Continuous flow synthesis of aryl aldehydes by Pd-catalyzed formylation of phenol-derived aryl fluorosulfonates using syngas

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1. Materials and Methods

All solvents and chemicals were obtained from standard commercial vendors (Sigma-Aldrich/Merck or VWR) and were used without any further purification, unless otherwise noted.

NMR spectra: $^1$H NMR spectra were recorded on a Bruker 300 MHz or 500 MHz instrument. $^{13}$C NMR spectra were recorded on a 300 MHz instrument at 75 MHz. $^{19}$F NMR spectra were recorded on the 300 MHz instrument at 282 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet.

GC-MS spectra were recorded using a Shimadzu GCMS-QP 2010 SE coupled with a DSQ II (EI, 70 eV). A RTX-5MS column (30 m × 0.25 mm × 0.25 μm) was used, with helium as carrier gas (40 cm/sec linear velocity). The injector temperature was set at 280 °C. Within the GC oven, after 1 min at 50 °C, the temperature was increased by 25 °C/min to 300 °C and kept at 300 °C for 3 min.

GC-FID analysis was performed on a Shimadzu GC-FID 2030 with a flame ionization detector, using a RTX -5MS column (30 m × 0.25 mm ID × 0.25 μm) and helium as carrier gas (40 cm/sec linear velocity). The injector temperature was set at 280 °C. Within the GC oven, after 1 min at 50 °C, the temperature was increased by 25 °C/min to 300 °C and kept constant at 300 °C for 4 min. The detector gases used for flame ionization were hydrogen and synthetic air (5.0 quality).

Identity and purity of compounds (2a – 2u) after reductive carbonylation reaction was established via GC-MS and GC-FID with internal standard respectively. Isolation, with exception of 2a, 2b, 2c and 2p, was not attempted due to volatility of the products.

CAUTION NOTE: CO is an odorless, toxic, and flammable gas. All of the experiments must be performed in a well-ventilated fume cupboard with a fitted CO detector. H$_2$ is extremely flammable. A N$_2$ purge should be used at the outlet. Care should be taken when operating pressurized equipment. A thorough safety assessment should be made before conducting any experiments.
2. General Procedure A for the Preparation of Sulfurofluoridates 1a-1u

A 20 mL microwave vial equipped with stirrer bar and charged with phenol (10 mmol, 1 equiv), Et₃N (2.79 mL, 20 mmol) and CH₂Cl₂ (12.5 mL). After sealing of the reaction vessel with a septum, a slight vacuum was applied. Subsequently a balloon filled with SO₂F₂ was attached to the reaction vessel via a syringe. The reaction mixture was stirred (1-16 h). The reaction mixture was concentrated under reduced pressure after complete conversion of starting material was observed via GC-FID. The crude product was diluted with EtOAc (20 mL) and washed with 1 M HCl (2 x 30 mL) and brine (30 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure.

2.1. 4-Methoxyphenyl Sulfurofluoridate (1a)

Product 1a was obtained as a colorless oil (2.04 g, 99% yield). ¹H NMR (CDCl₃), ¹⁹F NMR (CDCl₃), and ¹³C NMR (CDCl₃) spectra matched those previously reported in the literature.² MS EI (m/z): [M]+ calcd. for C₇H₇FO₄S, 206; found, 206.

2.2. 4-Chlorophenyl Sulfurofluoridate (1b)

Product 1b was obtained as a colorless oil (2.10 g, 98% yield). ¹H NMR (CDCl₃), ¹⁹F NMR (CDCl₃), and ¹³C NMR (CDCl₃) spectra matched those previously reported in the literature.³ MS EI (m/z): [M]+ calcd. for C₆H₄ClFO₃S, 210; found, 210.

2.3. 3-Chlorophenyl Sulfurofluoridate (1c)

Product 1c was obtained as an orange oil (2.06 g, 98% yield). ¹H NMR (CDCl₃), ¹⁹F NMR (CDCl₃), and ¹³C NMR (CDCl₃) spectra matched those previously reported in the literature.⁴ MS EI (m/z): [M]+ calcd. for C₆H₄ClFO₃S, 210; found, 210.

