Supporting Information

Metal-Free Electrochemical Synthesis of Sulfonamides Directly from (Hetero)arenes, SO$_2$, and Amines

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1. General Information

**All reagents and solvents** used were obtained as analytical grade from commercial suppliers or purified with standard methods. Sulfur dioxide (99.98%) was purchased from Linde AG in a 10 L pressure bottle. Electrochemical reactions were carried out at boron-doped diamond (BDD) electrodes. BDD electrodes (DIACHEM®, 15 μm boron-doped diamond layer on 3 mm silicon support/wafer) were purchased from CONDIAS GmbH, Itzhoe, Germany. The glass frits were purchased from ROBU® Glasfilter-Geräte GmbH (VitraPOR filter-disc; centred; porosity: P4; diameter: 10 mm; thickness standard: apx. 2.8 mm). Isostatic graphite Sigrafine® electrodes were purchased from SGL Carbon (Bonn-Bad Godesberg, Germany). Glassy carbon electrodes (SIGRADUR® G) were obtained from HTW Hochtemperatur-Werkstoffe GmbH (Thierhaupten, 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 employed. 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 μm, 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 μm, 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 $^1$H (400 MHz), $^{13}$C{$^1$H} (101 MHz), and $^{19}$F (376 MHz) were recorded at 23 °C by Bruker Avance II 400 (400 MHz, 5 mm BBFO-SmartProbe with z gradient and ATM,
SampleXPress 60 sample changer, Analytische Messtechnik, Karlsruhe, Germany). Chemical shifts (δ) are reported in parts per million (ppm) relative to traces of CHCl₃ (7.26 ppm in ¹H, 77.16 ppm in ¹³C{¹H}). For ¹⁹F spectra, CFCl₃ serves as reference compound.[²]

High-resolution mass spectra were obtained with QT of Ultima 3 (Waters, Milford, Massachusetts) using ESI⁺ ionization mode.

X-ray analysis data were collected on a STOE IPDS-2T diffractometer (STOE & Cie GmbH, Darmstadt, Germany) using graphite monochromated Mo-Kα radiation (λ= 0.71073 Å). Intensities were measured using fine-slicing ω 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. v = 100 mV/s, room temperature, c = 0.01 M, supporting electrolyte: NB₄BF₄, c (NB₄BF₄) = 0.1 M.
2. Experimental Procedures

Preparation of SO$_2$ stock solution:

According to Figure 1, 160 mL of the solvent(mixture) (HFIP, MeCN or HFIP:MeCN-mixture) was transferred into a dry two-neck round bottom flask. (Please note: low heat build-up occurs when mixing MeCN with HFIP). Sulfur dioxide was inserted for 45 minutes while constant stirring at 0 °C. After usage, the gas-inlet apparatus was flushed with argon. Excess SO$_2$ was quenched with aqueous NaOH (20 wt-%). The SO$_2$ stock solution was stored at +4 °C.

Determination of the SO$_2$ concentration of the stock solution:

The SO$_2$ molarity was determined according to the principles of iodometry.$^{[3]}$

An aliquot of the SO$_2$ stock solution (0.5 mL) was slowly added under stirring to an aq. solution of I$_2$ (1.27 g, 5.00 mmol) and KI (2.20 g, 13.3 mmol) in distilled water (100 mL) (equation 1). (Please note: Low heat build-up was observed). The solution was then back titrated with a freshly prepared aq. Na$_2$S$_2$O$_3$ solution (0.2 M) as titrant (equation 2). (Optional: On the verge of the transition point (decolorization), a few drops of a freshly prepared starch solution can be added for better visualization). After full reduction of the iodine, the concentration of SO$_2$ was calculated according to the previously reduced amount of iodine by SO$_2$. The procedure was
repeated twice. A SO2 concentration not higher than 3.0 m is highly recommended by the authors. (Please note: The solubility of SO2 in pure MeCN is superior compared to pure HFIP). If the concentration was too excessive, the stock-solution was diluted, and the titration was repeated. In case the stock solution was too diluted, SO2 was again injected for several minutes and the titration was repeated.

\[
\begin{align*}
\text{SO}_2 + 2 \text{H}_2\text{O} + \text{I}_2 & \rightarrow \text{H}_2\text{SO}_4 + 2 \text{HI} \\
2 \text{Na}_2\text{S}_2\text{O}_3 + \text{I}_2 & \rightarrow \text{Na}_2\text{S}_4\text{O}_6 + 2 \text{NaI}
\end{align*}
\]

(1) (2)

Experimental set-up and general protocol for the synthesis of sulfonamides in divided cells:
The electrochemical conversion was conducted in divided cells made of Teflon according to Figure 2.[4] A porous glass frit (porosity: 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 is placed in each compartment of the cell. In total, six divided cells can be placed in a screening block, which can be located on a magnetic stirrer. This reaction set-up can be commercially obtained as IKA screening system package (6 cells) from IKA®-Werke GmbH & Co. KG.

![Figure 2. Screening system with 6 divided electrolysis cells fitting on a common magnetic stirrer; electrode gap: 2 cm; active surface of each planar electrode: 3.2 cm².](image)

Scale-up Reaction:
The scale-up reaction was performed in an H-type glass cell, which is divided by a glass frit (Figure 3). Total volume was 160 mL (80 mL in each compartment). A star-shaped stirring bar was used on each side for efficient mixing. BDD electrodes (dimensions: (6.0 x 2.0 x 0.3) cm) were employed.
**General procedure for optimization reactions (GP1):**

The anodic compartment of a divided screening cell was charged with 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.). Preparation of the electrolyte: A ready-made solution of solvents,
SO₂ in MeCN/HFIP/HFIP:MeCN (1:1), morpholine (314 mg, 3.60 mmol, 6.00 eq.) and \(N,N\)-diisopropylethylamine (620 mg, 4.80 mmol, 8.00 eq.) were added into a pre-dried pear-shaped flask with septum at 0 °C under stirring so that a total volume of 12.0 mL and the desired SO₂ concentration was reached. The reaction mixture was then transferred into the two compartments of the divided cell (6.0 mL into each compartment). The electrodes were connected to a DC power device and the electrolysis was started under constant stirring (300 rpm, r.t., 14 h). The NMR yield was calculated by internal standard via addition of 1,3,5-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.) to the crude reaction mixture.

**General procedure for the synthesis of sulfonamides [arene substrate scope] (GP2):**
The anodic compartment of a divided screening cell was charged with the arene (0.60 mmol, 1.00 eq.). Preparation of the electrolyte: HFIP:MeCN (1:1), SO₂ in HFIP:MeCN (1:1), morpholine (314 mg, 3.60 mmol, 6.00 eq.) and \(N,N\)-diisopropylethylamine (620 mg, 4.80 mmol, 8.00 eq.) were transferred into a pre-dried pear-shaped flask with septum at 0 °C under stirring so that a total volume of 12.0 mL and a SO₂ concentration of 1.5 M was reached. The reaction mixture was then transferred into the two compartments of the divided cell (6.0 mL into each compartment). The BDD electrodes were connected to a DC power device and the electrolysis (12.0 mA/cm², 3.50 F) was started under constant stirring (300 rpm, r.t., 14 h). GC spectra of the crude reaction mixture were recorded. The solvents were removed at reduced pressure. Distilled water (30.0 mL) was added to the crude product, which was then extracted in ethyl acetate (3 x 30.0 mL). The combined organic fractions were dried over MgSO₄. The organic solvent was removed at reduced pressure and the crude product was purified via column chromatography with an ethyl acetate/cyclohexane solvent gradient (mostly 1:9 to 5:5).

