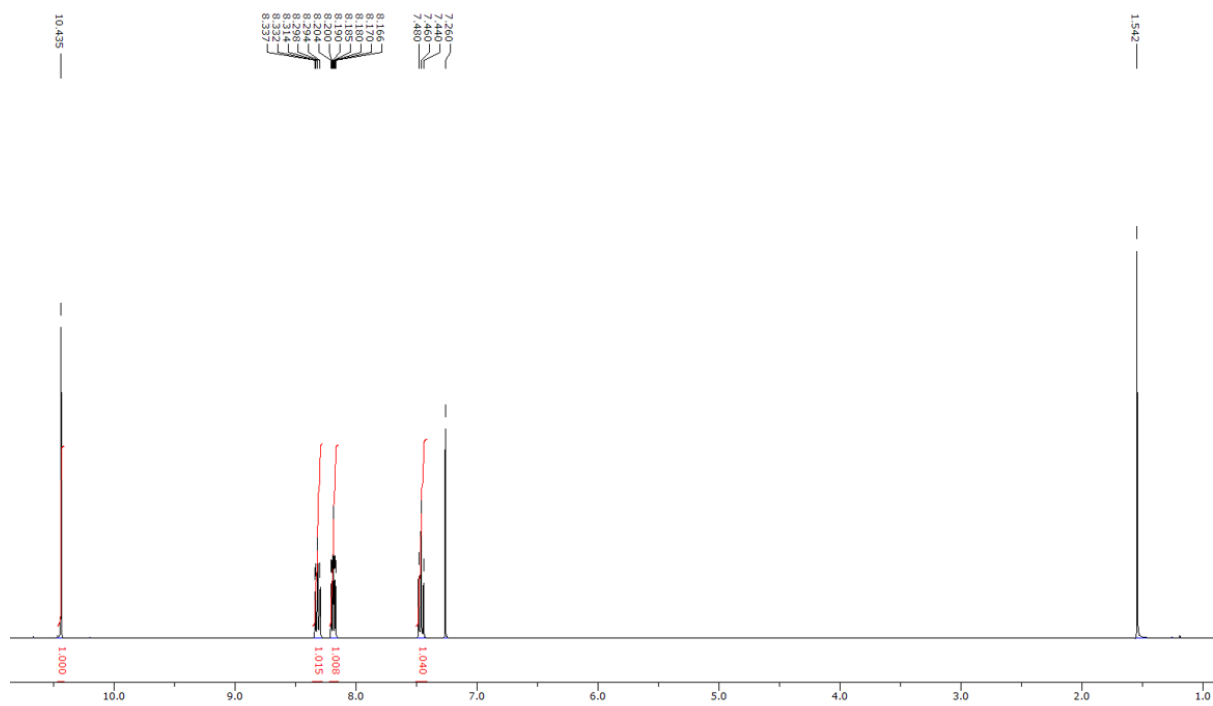
**Fig S22:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of isolated product **5g**.

**2-Fluoro-3-nitrobenzaldehyde **5f**:** match with reported data<sup>9</sup>



Obtained using standard procedure with 59% yield (550 mg isolated from 932 mg of alcohol **4f**) as yellow oil. The reaction was monitoring by TLC (DCM). Purification was performed by flash chromatography with Dichloromethane/MethylCycloHexane (70/30).

<sup>9</sup> Spectral data were obtained from Enamine Ltd.



**Fig S23:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of isolated product **5f**.