A Unified Approach to the Chemoselective α-Functionalization of Amides with Heteroatom Nucleophiles

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General Information

Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. Triflic anhydride was distilled over $P_4O_{10}$ prior to use. All other reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers ($\nu_{\max}$) are reported in cm$^{-1}$. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All $^1H$ NMR and $^{13}C$ NMR spectra were recorded using a Bruker AV-400, AV-600 and AV-700 spectrometer at 300K. Chemical shifts were given in parts per million (ppm, $\delta$), referenced to the solvent peak of CDCl$_3$, defined at $\delta = 7.26$ ppm ($^1H$ NMR) and $\delta = 77.16$ ($^{13}C$ NMR). Coupling constants are quoted in Hz (J). $^1H$ NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Selected $^{13}C$ NMR spectra were recorded using the attached proton test (APT) to facilitate the confirmation and assignment of the structure.

General Procedure for Nucleophilic $\alpha$-Functionalisation of Amides

To a mixture of amide (0.20 mmol), 2-iodopyridine (0.44 mmol) in DCM (2.0 mL) was added triflic anhydride (37 $\mu$L, 0.22 mmol) dropwise under Ar at 0 °C. After stirring for 15 min at 0 °C, 2,6-lutidine N-oxide (22.4 $\mu$L, 0.20 mmol,) was added and the reaction stirred for a further 5 min at 0 °C. Then the nucleophile (vide infra for details) was added in one portion (3 equiv.). The reaction mixture was stirred at room temperature for 3 h before being quenched with NH$_4$Cl solution. The layers were separated and the aqueous extracted with DCM. The combined organic layers were washed with brine before being dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by column chromatography.
Mechanistic studies

2o: 2-hydroxy-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

A flamed dried Schlenk tube containing 4-Phenyl-1-(pyrrolidin-1-yl)butan-1-one (0.434 g, 2.0 mmol) in 25 mL of DCM was cooled down to -78 °C for 15 minutes before the addition of 1.2 equiv. of LiHMDS (2.1 mL, 1M in DCM). The mixture was stirred for 1 hour before oxygen gas saturated the solution. After 3 hours the reaction was then allowed to slowly warm up to rt. At this point 3 equiv. of triethylphosphite were added. After 1 hour the mixture was quenched with saturated NH₄Cl and washed 3x times with DCM. The combined organic phases were dried using MgSO₄ and evaporated. Purification by column chromatography on silica gel (EtOAc: heptane = 2:1) yielded the product as a yellow oil (0.251 g, 54%).

¹H NMR (400 MHz, CDCl₃): δ 7.30 – 7.27 (m, 3H), 7.24 – 7.16 (m, 2H), 4.17 – 4.14 (m, 1H), 3.71 (d, J = 7.2 Hz, 1H), 3.55 – 3.52 (m, 1H), 3.43 – 3.39 (m, 1H), 3.31 – 3.26 (m, 1H), 3.19 – 3.14 (m, 1H), 2.89 – 2.77 (m, 2H), 1.95 – 1.79 (m, 6H); ¹³C NMR (151 MHz, CDCl₃): δ 172.9, 141.6, 128.7 (2C), 128.6 (2C), 126.2, 68.6, 46.4, 45.9, 36.2, 31.4, 26.2, 24.0; HRMS (ESI): calculated for [M+H]^+ (C₁₄H₁₉NO₂) m/z : 256.1313 found [M+H]^+:256.1316; IR (neat, cm⁻¹): 3400, 3059, 2936, 1645.
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
Independent formation and isolation of the α-triflate amide.

To a solution of the amide 2m (0.2 mmol, 1 equiv.) and distilled lutidine (1 equiv.) in d$_2$-DCM (0.1 M, 2 mL) at 0 °C, triflic anhydride (35 µL, 1.1 equiv.) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature while stirring for 1 hour. After this time, the reaction mixture was quickly purified by column chromatography (Ethyl acetate/heptane 1:1 – 3:1) at -30 °C (cryostat - isopropanol) to afford the alpha triflate amide in 70% yield (50.0 mg) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.36 – 7.28 (m, $J = 8.5, 1.5$ Hz, 2H), 7.25 – 7.17 (m, 3H), 5.21 (dd, $J = 8.7, 4.4$ Hz, 1H), 3.62 – 3.48 (m, 1H), 3.48 – 3.36 (m, 2H), 3.14 – 3.04 (m, $J = 9.9, 6.9$ Hz, 1H), 2.91 – 2.80 (m, $J = 14.3, 8.8, 5.6$ Hz, 1H), 2.78 – 2.67 (m, 1H), 2.46 – 2.33 (m, $J = 14.2, 8.6, 5.6$ Hz, 1H), 2.24 – 2.14 (m, 1H), 1.94 – 1.79 (m, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 164.5 , 139.3 , 128.9 , 128.7 , 128.6 , 128.5 , 126.9 , 118.6 (q, $J = 320$ Hz), 83.1 , 46.6 , 46.2 , 33.4 , 30.8 , 26.2 , 23.9; $^{19}$F NMR (565 MHz, CDCl$_3$): δ -75.4, -78.9 (OTf); HRMS (ESI): calculated for [M+H]$^+$ (C$_{15}$H$_{19}$F$_3$NO$_4$S) m/z: 366.0981 found [M+H]$^+$: 366.0969.
A flamed dried Schelenk tube containing $N,N$-dibenzyl-4-phenylbutanamide (0.69 g, 2.0 mmol) in 25 mL of DCM was cooled down to -78 °C for 15 minutes before the addition of 1.2 equiv. of LiHMDS (2.1 mL, 1 M in DCM). The mixture was stirred for 1 hour before oxygen gas saturated the solution. After 3 hours the reaction was then allowed to slowly warm up to rt. At this point 3 equiv. of triethylphosphite were added. After 1 hour the mixture was quenched with saturated NH$_4$Cl and washed 3x times with DCM. The combined organic phases were dried using MgSO$_4$ and evaporated. Purification by column chromatography on silica gel (EtOAc: heptane = 2:1) yielded the product as a yellow oil (0.373 g, 52%).
$^1$H NMR (600 MHz, CDCl$_3$): δ 7.38 – 7.26 (m, 6H), 7.25 – 7.23 (m, 2H), 7.17 – 7.15 (m, 3H), 7.12 – 7.11 (m, 2H), 7.04 – 7.03 (m, 2H), 4.98 (d, $J = 14.8$ Hz, 1H), 4.39 (dd, $J = 8.6$, 2.6 Hz, 1H), 4.27 (d, $J = 16.6$ Hz, 1H), 4.21 (d, $J = 14.8$ Hz, 1H), 4.10 (d, $J = 16.6$ Hz, 1H), 3.92 – 3.53 (brs, 1H), 2.87 – 2.76 (m, 2H), 1.97 – 1.92 (m, 1H), 1.83 – 1.82 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 175.4, 141.3, 136.6, 135.4, 129.2 (C2), 128.9 (C2), 128.7 (C2), 128.6 (C2), 128.4 (C2), 128.1, 127.9, 126.8 (2C), 126.2, 67.5, 48.9, 48.4, 37.5, 31.4; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{24}$H$_{25}$NONa) m/z : 366.1834 found [M+Na]$^+$: 366.1823; IR (neat, cm$^{-1}$): 3062, 3032, 2928, 1644, 1494, 1452.
Isolation of the alpha triflate amide from an Umplung reaction.

To a mixture of amide 4-Phenyl-1-(pyrrolidin-1-yl)butan-1-one (0.2 mmol), 2-iodopyridine (0.44 mmol) in DCM (2 mL) was added triflic anhydride (37 µL, 0.22 mmol) dropwise under Ar at 0 °C. After stirring for 15 min at 0 °C, lutidine N-oxide (22.4 µL, 0.22 mmol) was added and the reaction stirred for a further 5 min at 0 °C. After 1 hour the reaction was quenched with water and extracted 2 x with DCM. The combined organic layers were dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. The crude mixture was quickly columned at -30 °C (cryostat / isopropanol) to afford the desired compound in 95% yield (69.0 mg) as a yellow oil.

Disclosure

One important fact to disclose was that the formation of the alpha triflate from the corresponding alpha hydroxamide proved to proceed in consistently higher yields when 2,6-lutidine was used as a base. For instance, when 2-I-Pyridine was used the yield was significantly lower and the ¹H-NMR analysis became less straightforward.

In order to access whether the intermediate (α-triflate) could be transformed to the intramolecular fridelcraft product we scoped a wide array of conditions. We soon realized that forcing conditions, such as the one encountered previously in the literature (enolnium ref paper) where ideal. After careful examination we became aware that 2-I-Pyridine as a base, combined with extreme temperatures (110 °C) in acetonitrile were crucial for the reaction to take place (vide infra).
| Entry | Base           | Temperature (°C) | Yield (NMR) |
|-------|----------------|-----------------|-------------|
| 1     | 2,6-lutidine   | 0               | -           |
| 2     | 2,6-lutidine   | 110             | -           |
| 3     | 2-I-Pyridine   | 0               | -           |
| 4     | 2-I-Pyridine   | 80              | -           |
| 5     | 2-I-Pyridine   | 110 (3 hours)   | 18          |
| 6     | 2-I-Pyridine   | 110 (14 hours)  | 47          |

2-benzyl-4-phenethyl-1,4-dihydroisoquinolin-3(2H)-one

1H NMR (600 MHz, CDCl3): δ 7.37 – 7.26 (m, 7H), 7.25 – 7.19 (m, 2H), 7.17 (dd, J = 14.0, 7.0 Hz, 4H), 7.09 (d, J = 7.7 Hz, 1H), 4.88 (d, J = 14.8 Hz, 1H), 4.64 (d, J = 14.8 Hz, 1H), 4.54 (d, J = 15.9 Hz, 1H), 4.21 (d, J = 15.9 Hz, 1H), 3.70 (t, J = 6.8 Hz, 1H), 2.70 – 2.64 (m, 2H), 2.25 – 2.14 (m, 1H), 2.14 – 2.01 (m, 1H); 13C NMR (151 MHz, CDCl3): δ 171.7, 141.5, 137.0, 136.6, 131.2, 128.9 (2C), 128.6 (2C), 128.5 (2C), 128.1 (2C), 127.7 (2C), 127.6, 126.8, 126.1, 125.6, 50.4, 50.0, 47.6, 35.7, 33.0; HRMS (ESI): calculated for [M+H]+ (C24H23NO) m/z: 342.1852 found [M+H]+: 342.1854; IR (neat, cm−1): 3060, 3034, 2932, 1655, 1495, 1452.
Substitution on an independently formed $\alpha$-OTf amide.

To a solution of the amide 2m (0.2 mmol, 1 equiv.) and distilled 2,6-lutidine (1 equiv.) in DCM (0.1 M, 2 mL) at 0 °C, triflic anhydride (35 µL, 1.1 equiv.) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature while stirring for 1 hour. TBAI (0.6 mmol, 3 equiv.) was added and the reaction mixture was stirred at room temperature for 3 h before being quenched with NH$_4$Cl solution. The layers were separated and the aqueous extracted with DCM. The combined organic layers were washed with brine before being dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc in heptane 10% – 40%) to afford the product as a yellow oil in 69% (47.1 mg) yield.

