Metal- and Reagent-Free Electrochemical Synthesis of Alkyl Arylsulfonates in a Multi-Component Reaction

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1. General Aspects

All reagents and solvents used were obtained as analytical grade from commercial suppliers or purified with standard methods.\textsuperscript{[1]} Sulfur dioxide 3.8 was purchased from Linde AG in a 10 L gas bottle. Electrochemical reactions were carried out at boron-doped diamond (BDD) electrodes. BDD electrodes (DIACHEM\textsuperscript{®}, 15 \textmu m boron-doped diamond layer on 3 mm silicon support/wafer) were purchased from CONDIAS GmbH, Itzhoe, Germany.

Column chromatography was performed on silica gel 60 M (0.040–0.063 mm, Macherey-Nagel GmbH & Co, Düren, Germany). Therefore, a preparative chromatography system (Büchi, Flawil, Switzerland) was used with a Büchi Control Unit C-620, an UV detector Büchi UV photometer C-635, a Büchi fraction collector C-660 and two Pump Modules C-605 for adjusting the solvent mixtures. As eluent, mixtures of cyclohexane and ethyl acetate were used. Silica gel 60 sheets on aluminium (F254, Merck KGaA, Darmstadt, Germany) were employed for thin layer chromatography.

Gas chromatography was performed on a Shimadzu GC-2025 (Shimadzu, Japan) using a HP-5 column (Agilent Technologies, Santa Clara, California; length: 30 m, inner diameter: 0.25 mm, film: 0.25 \textmu m, carrier gas: hydrogen). GC-MS measurements were carried out on a Shimadzu GC-2010 (Shimadzu, Japan) using a HP-1 column (Agilent Technologies, Santa Clara, California; length: 30 m, inner diameter: 0.25 mm, film: 0.25 \textmu m, carrier gas: helium). The chromatograph was coupled to a mass spectrometer Shimadzu GC-MS-QP2010.

Melting points were determined with a Melting Point Apparatus B-565 (Büchi, Flawil, Switzerland) and are uncorrected. Heating rate: 1°C/min.

NMR spectra of \textsuperscript{1}H (300.13 MHz), \textsuperscript{19}F (282.38 MHz) and \textsuperscript{13}C{\textsuperscript{1}H} (75.48 MHz) were recorded at 23 °C by Bruker Avance III HD spectrometer. Chemical shifts (\delta) are reported in parts per million (ppm) relative to traces of CHCl\textsubscript{3} (7.26 ppm in \textsuperscript{1}H, 77.16 ppm in \textsuperscript{13}C{\textsuperscript{1}H}). For \textsuperscript{19}F spectra CFCl\textsubscript{3} serves as reference compound.\textsuperscript{[2]}
Infrared spectra (IR) were recorded from 4000 cm\(^{-1}\) to 400 cm\(^{-1}\) on a Bruker ALPHA FT-IR spectrometer by using the Attenuated Total Reflection (ATR) sampling technique with a diamond sensor. Samples were prepared as a neat film or a thin powder layer. IR data in frequency of absorption (cm\(^{-1}\)) is reported as follows: w = weak, m = medium, s = strong, br = broad or combinations thereof.

High-resolution mass spectra were obtained with QT of Ultima 3 (Waters, Milford, Massachusetts) using ESI\(^+\) and APCI\(^+\) ionization modes.

X-ray analysis data were collected on a STOE IPDS-2T diffractometer (STOE & Cie GmbH, Darmstadt, Germany) using graphite monochromated Mo-K\(\alpha\) radiation (\(\lambda = 0.71073 \text{ Å}\)). Intensities were measured using fine-slicing \(\omega\) and \(\varphi\)-scans and corrected for background, polarization and Lorentz effects. The structures were solved by direct methods and refined anisotropically by the least-squares procedure implemented in the SHELX program system. The supplementary crystallographic data for this paper can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. Deposition numbers and further details are given with the individual characterization data.

Cyclic voltammetry was performed in a 10 mL snap-cap vial equipped with an Autolab PGSTAT101 potentiostat (Metrohm AG, Herisau, Switzerland). WE: BDD electrode tip, 2 mm diameter; CE: glassy carbon rod; RE: Ag/AgCl in saturated LiCl/EtOH. Solvent: HFIP:MeCN = 1:1. \(\nu = 100 \text{ mV/s, } T = 20^\circ \text{C, } c = 0.01 \text{ M, supporting electrolyte: NBu}_4\text{BF}_4, c (\text{NBu}_4\text{BF}_4) = 0.1 \text{ M.}\)
2. Experimental Considerations

The SO$_2$ stock solution was prepared as follows:
In a gas-inlet apparatus, acetonitrile (90 mL) was saturated in a container with SO$_2$ at 0 °C under constant stirring. The mixture was further diluted with acetonitrile, so that a SO$_2$ stock solution with 500 mL total volume was obtained. Excess SO$_2$ in the gas apparatus was quenched in three successive washing bottles, filled with aq. NaOH (20 wt-%). Wolff bottles were placed before and after the washing bottles. After usage, the gas-inlet apparatus was flushed with Argon.