**General procedure for the synthesis of sulfonamides [amine substrate scope] (GP3):**
The anodic compartment of a divided screening cell was charged with 1,4-dimethoxybenzene (83 mg, 0.60 mmol, 1.00 eq.). Preparation of the electrolyte: HFIP:MeCN (1:1), SO₂ in HFIP:MeCN (1:1), the amine (3.60 mmol, 6.00 eq.) and \(N,N\)-diisopropylethylamine (620 mg, 4.80 mmol, 8.00 eq.) were transferred into a pre-dried pear-shaped flask with septum at 0 °C under stirring so that a total volume of 12.0 mL and a SO₂ concentration of 1.5 M was reached. The reaction mixture was then transferred into the two compartments of the divided cell (6.0 mL into each compartment). The BDD electrodes were connected to a DC power device and the electrolysis (12.0 mA/cm², 3.50 F) was started under constant stirring (300 rpm, r.t., 14 h). GC spectra of the crude reaction mixture were recorded. The solvents were removed at reduced
pressure. Distilled water (30.0 mL) was added to the crude product, which was then extracted in ethyl acetate (3 x 30.0 mL). The combined organic fractions were dried over MgSO$_4$. The organic solvent was removed at reduced pressure and the crude product was purified via column chromatography with an ethyl acetate/cyclohexane solvent gradient (mostly 1:9 to 5:5).

**Important Considerations**

Low heat buildup was observed while mixing HFIP with MeCN. In few cases, the amine-SO$_2$ complex precipitated. However, sonication improved the dissolution rate. MeCN, HFIP and DIPEA were dried with 3 Å MS. The Teflon cells were sealed with Parafilm, but were not pre-dried. The BDD electrodes were cleaned with DMSO after usage. After electrolysis, precipitation occurred in the cathodic compartment when the reaction mixture was left overnight. Therefore, direct work-up is recommended.

3. **Cyclic Voltammetry**

CV investigations were performed for reaction mechanism elucidation. Unless otherwise noted, 0.1 M NBu$_4$BF$_4$ (165 mg, 0.50 mmol) was dissolved in HFIP:MeCN (1:1; 5.0 mL). The different substrates used can be retrieved from Table 1 and Graph 1. Ferrocene/ferrocenium (FcH/FcH$^+$) was used as internal reference (unless otherwise noted: half-wave potential 0.36 V versus Ag/AgCl).$^{[5]}$

| Table 1. Substrates used for CV studies (also see Graph 1). |
|------------------------------------------------------------|
| **Graph** | **Substrates** | **m [mg]** | **n [mmol]** |
| --- | --- | --- | --- |
| Red graph[a] | Morpholine | 131 | 1.50 |
| | N,N-Diisopropanylamine | 259 | 2.00 |
| Blue graph | SO$_2$ stock solution[b] | 480 | 7.50 |
| Green graph | 1,2,3-Trimethoxybenzene | 8 | 0.05 |
| Black graph | 1,4-Dimethoxybenzene | 7 | 0.05 |
| | 6 | 14 | 0.05 |

[a] No supporting electrolyte was used; half-wave potential: 0.43 V;
[b] A HFIP:MeCN (1:1) SO$_2$ stock solution (3 M) was used (total volume of all components = 5 mL).
4. Mechanistic Proposal

As depicted by Graph 1, the oxidation potentials increase in the following order: 1,4-dimethoxybenzene (1.05 V, green), 1,2,3-trimethoxybenzene (1.13 V, blue), sulfonamide 6 (1.26 V, black), amidosulfinate (red). It is noteworthy, that the electron-rich arenes undergo initial anodic oxidation in comparison to the amidosulfinate species. Furthermore, 6 is not prone to overoxidization due to its significantly higher oxidation potential compared to 1,4-dimethoxybenzene.

![Graph 1](image)

**Graph 1.** Cyclic Voltammetry measurements of 1,4-dimethoxybenzene, 1,2,3-trimethoxybenzene, amidosulfinate and sulfonamide 6.

The reaction mechanism proposal is depicted in Scheme 1. Sulfur dioxide and the amine form Lewis acid-base adducts, generating amidosulfinates in an equilibrium reaction after deprotonation by an organic base. Initial anodic oxidation of the arene substrate forms the radical cation intermediate. Subsequent nucleophilic attack of the amidosulfinate, followed by a second oxidation step provides the sulfonamide. As cathodic reaction, SO$_2$ reduction occurs.
Scheme 1. Proposed reaction mechanism.
5. **Optimization of the Reaction Conditions**

The reaction conditions were optimized in a step-by-step approach (GP1). The SO\textsubscript{2} concentration, solvent ratio, current density, amount of applied charge, electrode material, role of the base and cell type were screened.

### 5.1 Optimization of the SO\textsubscript{2} Concentration and Solvent Ratio

According to Scheme 2, a series of reactions was executed by varying the SO\textsubscript{2} concentration and solvent ratios. For this purpose, different amounts of the SO\textsubscript{2} stock solution in MeCN (2.75 M) were filled up with HFIP in order to find a first reference point for further investigations (Table 2).

![Scheme 2](image.png)

**Scheme 2.** Model reaction for optimization of reaction conditions; DIPEA = N,N-diisopropylethylamine.

**Table 2.** Optimization of the reaction by variation of SO\textsubscript{2} concentration and HFIP:MeCN-ratio.

| Entry | SO\textsubscript{2} [M] | Ratio (HFIP:MeCN) | Yield 5a\textsuperscript{[a]} [%] | Yield 5b\textsuperscript{[a]} [%] | Combined yield\textsuperscript{[a]} [%] |
|-------|----------------|------------------|----------------------------|----------------------------|----------------------------------|
| 1     | 0.6            | 3.15 : 1.00      | 22                         | 5                         | 27                               |
| 2     | 0.9            | 1.80 : 1.00      | 32                         | 5                         | 37                               |
| 3     | 1.2            | 1.00 : 1.00      | 46                         | 8                         | 54                               |
| 4     | 1.5            | 1.00 : 1.50      | 44                         | 7                         | 51                               |
| 5     | 1.8            | 1.00 : 2.60      | 34                         | 5                         | 39                               |

\textsuperscript{[a]} Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene).

The highest NMR yield was observed with 1.2 M SO\textsubscript{2} and a solvent ratio of HFIP:MeCN (1:1). Further optimization reactions were executed in order to determine the best solvent mratio:
Table 3. Optimization of the reaction by variation of HFIP:MeCN ratio at constant SO₂ concentration (1.2 M).

| Entry | Ratio (HFIP:MeCN) | Voltage\(^{[a]}\) [V] | Yield\(^{[b]}\) 5a [%] | Yield\(^{[b]}\) 5b [%] | Combined Yield\(^{[b]}\) [%] |
|-------|------------------|-----------------|-----------------|-----------------|-----------------|
| 6     | 9 : 1            | 18.3            | 30              | 9               | 39              |
| 7     | 9 : 1\(^{[c]}\)  | 18.1            | 28              | 7               | 35              |
| 8     | 7 : 3            | 11.3            | 40              | 7               | 47              |
| 9     | 6 : 4            | 9.90            | 41              | 7               | 48              |
| 3     | 1 : 1            | 9.20            | 46              | 8               | 54              |
| 10    | 4 : 6            | 8.30            | 37              | 6               | 43              |
| 11    | 3 : 7            | 8.00            | 33              | 5               | 38              |
| 12    | 1 : 9            | 10.4            | –               | –               | traces          |

\(^{[a]}\) Terminal voltage;  
\(^{[b]}\) Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene);  
\(^{[c]}\) A few pellets of 3 Å MS were added into the anodic compartment.

The optimal HFIP:MeCN solvent ratio was fixed at 1:1 (entry 3). It can be noted that a higher MeCN content provides improved conductivity (lower terminal voltage). Furthermore, it can be concluded that the addition of molecular sieves had no influence (entry 7).

Further solvent screening can be seen in Table 4.