To a solution of the amide 2m (0.2 mmol, 1 equiv.) and distilled 2,6-lutidine (1 equiv.) in DCM (0.1 M, 2 mL) at 0 °C, triflic anhydride (35 µL, 1.1 equiv.) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature while stirring for 1 hour. Then, a solution of the deprotonated nucleophile was generated from addition of the N-Methyl-p-toluenesulfonamide (0.6 mmol, 3 equiv.) to a suspension of NaH (0.6 mmol, 3 equiv.) in DMF (3.0 mL) was added. The reaction mixture was stirred at room temperature for 3 h before being quenched with NH$_4$Cl solution. The layers were separated and the aqueous extracted with DCM. The combined organic layers were washed with brine before being dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc in heptane 20% – 40%) to afford the product as a yellow oil in 82% (65.9 mg) yield.
Optimization

Regarding the mode of addition of the sulfonamide

| entry | T (°C) | Time (h) | solvent | Nucleophile addition conditions | NMR yield | NMR yield |
|-------|-------|----------|---------|---------------------------------|-----------|-----------|
| 1     | r.t.  | 1        | DCM     | no base                         | 0         |           |
| 2     | r.t.  | 1        | DCM     | NaH + sulfonamide added directly| 0         |           |
| 3     | r.t.  | 1        | DCM     | Cs$_2$CO$_3$ + sulfonamide added directly | 0         |           |
| 4     | r.t.  | 1        | DCM     | no base + TBAHFP                | 0         |           |
| 5     | r.t.  | 1        | MeCN    | NaH + sulfonamide added as a MeCN suspension | 37        |           |
| 6     | r.t.  | 1        | MeCN    | direct addition of Na-sulfonamidate | 44        |           |
| 7     | r.t.  | 20       | MeCN    | direct addition of Na-sulfonamidate | 43        |           |
| 8     | r.t.  | 2        | MeCN    | KHMS + sulfonamide added directly | 25        |           |
| 9     | r.t.  | 2        | MeCN    | Na-sulfonamidate dissolved in 0.5 mL DMF | 45        |           |
| 10    | 80    | 2        | MeCN    | direct addition of Na-sulfonamidate salt | 31        |           |

Attempts towards an Umpolung – Smiles rearrangement one pot reaction

| entry | solvent | Step 1 | Step 2 | NMR yield $4f^a$ | NMR yield $7a^a$ |
|-------|---------|--------|--------|-----------------|-----------------|
| 1     | MeCN    | NaH + sulfonamide suspended in MeCN (0.12 M) | 3 eq. Pr$_4$NOH | 32              | 0               |
| 2     | MeCN    | Na-sulfonamidate | 10 eq. Pr$_4$NOH | 4               | 19              |
| 3     | MeCN    | Na-sulfonamidate + 2 eq. TBAHFP | 10 eq. Pr$_4$NOH | 1               | 15              |
| 4     | DCM     | NaH + sulfonamide in DMF (0.6 M) | Addition of 3 mL MeCN, 10 eq. Bu$_4$NOH | 70   | 0               |
| 5     | DCM     | NaH + sulfonamide in DMF (0.6 M) | Addition of 3 mL dioxane, 10 eq. Bu$_4$NOH | 69   | 0               |

$^a$ Using 1,3,5-trimethoxybenzene as an internal standard in $^1$H NMR.
General procedures for the synthesis of carboxamides and sulfonamides

**Carboxamides – Procedure A**

To a solution of the amine (1.0 equiv.) and triethylamine (2.0 equiv.) in DCM (0.1 M) at 0 °C, the corresponding acyl chloride (1.2 equiv.) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature while stirring overnight (14 h). After this time, a saturated aqueous solution of sodium bicarbonate was added and the biphasic system was separated. The aqueous phase was extracted with DCM (1×) and the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired compound.

**Carboxamides – Procedure B**

To a solution of the amine (1.0 equiv.), triethylamine (1.0 equiv.), hydroxybenzotriazole (HOBt, 1.0 equiv.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI*HCl, 1.0 equiv.) in DCM (0.1 M), the corresponding carboxylic acid was added and the resulting solution was stirred at room temperature overnight (14 h). After this time, the organic solution was extracted sequentially with 0.5 M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The washed solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired compound.

**Sulfonamides – Procedure C**

To a solution of sulfonyl chloride (1.0 equiv.) in THF (1 M) was added the primary amine (3.0 equiv.) or the primary amine hydrochloride salt (1.0 equiv.) in combination with triethylamine (2.5 equiv.) at room temperature. The mixture was stirred for 16 h while a precipitate formed. Then a solution of HCl (1 M) was added until a pH of 2 was reached. The solution was extracted with EtOAc. The combined organic layers were washed with a saturated solution of NaCl and dried over MgSO₄. The solvent was removed under reduced pressure which yielded the product. The crude product was used without further purification.
Characterization

4-Phenyl-1-(pyrrolidin-1-yl)butan-1-one

The product was prepared according to general procedure B from 2.46 g (15.0 mmol) 4-phenylbutyric acid and 1.07 g (1.24 mL, 15.0 mmol) pyrrolidine in 93% (3.04 g) yield. All spectroscopic properties are in good accordance with reported data.[1]

N,N-dimethyl-4-phenylbutanamide

The product was prepared according to general procedure B from 2.46 g (15.0 mmol) 4-phenylbutyric acid and 4-nitrobenzenesulfonyl chloride and 7.5 mL (15.0 mmol) dimethylamine (2.0 M in THF) in 71% (2.04 g) yield. All spectroscopic properties are in good accordance with reported data. [2]

6-chloro-1-(pyrrolidin-1-yl)hexan-1-one

The product was prepared according to general procedure A from 507 mg (3.0 mmol) 6-chlorohexanoyl chloride and 213 mg (0.25 mL, 3 mmol) pyrrolidine in 98% (600 mg) yield. All spectroscopic properties are in good accordance with reported data.[1]

Methyl 9-oxo-9-(pyrrolidin-1-yl)nonanoate
The product was prepared according to general procedure B from 1.42 g (7.0 mmol) monomethyl azelate and 0.50 g (0.57 mL, 7.0 mmol) pyrrolidine in 99% (1.77 g) yield. All spectroscopic properties are in good accordance with reported data.[1]

1-(Pyrrolidin-1-yl)undecane-1,10-dione

Prepared according to the procedure reported in the literature.[3] All analytical data were in good accordance with data reported in the literature.

1-(pyrrolidin-1-yl)undec-10-en-1-one

The product was prepared according to general procedure A from 1.22 g (6.0 mmol) 10-undecenoyl chloride and 866 mg (1.0 mL, 5.0 mmol) pyrrolidine in 99% (1.19 g) yield. All spectroscopic properties are in good accordance with reported data.[4]

1-(Pyrrolidin-1-yl)hex-5-yn-1-one

The product was prepared according to general procedure B from 135 mg (1.2 mmol) 5-hexynoic acid and 85 mg (0.1 mL, 1.2 mmol) pyrrolidine in 96% (190 mg) yield. All spectroscopic properties are in good accordance with reported data.[5]
7-Oxo-7-(pyrrolidin-1-yl)heptanenitrile

\[
\text{NC} \quad \text{O} \quad \text{N}
\]

Prepared according to the procedure reported in the literature.[3] All analytical data were in good accordance with data reported in the literature.

3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one

The product was prepared according to general procedure A from 674 mg (4.0 mmol) hydrocinnamoyl chloride and 341 mg (0.4 mL, 4.8 mmol) pyrrolidine in 99% (810 mg) yield. All spectroscopic properties are in good accordance with reported data.[6]

1-(Azepan-1-yl)-4-phenylbutan-1-one

The product was prepared according to general procedure B from 821 mg (5.0 mmol) 4-phenylbutyric acid and 496 mg (546 µL, 5.0 mmol) hexamethyleneimine. Purification by column chromatography on silica gel (20–50% EtOAc:heptane) yielded the product (1.07 g, 88%) as a pale yellow oil.

\[^1\text{H NMR (400 MHz, CDCl}_3\text{):} \delta = 7.30 - 7.25 (m, 2H), 7.21 - 7.15 (m, 3H), 3.52 (t, J = 6.0 Hz, 2H), 3.35 (t, J = 6.0 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 2.06 - 1.95 (m, 2H), 1.74 - 1.62 (m, 4H), 1.59 - 1.51 (m, 4H);\]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{):} \delta = 172.4, 142.1, 128.7 (2C), 128.5 (2C), 126.0, 48.0, 46.1, 35.6, 32.5, 29.3, 27.8, 27.2, 27.0, 26.9;\]

HRMS (ESI): calculated for [M+Na\(^+\)]\((\text{C}_{18}\text{H}_{23}\text{NNaO})\) 268.1672, found 268.1684; IR (neat, \text{cm}^{-1}): = 2925, 2854, 1635, 1425, 1262, 1194, 746, 700.
**N-Methyl-4-nitrobenzenesulfonamide**

![Chemical structure of N-Methyl-4-nitrobenzenesulfonamide](image)

The product was prepared according to general procedure C from 2.22 g (10.0 mmol) 4-nitrobenzenesulfonyl chloride and 15.0 mL (30.0 mmol) methylamine (2.0 M in THF) in 96% (2.12 g) yield. All spectroscopic properties are in good accordance with reported data.[7]

**N-Isopropyl-4-methylbenzenesulfonamide**

![Chemical structure of N-Isopropyl-4-methylbenzenesulfonamide](image)

The product was prepared according to general procedure C from 381 mg (2.0 mmol) 4-methylbenzenesulfonyl chloride and 355 mg (0.49 mL, 6.0 mmol) iso-propylamine in 95% (404 mg) yield. All spectroscopic properties are in good accordance with reported data.[8]

**N-Benzyl-4-methylbenzenesulfonamide**

![Chemical structure of N-Benzyl-4-methylbenzenesulfonamide](image)

The product was prepared according to general procedure C from 381 mg (2.0 mmol) 4-methylbenzenesulfonyl chloride and 643 mg (0.65 mL, 6.0 mmol) benzyamine in 94% (489 mg) yield. All spectroscopic properties are in good accordance with reported data.[9]

**4-Methyl-N-phenylbenzenesulfonamide**

![Chemical structure of 4-Methyl-N-phenylbenzenesulfonamide](image)

The product was prepared according to general procedure C from 381 mg (2.0 mmol) 4-methylbenzenesulfonyl chloride and 559 mg (0.55 mL, 6.0 mmol) aniline in 87% (432 mg) yield. All spectroscopic properties are in good accordance with reported data.[9]
**N-(4-methoxyphenyl)-4-methylbenzenesulfonamide**

![Chemical Structure]

The product was prepared according to general procedure C from 4.58 g (24.0 mmol) 4-methylbenzenesulfonyl chloride, 2.46 g (20.0 mmol) 4-methoxyaniline, 2.43 g (24.0 mmol) triethylamine in 89% (4.93 g) yield. All spectroscopic properties are in good accordance with reported data.[9]

**Methyl tosylglycinate**

![Chemical Structure]

The product was prepared according to general procedure C from 381 mg (2.0 mmol) 4-methylbenzenesulfonyl chloride, 281 mg (2.0 mmol) glycine methyl ester hydrochloride and 506 mg (0.76 mL, 5 mmol) trimethylamine in 91% (445 mg) yield. All spectroscopic properties are in good accordance with reported data.[10]

**N-Methyl-2-nitrobenzenesulfonamide**

![Chemical Structure]

The product was prepared according to general procedure C from 665 mg (3.0 mmol) 2-nitrobenzenesulfonyl chloride and 4.5 mL (9.0 mmol) methylamine (2.0 M in THF) in 93% (600 mg) yield. All spectroscopic properties are in good accordance with reported data.[11]

**N-Methylnaphthalene-2-sulfonamide**

![Chemical Structure]
The product was prepared according to general procedure C from 453 mg (2.0 mmol) naphthalene-2-sulfonyl chloride and 3.0 mL (6.0 mmol) methylamine (2.0 M in THF) in 96% (423 mg) yield. All spectroscopic properties are in good accordance with reported data.[12]

**N-Methylpyridine-2-sulfonamide**

![N-Methylpyridine-2-sulfonamide](image)

2-Mercaptopyridine (0.561 g, 5.0 mmol) was stirred in a mixture of 25.0 mL of DCM and 25.0 mL of a 1.0 M solution of HCl for 10 min at -10 to -5 °C. Then, a cold (5 °C) solution of sodium hypochlorite (11% (aq.), 9.3 mL, 16.5 mmol) was added dropwise under vigorous stirring. After the addition was completed, the mixture was stirred for 15 min from -10 to -5 °C. It was transferred to a separatory funnel (pre-cooled in the freezer) and the organic layer was rapidly separated and collected in an Erlenmeyer flask cooled in a dry ice-acetone bath. Methylamine (2.0 M in THF, 6.25 mL, 12.5 mmol) was added while stirring, whereupon the organic layer became a white suspension. The suspension was stirred for 30 min at 0 °C. Then, the mixture was washed with 1.0 M solution of HCl, water and a solution of saturated NaCl, dried with MgSO₄ and concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc:heptane = 1:1) yielded the product as a white solid (400 mg, 47%).[13]

**1H NMR (400 MHz, CDCl₃)**: δ = 8.75 – 8.69 (m, 1H), 8.02 (dt, J = 7.7, 0.9 Hz, 1H), 7.93 (td, J = 7.7, 1.7 Hz, 1H), 7.51 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 4.94 (s,br, 1H), 2.75 (d, J = 5.3 Hz, 3H); **13C NMR (175 MHz, CDCl₃)**: δ = 156.7, 150.2, 138.2, 126.9, 122.8, 29.9; **HRMS (ESI)**: calculated for [M+Na]⁺ (C₆H₈N₂O₂SNa) m/z: 195.0199, found 195.0198; **IR (neat, cm⁻¹)**: 3289, 1579, 1454, 1428, 1325, 1174, 1117, 1086, 992, 844, 777, 738, 590.