**Determination of the SO$_2$ concentration of the stock solution:**
The SO$_2$ molarity was determined according to the principles of the “Excess Iodine Method” described by Ferguson.[3]
To an aq. solution of I$_2$ (1.27 g, 5.00 mmol) and KI (2.20 g, 13.3 mmol) was slowly added 1.0 mL of the freshly prepared SO$_2$ stock solution. The solution was then back titrated with a freshly prepared aq. Na$_2$S$_2$O$_3$ solution (0.1 M) as titrant. On the verge of the transition point (decolorization), a few drops of a freshly prepared starch solution were added to the iodine solution for better visualization. After full reduction of the iodine, the concentration of SO$_2$ (mostly 2–2.5 M) was calculated according to the previously reduced iodine by aq. SO$_2$.

**Experimental set-up for the screening reactions in undivided cells:**
The undivided PTFE cells (figure 1) used are homemade by the university's own mechanical shop, which are described in literature.[4] The complete setup of these cells with screening block is also commercially available as IKA Screening System, IKA-Werke GmbH & Co. KG, Staufen, Germany. The cells are operated with boron-doped diamond electrodes (BDD).
Experimental set-up and general protocol for the synthesis of sulfonate esters in divided cells (GP1):

The electrochemical conversion was conducted in divided cells made of Teflon according to figure 2.[4] A porous glass frit (P4) was used as separator, sealed by an EPDM ring. As cathode and anode material, boron-doped diamond electrodes (BDD) were utilized, which can be fixed by Teflon screws. One round-shaped stirring bar can be placed in each compartment of each cell. In total, six divided cells can be placed in a screening block, which can be attached to a magnetic stirrer.

The anode compartment of the cell was charged with the arene substrate (0.60 mmol, 1.00 eq.). Acetonitrile, SO$_2$ in acetonitrile (2.19 M, 15.0 eq.) and the alcohol (8.00 eq.) were combined in a pear-shaped flask. The mixture was cooled to 0 °C and N-ethyl-
N-isopropylpropan-2-amine (816 µL, 4.80 mmol, 8.00 eq.) was added slowly under stirring through a septum. The reaction mixture was stirred for 5 min and HFIP was added slowly at 0 °C, so that a total volume of 12.0 mL and a solvent ratio of HFIP:MeCN = 1:1 was obtained. 6.0 mL of the reaction mixture was transferred into the cathode compartment and the other 6.0 mL of the electrolyte was then immediately transferred to the anode compartment of the divided cell via syringe. The amperage was set accordingly, so that a current density of 11.25 mA/cm² was reached. The amount of charge was set to 3.50 Faraday. The electrolysis was conducted at r.t. under stirring (300 rpm). The reaction mixture was stirred for 14 h in total. The anolyte and catholyte were combined and the solvents were distilled under reduced pressure for reutilization. Cold distilled water (30.0 mL) was added to the remaining reaction mixture, which was then extracted in ethyl acetate (3 x 30.0 mL). The combined organic fractions were dried over Na₂SO₄. The organic solvent was removed under reduced pressure and the crude product was purified via column chromatography with a cyclohexane/ethyl acetate solvent gradient. The NMR yield was calculated via addition of 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol, 1.00 eq.) to the crude reaction mixture as internal standard.

3. General Procedure of Cyclic Voltammetry

The general procedure of cyclic voltammetry is described as follows (GP2): All cyclic voltammograms were recorded in a HFIP:MeCN = 1:1 mixture (5 mL total volume in a 10 mL vial). Unless otherwise noted, 0.1 M N,N,N,N-tetrabutylammonium tetrafluoroborate (165 mg, 0.50 mmol) was used as supporting electrolyte. Cyclic voltammetry was performed with a 0.1 V/s scan rate using a BDD working electrode (tip, 2 mm diameter), a glassy carbon rod as counter electrode and an Ag/AgCl reference electrode in saturated LiCl/EtOH. Ferrocene/Ferrocenium (FcH/FcH⁺) was used as internal reference (unless otherwise noted: half-wave potential 0.36 V versus Ag/AgCl).[5]
4. Cyclic Voltammetry Results and Mechanistic Proposal

The results of cyclic voltammetry were used for the postulation of a reaction mechanism: The initial oxidation step is confirmed by cyclic voltammetry measurements. Figure 3 clearly depicts that the oxidation of 1,2,3-trimethoxybenzene (brown) occurs before the oxidation of the monoalkyl sulfite (green graph). This indicates that an initial formation of the radical cation can be assumed. Please note that the concentration of DIPEA, 2,2-dimethyl-1-propanol and SO₂ were chosen accordingly to the reaction conditions of GP2.