2.4. 2-Chlorophenyl Sulfurofluoridate (1d)

Product 1d was obtained as a colorless oil (1.81 g, 86% yield). ¹H NMR (CDCl₃), ¹⁹F NMR (CDCl₃), and ¹³C NMR (CDCl₃) spectra matched those previously reported in the literature.⁵ MS EI (m/z): [M]+ calcd. for C₆H₄ClFO₃S, 210; found, 210.
2.5. 4-Bromophenyl Sulfurofluoridate (1e)

Product 1e was obtained as a colorless oil (2.54 g, 99% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^7$ MS El (m/z): [M]$^+$ calcd. for C$_6$H$_4$BrFO$_3$S, 254; found, 254.

2.6. 4-Iodophenyl Sulfurofluoridate (1f)

Product 1f was obtained as a beige crystalline solid (2.96 g, 98% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^9$ MS El (m/z): [M]$^+$ calcd. for C$_6$H$_4$FO$_3$S, 302; found, 302.

2.7. 4-Cyanophenyl Sulfurofluoridate (1g)

Product 1g was obtained as a white solid (2.01 g, 99% yield, mp = 37.7–39.5 °C). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^3$ MS El (m/z): [M]$^+$ calcd. for C$_7$H$_4$FNO$_3$S, 201; found, 201.

2.8. Methyl 4-((fluorosulfonyl)oxy)benzoate (1h)

Product 1h was obtained as a colorless oil (2.17 g, 93% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^8$ MS El (m/z): [M]$^+$ calcd. for C$_8$H$_7$FO$_5$S, 234; found, 234.

2.9. 4-Formylphenyl Sulfurofluoridate (1i)
Product 1i was obtained as a yellow oil (2.03 g, 99% yield). 1H NMR (CDCl₃), 19F NMR (CDCl₃), and 13C NMR (CDCl₃) spectra matched those previously reported in the literature. MS EI (m/z): [M]+ calcd. for C₇H₅FO₄S, 204; found, 204.

2.10.4-Acetylphenyl Sulfurofluoridate (1j)

Product 1j was obtained as a yellow oil (2.17 g, 99% yield). The 1H NMR (CDCl₃), 19F NMR (CDCl₃), and 13C NMR (CDCl₃) spectra matched those previously reported in the literature. MS EI (m/z): [M]+ calcd. for C₈H₇FO₄S, 218; found, 218.

2.11.4-Fluorophenyl Sulfurofluoridate (1k)

Product 1k was obtained as a colorless oil (1.45 g, 75% yield). 1H NMR (CDCl₃), 19F NMR (CDCl₃), and 13C NMR (CDCl₃) spectra matched those previously reported in the literature. MS EI (m/z): [M]+ calcd. for C₆H₄FO₃S, 194; found, 194.

2.12.4-(Trifluoromethyl)phenyl Sulfurofluoridate (1l)

Product 1l was obtained as a colorless oil (2.17 g, 89% yield). 1H NMR (CDCl₃), 19F NMR (CDCl₃), and 13C NMR (CDCl₃) spectra matched those previously reported in the literature. MS EI (m/z): [M]+ calcd. for C₇H₄F₃O₃S, 244; found, 244.

2.13.4-Nitrophenyl Sulfurofluoridate (1m)

Product 1m was obtained as a yellow oil (2.11 g, 95% yield). 1H NMR (CDCl₃), 19F NMR (CDCl₃), and 13C NMR (CDCl₃) spectra matched those previously reported in the literature. MS EI (m/z): [M]+ calcd. for C₆H₄FNO₅S, 221; found, 221.
2.14. 3-Methoxyphenyl Sulfurofluoridate (1n)

Product 1n was obtained as a colorless oil (2.04 g, 99% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^4$ MS El (m/z): [M]$^+$ calcd. for C$_7$H$_7$FO$_4$S, 206; found, 206.

2.15. 2-Methoxyphenyl Sulfurofluoridate (1o)

Product 1o was obtained as a colorless oil (1.77 g, 86% yield). The $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^2$ MS El (m/z): [M]$^+$ calcd. for C$_7$H$_7$FO$_4$S, 206; found, 206.