Table 4. Optimization of the reactions by varying the solvents.

| Entry | Solvent (HFIP:X = 1:1) | Voltage\(^{[a]}\) [V] | SM\(^{[b]}\) [%] | Combined Yield\(^{[b]}\) [%] |
|-------|------------------------|-----------------|----------------|-----------------|
| 3     | X = MeCN               | 9.20            | 29             | 54              |
| 13    | X = CH₂Cl₂             | 27.8            | 19             | 57              |
| 14    | X = DMSO               | 18.8            | 77             | traces          |

\(^{[a]}\) Terminal voltage;  
\(^{[b]}\) Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene).  
SM = starting material

It can be clearly stated that DMSO is ineligible for this reaction. However, CH₂Cl₂ provides slightly higher combined yields in comparison to MeCN. But in contrast, the reaction with MeCN leaves more starting material and provides superior conductivity compared to CH₂Cl₂. Therefore, more possibilities to achieve higher yields through further optimization (e.g. amount of charge) are available.
Finally, the SO\textsubscript{2} concentration was screened at constant solvent ratios (Table 5).

Table 5. Investigation of varying SO\textsubscript{2} concentration in HFIP:MeCN = 1:1.

| Entry | SO\textsubscript{2} [M] | Yield\textsuperscript{[a]} 5a [%] | Yield\textsuperscript{[a]} 5b [%] | Combined Yield\textsuperscript{[a]} [%] |
|-------|----------------|----------------|----------------|----------------|
| 15    | 0.9           | 28             | 5              | 33             |
| 3     | 1.2           | 46             | 8              | 54             |
| 16    | 1.5           | 45             | 8              | 53             |
| 17    | 1.8           | 40             | 7              | 47             |

\textsuperscript{[a]} Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene).

The reactions from entry 3 and 16 provided best results. For further investigations, the SO\textsubscript{2} concentration was fixed at 1.5 M.

5.2 Optimization of the Current Density

According to Scheme 3, the influence of the current density was investigated. Hence, the \( j \) values were varied from 5.00 to 15.5 mA/cm\(^2\) (Table 6).

Table 6. Variation of the current density.

| Entry | \( j \) [mA/cm\(^2\)] | Yield\textsuperscript{[a]} 5a [%] | Yield\textsuperscript{[a]} 5b [%] | Combined Yield\textsuperscript{[a]} [%] |
|-------|----------------|----------------|----------------|----------------|
| 18    | 5.00          | 33             | 6              | 39             |
| 16    | 7.00          | 45             | 8              | 53             |
| 19    | 9.00          | 46             | 8              | 54             |
| 20    | 11.0          | 41             | 7              | 48             |
| 21    | 12.0          | 47             | 8              | 55             |
| 22    | 13.0          | 46             | 7              | 53             |
| 23    | 15.5          | 39             | 6              | 45             |

\textsuperscript{[a]} Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene).

\( j = \) current density
The yields from entries 19 to 22 (Table 6) provided similar results and subsequently we concluded that the current density does not have a major influence on the reaction. In general, higher current densities are preferred to lower ones. Therefore, we decided to fix this parameter at 12.0 mA/cm² for upcoming reactions.

5.3 Optimization of the Amount of Applied Charge

Scheme 4. Reaction conditions for the optimization of the amount of applied charge.

At this optimization step the amount of applied charge referred to the arene was varied. As there was still starting material left at 2.50 F, different Q values were screened from this value upwards to 5.50 F (Table 7). The reaction conditions are shown in Scheme 4.

Table 7. Reaction optimization by varying the amount of applied charge.

| Entry | Q [F] | SM[a] [%] | Yield[a] 5a [%] | Yield[a] 5b [%] | Combined Yield[a] [%] |
|-------|-------|----------|----------------|----------------|-----------------------|
| 24    | 0     | 98       | 0              | 0              | 0                     |
| 25    | 3.00  | 24       | 45             | 8              | 53                    |
| 26    | 3.50  | 6        | 61             | 11             | 72                    |
| 27    | 4.00  | 10       | 55             | 10             | 65                    |
| 28    | 4.50  | 4        | 49             | 10             | 59                    |
| 29    | 5.00  | 9        | 52             | 8              | 60                    |
| 30    | 5.50  | 3        | 32             | 8              | 40                    |

[a] Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene).

The highest yield was achieved with 3.50 F (entry 26). Values above 3.50 F (entry 27–30) led to product degradation. The results of entry 24 show that electricity is inevitable for this reaction.
5.4 Screening of the Electrode Material

Further electrode materials were screened (Table 8, Scheme 5).

Table 8. Optimization of the reaction by varying the electrode material.

| Entry | Electrode Material | SM[a] [%] | Yield[a] 5a [%] | Yield[a] 5b [%] | Combined Yield[a] [%] |
|-------|--------------------|-----------|----------------|----------------|-----------------------|
| 26    | BDD                | 6         | 61             | 11             | 72                    |
| 31    | Platinum           | 14        | 51             | 8              | 59                    |
| 32    | Glassy carbon      | 8         | 60             | 12             | 72                    |
| 33    | Graphite           | 37        | 41             | 8              | 49                    |

[a] Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene).
Q = amount of charge; SM = starting material.

Graphite and platinum provided worse results compared to BDD (entry 26) and glassy carbon (entry 32). However, we decided to further use BDD as electrode material due to practical reasons.

5.5 Further Optimization Reactions

Graphite and platinum provided worse results compared to BDD (entry 26) and glassy carbon (entry 32). However, we decided to further use BDD as electrode material due to practical reasons.
Further factors were investigated. Initially, the reaction was carried out without DIPEA (Table 9, entry 34). Additionally, the morpholine concentration (no DIPEA) was increased (entry 35). Finally, the reaction was performed in an undivided cell (entry 36).

### Table 9. Optimization of reactions without adding DIPEA and varying concentration of morpholine.

| Entry | Morpholine [eq.] | SM[a] [%] | Yield[a] 5a [%] | Yield[a] 5b [%] | Combined Yield[a] [%] |
|-------|------------------|-----------|-----------------|-----------------|-----------------------|
| 34    | 3.00             | 29        | 31              | traces          | 31                    |
| 35    | 5.00             | 34        | 26              | 5               | 31                    |
| 36[b] | 3.00             | 62        | 13              | traces          | 13                    |

[a] Yield was determined by internal NMR standard (1,3,5-trimethoxybenzene);  
[b] Electrolysis was conducted in an undivided cell; DIPEA (4.00 eq.) was used.  
Q = amount of charge; SM = starting material

The results show that the omission of DIPEA leads to lower yields which cannot be increased by enhancing the morpholine concentration (entry 35). The reaction in the undivided cell (entry 36) provided only 13% NMR yield with 62% starting material being left. Cathodic reduction of SO₂ to with subsequent anodic reoxidation could result in lower current efficiencies.
6. **Unsuccessful Substrates**

Herein, we include a list of unsuccessful arene substrates (Scheme 7) and amine substrates (Scheme 8). However, in some cases, the product formation was low. A brief description to each substrate was added according to TLC, GC, and GC/MS results.

![Chemical diagrams showing unsuccessful substrates](image)

**Scheme 7.** Unsuccessful arene substrates in the sulfonamide synthesis.
**Scheme 8.** Unsuccessful amine components in the sulfonamide synthesis.
7. Product Characterization

7.1 4-((3,4,5-Trimethoxyphenyl)sulfonyl)morpholine (5a) & 4-((2,3,4-Trimethoxyphenyl)sulfonyl)morpholine (5b)

According to GP2, 1,2,3-trimethoxybenzene (101 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 5a and 5b (6:1 (5a:5b) NMR ratio, 127 mg, 0.40 mmol, 67%) were obtained as regioisomer mixture (colorless solid). An aliquot (50 mg) of the mixture was taken for regioisomer separation, which was accomplished by RP-HPLC. 5a was obtained as colorless solid and 5b as colorless waxy solid.