![Graph](image-url)

**Figure 3.** Two cyclic voltammograms plotted in one graphic. Brown graph: HFIP:MeCN = 1:1, 0.01 M 1,2,3-trimethoxybenzene, 0.1 M n-BuNBF₄; orange graph: HFIP:MeCN = 1:1, 0.75 M SO₂, 0.40 M DIPEA, 0.40 M 2,2-dimethyl-1-propanol (no additional supporting electrolyte was used; half-wave potential 0.52 V versus Ag/AgCl).
Figure 4. Two cyclic voltammograms plotted in one graphic. Orange graph: HFIP:MeCN = 1:1, 0.1 M n-Bu4NBF₄; blue graph: HFIP:MeCN = 1:1, 0.75 M SO₂, 0.1 M n-Bu4NBF₄.

Furthermore, figure 4 indicates that SO₂ reduction occurs. The comparison of the orange and the blue graph clearly shows the difference of the potential windows. The presence of SO₂ (blue graph) in the solvent mixture clearly evidences a reduction at lower potential. Please note that the concentration of SO₂ was chosen accordingly to the reaction conditions of GP1.

5. Optimization of the Reaction Conditions

According to the general experimental set-up for undivided cells, different organic bases were screened (scheme 1):

Scheme 1. General reaction scheme for the base screening.
Table 1. NMR Yields of the screening-reactions. Yields were determined by internal standard.

| Entry | Base   | NMR Yield |
|-------|--------|-----------|
| 1     | DBU    | 23%       |
| 2     | TMG    | 20%       |
| 3     | DABCO  | 18%       |
| 4     | pyridine | 0%       |
| 5     | TEA    | 27%       |
| 6     | DIPEA  | 33%       |

DBU = 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine; TMG = 1,1,3,3-tetramethylguanidine; DABCO = 1,4-diazabicyclo[2.2.2]octane; TEA = N,N-diethylethanamine; DIPEA = N-ethyl-N-(propan-2-yl)propan-2-amine.

An undivided screening cell was charged with 1,2,3-trimethoxybenzene (84 mg, 0.50 mmol, 1.00 eq.). Acetonitrile, SO₂ in acetonitrile (2.19 M, 3.75 eq.) and 2,2-dimethyl-1-propanol (132 mg, 1.50 mmol, 3.00 eq.) were combined in a pear-shaped flask. The mixture was cooled to 0 °C. As base DBU (223 µL, 228 mg, 1.50 mmol, 3.0 eq., entry 1), or TMG (187 µL, 173 mg, 1.50 mmol, 3.00 eq., entry 2), or DABCO (168 mg, 147 µL, 1.50 mmol, 3.00 eq., entry 3), or pyridine (121 µL, 119 mg, 1.50 mmol, 3.00 eq., entry 4), or TEA (207 µL, 152 mg, 1.50 mmol, 3.00 eq., entry 5), or DIPEA (255 µL, 194 mg 1.50 mmol, 3.00 eq., entry 6) was added slowly under stirring through a septum. The reaction mixture was stirred for 5 min and HFIP was added slowly at 0 °C under stirring, so that a total volume of 5.0 mL and a solvent ratio of HFIP:MeCN = 3:1 was obtained. The electrolyte was transferred into the undivided screening cell. The electrolysis was conducted at r.t. under constant stirring (300 rpm) with galvanostatic experimental set-up. The amperage was set accordingly, so that a current density of 12.00 mA/cm² was reached. The amount of charge was set to 2.50 Faraday. The reaction mixture was stirred for 14 h in total. NMR yield was calculated via addition of 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol, 1.00 eq.) to the crude reaction mixture as internal standard. The calculated yields can be seen in table 1.
6. Product Characterization

6.1 2,2-Dimethoxypropyl 3,4,5-trimethoxybenzenesulfonate (7a)

According to the general protocol (GP1), 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.) was used as substrate and 2,2-dimethylpropan-1-ol (424 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 7:3), 2,2-dimethylpropyl 3,4,5-trimethoxybenzenesulfonate (73%, 139 mg, 0.44 mmol) was obtained as an off-white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ [ppm] = 7.11 (s, 2H), 3.92 (s, 3H), 3.91 (s, 6H), 3.68 (s, 2H), 0.93 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ [ppm] = 153.5, 142.4, 130.7, 105.3, 79.9, 61.2, 56.6, 31.8, 26.2; IR (ATR): $\nu_{\text{max}}$ (cm$^{-1}$) = 413 (w), 450 (w), 461 (w), 526 (m), 544 (m), 614 (s), 627 (m), 666 (w), 687 (w), 741 (w), 754 (w), 773 (w), 824 (s), 901 (m), 937 (m), 958 (s), 1104 (s), 1120 (s), 1169 (s), 1230 (m), 1268 (w), 1313 (m), 1351 (m), 1407 (m), 1432 (w), 1444 (w), 1465 (m), 1498 (m), 1587 (m), 2959 (w, br), 3099 (w); m$\text{R}$: 92–93°C; HRMS for C$_{14}$H$_{22}$NaO$_6$S$^+$ (ESI+) [M+Na]$^+$: calc.: 341.1035, found: 341.1032.