2.16. 6-Methoxynaphthalen-2-yl Sulfurofluoridate (1p)

Product 1p was obtained as a brown solid (2.14 g, 84% yield). $^1$H NMR (300.36 MHz, CDCl$_3$): $\delta$ = 7.90 – 7.71 (m, 3H), 7.41 (ddd, J = 9.0, 2.6, 1.0 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.19 (d, J = 2.5 Hz, 1H), 3.96 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 158.8, 146.2, 134.1, 129.6, 129.4, 128.7, 120.8, 119.6, 118.9, 105.9, 55.6. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ = 37.28 ppm. MS El (m/z): [M]$^+$ calcd. for C$_{11}$H$_9$FO$_4$S, 256; found, 256.

2.17. Phenyl Sulfurofluoridate (1q)

Product 1q was obtained as a colorless oil (0.704 g, 40% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^3$ MS El (m/z): [M]$^+$ calcd. for C$_6$H$_5$FO$_3$S, 176; found, 176.

2.18. o-Tolyl Sulfurofluoridate (1r)

Product 1r was obtained as a colorless oil (1.58 g, 83% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^2$ MS El (m/z): [M]$^+$ calcd. for C$_7$H$_7$FO$_3$S, 190; found, 190.
2.19. m-Toly1 Sulfurofluoridate (1s)

Product 1s was obtained as a colorless oil (1.73 g, 91% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^3$ MS EI (m/z): [M]$^+$ calcd. for C$_7$H$_7$FO$_3$S, 190; found, 190.

2.20. p-Toly1 Sulfurofluoridate (1t)

Product 1t was obtained as a colorless oil (1.62 g, 85% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^3$ MS EI (m/z): [M]$^+$ calcd. for C$_7$H$_7$FO$_3$S, 190; found, 190.

2.21. 2,6-Dimethylphenyl Sulfurofluoridate (1u)

Product 1u was obtained as a colorless oil (1.82 g, 89% yield). $^1$H NMR (CDCl$_3$), $^{19}$F NMR (CDCl$_3$), and $^{13}$C NMR (CDCl$_3$) spectra matched those previously reported in the literature.$^4$ MS EI (m/z): [M]$^+$ calcd. for C$_8$H$_9$FO$_3$S, 204; found, 204.
3. General Procedure B for the Formylation of EWG Containing Aryl Fluorosulfonates 2a-2m

The flow setup consisted of two HPLC pumps (Uniqsis FlowSyn, Feed 1 and 2). Input solutions for feeds 1 and 2 were prepared with DMSO, in oven-dried volumetric flasks as follows:

Feed 1: 0.2 M fluorosulfonates (2 mmol, 1 equiv) and pyridine (3 mmol, 1.5 equiv) in DMSO within a 10 mL volumetric flask.

Feed 2: 0.0025 M Pd(OAc)$_2$ (14 mg, 62.5 µmol) and 0.005 M dppp (48 mg, 0.125 mmol) in DMSO within a 25 mL volumetric flask.

Feeds 1 and 2 were introduced through sample loops (Feed 1, 2 mL, 0.4 mmol, Feed 2, 3 mL) using DMSO as carrier solvent.

Before commencing the experiment, the reactor setup was flushed by pumping DMSO with a flow rate of 0.30 mL/min; using the pump for feed 1; and 0.30 mL/min using the pump for feed 2. Gas flow rates were measured in units of mL$_n$ /min$^{-1}$, where $n$ represents measurement under standard conditions, i.e., $T_n = 0 \ $°C, $P_n = 1.01$ bar. Hydrogen was introduced into the reactor with a flow rate of 1.87 mL$_n$ /min (1.4 equiv) using a calibrated mass flow controller (MFC, Bronkhorst, EL-FLOW). Carbon monoxide was introduced into the reactor with a flow rate of 1.87 mL$_n$ /min (1.4 equiv) using a calibrated mass flow controller (MFC, Bronkhorst, EL-FLOW). To commence the experiment, the pumping of DMSO at pumps 1 and 2 was switched to their respective input solution whilst maintaining their flow rate. Feed 1 and 2 were combined within an arrowhead mixer at room temperature. The combined reaction feed was mixed with CO and H$_2$ in a four-way mixer. The biphasic gas liquid mixture was passed through a stainless-steel reaction coil before exiting the system through a back-pressure regulator (Zaiput BPR-10). The system was maintained at 120 °C and 20 bar pressure to provide ~43 min residence time. The residence time was measured from the three streams combining at the mixer until color was observed at the BPR. The liquid pump
flow rates, temperature, and pressure were measured and monitored by the control platform of the pumping system. Once color was observed at the BPR, a fraction was collected until there was no color observed.