5a:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 6.94 (s, 2H), 3.90 (s, 9H), 3.77–3.71 (m, 4H), 3.04–2.98 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ [ppm] = 153.5, 142.0, 129.9, 105.2, 66.2, 61.1, 56.6, 46.1; mR: 108–110 °C; HRMS for C$_{13}$H$_{19}$NO$_6$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 318.1012, found: 318.1012.

Analytical data of 5a corresponds to those reported in the reference.[5]

Crystallization was performed by dissolving 5a (15 mg) in dichloromethane (1 mL) and pentane (1 mL) at room temperature. Crystal structure determination of 5a (also see Figure 4): C$_{13}$H$_{19}$NO$_6$S, M = 317.35 g/mol; colorless plates (0.09 x 0.41 x 0.60 mm$^3$), T = 120 K, $\lambda$(Mo-K$_{α}$) = 0.71073 Å, monoclinic space group P5$_2$/n, (14), a = 10.6703(5) Å, b = 7.8425(3) Å, c = 18.7446(8) Å, $\beta$ = 103.876(3)$^o$, V = 1522.81(11) Å$^3$, z = 4, $\rho_{\text{ray}}$ = 1.384 g/cm$^{-3}$, $\theta_{\text{max}}$ = 57.2$^o$, $\mu$ = 0.238 mm$^{-1}$, F(000) = 672, 7299 reflections, 3623 unique reflections (R$_{\text{int}}$ = 0.0155), final R-values [I > 2$\sigma$(I)]: R$_1$ = 0.0323, wR$_2$ = 0.0836, R-values (all data): R$_1$ = 0.0345, wR$_2$ = 0.0858, CCDC-2032478.
The morpholine ring has a chair conformation. As shown in Figure 4, the 4-methoxy group is axial while the 3- and 5-methoxy groups are equatorial to the phenyl ring.

5b:
\[ ^1H \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \ \delta [\text{ppm}] = 7.56 \ (d, \ J = 8.9 \text{ Hz}, 1H), \ 6.72 \ (d, \ J = 8.9 \text{ Hz}, 1H), \ 3.97 \ (s, 3H), \ 3.92 \ (s, 3H), \ 3.90 \ (s, 3H), \ 3.74 - 3.69 \ (m, 4H), \ 3.21 - 3.15 \ (m, 4H); \ ^{13}C \ \text{NMR} \ (101 \text{ MHz}, \text{CDCl}_3) \ \delta [\text{ppm}] = 158.0, \ 152.2, \ 143.3, \ 126.7, \ 123.3, \ 106.7, \ 66.7, \ 61.9, \ 61.1, \ 56.3, \ 46.2; \ \text{HRMS} \ \text{for} \ C_{13}H_{19}NaNO_6S^+ \ (\text{ESI}^+) \ [\text{M+Na}]^+: \ \text{calc.:} \ 340.0825, \ \text{found:} \ 340.0832.\]

7.2 4-((2,5-Dimethoxyphenyl)sulfonyl)morpholine (6)

According to GP2, 1,4-dimethoxybenzene (83 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 $\rightarrow$ 5:5). The title compound (138 mg, 0.48 mmol, 80%) was obtained as colorless solid.
**Scale-up of electrolysis:**

The anodic compartment of a divided H-type glass cell was charged with 1,4-dimethoxybenzene (1.11 g, 8.00 mmol, 1.0 eq.). Preparation of the electrolyte: HFIP:MeCN (1:1), SO\(_2\) in HFIP:MeCN (1:1), morpholine (4.18 g, 48.0 mmol, 6.0 eq.) and N,N-diisopropylethylamine (8.27 g, 64.0 mmol, 8.0 eq.) were transferred into a pre-dried pear-shaped flask with septum at 0 °C under stirring so that a total volume of 160 mL and a SO\(_2\) concentration of 1.5 m was reached. The reaction mixture was then transferred into the two compartments of the divided cell (80.0 mL into each compartment). The BDD electrodes were connected to a DC power device and the electrolysis (\(A = 7.20 \text{ cm}^2; j = 12.0 \text{ mA/cm}^2, Q = 3.50 \text{ F}\)) was started under constant stirring (300 rpm, 14 h, room temperature). The solvents were removed at reduced pressure. Distilled water (400 mL) was added to the crude product, which was then extracted in EA (400 mL), washed with distilled water (200 mL) and brine (200 mL) in order to remove all amine residues. The aqueous fractions were rewashed with EA (2 x 200 mL). The combined organic fractions were dried over MgSO\(_4\). The organic solvent was removed at reduced pressure and the crude product was purified via column chromatography with an ethyl acetate:cyclohexane solvent gradient (1:9 → 5:5). The title compound (1.95 g, 6.79 mmol, 85%) was obtained as colorless solid.

**6:**

\(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta [ppm] = 7.41 (d, J = 3.1 \text{ Hz}, 1H), 7.06 (dd, J = 9.0, 3.1 \text{ Hz}, 1H), 6.96 (d, J = 9.0 \text{ Hz}, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.73–3.68 (m, 4H), 3.26–3.19 (m, 4H); \(^{13}\text{C NMR (101 MHz, CDCl}_3\) \(\delta [ppm] = 153.2, 151.2, 126.4, 120.6, 116.3, 114.1, 66.8, 56.7, 56.1, 46.2; m\text{r}: 97–98 °C; HRMS for C\(_{12}\)H\(_{18}\)NO\(_5\)S\(^+\) (ESI\(^+\)) [M+H]\(^+\): calc.: 288.0906, found: 288.0904.**
7.3 4-((4-Bromo-2,5-dimethoxy-phenyl)sulfonyl)-morpholine (7a) & 4-((3-Bromo-2,5-dimethoxyphenyl)-sulfonyl)-morpholine (7b)

According to GP2, 1-bromo-2,5-dimethoxybenzene (157 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 7a (126 mg, 0.34 mmol, 57%) and 7b (45 mg, 0.12 mmol, 20%) were both obtained as colorless solids.

7a:
$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.40 (s, 1H), 7.24 (s, 1H), 3.88 (s, 6H), 3.73–3.68 (m, 4H), 3.24–3.20 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 151.0, 149.9, 125.7, 118.4, 118.0, 114.4, 66.8, 57.1, 57.0, 46.1; mR: 89–90 °C; HRMS for C$_{12}$H$_{16}$Na$_7$9BrNO$_5$S$^+$ (ESI+) [M+Na]$^+$: calc.: 387.9825, found: 387.9832.

7b:
$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.32 (d, $J = 3.1$ Hz, 1H), 7.29 (d, $J = 3.1$ Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.73–3.68 (m, 4H), 3.21–3.17 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 155.7, 148.6, 133.0, 124.0, 119.9, 115.6, 66.6, 62.4, 56.3, 46.2; mR: 82–84 °C; HRMS for C$_{12}$H$_{16}$Na$_7$9BrNO$_5$S$^+$ (ESI+) [M+Na]$^+$: calc.: 387.9825, found: 387.9836.
7.4 4-((4-Chloro-2,5-dimethoxy-phenyl)sulfonyl)-morpholine (8a) & 4-((3-Chloro-2,5-dimethoxyphenyl)-sulfonyl)-morpholine (8b)

According to GP2, 1-chloro-2,5-dimethoxybenzene (104 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 8a (80 mg, 0.25 mmol, 42%) was obtained as off-white solid and 8b (37 mg, 0.11 mmol, 19%) as colorless waxy solid.

8a:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.44 (s, 1H), 7.07 (s, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 3.7–3.69 (m, 4H), 3.24–3.20 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 150.8, 148.8, 128.6, 124.9, 115.3, 114.8, 66.7, 57.0, 56.9, 46.0; $m_r$: 152–153 °C; HRMS for C$_{12}$H$_7$ClNO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 322.0511, found: 322.0523.