**N,N-dibenzyl-4-phenylbutanamide**

![N,N-dibenzyl-4-phenylbutanamide](image)

The product was prepared according to general procedure A. Purification by flash column chromatography yielded the product as a yellow oil (84%).
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.35 (t, $J = 7.4$ Hz, 2H), 7.33 – 7.26 (m, 4H), 7.25 (d, $J = 7.6$ Hz, 2H), 7.22 (d, $J = 7.3$ Hz, 2H), 7.18 – 7.15 (m, 3H), 7.10 (d, $J = 7.4$ Hz, 2H), 4.61 (s, 2H), 4.38 (s, 2H), 2.68 (t, $J = 7.6$ Hz, 2H), 2.43 (t, $J = 7.4$ Hz, 2H), 2.08 – 2.02 (m, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 173.4, 141.8, 137.7, 136.8, 129.1 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 127.7 (2C), 127.5, 126.5, 126.0, 50.0, 48.3, 35.4, 32.6, 27.0; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{26}$H$_{25}$NO$\text{Na}$) m/z: 366.1834 found [M+Na]$^+$: 366.1823; IR (neat, cm$^{-1}$): 3062, 3032, 2928, 1644, 1494, 1452.
NMR Spectra

$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
175 MHz
$^{1}H$ NMR
CDCl$_3$
400 MHz

$^{13}C$ NMR
CDCl$_3$
175 MHz
General procedures for the $\alpha$-functionalization of amides

**Halogens – Procedure D**

To a mixture of amide (0.20 mmol), 2-iodopyridine (0.44 mmol) in DCM (2.0 mL) was added triflic anhydride (37 $\mu$L, 0.22 mmol) dropwise under Ar at 0 °C. After stirring for 15 min at 0 °C, 2,6-lutidine $N$-oxide (22.4 $\mu$L, 0.20 mmol,) was added and the reaction stirred for a further 5 min at 0 °C. Then a tetrabutylammonium salt of the halogen was added in one portion (3 equiv.). The reaction mixture was stirred at room temperature for 3 h before being quenched with NH$_4$Cl solution. The layers were separated and the aqueous extracted with DCM. The combined organic layers were washed with brine before being dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure.

**O-,S- and N-Nucleophiles – Procedure E**

To a mixture of amide (0.20 mmol), 2-iodopyridine (0.44 mmol) in DCM (2.0 mL) was added triflic anhydride (37 $\mu$L, 0.22 mmol) dropwise under Ar at 0 °C. After stirring for 15 min, 2,6-lutidine $N$-oxide (22.4 $\mu$L, 0.20 mmol,) was added and the reaction stirred for a further 5 min at 0 °C. Then, a solution of the deprotonated nucleophile was generated from addition of the nucleophile (0.60 mmol) to a suspension of NaH (0.60 mmol) in DMF (3.0 mL) was added. The reaction mixture was stirred at room temperature for 3 h before being quenched with NH$_4$Cl solution. The layers were separated and the aqueous extracted with DCM. The combined organic layers were washed with brine before being dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure.

**$\alpha$-Arylation via Smiles rearrangement – Procedure F**

To a solution of the amide (1 equiv.) in MeCN (0.1 M) was added tetrapropyl ammonium hydroxide (40% (aq.), 2 eq.) The solution was stirred for 16 h. Then it was washed with saturated NH$_4$Cl solution and brine. The organic layer was dried with MgSO$_4$, the solvent evaporated under reduced pressure and the crude product purified by column chromatography on silica gel.
Characterization

1aa: 2-Chloro-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (42.0 mg, 84% / 10mmol scale - 1.85 g, 75%). When NaCl (95%) was used as a halide source the reaction was stirred for 20 hours instead and yielded the product in 90% (45.1 mg).

$^1$H NMR (700 MHz, CDCl$_3$): $\delta$ = 7.29 (t, $J = 7.5$ Hz, 2H), 7.21 – 7.17 (m, 3H), 4.14 (t, $J = 7.3$ Hz, 1H), 3.52 – 3.46 (m, 3H), 3.14 (dt, $J = 9.8$, 7.0 Hz, 1H), 2.76 (t, $J = 7.3$ Hz, 2H), 2.47 – 2.45 (m, 1H), 2.37 – 2.35 (m, 1H), 1.95 – 1.93 (m, 2H), 1.88 – 1.85 (m, 2H); $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ = 167.0, 140.4, 128.7 (2C), 128.6 (2C), 126.4, 46.5 (2C), 44.9, 36.0, 33.4, 26.1, 24.3; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{14}$H$_{18}$ClNO Na) m/z: 274.0969 found [M+Na]$^+$: 274.0971; IR (neat, cm$^{-1}$): 3025, 2950, 2874, 1643, 1495, 1433, 1340, 1189.

1ab: 2-Bromo-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (44.2 mg, 75%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.31 – 7.26 (m, 2H), 7.22 – 7.18 (m, 3H), 4.18 (dd, $J = 7.9$, 6.4Hz, 1H), 3.55 – 3.47 (m, 3H), 3.21 – 3.18 (m, 1H), 2.80 – 2.77 (m, 2H), 2.39 – 2.36 (m, 1H), 2.30 – 2.27 (m, 1H), 1.95 – 1.83 (m, 4H); $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ = 166.9, 140.5, 128.7 (2C), 128.7 (2C), 126.4, 55.0, 46.5, 46.4, 35.6, 32.3, 26.2, 24.3; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{14}$H$_{18}$BrNONa) m/z: 318.0464 found [M+Na]$^+$: 318.0462; IR (neat, cm$^{-1}$): 2972, 2875, 1651, 1438, 752, 700.

1ac: 2-Iodo-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one
The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (58.5 mg, 80%).

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) : \delta = 7.30 - 7.28 (m, 2H), 7.21 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 7.4 Hz, 2H), 4.15 (t, J = 7.4 Hz, 1H), 3.46 (t, J = 6.9 Hz, 2H), 3.35 (dt, J = 9.7, 6.7 Hz, 1H), 3.05 – 3.01 (m, 1H), 2.73 – 2.69 (m, 2H), 2.44 (td, J = 14.2, 7.5 Hz, 1H), 2.36 (td, J = 14.5, 7.3 Hz, 1H), 1.98 – 1.91 (m, 2H), 1.89 – 1.81 (m, 2H); \]

\[ ^13C \text{ NMR (151 MHz, CDCl}_3) : \delta = 168.5, 140.3, 128.7 (2C), 128.7 (2C), 126.4, 46.8, 46.7, 37.7, 35.2, 26.1, 24.4, 22.3; \]

\[ \text{HRMS (ESI): calculated for [M+Na]^+ (C}_{14}H_{18}INO Na) m/z: 366.0325 found [M+Na]^+: 366.0331; IR (neat, cm}^{-1}) : 2969, 2928, 2873, 1642, 1430, 1341, 750, 700. \]

1ba: 2-Chloro-\(N,N\)-dimethyl-4-phenylbutanamide

\[ \text{The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (38.7 mg, 86%).} \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) : \delta = 7.31 – 7.28 (m, 2H), 7.22 – 7.18 (m, 3H), 4.32 (t, J = 7.0 Hz, 1H), 2.98 (s, 3H), 2.97 (s, 3H), 2.78 (t, J = 7.3 Hz, 2H), 2.38 – 2.26 (m, 2H); \]

\[ ^13C \text{ NMR (151 MHz, CDCl}_3) : \delta = 168.4, 140.5, 128.7 (2C), 128.6 (2C), 126.4, 53.0, 37.3, 36.3, 35.8, 32.3; \]

\[ \text{HRMS (ESI): calculated for [M+Na]^+ (C}_{12}H_{16}ClNO Na) m/z: 248.0818 found [M+Na]^+: 248.0812; IR (neat, cm}^{-1}) : 2933, 2867, 1656, 1495, 1545, 1401. \]

1bb: 2-Bromo-\(N,N\)-dimethyl-4-phenylbutanamide

\[ \text{The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (49.5 mg, 92%).} \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) : \delta = 7.31 – 7.29 (m, 2H), 7.22 – 7.19 (m, 3H), 4.32 (t, J = 7.0 Hz, 1H), 2.99 (s, 3H), 2.98 (s, 3H), 2.78 (t, J = 7.3 Hz, 2H), 2.38 – 2.26 (m, 2H); \]

\[ ^13C \text{ NMR (151 MHz, CDCl}_3) : \delta = 168.5, 140.5, 128.7 (2C), 128.7 (2C), 126.4, 53.0, 37.3, 36.3, 35.9, 32.3, 32.3; \]

\[ \text{HRMS (ESI): calculated for [M+Na]^+ (C}_{12}H_{16}BrNO Na) m/z: 292.0313 found [M+Na]^+: 292.0303; IR (neat, cm}^{-1}) : 3026, 2929, 2859, 1652, 1494, 1453, 1400, 1135. \]
1bc: 2-Iodo-\(N,N\)-dimethyl-4-phenylbutanamide

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (57.0 mg, 90%). (Rotamers present in a 1:3 ratio at room temperature)

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.30 – 7.28\) (m, 2H), 7.22 – 7.16 (m, 3H), 4.32 (t, \(J = 7.3\) Hz, 1H), 2.99 – 2.97 (m, 1H), 2.97 (s, 3H), 2.87 (s, 3H), 2.70 – 2.65 (m, 2H), 2.45 – 2.30 (m, 2H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta = 170.1\), 140.3, 128.7 (2C), 128.7 (2C), 128.6, 126.4, 53.0 (minor), 38.1 (major), 37.8 (major), 37.3 (minor), 36.6 (major), 36.3 (minor), 35.9 (minor), 35.2 (major), 32.4 (minor), 19.9 (major); HRMS (ESI): calculated for [M+Na]\(^+\) (C\(_{12}\)H\(_{16}\)INONa) m/z: 340.0174 found [M+Na]\(^+\): 340.0170; IR (neat, cm\(^{-1}\)): 2927, 2857, 1645, 1494, 1453, 1399.

1ca: 2,6-Dichloro-1-(pyrrolidin-1-yl)hexan-1-one

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (44.6 mg, 94%).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 4.29 – 4.26\) (m, 1H), 3.69 – 3.67 (m, 1H), 3.54 – 3.44 (m, 5H), 2.12 – 2.06 (m, 1H), 2.03 – 1.93 (m, 3H), 1.91 – 1.88 (m, 2H), 1.83 – 1.81 (m, 2H), 1.66 – 1.64 (m, 1H), 1.51 – 1.49 (m, 1H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta = 166.9\), 55.8, 46.6, 46.5, 44.8, 33.5, 32.2, 26.2, 24.3, 23.9; HRMS (ESI): calculated for [M+Na]\(^+\) (C\(_{10}\)H\(_{17}\)Cl\(_2\)NONa) m/z: 260.0585 found [M+Na]\(^+\): 260.0570; IR (neat, cm\(^{-1}\)): 2952, 2857, 1650, 1440, 1314.