The collected process stream was diluted with Et₂O (1/1 = v/v) and washed (2x 1/1 = v/v) with aqueous 5 wt% LiCl solution. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure.

3.1. 4-Chlorobenzaldehyde (2b)

Product 2b was obtained as after flash column chromatography (EtOAc/petroleum ether a colorless crystalline solid (50 mg, 89% yield, Mp. = 46 °C). ¹H NMR (300.36 MHz, CDCl₃): δ = 9.98 (s, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H) ppm. MS EI (m/z): [M]+ calcd. for C₇H₅ClO, 140; found, 140.

3.2. 3-Chlorobenzaldehyde (2c)

Product 2c was obtained as after flash column chromatography (EtOAc/petroleum ether a colorless oil (49 mg, 88% yield). ¹H NMR (300.36 MHz, CDCl₃): δ = 9.98 (s, 1H), 7.89 – 7.83 (m, 1H), 7.77 (dt, J = 7.5, 1.4 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.49 (t, J = 7.8 Hz, 1H). MS EI (m/z): [M]+ calcd. for C₇H₅ClO, 140; found, 140.

4. General Procedure C for the Formylation of EWG Containing Aryl Fluorosulfonates 2k-2u

The flow setup consisted of two HPLC pumps (Uniqsis FlowSyn, Feed 1 and 2). Input solutions for feeds 1 and 2 were prepared with DMSO, in oven-dried volumetric flasks as follows:
Feed 1: 0.2 M fluorosulfonate (2 mmol, 1 equiv) and pyridine (3 mmol, 1.5 equiv) in DMSO within a 10 mL volumetric flask.

Feed 2: 0.0025 M Pd(OAc)$_2$ (14 mg, 62.5 µmol) and 0.005 M dppp (48 mg, 0.125 mmol) in DMSO within a 25 mL volumetric flask.

Feeds 1 and 2 were introduced through sample loops (Feed 1, 2 mL, 0.4 mmol; Feed 2, 3 mL) using DMSO as carrier solvent.

Before commencing the experiment, the reactor setup was flushed by pumping DMSO with a flow rate of 0.08 mL/min; using the pump for feed 1; and 0.08 mL/min using the pump for feed 2. Hydrogen was introduced into the reactor with a flow rate of 1.5 mL/min (4.5 equiv) using a calibrated mass flow controller (MFC, Bronkhorst, EL-FLOW). Carbon monoxide was introduced into the reactor with a flow rate of 0.5 mL/min (1.5 equiv) using a calibrated mass flow controller (MFC, Bronkhorst, EL-FLOW). To commence the experiment, the pumping of DMSO at pumps 1 and 2 was switched to their respective input solution whilst maintaining their flow rate. Feed 1 and 2 were combined within an arrowhead mixer at room temperature. The combined reaction feed was mixed with CO and H$_2$ in a four-way mixer. The biphasic gas liquid mixture was passed through a stainless-steel reaction coil before exiting the system through a back-pressure regulator (Zaiput BPR-10). The system was maintained at 120 °C and 20 bar pressure to provide ~120 min residence time. The residence time was measured from the three streams mixing at the mixer until colour was observed at the BPR. The liquid pump flow rates, temperature, and pressure were measured and monitored by the control platform of the pumping system. Once colour was observed at the BPR, a fraction was collected until there was no colour observed.

The collected process stream was diluted with Et$_2$O (1/1 = v/v) and washed (2x 1/1 = v/v) with an aqueous 5 wt% LiCl solution. The organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure.