8b:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.29 (d, $J = 3.1$ Hz, 1H), 7.14 (d, $J = 3.1$ Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.74–3.69 (m, 4H), 3.23–3.19 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 155.5, 147.7, 133.2, 130.8, 121.1, 114.8, 66.6, 62.2, 56.3, 46.3; HRMS for C$_{12}$H$_7$ClNO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 322.0511, found: 322.0521.
7.5 4-((4-Fluoro-2,5-dimethoxy-phenyl)sulfonyl)-morpholine (9a) & 4-((3-Fluoro-2,5-dimethoxyphenyl)-sulfonyl)-morpholine (9b)

According to GP2, 2-fluoro-1,4-dimethoxybenzene (94 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 9a (91 mg, 0.30 mmol, 50%) was obtained as off-white solid and 9b (36 mg, 0.12 mmol, 20%) as colorless waxy solid.

9a:
\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta [ppm] = 7.50 (d, J = 9.2 Hz, 1H), 6.81 (d, J = 12.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.75–3.68 (m, 4H), 3.24–3.17 (m, 4H); }^{13}\text{C NMR (101 MHz, CDCl}_3 \text{)} \delta [ppm] = 155.7 (d, J = 255.7 Hz), 151.7 (d, J = 8.9 Hz), 141.1 (d, J = 11.2 Hz), 121.2 (d, J = 3.7 Hz), 117.0 (d, J = 4.2 Hz), 102.4 (d, J = 23.0 Hz), 66.7, 57.1, 56.8, 46.0; }^{19}\text{F NMR (376 MHz, CDCl}_3 \text{)} \delta [ppm] = -123.88 (dd, J = 12.1, 9.3 Hz); \text{ mR: 118–120 °C; HRMS for C}_{12}\text{H}_{17}\text{FNO}_{5}\text{S}^+ (ESI+) [M+H]^+: calc.: 306.0806, found: 306.0813.}

9b:
\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta [ppm] = 7.14 (dd, J = 3.1, 1.7 Hz, 1H), 6.88 (dd, J = 12.1, 3.1 Hz, 1H), 3.92 (d, J = 1.0 Hz, 3H), 3.81 (s, 3H), 3.74–3.69 (m, 4H), 3.24–3.20 (m, 4H); }^{13}\text{C NMR (101 MHz, CDCl}_3 \text{)} \delta [ppm] = 156.9 (d, J = 251.2 Hz), 155.2 (d, J = 10.3 Hz), 139.5 (d, J = 13.8 Hz), 132.6 (d, J = 2.7 Hz), 110.5 (d, J = 2.8 Hz), 108.4 (d, J = 22.6 Hz), 66.5, 62.4 (d, J = 4.6 Hz), 56.1, 46.1; }^{19}\text{F NMR (376 MHz, CDCl}_3 \text{)} \delta [ppm] = -126.23 (d, J = 12.2 Hz); \text{ HRMS for C}_{12}\text{H}_{17}\text{FNO}_{5}\text{S}^+ (ESI+) [M+H]^+: calc.: 306.0806, found: 306.0817.}
7.6 4-((2-Fluoro-4,5-dimethoxyphenyl)sulfonyl)morpholine (10)

According to GP2, 4-fluoroveratrole (94 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 10 (63 mg, 0.21 mmol, 34%) was obtained as colorless waxy solid. A minor regioisomer was detected in GC and GC/MS spectra of the crude reaction mixture according to their mass fragmentation pattern.

10:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.21 (d, $J = 6.4$ Hz, 1H), 6.75 (d, $J = 11.2$ Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.78–3.74 (m, 4H), 3.19–3.14 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 154.3 (d, $J = 249.8$ Hz), 154.1 (d, $J = 9.6$ Hz), 145.1 (d, $J = 2.5$ Hz), 114.4 (d, $J = 15.8$ Hz), 112.0 (d, $J = 2.2$ Hz), 100.9 (d, $J = 28.1$ Hz), 66.3, 56.7, 56.6, 45.8; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ [ppm] = −114.2 (dd, $J = 11.0$, 6.2 Hz); HRMS for C$_{12}$H$_{17}$FNO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 306.0806, found: 306.0808.
7.7 4-((2-Bromo-4,5-dimethoxyphenyl)sulfonyl)morpholine (11)

According to GP2, 4-bromoveratrole (130 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 11 (38 mg, 0.10 mmol, 17%) was obtained as off-white solid. Two minor regioisomers were detected in GC and GC/MS spectra of the crude reaction mixture according to their mass fragmentation pattern.

11:
\[ \text{H NMR (400 MHz, CDCl}_3) \delta [ppm] = 7.55 (s, 1H), 7.18 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.76–3.73 (m, 4H), 3.31–3.27 (m, 4H); } \]
\[ \text{C NMR (101 MHz, CDCl}_3) \delta [ppm] = 152.5, 147.9, 128.5, 117.8, 114.6, 112.2, 66.4, 56.5, 56.4, 45.7; mR: 109–111 °C; HRMS for C}_{12}H_{17}BrNO_5S^+ (ESI+) [M+H]^+: calc.: 366.0006, found: 366.0001. \]
According to GP2, 1-iodo-3,4-dimethoxy-2-methylbenzene (167 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 3:97 → 50:50), 12 (71 mg, 0.17 mmol, 28%) was obtained as colorless waxy solid. Two minor regioisomers were detected in GC and GC/MS spectra of the crude reaction mixture according to their mass fragmentation pattern.

12:
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta [ppm] = 7.74 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.81–3.66 (m, 4H), 3.46–3.25 (m, 4H), 2.53 (s, 3H); ^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta [ppm] = 151.8, 149.9, 139.1, 135.4, 114.5, 90.8, 66.1, 60.6, 56.2, 45.4, 23.2; \)HRMS for C\(_{13}\)H\(_{19}\)INO\(_5\)S\(^+\) (ESI\(^+\)) [M+H]\(^+\): calc.: 428.0023, found: 428.0016.
According to GP2, veratrole (83 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 13a (108 mg, 0.38 mmol, 63%) was obtained as colorless solid. A minor regioisomer 13b (28 mg, 0.10 mmol, 16%) was obtained as colorless solid.

13a: 
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.36 (dd, $J = 8.4$, 2.1 Hz, 1H), 7.19 (d, $J = 2.2$ Hz, 1H), 6.97 (d, $J = 8.5$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.76–3.71 (m, 4H), 3.02–2.96 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 153.0, 149.2, 126.9, 121.9, 110.8, 110.4, 66.2, 56.4, 56.3, 46.1; m$_R$: 162–164°C; HRMS for C$_{12}$H$_{13}$NO$_5$S$^+$ (ESI+) [M+H]$^+$: calc.: 288.0900, found: 288.0905. Analytical data of 13a corresponds to those reported in the reference.[6]

13b: 
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.42 (dd, $J = 7.0$, 2.5 Hz, 1H), 7.19–7.11 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.73–3.68 (m, 4H), 3.23–3.18 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 154.1, 147.3, 131.7, 124.1, 122.4, 117.0, 66.7, 61.6, 56.3, 46.2; m$_R$: 96–97°C; HRMS for C$_{12}$H$_{13}$NO$_5$S$^+$ (ESI+) [M+H]$^+$: calc.: 288,0900; found: 288,0902.
7.10 4-((2,5-Dimethoxy-4-methylphenyl)sulfonyl)morpholine (14a) & 4-((2,5-Dimethoxy-3-methylphenyl)sulfonyl)morpholine (14b)

According to GP2, 2-methyl-1,4-dimethoxybenzene (91 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 14a (53 mg, 0.18 mmol, 29%) and 14b (58 mg, 0.19 mmol, 32%) were both obtained as colorless solids.