1cb: 2-Bromo-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (44.5 mg, 79%).
1H NMR (600 MHz, CDCl₃): δ = 4.29 – 4.27 (m, 1H), 3.71 – 3.67 (m, 1H), 3.57 – 3.43 (m, 5H), 2.12 – 2.06 (m, 1H), 2.01 – 1.98 (m, 3H), 1.91 – 1.87 (m, 2H), 1.83 – 1.80 (m, 2H), 1.68 – 1.60 (m, 1H), 1.54 – 1.47 (m, 1H); 13C NMR (151 MHz, CDCl₃): δ = 166.9, 55.8, 46.6, 46.5, 44.8, 33.6, 32.2, 26.2, 24.3, 23.9; HRMS (ESI): calculated for [M+H]+ (C₁₀H₁₇BrClNO) m/z: 282.0260 found [M+H]+: 282.0250; IR (neat, cm⁻¹): 2954, 2874, 1674, 1438, 1340, 1311, 736, 648.

1cc: 2-iodo-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (59.8 mg, 91%). (Rotamers present with a ratio of 6/4 at room temperature)

1H NMR (700 MHz, CDCl₃): δ = 4.27 (t, J = 7.4 Hz, 1H), 3.69 – 3.66 {minor}(m, 0.4H), 3.57 – 3.50 (m, 3H), 3.49 – 3.42 {minor}(m, 2H), 3.33 – 3.29 {major} (m, 0.6H), 2.10 – 2.03 (m, 2H), 2.02 – 1.94 (m, 2H), 1.91 – 1.79 (m, 4H), 1.67 – 1.56 (m, 1H), 1.51 – 1.40 (m, 1H); 13C NMR (176 MHz, CDCl₃): δ = 168.5 (major), 166.8 (minor), 55.7 (minor), 47.0, 46.8, 44.8, 35.6, 32.0, 27.1, 26.2, 24.4, 22.9 (major); HRMS (ESI): calculated for [M+Na]+ (C₁₀H₁₇ClINO) m/z: 351.9941 found [M+Na]+: 351.9936; IR (neat, cm⁻¹): 2951, 2872, 1735, 1651, 1436, 1340, 1311, 736, 648.

1da: Methyl 8-chloro-9-oxo-9-(pyrrolidin-1-yl)nonanoate

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (49.7 mg, 86%). (Rotamers present)

1H NMR (600 MHz, CDCl₃): δ = 4.28 – 4.25 (m, 1H), 3.66 (s, 3H), 3.54 – 3.48 (m, 2H), 3.47 – 3.42 (m, 1H), 2.30 (t, J = 7.5 Hz, 2H), 2.04 – 1.97 (m, 3H), 1.94 – 1.86 (m, 3H), 1.64 – 1.60 (m, 2H), 1.48 – 1.44 (m, 1H), 1.37 – 1.32 (m, 6H); 13C NMR (151 MHz, CDCl₃): δ = 174.4, 167.2, 56.1, 51.7, 46.6, 46.5, 34.2, 34.1, 29.0, 28.9, 26.3, 26.2, 24.9, 24.3; HRMS (ESI): calculated for [M+Na]+ (C₁₄H₂₄ClNO₃Na) m/z: 312.1337 found [M+Na]+: 312.1338; IR (neat, cm⁻¹): 2927, 2856, 1735, 1651, 1436, 1341, 1170.
1db: Methyl 8-bromo-9-oxo-9-(pyrrolidin-1-yl)nonanoate

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (59.9 mg, 90%). (Rotamers present with a ratio of 1:3 at room temperature using $^{13}$CNMR)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 4.27$ (t, $J = 7.2$ Hz, 1H), 3.68 (m, 3H), 3.55 – 3.36 (m, 3H), 2.30 (t, $J = 7.5$ Hz, 2H), 2.01 – 1.98 (m, 2H), 1.91 – 1.87 (m, 3H), 1.65 – 1.60 (m, 2H), 1.46 – 1.44 (m, 1H), 1.36 – 1.33 (m, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta =$ 174.4 , 167.3 (minor), 167.2 (major), 56.1 , 51.7 , 46.7 , 46.6 , 46.5 , 46.1 , 34.6 , 34.2 , 34.1 , 29.0 , 28.9 , 28.9 , 27.5 , 26.3 , 26.2 , 26.2 , 24.9 , 24.4 , 24.3 ; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{14}$H$_{24}$BrNO$_3$Na) m/z: 356.0832 found [M+Na]$^+$: 356.0832; IR (neat, cm$^{-1}$): 2930, 2858, 1734, 1649, 1434, 1340, 1193, 1169.

1dc: Methyl 8-iodo-9-oxo-9-(pyrrolidin-1-yl)nonanoate

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (64.8 mg, 85%). (Rotamers present with a ratio of 1/2 at room temperature using $^{13}$CNMR)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 4.27$ (t, $J = 7.3$ Hz, 1H), 3.66 (s, 3H), 3.51 – 3.48 (m, 1H), 3.45 – 3.43 (m, 2H), 3.32 – 3.28 (m, 1H), 2.30 – 2.27 (m, 2H), 2.03 – 1.99 (m, 4H), 1.90 – 1.85 (m, 2H), 1.61 – 1.59 (m, 2H), 1.35 – 1.25 (m, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta =$ 174.4 , 168.8 (major), 167.2 (minor), 56.1 (minor) , 51.7 , 46.9 (2C, major) , 46.7 (major) , 46.6 (minor) , 46.5 (minor) , 36.2 , 34.2 , 34.1 , 29.5 , 29.0 , 29.0 , 28.9 , 28.7 , 26.2 , 26.2 , 24.9 , 24.4 , 24.3 , 23.7 (major); HRMS (ESI): calculated for [M+Na]$^+$ (C$_{14}$H$_{24}$INO$_3$Na) m/z: 404.0693 found [M+Na]$^+$: 404.0693; IR (neat, cm$^{-1}$): 2924, 2854, 1734, 1642, 1431, 1340, 1249.
1e: 2-Iodo-1-(pyrrolidin-1-yl)undecane-1,10-dione

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (58.3 mg, 77%). *(Rotamers present with a ratio of 1:1 at room temperature using $^{13}$C NMR)*

$^{1}$H NMR (600 MHz, CDCl$_3$): $\delta$ = 4.27 (t, $J$ = 7.3 Hz, 1H), 3.68 – 3.66 (m, 0.7H, major), 3.53 – 3.42 (m, 3H), 3.32 – 3.30 (m, 0.4H, minor), 2.41 (t, $J$ = 7.4 Hz, 2H), 2.13 (s, 3H), 2.03 – 2.00 (m, 3H), 1.92 – 1.84 (m, 2H), 1.56 – 1.54 (m, 2H), 1.45 – 1.43 (m, 1H), 1.35 – 1.19 (m, 8H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 209.5, 168.8 (major), 167.2 (minor), 56.2, 46.9, 46.7, 46.6, 46.5, 43.9, 36.3, 34.3, 30.1, 29.3, 29.1 (2C), 26.4, 26.2, 26.2, 24.4, 24.3, 23.9; HRMS (ESI): calculated for [M+Na]$^+$ ([C$_{15}$H$_{26}$INO]Na) m/z: 402.0906 found [M+Na]$^+$: 402.0897; IR (neat, cm$^{-1}$): 2926, 2855, 1721, 1648, 1433, 1358, 1167.

1f: 6-Iodo-7-oxo-7-(pyrrolidin-1-yl)heptanenitrile

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:1-20:1) yielded the product as a yellow oil (57.6 mg, 90%). *(Rotamers present with a ratio of 4/1 at room temperature using $^{13}$C NMR)*

$^{1}$H NMR (600 MHz, CDCl$_3$): $\delta$ = 4.27 – 4.25 (m, 1H), 3.70 – 3.66 (m, 0.2H, minor), 3.51 – 3.43 (m, 3H), 3.32 – 3.28 (m, 0.8H, major), 2.39 – 2.34 (m, 2H), 2.10 – 1.99 (m, 4H), 1.91 – 1.85 (m, 2H), 1.72 – 1.67 (m, 2H), 1.58 – 1.53 (m, 1H), 1.47 – 1.44 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 168.4 (major), 167.7 (minor), 119.6, 55.4 (minor), 47.0 (major), 46.8 (major), 46.6 (minor), 46.5 (minor), 35.5 (major), 33.4 (major), 28.8, 26.2, 26.2, 24.8, 24.4, 22.3 (major), 17.2 (2C); HRMS (ESI): calculated for [M+Na]$^+$ ([C$_{11}$H$_{17}$ClNONa] m/z: 343.0283 found [M+Na]$^+$: 343.0271; IR (neat, cm$^{-1}$): 3362, 2955, 2923, 2853, 2334, 1640, 1432, 1342, 748.
1g: 2-Bromo-1-(pyrrolidin-1-yl)undec-10-en-1-one

\[
\text{\begin{tikzpicture}
\draw (-1,0) -- (0,0) -- (1,0) -- (2,0) -- (3,0) -- (4,0);
\draw (1,0) -- (1,1) node[anchor=west] {Br};
\draw (3,0) -- (3,1) node[anchor=west] {O};
\draw (4,0) -- (4,1) node[anchor=west] {N};
\end{tikzpicture}}
\]

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:3-2:1) yielded the product as a yellow oil (53.5 mg, 85%).

\[\text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3\text{)}: \delta = 5.82 - 5.76 \text{ (m, 1H)}, 4.99 - 4.91 \text{ (m, 2H)}, 4.28 - 4.26 \text{ (m, 1H)}, 3.68 - 3.65 \text{ (m, 1H)}, 3.51 - 3.42 \text{ (m, 3H)}, 2.04 - 1.96 \text{ (m, 5H)}, 1.93 - 1.86 \text{ (m, 3H)}, 1.37 - 1.29 \text{ (m, 10H)}; \text{\textsuperscript{13}C NMR (151 MHz, CDCl}_3\text{)}: \delta = 167.2, 139.3, 114.3, 56.2, 46.6, 46.5, 34.3, 33.9, 29.4, 29.2, 29.1, 29.0, 26.5, 26.2, 24.3; HRMS (ESI): calculated for [M+Na\textsuperscript{+}] (C\textsubscript{15}H\textsubscript{26}BrNONa) m/z: 338.1095 found [M+Na\textsuperscript{+}]: 338.1073; IR (neat, cm\textsuperscript{-1}): 2924, 2853, 1738, 1651, 1435, 909.

1h: 2-Chloro-1-(pyrrolidin-1-yl)hex-5-yn-1-one

\[
\text{\begin{tikzpicture}
\draw (-1,0) -- (0,0) -- (1,0) -- (2,0) -- (3,0) -- (4,0);
\draw (1,0) -- (1,1) node[anchor=west] {Cl};
\draw (3,0) -- (3,1) node[anchor=west] {O};
\draw (4,0) -- (4,1) node[anchor=west] {N};
\end{tikzpicture}}
\]

The product was prepared according to general procedure D. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (29.8 mg, 75%). (Rotamers present with a ration of 1:10 in \textsuperscript{13}CNMR)

\[\text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3\text{)}: \delta = 4.59 - 4.56 \text{ (m, 1H)}, 3.71 - 3.67 \text{ (m, 1H)}, 3.55 - 3.47 \text{ (m, 3H)}, 2.47 - 2.42 \text{ (m, 1H)}, 2.39 - 2.35 \text{ (m, 1H)}, 2.28 - 2.25 \text{ (m, 1H)}, 2.22 - 2.13 \text{ (m, 1H)}, 2.03 - 1.98 \text{ (m, 3H)}, 1.94 - 1.86 \text{ (m, 2H)}; \text{\textsuperscript{13}C NMR (151 MHz, CDCl}_3\text{)}: \delta = 166.6, 82.6, 69.8, 54.3, 46.6 \text{ (major), 46.5 \text{ (major), 45.6 \text{ (minor), 35.7 \text{ (minor), 33.8 \text{ (minor), 32.7 \text{ (major), 26.2 \text{ (major), 24.3 \text{ (minor), 23.0 \text{ (major), 18.0 \text{ (minor), 17.4 \text{ (minor), 15.6 \text{ (major); HRMS (ESI): calculated for [M+Na\textsuperscript{+}] (C\textsubscript{10}H\textsubscript{14}ClNONa) m/z: 222.0662 found [M+Na\textsuperscript{+}]: 222.0648; IR (neat, cm\textsuperscript{-1}): 3296, 3239, 2972, 2877, 1737, 1646, 1440, 1342.}

1i: 1-(Azepan-1-yl)-2-iodo-4-phenylbutan-1-one

\[
\text{\begin{tikzpicture}
\draw (-1,0) -- (0,0) -- (1,0) -- (2,0) -- (3,0) -- (4,0);
\draw (1,0) -- (1,1) node[anchor=west] {I};
\draw (3,0) -- (3,1) node[anchor=west] {O};
\draw (4,0) -- (4,1) node[anchor=west] {N};
\end{tikzpicture}}
\]
The product was prepared according to general procedure D. Purification by column chromatography on silica gel (10–40% EtOAc in heptane) yielded the product (56.6 mg, 76%) as a pale yellow oil. (Rotamers present in a 1:4 ratio at room temperature)

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.32 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 4.32 (apt, $J$ = 7.4 Hz, 1H), 3.74 – 3.66 {major}(m, 0.8H), 3.64 – 3.56 {minor}(m, 0.2H), 3.51 – 3.17 (m, 3H), 2.80 – 2.74 {minor}(m, 0.4H), 2.74 – 2.62 {major}(m, 1.6H), 2.50 – 2.26 (m, 2H), 1.84 – 1.36 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 169.8, 140.4, 128.7 (2C), 128.6 (2C), 126.4, 53.1 (minor), 48.4 (major), 47.9 (minor), 46.8 (minor), 46.6 (major), 38.3, 36.1 (minor), 35.2 (major), 32.4 (minor), 29.2 (minor), 28.7 (major), 27.6 (major), 27.5 (minor), 27.2 (major), 27.0 (major), 26.8 (minor), 20.6 (major); HRMS (ESI): calculated for [M+Na]$^+$ (C$_{16}$H$_{22}$NNaO) 394.0638, found 394.0642; IR (neat, cm$^{-1}$): = 2926, 2854, 1639, 1429, 1192, 1152, 749, 700.