Crystallization was performed by dissolving 7a (50 mg) in dichloromethane (1 mL) and slow diffusion of over layered n-heptane (4 mL) and cyclohexane (1 mL) into the solution at 23°C.

Crystal structure determination of 7a (also see figure 5): C$_{14}$H$_{22}$O$_6$S, $M_r$ = 318.39; colorless pads (0.06 x 0.323 x 0.54 mm$^3$), $T$ = 120 K, $\lambda$(Mo-K$\alpha$) = 0.71073 Å, triklin space group $P$ 1, $a$ = 22.545(2) Å, $b$ = 5.9659(5) Å, $c$ = 11.9208(10) Å, $\alpha$ = 91.489(7)$^\circ$, $\beta$ = 95.742(8)$^\circ$, $\gamma$ = 90.095(8)$^\circ$, $V$ = 1594.8(2) Å$^3$, $z$ = 4, $\rho_{\text{rön}}$ = 1.326 g/cm$^3$, $\theta_{\text{max}}$ = 56$^\circ$, $\mu$ = 0.23 mm$^{-1}$, $F$(000) = 680, 13924 reflections, 7617 unique reflections ($R_{\text{int}}$ = 0.0945), $w$ = 1/[$\sigma^2(F_0^2) + (0.1626 \cdot P)^2 + 17.54 \cdot P$] while $P$ = (Max(Fo$^2$,0) + 2 · Fo$^2$)/3, $R_{1}$ = 0.1606 [$I > 2\sigma(I)$], $R_{1}$ = 0.2196 [all data], $wR_{2}$ = 0.4603, CCDC-1988057.
6.2 2-Methylpropyl 3,4,5-trimethoxybenzenesulfonate (7b)

According to the general protocol (GP1), 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.) was used as substrate and 2-methylpropan-1-ol (445 µL, 356 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 7:3), 2-methylpropyl 3,4,5-trimethoxybenzenesulfonate (69%, 126 mg, 0.41 mmol) was obtained as an off-white solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ [ppm] = 7.11 (s, 2H), 3.91 (s, 3H), 3.91 (s, 6H), 3.81 (d, J = 6.5 Hz, 2H), 1.97 (dp, J = 13.3, 6.9 Hz, 1H), 0.93 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ [ppm] = 153.5, 142.4, 130.7, 105.3, 76.7, 61.2, 56.6, 28.2, 18.8; IR (ATR): $\nu_{\text{max}}$ (cm$^{-1}$) = 411 (w), 430 (w), 450 (w), 521 (m), 541 (m), 613 (s), 627 (m), 645 (w), 666 (w), 687 (w), 741 (w), 773 (m), 789 (m), 810 (s), 835 (m), 901 (m), 913 (m), 946 (m), 972 (s), 991 (m), 1023 (w), 1104 (s), 1123 (s), 1168 (s), 1231 (m), 1311 (m), 1356 (m), 1408 (m), 1432 (w), 1467 (m), 1498 (m), 1587 (m), 1738 (w, br), 2963 (w,
6.3 Ethyl 3,4,5-trimethoxybenzenesulfonate (7c)

According to the general protocol (GP1), 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.) was used as substrate and ethanol (280 µL, 221 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 6:4), ethyl 3,4,5-trimethoxybenzenesulfonate (65%, 108 mg, 0.39 mmol) was obtained as an off-white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ [ppm] = 7.12 (s, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.92 (s, 9H), 1.34 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ [ppm] = 153.6, 142.5, 130.6, 105.3, 67.2, 61.2, 56.6, 14.9; IR (ATR): $\nu_{\text{max}}$ (cm$^{-1}$) = 415 (w), 454 (w), 478 (m), 529 (w), 548 (m), 609 (s), 628 (m), 664 (w), 684 (w), 704 (w), 737 (w), 775 (m), 789 (m), 822 (w), 841 (m), 915 (s), 996 (s), 1030 (w), 1093 (s), 1105 (m), 1123 (s), 1151 (m), 1167 (m), 1185 (w), 1232 (w), 1230 (w), 1311 (m), 1348 (s), 1433 (w), 1457 (m), 1476 (w), 1499 (w), 1588 (m), 2942 (w, br), 3105 (w); m$_r$: 91–93 °C; HRMS for C$_{12}$H$_{18}$NaO$_6$S$^+$ (ESI$^+$) [M+Na]$^+$: calc.: 299.0566, found: 299.0565.