14a:
$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.28 (s, 1H), 6.83 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.72–3.68 (m, 4H), 3.21–3.17 (m, 4H), 2.25 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 151.3, 150.9, 134.4, 123.0, 115.7, 112.7, 66.8, 56.7, 56.1, 46.2, 16.8; m$_R$: 146–148 °C; HRMS for C$_{13}$H$_{19}$NNaO$_5$S$^+$ (ESI$^+$) [M+Na]$^+$: calc.: 324.0876, found: 324.0881.

14b:
$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.17 (d, $J$ = 3.1 Hz, 1H), 6.92 (d, $J$ = 3.2, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.71–3.66 (m, 4H), 3.18–3.14 (m, 4H), 2.31 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 155.1, 150.1, 135.0, 131.0, 122.4, 113.0, 66.6, 61.8, 55.9, 46.2, 16.4; m$_R$: 69–71 °C; HRMS for C$_{13}$H$_{20}$NO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 302.1057, found: 302.1056.
7.11 4-((4-Methoxy-2,6-dimethylphenyl)sulfonyl)morpholine (15a) & 4-((2-Methoxy-4,6-dimethylphenyl)sulfonyl)morpholine (15b)

According to GP2, 3,5-dimethylanisole (82 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 15a (24 mg, 0.08 mmol, 14%) and 15b (29 mg, 0.10 mmol, 17%) were both obtained as off-white solids.

15a:  
$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 6.65 (s, 2H), 3.83 (s, 3H), 3.73–3.66 (m, 4H), 3.17–3.10 (m, 4H), 2.65 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 161.8, 143.5, 125.7, 116.3, 66.3, 55.4, 44.5, 23.6; m$_R$: 80–83 °C; HRMS for C$_{13}$H$_{20}$NO$_4$S$^+$ (ESI+) [M+Na]$^+$: calc.: 286.1108, found: 286.1107.

15b:  
$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 6.71 (s, 1H), 6.70 (s, 1H), 3.90 (s, 3H), 3.76–3.72 (m, 4H), 3.31–3.23 (m, 4H), 2.63 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 158.2, 144.0, 141.4, 126.3, 123.1, 111.2, 67.0, 56.3, 45.8, 23.4, 21.6.; m$_R$: 116–118 °C; HRMS for C$_{13}$H$_{20}$NO$_4$S$^+$ (ESI+) [M+H]$^+$: calc.: 286.1108, found: 286.1109.
7.12 4-((5-tert-Butyl)-2,4-dimethoxyphenyl)sulfonyl)morpholine (16)

According to GP2, 1-tert-butyl-2,4-dimethoxybenzene (117 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 16 (76 mg, 0.22 mmol, 37%) was obtained as an off-white solid.

16:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.71 (s, 1H), 6.47 (s, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.73–3.69 (m, 4H), 3.19–3.14 (m, 4H), 1.33 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 163.4, 157.1, 130.7, 130.1, 116.0, 96.6, 66.8, 56.2, 55.5, 46.1, 34.6, 29.7; m$_R$: 160–163 °C; HRMS for C$_{16}$H$_{25}$NNaO$_5$S$^+$ (ESI$^+$) [M+Na]$^+$: calc.: 366.1345, found: 366.1352.
7.13 4-((1,4-Dimethoxynaphthalen-2-yl)sulfonyl)morpholine (17)

According to GP2, 1,4-dimethoxynaphthalene (113 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 17 (68 mg, 0.20 mmol, 34%) was obtained as colorless waxy solid.

17:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 8.32–8.26 (m, 1H), 8.17–8.11 (m, 1H), 7.68–7.59 (m, 2H), 7.13 (s, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.74–3.69 (m, 4H), 3.25–3.20 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 151.9, 149.6, 129.0, 129.0, 128.3, 127.8, 125.5, 123.3, 122.9, 103.0, 66.5, 64.0, 56.1, 46.4; HRMS for C$_{16}$H$_{19}$NNaO$_5$S$^+$(ESI$^+$) [M+Na]$^+$: calc.: 360.0876, found: 360.0878.
7.14 4-((2,3-Dihydrobenzo[b]-1,4-dioxin-6-yl)sulfonyl)morpholine (18a) & 4-((2,3-Dihydrobenzo[b]-1,4-dioxin-5-yl)sulfonyl)morpholine (18b)

According to GP2, benzo-1,4-dioxane (82 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 18a (112 mg, 0.39 mmol, 65%) was obtained as colorless solid. A minor regioisomer 18b (24 mg, 0.08 mmol, 14%) was obtained as colorless solid.

18a:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.25 (d, $J = 2.2$ Hz, 1H), 7.21 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 4.35–4.24 (m, 4H), 3.77–3.65 (m, 4H), 3.01–2.91 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 147.8, 143.7, 127.4, 121.6, 117.9, 117.5, 66.2, 64.6, 64.3, 46.1; mR: 133–135 ºC; HRMS for C$_{12}$H$_{16}$NO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 286.0744, found: 286.0753. Analytical data of 18a corresponds to those reported in the reference.[5]

18b:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.39 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.07 (dd, $J = 8.2, 1.5$ Hz, 1H), 6.91 (t, $J = 8.0$ Hz, 1H), 4.39–4.29 (m, 4H), 3.77–3.69 (m, 4H), 3.25–3.17 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 144.5, 141.8, 125.5, 123.7, 122.6, 120.8, 66.7, 64.7, 63.9, 46.1; mR: 162–163 ºC; HRMS for C$_{12}$H$_{16}$NO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 286.0744, found: 286.0742.
According to GP2, 3,4-dimethoxythiophene (87 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 19 (20 mg, 0.07 mmol, 11%) was obtained as yellowish waxy solid.

19: 
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 6.49 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.76–3.72 (m, 4H), 3.19–3.15 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 150.8, 148.5, 119.5, 102.5, 66.3, 61.5, 57.7, 46.3; HRMS for C$_{10}$H$_{16}$NO$_5$S$_2$ $^\dagger$ (ESI$^+$) [M+H]$^+$: calc.: 294.0465, found: 294.0466.
7.16 4-(Benzo[d]-1,3-dioxol-5-ylsulfonyl)morpholine (20)

According to GP2, 1,3-benzodioxole (73 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 20 (68 mg, 0.25 mmol, 42%) was obtained as colorless solid. A minor regioisomer was detected in GC and GC/MS spectra of the crude reaction mixture according to their mass fragmentation pattern.

20:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.31 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.16 (d, $J = 1.8$ Hz, 1H), 6.92 (d, $J = 8.2$ Hz, 1H), 6.09 (s, 2H), 3.76–3.72 (m, 4H), 3.01–2.96 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 151.8, 148.4, 128.5, 123.7, 108.5, 108.1, 102.5, 66.2, 46.2; m$\text{R}$: 138–140 °C; HRMS for C$_{11}$H$_{14}$NO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 272.0587, found: 272.0587.

Analytical data of 20 corresponds to those reported in the reference.$^5$
7.17 4-((6-Bromobenzo[d]-1,3-dioxol-5-yl)sulfonyl)morpholine (21)

According to GP2, 5-bromo-1,3-benzodioxole (121 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 21 (54 mg, 0.15 mmol, 26%) was obtained as off-white solid. Two minor regioisomers were detected in GC and GC/MS spectra of the crude reaction mixture according to their mass fragmentation pattern.

21:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.53 (s, 1H), 7.16 (s, 1H), 6.10 (s, 2H), 3.76–3.68 (m, 4H), 3.30–3.24 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 151.9, 147.5, 130.3, 115.4, 113.6, 112.2, 103.2, 66.5, 45.9; $\text{mR}$: 156–158 °C; HRMS for C$_{11}$H$_{13}$BrNO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 349.9693, found: 349.9692.
According to GP2, 5-chloro-1,3-benzodioxole (94 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 \(\rightarrow\) 5:5), 22 (46 mg, 0.15 mmol, 25%) was obtained as off-white solid. Two minor regioisomers were detected in GC and GC/MS spectra of the crude reaction mixture according to their mass fragmentation pattern.

\[
\text{22:} \\
\text{\ }^1H\text{ NMR (400 MHz, CDCl}_3\text{) }\delta\text{ [ppm] } = 7.48 \text{ (s, 1H), 6.97 \text{ (s, 1H), 6.12 \text{ (s, 2H), 3.76–3.71 (m, 4H), 3.30–3.24 (m, 4H);} \text{ }^{13}C\text{ NMR (101 MHz, CDCl}_3\text{) }\delta\text{ [ppm] } = 151.7, 146.7, 128.5, 126.6, 112.0, 111.5, 103.1, 66.4, 45.8;} \text{ mR: } 159–161 ^\circ\text{C; HRMS for C}_{11}H_{13}ClNO_5S^+ (ESI+) [M+H]^+: }\text{ calc.: 306.0198, found: 306.0195.} 
\]
According to GP2, methyleugenol (107 mg, 0.60 mmol, 1.00 eq.) was used as substrate. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 23 (46 mg, 0.14 mmol, 23%) was obtained as colorless solid.

23:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.40 (s, 1H), 6.82 (s, 1H), 5.96 (ddt, $J$ = 16.7, 10.1, 6.5 Hz, 1H), 5.16–5.06 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.74 (dt, $J$ = 6.5, 1.6 Hz, 2H), 3.73–3.69 (m, 4H), 3.13–3.09 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 152.6, 146.9, 136.9, 134.1, 125.7, 116.9, 114.1, 113.4, 66.4, 56.4, 56.2, 45.4, 36.7; m$_R$: 84–86 °C; HRMS for C$_{15}$H$_{22}$NO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 328.1213, found: 328.1212.
According to GP2, safrole (97 mg, 0.60 mmol, 1.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 24 (30 mg, 0.10 mmol, 16%) was obtained as colorless solid.

**24:**

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.38 (s, 1H), 6.83 (s, 1H), 6.05 (s, 2H), 5.94 (ddt, $J = 16.8$, 10.1, 6.5 Hz, 1H), 5.15–5.06 (m, 2H), 3.73–3.70 (m, 6H), 3.14–3.10 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 151.7, 146.2, 136.7, 136.4, 127.4, 117.0, 111.6, 110.6, 102.4, 66.4, 45.5, 37.0; m$_R$: 106–108 °C; HRMS for C$_{14}$H$_{18}$NO$_5$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 312.0900, found: 312.0904.
7.21 *N,N*-Diisobutyl-2,5-dimethoxybenzenesulfonamide (25)

![Structural formula of 25]

According to GP3, diisobutylamine (465 mg, 3.60 mmol, 6.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 25 (125 mg, 0.38 mmol, 63%) was obtained as off-white solid.

25:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.46 (d, $J$ = 3.1 Hz, 1H), 7.00 (dd, $J$ = 9.0, 3.2 Hz, 1H), 6.88 (d, $J$ = 9.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.01 (d, $J$ = 7.6 Hz, 4H), 1.82 (hept, $J$ = 7.4, 7.0 Hz, 2H), 0.82 (s, 6H), 0.81 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 152.9, 150.7, 129.3, 119.7, 116.1, 113.4, 56.4, 56.1, 55.8, 26.8, 20.1; m$_R$: 79–81 °C; HRMS for C$_{16}$H$_{28}$NO$_4$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 352.1553, found: 352.1558.

7.22 1-((2,5-Dimethoxyphenyl)sulfonyl)azepane (26)

![Structural formula of 26]

According to GP3, azepane (357 mg, 3.60 mmol, 6.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 26 (101 mg, 0.34 mmol, 56%) was obtained as off-white solid.

26:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.42 (d, $J$ = 3.1 Hz, 1H), 6.98 (dd, $J$ = 9.0, 3.1 Hz, 1H), 6.89 (d, $J$ = 9.0 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.32–3.26 (m, 4H), 1.71–1.64 (m, 4H), 1.60–1.55 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 152.8, 150.7, 128.5, 119.6, 116.1, 113.5, 56.4, 56.0, 48.4, 29.5, 27.0; m$_R$: 39–41 °C; HRMS for C$_{14}$H$_{21}$NaO$_4$S$^+$ (ESI$^+$) [M+Na]$^+$: calc.: 322.1083, found: 322.1089.
7.23 1-((2,5-Dimethoxyphenyl)sulfonyl)-3-methylpiperidine (27)

According to GP3, 3-methylpiperidine (357 mg, 3.60 mmol, 6.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 27 (98 mg, 0.33 mmol, 55%) was obtained as colorless highly viscous oil.

27:

$\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ [ppm]} = 7.42 \text{ (d, } J = 3.2 \text{ Hz, 1H), } 7.02 \text{ (dd, } J = 9.0 \text{, } 3.1 \text{ Hz, 1H), } 6.93 \text{ (d, } J = 9.0 \text{ Hz, 1H), } 3.85 \text{ (s, 3H), } 3.78 \text{ (s, 3H), } 3.77-3.62 \text{ (m, 2H), } 3.58 \text{ (td, } J = 11.9, 2.9 \text{ Hz, 1H), } 2.22 \text{ (dd, } J = 12.1, 10.3 \text{ Hz, 1H), } 1.99-1.21 \text{ (m, 4H), } 0.92 \text{ (td, } J = 12.0, 10.6, 3.7 \text{ Hz, 1H), } 0.85 \text{ (d, } J = 6.5 \text{ Hz, 3H);} ^{13}\text{C NMR (101 MHz, CDCl}_3\text{) } \delta \text{ [ppm]} = 153.0, 151.1, 127.6, 120.0, 116.3, 113.9, 56.7, 56.1, 53.1, 46.5, 32.5, 31.1, 25.3, 19.0; \text{ HRMS for } C_{14}H_{21}NNaO_4S^+ \text{ (ESI+) [M+Na]^+: } \text{calc.: } 322.1083, \text{ found: } 322.1087.$
7.24 2-((2,5-Dimethoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (28)

According to GP3, 1,2,3,4-tetrahydroisoquinoline (479 mg, 3.60 mmol, 6.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 28 (104 mg, 0.31 mmol, 52%) was obtained as colorless solid.

28: 
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.53 (d, $J = 3.2$ Hz, 1H), 7.15 (tt, $J = 7.2$, 5.3 Hz, 2H), 7.09–7.02 (m, 3H), 6.86 (d, $J = 9.0$ Hz, 1H), 4.52 (d, $J = 1.2$ Hz, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 3.60 (t, $J = 5.9$ Hz, 2H), 2.84–2.69 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 153.0, 151.1, 133.8, 132.8, 129.0, 127.7, 126.6, 126.4, 126.2, 120.4, 116.2, 113.6, 56.3, 56.2, 47.2, 43.5, 28.8; m$_R$: 125–126 °C; HRMS for C$_{17}$H$_{19}$NNaO$_4$S$^+$ (ESI$^+$) [M+Na]$^+$: calc.: 356.0927, found: 356.0932.
7.25 2,5-Dimethoxy-\(N,N\)-dipropylbenzenesulfonamide (29)

According to GP3, dipropylamine (364 mg, 3.60 mmol, 6.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 29 (70 mg, 0.23 mmol, 39%) was obtained as colorless highly viscous oil.