2a: 2-(Benzyloxy)-4-phenyl-1-{pyrrolidin-1-yl}butan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4:1:1) yielded the product as a yellow oil (52.3 mg, 81%)(rotamer ratio of 1:4 in $^1$HNMR).

$^1$H NMR (600 MHz, CDCl$_3$): δ = 7.39 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 7.26 – 7.22 (m, 2H), 7.19 – 7.15 (m, 1H), 7.15 – 7.11 (m, 2H), 4.68 – 4.62 (m, 1H, R1/R2), 4.38 (d, $J$ = 11.8 Hz, 0.8H, Rmajor), 4.35 (d, $J$ = 11.8 Hz, 0.2H, Rminor), 4.16 (dd, $J$ = 9.1, 4.1 Hz, 0.2H, Rminor), 4.01 (dd, $J$ = 9.1, 4.1 Hz, 0.8H, Rmajor), 3.54 – 3.42 (m, 2H), 3.31 – 3.20 (m, 2H), 2.89 – 2.84 (m, 1H), 2.73 – 2.64 (m, 1H), 2.18 – 2.10 (m, 1H), 1.98 – 1.92 (m, 1H), 1.86 – 1.73 (m, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ = 170.6 , 141.6 , 137.9 , 128.7 , 128.6 , 128.5 , 128.3 , 128. 0, 128.0 , 126.1 , 126.1 , 77.9 , 71.5 , 71.5 , 46.4 , 46.0 , 33.8 , 31.9 , 26.5 , 23.8; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{21}$H$_{25}$NO$_2$Na) m/z: 346.1783 found [M+Na]$^+$: 346.1777; IR (neat, cm$^{-1}$): 3060, 3027, 2950, 2926, 2871, 1641, 1495, 1433.
2b: 2-{allyloxy}-4-phenyl-1-{pyrrolidin-1-yl}butan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (39.3 mg, 72%).

\[ \begin{align*}
\text{H NMR (600 MHz, CDCl}_3\text{): } & \delta = 7.34 - 7.32 (m, 2H), 7.26 - 7.25 (m, 3H), 6.01 - 5.97 (m, 1H), 5.35 - 5.32 (m, 1H), 5.25 - 5.23 (m, 1H), 4.16 - 4.13 (m, 1H), 4.04 - 4.02 (m, 1H), 3.93 - 3.90 (m, 1H), 3.56 - 3.52 (m, 2H), 3.48 - 3.45 (m, 1H), 3.38 - 3.35 (m, 1H), 2.92 - 2.88 (m, 1H), 2.80 - 2.75 (m, 1H), 2.16 - 2.13 (m, 1H), 2.01 - 1.97 (m, 1H), 1.96 - 1.93 (m, 2H), 1.87 - 1.83 (m, 2H); 13C NMR (151 MHz, CDCl3): \delta = 170.6, 141.5, 134.6, 128.7 (2C), 128.5 (2C), 126.1, 117.6, 78.1, 70.6, 46.4, 46.0, 33.7, 31.8, 26.5, 23.8; HRMS (ESI): calculated for [M+Na]+ (C17H23NO2Na) m/z: 296.1626 found [M+Na]+: 296.1622; IR (neat, cm⁻¹): 3025, 2952, 2927, 2873, 1637, 1495, 1434. 
\end{align*} \]

2c: 2-{{(3-Methylbut-2-en-1-yl)oxy}-4-phenyl-1-{pyrrolidin-1-yl}butan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (51.8 mg, 86%).

\[ \begin{align*}
\text{H NMR (600 MHz, CDCl}_3\text{): } & \delta = 7.28 - 7.26 (m, 2H), 7.20 - 7.19 (m, 2H), 7.19 - 7.17 (m, 1H), 5.38 - 5.35 (m, 1H), 4.04 - 4.02 (m, 1H), 3.96 - 3.94 (m, 1H), 3.90 - 3.88 (m, 1H), 3.50 - 3.47 (m, 2H), 3.39 - 3.37 (m, 1H), 3.34 - 3.31 (m, 1H), 2.85 - 2.82 (m, 1H), 2.73 - 2.70 (m, 1H), 2.10 - 2.06 (m, 1H), 1.94 - 1.92 (m, 1H), 1.88 - 1.86 (m, 2H), 1.85 - 1.81 (m, 2H), 1.75 (s, 3H), 1.64 (s, 3H); 13C NMR (151 MHz, CDCl3): \delta = 170.9, 141.6, 137.6, 128.7 (2C), 128.5 (2C), 126.1, 120.9, 77.9, 65.9, 46.4, 46.0, 33.7, 31.9, 26.6, 26.0, 23.8, 18.2; HRMS (ESI): calculated for (C19H27NO3Na) [M+Na]+ m/z: 324.1939 found [M+Na]+: 324.1934; IR (neat, cm⁻¹): 3025, 2952, 2930, 2878, 1639, 1495, 1436. 
\end{align*} \]
2d: 2-(4-Nitrophenoxy)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:1) yielded the product (56.0 mg, 79%) as a pale yellow liquid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.16\) (d, \(J = 9.3\) Hz, 2H), 7.29 – 7.12 (m, 5H), 6.87 (d, \(J = 9.3\) Hz, 2H), 4.66 (dd, \(J = 9.1, 4.0\) Hz, 1H), 3.53–3.37 (m, 3H), 3.25–3.14 (m, 1H), 2.96 – 2.87 (m, 1H), 2.85 – 2.74 (m, 1H), 2.38 – 2.26 (m, 1H), 2.23 – 2.13 (m, 1H), 1.94 – 1.68 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 168.2, 162.8, 142.3, 140.5, 128.8 (2C), 128.7 (2C), 126.6, 126.2 (2C), 115.0 (2C), 77.8, 46.8, 46.1, 33.4, 31.8, 26.6, 23.6; HRMS (ESI): calculated for [M+Na]\(^+\) (C\(_{20}\)H\(_{22}\)N\(_2\)O\(_4\)Na) m/z: 377.1472, found 377.1475; IR (neat, cm\(^{-1}\)): 3082, 3027, 2956, 2878, 1652, 1590, 1512, 1494, 1441, 1338, 1256, 1110, 845, 751, 655.

2e: Ethyl 2-[(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)oxy]cyclohex-1-ene-1-carboxylate

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:2:1:1) yielded the product as a yellow oil (74.0 mg, 96%).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.28 – 7.26\) (m, 2H), 7.20 – 7.18 (m, 3H), 4.56 – 4.54 (m, 1H), 4.20 – 4.17 (m, J = 7.2 Hz, 2H), 3.49 – 3.45 (m, 4H), 2.88 – 2.84 (m, 1H), 2.82 – 2.77 (m, 1H), 2.36 – 2.28 (m, 2H), 2.20 – 2.17 (m, 2H), 2.10 – 2.04 (m, 2H), 1.89 – 1.76 (m, 4H), 1.64 – 1.63 (m, 2H), 1.55 – 1.54 (m, 2H), 1.30 – 1.28 (m, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta = 169.7, 168.1, 160.0, 141.1, 128.7 (2C), 128.6 (2C), 126.2, 108.1, 77.0, 60.0, 46.7, 46.1, 33.8, 31.5, 26.7, 26.6, 25.6, 23.6, 22.7, 22.1, 14.6; HRMS (ESI): calculated for [M+Na]\(^+\) (C\(_{23}\)H\(_{31}\)NO\(_4\)Na) m/z: 408.2151 found [M+Na]\(^+\): 408.2146; IR (neat, cm\(^{-1}\)): 3026, 2934, 2874, 1710, 1635, 1443.
2f: Methyl 8-(benzyloxy)-9-oxo-9-(pyrrolidin-1-yl)nonanoate

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (58.5 mg, 81%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.28 – 7.25 (m, 4H), 7.22 – 7.19 (m, 1H), 4.57 – 4.55 (m, 1H), 4.32 – 4.30 (m, 1H), 3.95 – 3.93 (m, 1H), 3.59 (s, 3H), 3.44 – 3.42 (m, 2H), 3.34 – 3.31 (m, 2H), 2.22 (t, $J$ = 7.8 Hz, 2H), 1.82 – 1.80 (m, 2H), 1.75 – 1.69 (m, 3H), 1.47 – 1.42 (m, 1H), 1.54 – 1.51 (m, 1H), 1.47 – 1.42 (m, 1H), 1.28 – 1.18 (m, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 174.4, 170.8, 137.9, 128.7, 128.5, 128.3, 128.1, 127.9, 79.0, 71.4, 66.2, 51.6, 46.4, 46.1, 34.2, 32.1, 29.1, 29.1, 26.5, 25.6, 25.0, 23.8; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{21}$H$_{31}$NO$_4$Na) m/z: 384.2151 found [M+Na]$^+$: 384.2150; IR (neat, cm$^{-1}$): 3029, 2932, 2860, 1736, 1646, 1495, 1435.

2g: 2-(Benzyloxy)-1-(pyrrolidin-1-yl)undecane-1,10-dione

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (54.5 mg, 76%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.28 – 7.25 (m, 4H), 7.22 – 7.20 (m, 1H), 4.57 – 4.55 (m, 1H), 4.32 – 4.30 (m, 1H), 3.95 (m, 1H), 3.46 – 3.43 (m, 2H), 3.41 – 3.32 (m, 2H), 2.35 – 2.32 (t, $J$ = 7.8 Hz, 2H), 2.06 (s, 3H), 1.82 – 1.80 (m, 2H), 1.75 – 1.71 (m, 3H), 1.60 – 1.57 (m, 1H), 1.48 – 1.43 (m, 2H), 1.26 – 1.18 (m, 8H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 209.6, 170.8, 137.9, 128.5 (2C), 128.1 (2C), 127.9, 79.1, 71.4, 46.4, 46.1, 43.9, 32.1, 30.0, 29.3, 29.3, 29.2, 26.5, 25.7, 23.9, 23.8; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{22}$H$_{33}$NO$_3$Na) m/z: 382.2358 found [M+Na]$^+$: 382.2357; IR (neat, cm$^{-1}$): 2928, 2856, 1712, 1647, 1435, 1342.
2h: 6-(Benzyloxy)-7-oxo-7-(pyrrolidin-1-yl)heptanenitrile

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:1-20:1) yielded the product as a yellow oil (52.2 mg, 87%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.39 – 7.26 (m, 5H), 4.64 (d, $J$ = 11.8 Hz, 1H), 4.39 (d, $J$ = 11.8 Hz, 1H), 4.03 (dd, $J$ = 8.5, 4.3 Hz, 1H), 3.57 – 3.43 (m, 3H), 3.41 (t, $J$ = 6.7 Hz, 1H), 2.33 (t, $J$ = 6.7 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.86 – 1.78 (m, 3H), 1.77 – 1.59 (m, 5H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 170.2, 137.7, 128.6 (2C), 128.2 (2C), 128.1, 119.7, 78.5, 71.5, 46.5, 46.2, 31.2, 26.6, 25.3, 25.0, 23.8, 17.2; HRMS (ESI): calculated for [M+Na]$^+$(C$_{18}$H$_{24}$N$_2$O$_2$Na) m/z: 323.1735 found [M+Na]$^+$: 323.1722; IR (neat, cm$^{-1}$): 3023, 3010, 2933, 2845, 1640, 1491, 1430.