6.4 Methyl 3,4,5-trimethoxybenzenesulfonate (7d)

According to the general protocol (GP1), 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.) was used as substrate and methanol (195 µL, 154 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography
(cyclohexane/ethyl acetate = 10:0 → 6:4), *methyl 3,4,5-trimethoxybenzene-sulfonate (48%, 75 mg, 0.29 mmol*) was obtained as an off-white solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ [ppm] = 7.12 (s, 2H), 3.92 (s, 9H), 3.78 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ [ppm] = 153.6, 142.7, 129.7, 105.5, 61.2, 56.7, 56.5; IR (ATR): v$_{max}$ (cm$^{-1}$) = ; IR (ATR): v$_{max}$ (cm$^{-1}$) = 416 (w), 451 (w), 480 (m), 515 (m), 528 (m), 543 (m), 555 (m), 604 (s), 626 (m), 665 (w), 686 (w), 771 (s), 781 (m), 822 (w), 845 (m), 901 (m), 919 (w), 927 (w), 975 (s), 989 (m), 1035 (m), 1102 (m), 1123 (s), 1166 (s), 1231 (m), 1313 (m), 1350 (s), 1410 (m), 1452 (m), 1498 (m), 1589 (m), 2947 (w, br), 3100 (w); m$_R$: 119–121 °C; HRMS for C$_{10}$H$_{14}$NaO$_6$S$^+$ (ESI+) [M+Na]$^+$: calc.: 285.0409, found: 285.0406.

6.5 1-Methylethyl 3,4,5-trimethoxybenzenesulfonate (7e)

According to the general protocol (GP1), 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.) was used as substrate and propan-2-ol (370 µL, 288 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification *via* column chromatography (cyclohexane/ethyl acetate = 10:0 → 7:3), *2-methylethyl 3,4,5-trimethoxybenzenesulfonate (41%, 72 mg, 0.25 mmol*) was obtained as an off-white solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ [ppm] = 7.12 (s, 2H), 4.74 (h, J = 6.2 Hz, 1H), 3.91 (s, 9H), 1.32 (s, 3H), 1.30 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ [ppm] = 153.5, 142.3, 132.1, 105.1, 77.6, 61.2, 56.6, 23.0; IR (ATR): v$_{max}$ (cm$^{-1}$) = 406 (w), 447 (w), 493 (m), 517 (w), 546 (m), 606 (s), 629 (m), 666 (w), 746 (w), 766 (m), 825 (w), 845 (w), 874 (s), 909 (s), 942 (w), 997 (m), 1031 (w), 1094 (s), 1109 (m), 1127 (s), 1166 (s), 1230 (m), 1313 (m), 1344 (m), 1377 (w), 1393 (w), 1412 (m), 1428 (w), 1589 (m), 2941 (w, br), 3098 (w); m$_R$: 69–71 °C; HRMS for C$_{12}$H$_{18}$NaO$_6$S$^+$ (ESI+) [M+Na]$^+$: calc.: 313.0722, found: 313.0717.
6.6 2,2-Dimethylpropyl 2,5-dimethoxybenzenesulfonate (8a)

According to the general protocol (GP1), 1,4-dimethoxybenzene (83 mg, 0.60 mmol, 1.00 eq.) was used as substrate and 2,2-dimethylpropan-1-ol (424 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 7:3), 2,2-dimethylpropyl 2,5-dimethoxybenzenesulfonate (58%, 100 mg, 0.35 mmol) was obtained as an off-white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ [ppm] = 7.46 (d, $J = 3.1$ Hz, 1H), 7.13 (dd, $J = 9.0$, 3.2 Hz, 1H), 6.97 (d, $J = 9.1$ Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.73 (s, 2H), 0.93 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ [ppm] = 152.9, 151.7, 124.3, 121.7, 115.8, 113.9, 80.3, 56.7, 56.2, 31.8, 26.2; IR (ATR): $\nu_{\text{max}}$ (cm$^{-1}$) = 452 (m), 465 (m), 513 (m), 541 (s), 576 (m), 612 (m), 633 (w), 696 (m), 715 (w), 738 (m), 760 (m), 819 (s), 848 (m), 886 (s), 921 (m), 935 (s), 951 (s), 1020 (m), 1047 (m), 1064 (w), 1087 (w), 1152 (m), 1174 (s), 1224 (s), 1278 (s), 1304 (w), 1368 (w), 1386 (w), 1402 (w), 1414 (m), 1435 (m), 1447 (m), 1461 (m), 1490 (m), 1573 (w), 2958 (w, br), 3087 (w); $mR$: 72–73 °C; HRMS for C$_{13}$H$_{20}$NaO$_5$S$^+$ (ESI$^+$) [M+Na]$^+$: calc.: 311.0921, found: 311.0929.