4.1. 4-Anisaldehyde (2a)

Product 2a was obtained as a colorless oil (49 mg, 90% yield). $^1$H NMR (300.36 MHz, CDCl$_3$): $\delta$ = 9.88 (s, 1H), 7.84 (d, $J$ = 8.8 Hz, 2H), 7.00 (d, $J$ = 8.6 Hz, 2H), 3.89 (s, 3H) ppm. MS EI (m/z): [M]$^+$ calcd. for C$_8$H$_8$O$_2$, 136; found, 136.

4.2. 6-Methoxy-2-naphthaldehyde (2p)
Product 2p was obtained after flash column chromatography (EtOAc/petroleum ether) as a colorless solid (61 mg, 82% yield, mp = 82 °C). $^1$H NMR (300.36 MHz, CDCl$_3$): $\delta$ = 10.10 (d, $J$ = 0.7 Hz, 1H), 8.35 – 8.17 (m, 1H), 8.01 – 7.71 (m, 3H), 7.31 – 7.14 (m, 2H), 3.96 (s, 3H) ppm. MS El (m/z): [M]$^+$ calcd. for C$_{12}$H$_{10}$O$_2$, 186; found, 186.
5. Optimization of Reaction Parameters

5.1. Pressure

Increasing the pressure to 20 bar suppressed the formation of the defunctionalized product. The GC yield of obtained 4-methoxybenzaldehyde (2a) remained similar.

![Figure S1](image1.png)

**Figure S1** Influence of pressure on 4-methoxybenzaldehyde (2a) GC yield. Conditions: Feed 1: 0.2 M 4-methoxy sulfurofluoridate (1a), 1.5 equiv pyridine and 0.15 equiv Ph₂O in DMF/DMSO = 40/60; Feed 2: 1.25 mol% Pd(OAc)₂ and 2.5 mol% dppp in DMSO. H₂ and CO were introduced via mass flow controller with flow rates for Feed 1/Feed 2/H₂/CO = 0.3:0.3:1.5:1.5 mL/min. System pressure was gradually increased for 2.5 bar every run, the residence time varied accordingly.

5.2. Catalyst Loading

![Figure S2](image2.png)

**Figure S2** Influence of catalyst loading on 4-chlorobenzaldehyde (2b) GC yield. Conditions: Feed 1: 0.2 M 4-chloro sulfurofluoridate (1b), 1.5 equiv pyridine and 0.15 equiv Ph₂O in DMSO; Feed 2: Pd(OAc)₂ and dppp in DMSO. Feed 1/Feed 2/H₂/CO = 0.3:0.3:1.5:1.5 mL/min resulting in a residence time of 43 min. System pressure was maintained at 20 bar.
5.3. Residence Time EWG

Figure S3 Influence of residence time on 4-chlorobenzaldehyde (2b). Conditions: Feed 1: 0.2 M 4-chloro sulfurofluoridate (1b), 1.5 equiv pyridine and 0.15 equiv Ph₂O in DMSO; Feed 2: 1.25 mol% Pd(OAc)₂ and 2.5 mol% dppp in DMSO. Flow rate ratio of H₂/CO = 1/1. System pressure was maintained at 20 bar.

5.4. Residence Time EDG

Figure S4 Influence of residence time on 4-methoxybenzaldehyde (2a) GC yield. Conditions: Feed 1: 0.2 M 4-methoxy sulfurofluoridate (1a), 1.5 equiv pyridine and 0.15 equiv Ph₂O in DMSO; Feed 2: 1.25 mol% Pd(OAc)₂ and 2.5 mol% dppp in DMSO. H₂/CO = 1/3. System pressure was maintained at 20 bar.

5.5. Ligand Screening

Table S1 4-Chlorobenzaldehyde (2b) for different ligand systems. Conditions: Feed 1: 0.2 M 4-chloro sulfurofluoridate (1b), 1.5 equiv pyridine and 0.15 equiv Ph₂O in DMSO; Feed 2: 1.25 mol% Pd(OAc)₂ and 2.5 mol%
ligand in DMSO. Feed 1/Feed 2/H₂/CO = 0.6:0.6:3:3 mL/min resulting in a residence time of 21 min. System pressure was maintained at 20 bar.

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6. NMR spectra

[Chemical structures and spectra]

1a
$1^h$
7. References