2i: 2-(Benzyloxy)-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (51.3 mg, 83%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.27 – 7.26 (m, 4H), 7.23 – 7.19 (m, 1H), 4.57 – 4.55 (m, 1H), 4.32 – 4.30 (m, 1H), 3.96 – 3.95 (m, 1H), 3.47 – 3.40 (m, 4H), 3.34 – 3.32 (m, 2H), 1.81 – 1.77 (m, 2H), 1.76 – 1.72 (m, 3H), 1.71 – 1.67 (m, 2H), 1.63 – 1.61 (m, 2H), 1.45 – 1.42 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 170.5, 137.8, 128.5 (2C), 128.1 (2C), 128.0, 78.7, 71.4, 46.4, 46.2, 44.9, 32.4, 31.3, 26.5, 23.8, 23.2; HRMS (ESI): calculated for [M+Na]$^+$(C$_{17}$H$_{24}$ClNO$_2$Na) m/z: 332.1393 found [M+Na]$^+$: 332.1388; IR (neat, cm$^{-1}$): 2942, 2888, 1640, 1494, 1450.
2j: \(2\)-\{benzyloxy\}-1-\{pyrrolidin-1-yl\}undec-10-en-1-one

\[
\begin{align*}
\text{The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (56.9 mg, 83%).}
\end{align*}
\]

\(^1\)H NMR (600 MHz, CDCl\(_3\)) δ: 7.28 – 7.22 (m, 4H), 7.21 – 7.19 (m, 1H), 5.76 – 5.70 (m, 1H), 4.93 – 4.85 (m, 2H), 4.57 – 4.55 (m, 1H), 4.33 – 4.31 (m, 1H), 3.96 – 3.94 (m, 1H), 3.47 – 3.41 (m, 2H), 3.35 – 3.32 (m, 2H), 1.97 – 1.94 (m, 2H), 1.82 – 1.80 (m, 2H), 1.75 – 1.71 (m, 2H), 1.61 – 1.58 (m, 1H), 1.44 – 1.43 (m, 1H), 1.29 – 1.28 (m, 3H), 1.20 – 1.18 (m, 7H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) δ: 170.9, 139.3, 138.0, 128.5 (2C), 128.1 (2C), 127.9, 114.3, 79.2, 71.4, 46.1, 33.9, 32.2, 29.5, 29.5, 29.2, 29.0, 26.6, 25.8, 23.8; HRMS (ESI): calculated for \([M+Na]^+\) (C\(_{22}\)H\(_{33}\)NO\(_2\)Na) m/z: 366.2409 found [M+Na]\(^+\): 366.2404; IR (neat, cm\(^{-1}\)): 3072, 3030, 2971, 2925, 1639, 1434.

2k: \(2\)-\{benzyloxy\}-1-\{pyrrolidin-1-yl\}hex-5-yn-1-one

\[
\begin{align*}
\text{The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-2:1) yielded the product as a yellow oil (40.0 mg, 73%).}
\end{align*}
\]

\(^1\)H NMR (600 MHz, CDCl\(_3\)) δ: 7.38 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 4.65 (d, \(J = 11.7\) Hz, 1H), 4.42 (d, \(J = 11.7\) Hz, 1H), 4.24 (dd, \(J = 9.2, 4.1\) Hz, 1H), 3.59 – 3.27 (m, 4H), 2.51 – 2.25 (m, 2H), 2.05 – 1.96 (m, 1H), 1.94 – 1.77 (m, 6H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) δ: 170.1, 137.8, 128.5 (2C), 128.2 (2C), 128.0, 76.6, 71.6, 69.1, 46.3, 46.1, 31.0, 26.5, 23.9, 15.0; HRMS: calculated for C\(_{17}\)H\(_{21}\)NO\(_2\) [M+Na]\(^+\) m/z: 294.1470 found [M+Na]\(^+\): 294.1459; IR (neat, cm\(^{-1}\)): 3061, 3028, 2938, 2871, 1632, 1492, 1429.
2l: 2-(Benzyloxy)-N,N-dimethyl-4-phenylbutanamide

![Chemical structure of 2l]

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:3) yielded the product (44.0 mg, 74%) as a pale yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.40 – 7.11 (m, 10H), 4.63 (d, $J$ = 11.6 Hz, 1H), 4.35 (d, $J$ = 11.6 Hz, 1H), 4.16 (dd, $J$ = 9.1, 4.2 Hz, 1H), 2.94 (s, 3H), 2.92 (s, 3H), 2.89 – 2.81 (m, 1H), 2.74 – 2.65 (m, 1H), 2.20 – 2.09 (m, 1H), 2.02 – 1.92 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 171.7, 141.5, 137.9, 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 128.0, 126.1, 77.5, 71.5, 36.5, 36.2, 33.9, 31.9; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{19}$H$_{23}$NO$_2$Na) m/z: 320.1621, found 320.1621; IR (neat, cm$^{-1}$): 3060, 3026, 2925, 2861, 1639, 1494, 1452, 1397, 1343, 1257, 1097, 981, 734, 697.

2m: 1-(Azepan-1-yl)-2-(benzyloxy)-4-phenylbutan-1-one

![Chemical structure of 2m]

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (10–30% EtOAc in heptane) yielded the product (32.2 mg, 46% (54% brsm)) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.40 – 7.28 (m, 5H), 7.25 – 7.09 (m, 5H), 4.67 (d, $J$ = 11.7 Hz, 1H), 4.35 (d, $J$ = 11.7 Hz, 1H), 4.14 (dd, $J$ = 11.7 Hz, 1H), 3.71 – 3.61 (m, 1H), 3.40 – 3.20 (m, 3H), 2.91 – 2.81 (m, 1H), 2.74 – 2.63 (m, 1H), 2.23 – 2.12 (m, 1H), 2.01 – 1.87 (m, 1H), 1.79 – 1.65 (m, 2H), 1.57 – 1.45 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 171.3, 141.6, 138.1, 128.7 (2C), 128.5 (4C), 128.3 (2C), 127.9, 126.1, 76.7, 71.3, 47.0, 46.8, 34.4, 32.0, 29.5, 27.5 (2C), 26.7; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{23}$H$_{28}$NNaO$_2$) 374.2091, found 374.2093; IR (neat, cm$^{-1}$): 2925, 2855, 1649, 1454, 1275, 1099, 746, 699.
2n: Benzyl 8-(benzyloxy)-9-((4-methoxybenzyl)(methyl)amino)-9-oxononanoate

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (5–50% EtOAc in heptane) yielded the product (34.0 mg, 33%) as a pale yellow solid. When the nucleophile was added 20 s after the addition of 2,6-lutidine N-oxide (instead of 5 min) the reaction yielded the product in (42.6 mg, 41%). (Rotamers present in a 1:2 ratio at room temperature)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.40 - 7.27$ (m, 10H), 7.19 {major}|d, J = 8.6 Hz, 1.3H), 7.03 {minor}|d, J = 8.6 Hz, 0.7H), 6.89 – 6.82 (m, 2H), 5.11 (s, 2H), 4.69 – 4.32 (m, 4H), 4.26 – 4.16 (m, 1H), 3.80 (s, 3H), 2.96 – 2.86 (m, 3H), 2.37 – 2.28 (m, 2H), 1.86 – 1.21 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 173.7, 171.8, 159.2, 137.9, 136.3, 129.7$ (2C), 129.5, 128.8, 128.7 (2C), 128.5 (2C), 128.3 (2C), 128.1 (major), 128.1 (minor), 128.0, 127.9, 114.4 (minor), 114.2 (major), 78.9 (major), 78.7 (minor), 71.5 (major), 71.4 (minor), 66.2, 55.4, 52.0, 51.0, 34.4, 34.2 (major), 33.9 (minor), 32.7 (minor), 32.2 (major), 29.1, 25.7, 25.0; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{32}$H$_{39}$NNaO$_5$) 540.2720, found 540.2734; IR (neat, cm$^{-1}$): $= 2933, 2857, 1733, 1650, 1511, 1455, 1246, 1174, 738, 698.$

3a: 2-(Benzylthio)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4:1:1) yielded the product as a yellow oil (63.7 mg, 94%).

$^1$H NMR (600 MHz, MeOD): $\delta = 7.31 - 7.28$ (m, 2H), 7.27 – 7.21 (m, 4H), 7.19 (d, $J = 7.2$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 2H), 3.75 (s, 2H), 3.45 – 3.35 (m, 2H), 3.30 – 3.28 (m, 1H), 3.18 – 3.16 (m, 1H), 2.86 – 2.82 (m, 1H), 2.78 – 2.72 (m, 2H), 2.61 – 2.56 (m, 1H), 2.35 – 2.29 (m, 1H), 2.09 – 2.03 (m, 1H), 1.91 – 1.87 (m, 1H), 1.80 – 1.74 (m, 4H); $^{13}$C NMR (151 MHz, MeOD): $\delta = 171.5, 142.3, 139.7, 130.2$ (2C), 129.7 (2C), 129.6 (2C), 129.5 (2C), 128.1, 127.2
The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (46.2 mg, 80%).

**1H NMR (600 MHz, CDCl$_3$)**: δ = 7.28 – 7.26 (m, 2H), 7.19 – 7.15 (m, 3H), 5.80 – 5.74 (m, 1H), 5.03 – 5.00 (m, 2H), 3.52 – 3.46 (m, 3H), 3.23 – 3.20 (m, 2H), 3.18 – 3.16 (m, 1H), 3.10 – 3.08 (m, 1H), 2.79 – 2.75 (m, 1H), 2.66 – 2.61 (m, 1H), 2.44 – 2.38 (m, 1H), 2.05 – 1.99 (m, 1H), 1.91 – 1.89 (m, 2H), 1.86 – 1.83 (m, 2H); **13C NMR (176 MHz, CDCl$_3$)**: δ = 169.1, 141.3, 134.5, 128.7 (2C), 128.5 (2C), 126.1, 117.4, 46.3, 46.2, 43.5, 33.5, 33.4, 32.7, 26.2, 24.4; **HRMS (ESI)**: calculated for [M+Na]$^+$ (C$_{17}$H$_{23}$NOSNa) m/z: 312.1398 found [M+Na]$^+$: 312.1396; **IR (neat, cm$^{-1}$)**: 3026, 2949, 2872, 1635, 1494, 1428.

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-4:1) yielded the product as a yellow solid (32.7 mg, 76%).