6.7 Ethyl 2,5-dimethoxybenzenesulfonate (8b)

According to the general protocol (GP1), 1,4-dimethoxybenzene (83 mg, 0.60 mmol, 1.00 eq.) was used as substrate and ethanol (280 µL, 221 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 6:4), ethyl 2,5-dimethoxybenzenesulfonate (66%, 98 mg, 0.40 mmol) was obtained as an off-white solid.
1H NMR (300 MHz, CDCl₃) δ [ppm] = 7.45 (d, J = 3.1 Hz, 1H), 7.12 (dd, J = 9.0, 3.2 Hz, 1H), 6.99 (d, J = 9.1 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.81 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl₃) δ [ppm] = 153.0, 151.7, 124.8, 121.7, 115.6, 114.2, 67.7, 57.0, 56.2, 15.1; IR (ATR): ν max (cm⁻¹) = 405 (w), 464 (m), 536 (m), 544 (m), 568 (s), 610 (s), 694 (m), 712 (w), 735 (m), 788 (m), 822 (m), 885 (m), 927 (s), 1001 (m), 1018 (m), 1045 (m), 1061 (w), 1106 (w), 1170 (s), 1186 (m), 1192 (m), 1224 (m), 1262 (m), 1282 (m), 1303 (w), 1345 (s), 1362 (w), 1395 (w), 1413 (m), 1442 (m), 1460 (m), 1472 (m), 1490 (m), 1502 (m), 1573 (w), 1586 (w), 2835 (w), 2946 (w, br), 3099 (w); mR: 52–53 °C; HRMS for C₁₀H₁₄NaO₅S⁺ (ESI⁺) [M+Na⁺]: calc.: 269.0460, found: 269.0452.

6.8 Ethyl 3,4-dimethoxybenzenesulfonate (9)

![Chemical structure image]

According to the general protocol (GP1), 1,2-dimethoxybenzene (76 μL, 83 mg, 0.60 mmol, 1.00 eq.) was used as substrate and ethanol (280 μL, 221 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 6:4), ethyl 3,4-dimethoxybenzenesulfonate (49%, 73 mg, 0.30 mmol) was obtained as a highly viscous colorless oil.

1H NMR (300 MHz, CDCl₃) δ [ppm] = 7.53 (dd, J = 8.5, 2.2 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl₃) δ [ppm] = 153.5, 149.4, 127.8, 122.2, 110.6, 110.1, 66.9, 56.4, 56.4, 14.6; IR (ATR): ν max (cm⁻¹) = 485 (m), 503 (w), 539 (w), 576 (s), 620 (m), 663 (m), 685 (w), 762 (m), 780 (m), 812 (w), 857 (w), 911 (s), 1000 (m), 1016 (m), 1096 (m), 1139 (m), 1166 (s), 1185 (m), 1238 (m), 1261 (m), 1350 (m, br), 1407 (w), 1441 (w), 1463 (w), 1509 (m), 1587 (w), 2940 (w, br), 3086 (w); HRMS for C₁₀H₁₄NaO₅S⁺ (ESI⁺) [M+Na⁺]: calc.: 269.0460, found: 269.0458.
6.9 Ethyl 4-bromo-2,5-dimethoxybenzenesulfonate (10)

\[
\text{Br} \\
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{S} \\
\text{O}
\end{array}
\]

According to the general protocol (GP1), 2-bromo-1,4-dimethoxybenzene (90 µL, 130 mg, 0.60 mmol, 1.00 eq.) was used as substrate and ethanol (280 µL, 221 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 6:4), ethyl 4-bromo-2,5-dimethoxybenzenesulfonate (40%, 78 mg, 0.24 mmol) was obtained as an off-white solid.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 7.43 (s, 1H), 7.27 (s, 1H), 4.22 (q, \(J = 7.1\) Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 1.34 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 151.5, 149.8, 123.9, 119.2, 118.5, 113.9, 67.9, 15.1; IR (ATR): \(\nu_{\text{max}}\) (cm\(^{-1}\)) = 416 (w), 448 (m), 482 (w), 505 (m), 552 (m), 595 (s), 637 (m), 653 (w), 699 (m), 749 (m), 764 (m), 799 (m), 830 (m), 870 (m), 909 (s), 930 (m), 1004 (m), 1018 (m), 1043 (m), 1080 (m), 1111 (w), 1169 (s), 1216 (m), 1254 (w), 1278 (w), 1301 (w), 1342 (m), 1371 (s), 1393 (w), 1439 (m), 1465 (m), 1481 (m), 1494 (m), 1528 (w), 1558 (w), 1601 (w), 1704 (w, br), 2841 (w, br), 2922 (w, br), 3076 (w); \(m_r\): 74–76 °C; HRMS for C\(_{10}\)H\(_{13}\)BrNaO\(_5\)S\(^+\) (ESI\(^+\)) [M+Na\(^+\)]\(^+\): calc.: 346.9565, found: 346.9559.