29:
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 7.46 (d, \(J = 3.1\) Hz, 1H), 6.99 (dd, \(J = 9.0, 3.1\) Hz, 1H), 6.89 (d, \(J = 9.0\) Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.17 (t, \(J = 7.7\) Hz, 4H), 1.50 (h, \(J = 7.4\) Hz, 4H), 0.81 (t, \(J = 7.4\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 152.9, 150.8, 129.5, 119.7, 116.0, 113.6, 56.4, 56.1, 49.7, 21.9, 11.2; HRMS for C\(_{14}\)H\(_{23}\)NNaO\(_4\)S\(^+\) (ESI\(^+\)) [M+Na]\(^+\): calc.: 324.1240, found: 324.1249.

7.26 1-((2,5-Dimethoxyphenyl)sulfonyl)pyrrolidine (30)

According to GP3, pyrrolidine (256 mg, 3.60 mmol, 6.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 30 (61 mg, 0.22 mmol, 37%) was obtained as off-white solid.

30:
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 7.46 (d, \(J = 3.2\) Hz, 1H), 7.02 (dd, \(J = 9.0, 3.1\) Hz, 1H), 6.93 (d, \(J = 9.0\) Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.40–3.32 (m, 4H), 1.85–1.77 (m, 4H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 153.0, 150.9, 127.6, 120.1, 116.5, 113.8, 56.6, 56.1, 47.9, 25.9; \(m_p\): 67–69 °C; HRMS for C\(_{12}\)H\(_{17}\)NNaO\(_4\)S\(^+\) (ESI\(^+\)) [M+Na]\(^+\): calc.: 294.0770, found: 294.0773.
7.27 *N*-Benzyl-2,5-dimethoxybenzenesulfonamide (31)

According to GP3, benzyamine (386 mg, 3.60 mmol, 6.00 eq.) was used as amine. After product purification via column chromatography (ethyl acetate:cyclohexane = 5:95 → 50:50), 31 (53 mg, 0.17 mmol, 29%) was obtained as off-white solid.

31:

$^1$H NMR (400 MHz, CDCl$_3$) δ [ppm] = 7.47 (d, $J = 3.1$ Hz, 1H), 7.28–7.22 (m, 3H), 7.19–7.14 (m, 2H), 7.07 (dd, $J = 9.0$, 3.2 Hz, 1H), 6.89 (d, $J = 9.0$ Hz, 1H), 5.28 (t, $J = 6.3$ Hz, 1H), 4.10 (d, $J = 6.3$ Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ [ppm] = 153.3, 150.1, 136.4, 128.6, 128.0, 127.9, 127.8, 120.5, 114.6, 113.6, 56.8, 56.1, 47.8; m$_R$: 91–93 °C; HRMS for C$_{15}$H$_{17}$NNaO$_4$S$^+$ (ESI$^+$) [M+Na]$^+$: calc.: 330.0770, found: 330.0783.
Analytical data of 31 corresponds to those reported in the reference.[7]
7.28 Methyl ((2,5-dimethoxyphenyl)sulfonyl)-L-prolinate (32)

According to GP3, (L)-proline methyl ester hydrochloride (596 mg, 3.60 mmol, 6.00 eq.) was used as amine and 10 eq. of DIPEA (776 mg, 6 mmol) were used (instead of 8.00 eq.). After product purification via column chromatography (ethyl acetate:cyclohexane = 1:9 → 5:5), 32 (48 mg, 0.15 mmol, 24%) was obtained as off-white solid.

32:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ [ppm] = 7.48 (d, $J = 3.1$ Hz, 1H), 7.04 (dd, $J = 9.0$, 3.1 Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 1H), 4.61 (dd, $J = 8.3$, 3.5 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.57 (ddd, $J = 9.6$, 7.5, 4.8 Hz, 1H), 3.32 (dt, $J = 9.5$, 7.2 Hz, 1H), 2.17–1.91 (m, 3H), 1.86–1.76 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ [ppm] = 173.0, 153.1, 150.9, 127.9, 120.4, 116.3, 113.9, 60.8, 56.8, 56.2, 52.4, 48.3, 31.0, 24.8; mR: 115–117 °C; HRMS for C$_{14}$H$_{20}$NO$_6$S$^+$ (ESI$^+$) [M+H]$^+$: calc.: 330.1006, found: 330.1009.
8. NMR Spectra of all Isolated Compounds
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 5b

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 5b
$\text{^1H NMR (400 MHz, CDCl}_2\text{298 K): 6}$

$\text{^13C NMR (101 MHz, CDCl}_2\text{298 K): 6}$
$^1$H NMR (400 MHz, CDCl$\text{$_3$}$, 298 K): 7a

$^{13}$C NMR (101 MHz, CDCl$\text{$_3$}$, 298 K): 7a
SUPPORTING INFORMATION

$^1$H NMR (400 MHz, CDCl$_3$/298 K): 8a

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 8a
SUPPORTING INFORMATION

$^1$H NMR (400 MHz, CDCl$_3$/298 K): 8b

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 8b
$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 9b

$^{19}$F NMR (376 MHz, CDCl$_3$/298 K): 9b
$^{19}$F NMR (376 MHz, CDCl$_3$ 298 K): 10
$^1$H NMR (400 MHz, CDCl$_3$298 K): 13a

$^{13}$C NMR (101 MHz, CDCl$_3$298 K): 13a
SUPPORTING INFORMATION

$^1$H NMR (400 MHz, CDCl$_3$/298 K): 13b

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 13b
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 14a

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 14a
SUPPORTING INFORMATION

$^1$H NMR (400 MHz, CDCl$_3$/298 K): 14b

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 14b
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 15a

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 15a
$^1$H NMR (400 MHz, CDC$_6$298 K): 15b

$^{13}$C NMR (101 MHz, CDC$_6$298 K): 15b
**SUPPORTING INFORMATION**

**$^1$H NMR (400 MHz, CDCl$_3$$^\circ$298 K): 16**

![NMR Spectrum](image1)

**$^{13}$C NMR (101 MHz, CDCl$_3$$^\circ$298 K): 16**

![NMR Spectrum](image2)
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 17

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 17
$^{1}H$ NMR (400 MHz, CDCl$_3$/298 K): 18a

$^{13}C$ NMR (101 MHz, CDCl$_3$/298 K): 18a
$^{1}H$ NMR (400 MHz, CDCl$_3$298 K): 21

$^{13}$C NMR (101 MHz, CDCl$_3$298 K): 21
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 22

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 22
$^1$H NMR (400 MHz, CDCl$_3$ 298 K): 23

$^{13}$C NMR (101 MHz, CDCl$_3$ 298 K): 23
**SUPPORTING INFORMATION**

**$^1$H NMR (400 MHz, CDCl$_3$/298 K):** 24

**$^{13}$C NMR (101 MHz, CDCl$_3$/298 K):** 24
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 28

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 28
$^1$H NMR (400 MHz, CDCl$_3$ 298 K): 30

$^{13}$C NMR (101 MHz, CDCl$_3$ 298 K): 30
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 31

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 31
$^1$H NMR (400 MHz, CDCl$_3$/298 K): 32

$^{13}$C NMR (101 MHz, CDCl$_3$/298 K): 32
9. References

[1] W. L. F. Armarego, C. Chai (Eds.) *Purification of Laboratory Chemicals (Seventh Edition)*, Butterworth-Heinemann, Boston, 2013.

[2] R. K. Harris, E. D. Becker, Cabral de Menezes, Sonia M, 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] Y. Chen, P. R. D. Murray, A. T. Davies, M. C. Willis, *J. Am. Chem. Soc.* 2018, 140, 8781–8787.

[6] E. M. Alvarez, M. B. Plutschack, F. Berger, T. Ritter, *Org. Lett.* 2020, 22, 4593–4596.

[7] A. F. Kornahrens, A. B. Cognetta, D. M. Brody, M. L. Matthews, B. F. Cravatt, D. L. Boger, *J. Am. Chem. Soc.* 2017, 139, 7052–7061.