**1H NMR (600 MHz, CDCl$_3$)**: δ = 7.27 – 7.25 (m, 2H), 7.18 – 7.16 (m, 3H), 3.48 – 3.46 (m, 2H), 3.42 – 3.36 (m, 2H), 3.26 – 3.23 (m, 1H), 2.77 – 2.73 (m, 1H), 2.67 – 2.63 (m, 1H), 2.39 – 2.33 (m, 1H), 2.07 – 2.02 (m, 1H), 1.91 – 1.86 (m, 2H), 1.83 – 1.77 (m, 2H), 1.29 (s, 9H); **13C NMR (151 MHz, CDCl$_3$)**: δ = 170.7, 141.3, 128.6 (2C), 128.5 (2C), 126.2, 46.5, 46.3, 44.2, 44.0, 35.8, 33.8, 31.7 (3C), 26.3, 24.2; **HRMS (ESI)**: calculated for [M+Na]$^+$ (C$_{18}$H$_{27}$NOSNa) m/z: 328.1711 found [M+Na]$^+$: 328.1708; **IR (neat, cm$^{-1}$)**: 2943, 1734, 1639, 1424, 1275.
3d: S-(1-Oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl) ethanethioate

![Chemical Structure](image)

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (55.9 mg, 96%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.30 – 7.28$ (m, 2H), 7.20 – 7.17 (m, 3H), 4.29 (t, $J = 7.5$ Hz, 1H), 3.50 – 3.41 (m, 3H), 3.20 – 3.18 (m, 1H), 2.70 – 2.68 (t, $J = 7.7$ Hz, 2H), 2.35 (s, 3H), 2.30 – 2.27 (m, 1H), 2.07 – 2.01 (m, 1H), 1.91 – 1.86 (m, 2H), 1.85 – 1.78 (m, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 195.2$, 169.0, 140.8, 128.5 (4C), 126.3, 46.6, 46.3, 44.4, 34.1, 33.3, 30.4, 26.1, 24.4; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{16}$H$_{21}$NO$_2$SNa) m/z: 314.1191 found [M+Na]$^+$: 314.1182; IR (neat, cm$^{-1}$): 2950, 2926, 2874, 1689, 1639, 1428, 1353, 1128.

3e: 2-((3-Oxobutan-2-yl)thio)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

![Chemical Structure](image)

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (45.9 mg, 72%, d.r. 1:1.3 – calculated from crude NMR).

$^1$H NMR (600 MHz, CDCl$_3$): (Diastereoisomers present) $\delta = 7.29 – 7.27$ (m, 2H), 7.20 – 7.15 (m, 3H), 3.71 (dd, $J = 14.4$, 7.2 Hz, 0.6H, d2), 3.63 – 3.57 (m, 0.4H, d1), 3.56 – 3.52 (m, 0.6H, d2), 3.48 – 3.45 (m, 2+0.4H), 3.31 – 3.28 (m, 0.4H, d1), 3.28 – 3.25 (m, 0.6H, d2), 3.09 – 3.06 (m, 1H), 2.75 – 2.66 (m, 2H), 2.35 – 2.31 (m, 1H), 2.27 (s, 1.3H, d1), 2.20 (s, 1.7H, d2), 2.02 (dq, $J = 15.0$, 7.3 Hz, 1H), 1.94 – 1.88 (m, 4H), 1.38 (d, $J = 7.2$ Hz, 1.7H, d2), 1.31 (d, $J = 7.1$ Hz, 1.3H, d1); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 206.6$ (d2), 206. 3 (d1), 169.0 (d1), 168.7 (d2), 140.7, 128.4 (2C), 126.2 (2C), 126.1, 47.1, 46.1, 46.1, 44.4 (d2), 43.9 (d1), 33.9, 33.6, 33.2, 26.2, 26.0 (d1), 26.0 (d2), 24.3 (d1), 24.2 (d2), 17.5 (d1), 17.0 (d2); HRMS (ESI): calculated for [M+Na]$^+$ (C$_{18}$H$_{35}$NO$_2$SNa) m/z: 342.1504 found [M+Na]$^+$: 342.1497; IR (neat, cm$^{-1}$): 2969, 2927, 2873, 1707, 1633, 1495, 1430, 1352.
3f: 4-Phenyl-2-(pyrimidin-2-ylthio)-1-(pyrrolidin-1-yl)butan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-3:1) yielded the product as a yellow oil (49.3 mg, 81%).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.52 \ (d, J = 4.8 \text{ Hz}, 2 \text{H}), 7.32 \ (d, J = 7.5 \text{ Hz}, 2 \text{H}), 7.28 – 7.23 \ (m, 3 \text{H}), 7.02 \ (t, J = 4.8 \text{ Hz}, 1 \text{H}), 4.76 – 4.73 \ (m, 1 \text{H}), 3.68 – 3.64 \ (m, 1 \text{H}), 3.61 – 3.51 \ (m, 2 \text{H}), 3.33 – 3.31 \ (m, 1 \text{H}), 2.91 – 2.78 \ (m, 2 \text{H}), 2.55 – 2.47 \ (m, 1 \text{H}), 2.35 – 2.23 \ (m, 1 \text{H}), 1.98 – 1.92 \ (m, 2 \text{H}), 1.92 – 1.88 \ (m, 2 \text{H}); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): = 171.7, 169.3, 157.4 (2C), 141.2, 128.6 (2C), 128.6, 128.4, 126.1, 116.8, 46.6, 45.6, 43.4, 34.1, 26.2, 24.4; HRMS (ESI): calculated for [M+Na]\(^+\) (C\(_{18}\)H\(_{21}\)N\(_3\)O\(_3\)SNa) m/z: 350.1303 found [M+Na]\(^+\): 350.1301; IR (neat, cm\(^{-1}\)): 3112, 3018, 2929, 2855, 1712, 1564, 1547, 1431, 1379, 1186, 748.

3g: Ethyl 2-((1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)thio)acetate

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:3-2:3) yielded the product as a yellow oil (60.3 mg, 90%).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.28 – 7.26 \ (m, 2 \text{H}), 7.19 – 7.16 \ (m, 3 \text{H}), 4.14 \ (q, J = 7.2 \text{ Hz}, 2 \text{H}), 3.58 – 3.55 \ (m, 1 \text{H}), 3.48 – 3.46 \ (m, 2 \text{H}) 3.44 – 3.34 \ (m, 1 \text{H}), 3.34- 3.33 \ (m, 2 \text{H}), 3.11 – 3.08 \ (m, 1 \text{H}), 2.78 – 2.75 \ (m, 1 \text{H}), 2.69 – 2.65 \ (m, 1 \text{H}), 2.37 – 2.34 \ (m, 1 \text{H}), 2.06 – 2.03 \ (m, 1 \text{H}), 1.93 – 1.80 \ (m, 4 \text{H}), 1.25 \ (t, J = 7.2Hz, 3 \text{H}); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta = 170.5, 168.5, 141.1, 128.6 \ (2C), 128.5 \ (2C), 126.2, 61.5, 46.3, 46.2, 43.6, 33.3, 33.0, 31.2, 26.1, 24.4, 14.2; HRMS (ESI): calculated for [M+Na]\(^+\) (C\(_{18}\)H\(_{25}\)NO\(_3\)SNa) m/z: 358.1453 found [M+Na]\(^+\): 358.1448; IR (neat, cm\(^{-1}\)): 2971, 2927, 2874, 1734, 1637, 1432.
3h: Methyl 8-(benzylthio)-9-oxo-9-(pyrrolidin-1-yl)nonanoate

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{C} & \quad \text{O} \\
\end{align*}
\]

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:3) yielded the product as a yellow oil (61.0 mg, 81%).

\(^1H\) NMR (600 MHz, \(\text{CDCl}_3\)): \(\delta = 7.27 – 7.23 \ (m, \ 4H), 7.18 – 7.16 \ (m, \ 1H), 3.77 – 3.72 \ (m, \ 2H), 3.61 \ (s, \ 3H), 3.41 – 3.39 \ (m, \ 1H), 3.37 – 3.34 \ (m, \ 1H), 3.26 – 3.24 \ (m, \ 1H), 3.17 – 3.13 \ (m, \ 2H), 2.25 – 2.22 \ (m, \ 2H), 1.97 – 1.95 \ (m, \ 1H), 1.82 – 1.80 \ (m, \ 2H), 1.76 – 1.74 \ (m, \ 2H), 1.67 – 1.65 \ (m, \ 1H), 1.56 – 1.53 \ (m, \ 2H), 1.28 – 1.21 \ (m, \ 6H); \ ^{13}C\ NMR (151 MHz, \text{CDCl}_3): \delta = 174.3, 169.3, 138.4, 129.1 (2C), 128.5 (2C), 127.1, 51.6, 46.2, 46.1, 45.2, 34.0, 31.8, 29.1, 29.0, 27.4, 26.1, 24.9, 24.3; \ HRMS (ESI): calculated for \([M+Na]^+ \ (C_{21}H_{31}NO_3SNa) \ m/z: 400.1922 \) found \([M+Na]^+ : 400.1912; \ IR (\text{neat, cm}^{-1}): 2930, 2876, 1736, 1639, 1431.\)

3i: 2-(Benzylthio)-1-(pyrrolidin-1-yl)undecane-1,10-dione

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{C} & \quad \text{O} \\
\end{align*}
\]

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (70.5 mg, 94%).

\(^1H\) NMR (600 MHz, \(\text{CDCl}_3\)): \(\delta = 7.28 – 7.23 \ (m, \ 4H), 7.19 – 7.16 \ (m, \ 1H), 3.75 – 3.74 \ (m, \ 2H), 3.42 – 3.34 \ (m, \ 2H), 3.26 – 3.24 \ (m, \ 1H), 3.18 – 3.14 \ (m, \ 2H), 2.38 – 2.36 \ (m, \ 2H), 2.09 \ (s, \ 3H), 1.97 – 1.94 \ (m, \ 1H), 1.84 – 1.77 \ (m, \ 2H), 1.76 – 1.73 \ (m, \ 2H), 1.69 – 1.65 \ (m, \ 1H), 1.53 – 1.49 \ (m, \ 2H), 1.27 – 1.22 \ (m, \ 8H); \ ^{13}C\ NMR (151 MHz, \text{CDCl}_3): \delta = 209.5, 169.4, 138.3, 129.1 (2C), 128.5 (2C), 127.1, 46.2, 46.1, 45.2, 43.9, 34.0, 31.9, 30.0, 29.3, 29.3, 29.2, 27.6, 26.1, 24.3, 23.9; \ HRMS (ESI): calculated for \([M+Na]^+ \ (C_{22}H_{33}NO_2SNa) \ m/z: 398.2130 \) found \([M+Na]^+ : 398.2121; \ IR (\text{neat, cm}^{-1}): 2973, 2855, 1713, 1638, 1493, 1427.\)
3j: 6-(Benzylthio)-7-oxo-7-(pyrrolidin-1-yl)heptanenitrile

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:2-20:1) yielded the product as a yellow oil (52.5 mg, 83%).

\[ ^1H \text{NMR (600 MHz, CDCl}_3\text{)}: \delta = 7.27 – 7.25 (m, 4H), 7.22 – 7.18 (m, 1H), 3.77 – 3.71 (m, 2H), 3.41 – 3.34 (m, 1H), 3.33 – 3.30 (m, 2H), 3.16 – 3.11 (m, 2H), 2.29 – 2.22 (m, 2H), 1.99 – 1.94 (m, 1H), 1.85 – 1.79 (m, 2H), 1.77 – 1.72 (m, 2H), 1.70 – 1.65 (m, 1H), 1.60 – 1.55 (m, 2H), 1.49 – 1.44 (m, 1H), 1.40 – 1.35 (m, 1H); \]^13C \text{NMR (151 MHz, CDCl}_3\text{)}: \delta = 168.7, 138.2, 129.1 (2C), 128.5 (2C), 127.2, 119.7, 46.2, 46.1, 44.9, 33.9, 31.0, 26.7, 26.1, 25.2, 24.3, 17.1; \text{HRMS (ESI)}: \text{calculated for [M+Na]}^+ (C_{18}H_{24}N_2O Na) \text{m/z: 339.1507 found [M+Na]}^+ : 339.1419; \text{IR (neat, cm}^{-1} \text{): 3061, 3028, 2931, 2872, 1634, 1493, 1429.}

3k: 2-(Benzylthio)-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (51.3 mg, 79%).

\[ ^1H \text{NMR (600 MHz, CDCl}_3\text{)}: \delta = 7.32 – 7.28 (m, 4H), 7.23 – 7.21 (m, 1H), 3.82 – 3.76 (m, 2H), 3.54 – 3.31 (m, 5H), 3.21 – 3.17 (m, 2H), 2.06 – 2.00 (m, 1H), 1.90 – 1.84 (m, 2H), 1.79 – 1.68 (m, 5H), 1.56 – 1.49 (m, 1H), 1.45 – 1.38 (m, 1H); \]^13C \text{NMR (151 MHz, CDCl}_3\text{)}: \delta = 169.0, 138.3, 129.2 (2C), 128.5 (2C), 127.2, 46.2, 46.1, 45.0, 45.0, 34.0, 32.4, 31.1, 26.1, 25.0, 24.3; \text{HRMS (ESI)}: \text{calculated for [M+Na]}^+ (C_{17}H_{24}ClNOS Na) \text{m/z: 348.1165 found [M+Na]}^+ : 348.1152; \text{IR (neat, cm}^{-1} \text{): 2951, 2871, 1634, 1493, 1428.}
The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (58.8 mg, 82%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.27 – 7.22 (m, 4H), 7.18 – 7.16 (m, 1H) 5.79 – 5.72 (m, 1H), 4.91 (m, 2H), 3.75 (s, 2H), 3.43 – 3.33 (m, 2H), 3.25 – 3.22 (m, 1H), 1.99 – 1.92 (m, 3H), 1.83 – 1.77 (m, 2H), 1.76 – 1.73 (m, 2H), 1.70 – 1.65 (m, 1H), 1.31 – 1.21 (m, 10H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 169.4, 139.3, 138.4, 129.1 (2C), 128.5 (2C), 127.1, 114.3, 46.2, 46.1, 45.2, 34.0, 33.9, 31.9, 29.4, 29.4, 29.1, 29.0, 27.6, 26.1, 24.3; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{22}$H$_{33}$NOSNa) m/z: 382.2181 found [M+Na]$^+$: 382.2177; IR (neat, cm$^{-1}$): 3027, 2971, 2853, 2362, 1736, 1639, 1425.