6.10 Ethyl 5-(1,1-dimethylethyl)-2,4-dimethoxybenzenesulfonate (11)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{S} \\
\text{O}
\end{array}
\]

According to the general protocol (GP1), 4-(1,1-dimethylethyl)-3-methoxyanisol (117 mg, 0.60 mmol, 1.00 eq.) was used as substrate and ethanol (280 µL, 221 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 6:4), ethyl 5-(1,1-dimethylethyl)-2,4-dimethoxybenzenesulfonate (45%, 82 mg, 0.27 mmol) was obtained as an off-white solid.
**6.11 Ethyl 4-methoxy-2,6-dimethylbenzenesulfonate (12)**

![Chemical structure](image)

According to the general protocol (GP1), 3,5-dimethylanisole (84 μL, 82 mg, 0.60 mmol, 1.00 eq.) was used as substrate and ethanol (280 μL, 221 mg, 4.80 mmol, 8.00 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 6:4), ethyl 4-methoxy-2,6-dimethylbenzenesulfonate (17%, 25 mg, 0.10 mmol) was obtained as an off-white solid.

$^1\text{H} \text{NMR}\ (300 \text{ MHz, CDCl}_3) \, \delta \ [\text{ppm}] = 7.43 \ (s, \ 1\text{H}), \ 7.27 \ (s, \ 1\text{H}), \ 4.22 \ (q, \ J = 7.1 \text{ Hz}, \ 2\text{H}), \ 3.93 \ (s, \ 3\text{H}), \ 3.90 \ (s, \ 3\text{H}), \ 1.34 \ (t, \ J = 7.1 \text{ Hz}, \ 3\text{H}); \ ^{13}\text{C} \text{ NMR}\ (75 \text{ MHz, CDCl}_3) \, \delta \ [\text{ppm}] = ^{13}\text{C} \text{ NMR}\ (75 \text{ MHz, CDCl}_3) \, \delta \ [\text{ppm}] = 151.5, \ 149.8, \ 123.9, \ 119.2, \ 118.5, \ 113.9, \ 57.2, \ 57.2, \ 67.9, \ 15.1; \ IR\ (\text{ATR}): \nu_{\text{max}} \ (\text{cm}^{-1}) = 414 \ (w), \ 472 \ (m), \ 528 \ (m), \ 542 \ (s), \ 554 \ (m), \ 610 \ (s), \ 662 \ (m), \ 691 \ (w), \ 715 \ (w), \ 779 \ (s), \ 816 \ (w), \ 859 \ (m), \ 914 \ (s), \ 937 \ (s), \ 957 \ (s), \ 1003 \ (s), \ 1037 \ (w), \ 1084 \ (m), \ 1104 \ (w), \ 1160 \ (s), \ 1179 \ (m), \ 1192 \ (w), \ 1240 \ (w), \ 1282 \ (w), \ 1316 \ (s), \ 1340 \ (s), \ 1365 \ (w), \ 1385 \ (w, \ br), \ 1443 \ (w), \ 1455 \ (w), \ 1470 \ (m), \ 1568 \ (w), \ 1593 \ (m), \ 1713 \ (w, \ br), \ 2944 \ (w, \ br); \ m_R: 48–49 \degree \text{C}; \ \text{HRMS for C}_{11}\text{H}_{16}\text{NaO}_4\text{S}^+ (\text{ESI}^+) [\text{M+Na}]^+: \text{calc.: 267.0667}, \ \text{found: 267.0660.}
6.12 1,1,1,3,3,3-Hexafluoropropan-2-yl 3,4,5-trimethoxybenzene-sulfonate (13a) and 2,2,2-trifluoroethyl 3,4,5-trimethoxybenzenesulfonate (13b)

According to the general protocol (GP1), 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.0 eq.) was used as substrate and 2,2,2-trifluoroethanol (350 µL, 480 mg, 4.80 mmol, 8.0 eq.) as alcohol. After product purification via column chromatography (cyclohexane/ethyl acetate = 10:0 → 7:3), 1,1,1,3,3,3-hexafluoropropan-2-yl 3,4,5-trimethoxybenzene-sulfonate (12%, 28 mg, 0.07 mmol) and 2,2,2-trifluoroethyl 3,4,5-trimethoxybenzenesulfonate (33%, 65 mg, 0.20 mmol) were obtained as off-white solids.

Analytics of 13a: $^1$H NMR (300 MHz, CDCl$_3$) δ [ppm] = 7.14 (s, 2H), 5.29 (hept, $J = 5.7$ Hz, 1H), 3.95 (s, 3H), 3.92 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ [ppm] = 153.6, 143.9, 129.0, 120.0 (q, $J = 285.2$ Hz), 105.7, 72.0 (h, $J = 35.6$ Hz), 61.3, 56.7; $^{19}$F NMR (282 MHz, CDCl$_3$) δ [ppm] = −74.21 (d, $J = 5.6$ Hz); IR (ATR): $\nu_{\text{max}}$ (cm$^{-1}$) = 420 (w), 448 (w), 510 (w), 528 (m), 546 (w), 578 (w), 616 (s), 628 (m), 688 (m), 731 (w), 747 (w), 779 (w), 799 (s), 851 (m), 874 (m), 905 (m), 992 (m), 1031 (w), 1063 (s), 1103 (s), 1131 (s), 1171 (s), 1182 (m), 1203 (s), 1231 (m), 1264 (w), 1292 (s), 1319 (m), 1360 (m), 1375 (m), 1382 (m), 1416 (m), 1432 (w), 1454 (w), 1467 (w), 1502 (w), 1595 (w), 2968 (w, br), 3099 (w); $m_R$: 76–78 °C; HRMS for C$_{12}$H$_{12}$F$_6$O$_6$S (APCI$^+$) [M]: calc.: 398.0259, found: 398.0259.

Analytics of 13b: $^1$H NMR (300 MHz, CDCl$_3$) δ [ppm] = 7.13 (s, 2H), 4.37 (q, $J = 7.9$ Hz, 2H), 3.93 (s, 3H), 3.92 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ [ppm] = 153.7, 143.4, 129.1, 122.1 (q, $J = 277.9$ Hz), 105.5, 64.8 (q, $J = 38.0$ Hz), 61.2, 56.7; $^{19}$F NMR (282 MHz, CDCl$_3$) δ [ppm] = −74.89 (t, $J = 7.9$ Hz); IR (ATR): $\nu_{\text{max}}$ (cm$^{-1}$) = 410 (w), 433 (w), 497 (m), 521 (w), 534 (w), 570 (m), 607 (s), 657 (w), 670 (w), 688 (w), 759 (m), 783 (s), 826 (w), 841 (m), 901 (m), 918 (w), 958 (m), 997 (m), 1028 (s), 1126 (s), 1164 (s), 1239 (w), 1282 (m), 1304 (m), 1336 (w), 1367 (m), 1415 (m), 1434 (w), 1457 (m), 1467 (w), 1502 (w), 1595 (w), 2968 (w, br), 3099 (w); $m_R$: 76–78 °C; HRMS for C$_{12}$H$_{12}$F$_6$O$_6$S (APCI$^+$) [M]: calc.: 398.0259, found: 398.0259.
1499 (w), 1593 (w), 2955 (w, br), 3019 (w), 3100 (w); mR: 97–98 °C; HRMS for \( \text{C}_{11}\text{H}_{13}\text{F}_{3}\text{O}_{6}\text{S} \) (APCI\(^+\)) [M]: calc.: 330.0385, found: 330.0385.
7. NMR Spectra of all Isolated Compounds

$^1$H NMR (300 MHz, CDCl$_3$/298 K): 7a

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 7a
$^1$H NMR (300 MHz, CDCl$_3$/298 K): 7b

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 7b
$^1$H NMR (300 MHz, CDCl$_3$/298 K): 7c

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 7c
$^1$H NMR (300 MHz, CDCl$_3$/298 K): 7d

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 7d

S23
$^1$H NMR (300 MHz, CDCl$_3$/298 K): 8a

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 8a
$^1$H NMR (300 MHz, CDCl$_3/298$ K): 9

$^{13}$C NMR (75 MHz, CDCl$_3/298$ K): 9
$^1$H NMR (300 MHz, CDCl$_3$/298 K): 10

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 10
$^1$H NMR (300 MHz, CDCl$_3$/298 K): 11

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 11
$^1$H NMR (300 MHz, CDCl$_3$/298 K): 12

$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): 12
$^1\text{H NMR (300 MHz, CDC}$_3$/298 K): 13a$

$^{13}\text{C NMR (75 MHz, CDC}$_3$/298 K): 13a$
$^{13}$C NMR (75 MHz, CDCl$_3$/298 K): $^{13}$b

$^{19}$F NMR (282 MHz, CDCl$_3$/298 K): $^{13}$b
8. ATR-IR Spectra of all Isolated Compounds

![Graphs of ATR-IR Spectra for compounds 7a, 7b, and 7c]
9. References

[1] W. L. F. Armarego, C. L. L. Chai, Purification of Laboratory Chemicals (7th Edition); Elsevier Ltd, Oxford, 2012.
[2] R. K. Harris, E. D. Becker, S. M. Cabral de Menezes, R. Goodfellow, P. Granger, Solid State Nucl. Magn. Reson. 2002, 22, 458–483.
[3] J. B. Ferguson, J. Am. Chem. Soc. 1917, 39, 364–373.
[4] C. Gütz, B. Klöckner, S. R. Waldvogel, Org. Process Res. Dev. 2016, 20, 26–32.
[5] a) N. Elgrishi, K. J. Rountree, B. D. McCarthy, E. S. Rountree, T. T. Eisenhart, J. L. Dempsey, J. Chem. Educ. 2018, 95, 197–206; b) J. Heinze, Angew. Chem. Int. Ed. 1984, 23, 831–847.