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (45.9 mg, 80%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.34 – 7.33 (m, 2H), 7.30 – 7.28 (m, 2H), 7.24 – 7.21 (m, 1H), 3.83 – 3.77 (m, 2H), 3.53 – 3.51 (m, 1H), 3.46 – 3.44 (m, 1H), 3.39 – 3.37 (m, 1H), 3.33 – 3.31 (m, 1H), 3.25 – 3.22 (m, 1H), 2.41 – 2.37 (m, 1H), 2.27 – 2.22 (m, 2H), 1.96 – 1.77 (m, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 168.6, 138.4, 129.3 (2C), 128.6 (2C), 127.2, 69.4, 46.1, 46.1, 43.5, 34.1, 30.5, 26.1, 24.4, 16.5; (the quaternary carbon of the alkyne is not relaxing) HRMS (ESI): calculated for [M+Na]$^+$ (C$_{17}$H$_{21}$NOSNa) m/z :310.1242 found [M+Na]$^+$: 310.1227; IR (neat, cm$^{-1}$): 3028, 2931, 2872, 1738, 1634, 1493.
3n: 2-(Benzylthio)-N,N-dimethyl-4-phenylbutanamide

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (51.9 mg, 83%).

$^1$H NMR (600 MHz, CDCl$_3$): δ = 7.36 – 7.26 (m, 8H), 7.22 – 7.20 (m, 2H), 3.80 (s, 2H), 3.35 – 3.32 (m, 1H), 3.00 (s, 3H), 2.84 – 2.82 (m, 1H), 2.72 (s, 3H), 2.67 – 2.64 (m, 1H), 2.53 – 2.48 (m, 1H) 2.13 – 2.10 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ = 170.4, 141.3, 138.1, 129.1 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 127.1, 126.1, 41.4, 36.9, 36.1, 34.0, 33.6, 33.5; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{19}$H$_{23}$NOSNa) m/z: 336.1398 found [M+Na]$^+$: 336.1394; IR (neat, cm$^{-1}$): 3060, 3026, 2925, 2858, 1641, 1493, 1453, 1395.

3o: Methyl 8-(benzylthio)-9-(diallylamino)-9-oxononanoate

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (10–30% EtOAc in heptane) yielded the product (30.0 mg, 37%) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.32 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 5.80 – 5.59 (m, 2H), 5.20 – 4.99 (m, 4H), 4.27 – 4.39 (m, 1H), 3.99 – 3.90 (m, 1H), 3.78 (dd, $J$ = 24.8, 12.8 Hz, 2H), 3.67 (s, 3H), 3.65 – 3.55 (m, 2H), 3.27 – 3.20 (m, 1H), 2.29 (t, $J$ = 7.4 Hz, 2H), 2.12 – 2.00 (m, 1H), 1.77 – 1.66 (m, 1H), 1.64 – 1.54 (m, 3H), 1.33 – 1.22 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 174.4, 170.9, 138.1, 133.6, 133.3, 129.3 (2C), 128.7 (2C), 127.2, 117.1, 116.2, 51.6, 49.2, 48.5, 43.0, 34.2, 33.9, 32.1, 29.2, 29.1, 27.6, 25.0; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{23}$H$_{33}$NNaO$_3$S) 426.2073, found 426.2081; IR (neat, cm$^{-1}$): 2926, 2855, 1736, 1639, 1453, 1193, 1173, 922, 703.
4a: *N*,*N*-Diethyl-*N*-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (57.0 mg, 71%) as a pale yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.58 (d, $J$ = 7.8 Hz, 2H), 7.32 – 7.26 (m, 4H), 7.23 – 7.18 (m, 1H), 7.09 (d, $J$ = 7.8 Hz, 2H), 4.59 (dd, $J$ = 9.8, 6.4 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.46 – 3.21 (m, 3H), 2.92 (s, 3H), 2.64 – 2.54 (m, 1H), 2.50 – 2.41 (m, 1H), 2.42 (s, 3H), 2.18 – 2.09 (m, 1H), 1.98 – 1.88 (m, 2H), 1.87 – 1.78 (m, 2H), 1.51 – 1.40 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 167.7, 143.6, 140.9, 136.3, 129.8 (2C), 128.6 (2C), 128.6 (2C), 127.4 (2C), 126.4, 56.5, 46.6, 46.1, 32.4, 30.5, 29.6, 26.3, 24.3, 21.7; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{22}$H$_{28}$N$_2$O$_3$SNa) m/z: 423.1713, found 423.1716; IR (neat; cm$^{-1}$): 3059, 3026, 2950, 2874, 1740, 1639, 1441, 1335, 1156, 1087, 933, 814, 696, 651.

4b: *N*-Isopropyl-*N*-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:3) yielded the product (54.6 mg, 64%) as a pale yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.60 (d, $J$ = 7.8 Hz, 2H), 7.31 – 7.17 (m, 5H), 7.04 (d, $J$ = 7.8 Hz, 2H), 4.40 (dd, $J$ = 10.3, 4.1 Hz, 1H), 4.15 – 4.05 (m, 1H), 3.72 – 3.64 (m, 1H), 3.56 – 3.47 (m, 1H), 3.47 – 3.38 (m, 1H), 3.24 – 3.16 (m, 1H), 2.65 – 2.56 (m, 1H), 2.42 (s, 3H), 2.41 – 2.24 (m, 2H), 1.94 – 1.78 (m, 4H), 1.52 – 1.42 (m, 1H), 1.33 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 167.5, 143.1, 141.0, 139.6, 129.6 (2C), 128.7 (2C), 128.6 (2C), 127.6 (2C), 126.4, 57.7, 50.4, 46.5, 46.5, 32.7, 31.2, 26.4, 24.2, 23.3, 22.4, 21.6; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{24}$H$_{32}$N$_2$O$_3$SNa) m/z: 451.2026, found 451.2022; IR (neat, cm$^{-1}$): 3026, 2970, 2873, 1637, 1599, 1439, 1328, 1151, 1085, 965, 936, 815, 698, 597.
4c: 4-Methyl-N-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)-N-phenylbenzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:3) yielded the product (69.7 mg, 75%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.36 (d, J = 8.6 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.26 – 7.19 (m, 5H), 7.18 – 7.10 (m, 3H), 7.98 – 7.93 (m, 2H), 5.04 – 4.96 (m, 1H), 3.88 – 3.78 (m, 1H), 3.40 – 3.22 (m, 3H), 2.59 – 2.42 (m, 2H), 2.31 (s, 3H), 2.03 – 1.75 (m, 5H), 1.74 – 1.64 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 167.8, 143.5, 140.9, 137.0, 136.0, 132.4 (2C), 129.3 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 127.9, 126.4, 59.1, 46.5, 46.3, 32.6, 32.4, 26.5, 24.3, 21.7; HRMS (ESI): calculated for [M+H]$^+$ (C$_{27}$H$_{31}$N$_2$O$_3$S) m/z: 463.2050, found 463.2046; IR (neat, cm$^{-1}$): 3061, 3026, 2951, 2874, 2242, 1643, 1597, 1491, 1439, 1342, 1159, 909, 729, 697, 657.

4d: N-(4-Methoxyphenyl)-4-methyl-N-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (70.4 mg, 72%) as a pale yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.40 (d, J = 8.3 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.23 – 7.16 (m, 5H), 7.13 – 7.08 (m, 2H), 6.77 (d, J = 9.0 Hz, 2H), 5.03 (dd, J = 8.1, 6.4 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.78 (s, 3H), 3.45 – 3.28 (m, 3H), 2.64 – 2.48 (m, 2H), 2.39 (s, 3H), 2.07 – 1.82 (m, 5H), 1.76 – 1.66 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 167.9, 159.7, 143.4, 141.0, 137.0, 133.5 (2C), 129.2 (2C), 128.6 (2C), 128.2, 127.9 (2C), 126.3, 113.9 (2C), 59.0, 55.4, 46.4, 46.2, 32.5, 32.4, 26.5, 24.3, 21.6; HRMS (ESI): calculated for [M+H]$^+$ (C$_{28}$H$_{33}$N$_2$O$_4$S) m/z: 493.2156, found 493.2164; IR (neat, cm$^{-1}$): 3062, 3026, 2952, 2874, 2240, 1644, 1602, 1505, 1439, 1341, 1249, 1158, 914, 727, 589.
4e: \( N\)-Benzyl-4-methyl-\( \text{N}-(1\text{-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl}) \text{benzenesulfonamide} \)

\[
\begin{align*}
\text{O=S=O} \\
\text{N} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\end{align*}
\]

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (67.0 mg, 70%) as a pale yellow solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.62 \) (d, \( J = 8.1 \) Hz, 2H), 7.44 (d, \( J = 7.1 \) Hz, 2H), 7.32 – 7.14 (m, 8H), 6.98 – 6.93 (m, 2H), 4.87 (d, \( J = 16.1 \) Hz, 1H), 4.53 (dd, \( J = 9.1, 4.8 \) Hz, 1H), 4.33 (d, \( J = 16.1 \) Hz, 1H), 3.55 – 3.46 (m, 1H), 2.68 – 2.59 (m, 1H), 2.55 – 2.47 (m, 1H), 2.43 (s, 3H), 2.37 – 2.27 (m, 1H), 2.24 – 2.13 (m, 1H), 1.80 – 1.61 (m, 3H), 1.53 – 1.42 (m, 1H), 1.41 – 1.31 (m, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 166.7, 143.7, 141.1, 137.9, 137.7, 129.8 \) (2C), 128.7 (2C), 128.5 (2C), 128.2 (2C), 127.5 (2C), 127.4, 126.3, 57.2, 48.6, 46.1, 45.9, 32.7, 30.2, 26.2, 23.9, 21.7; HRMS (ESI): calculated for [M+H]\(^+\) (C\(_{28}\)H\(_{33}\)N\(_2\)O\(_3\)S) m/z: 477.2206, found 477.2201; IR (neat, cm\(^{-1}\)): 3061, 3027, 2948, 2874, 1642, 1599, 1494, 1435, 1335, 1156, 1093, 698, 654.

4f: \( \text{N-Methyl-4-nitro-\text{N}-(1\text{-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl}) \text{benzenesulfonamide} } \)

\[
\begin{align*}
\text{O=S=O} \\
\text{N} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\text{\text{O} = \text{N} - \text{C}} \\
\end{align*}
\]

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (82.3 mg, 82%) as a pale yellow liquid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.30 \) (d, \( J = 9.0 \) Hz, 2H), 7.82 (d, \( J = 9.0 \) Hz, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.21 (m, 1H), 7.15 – 7.10 (m, 2H), 4.63 (apt, \( J = 7.5 \) Hz, 1H), 3.64 – 3.57 (m, 1H), 3.41 – 3.19 (m, 3H), 3.03 (s, 3H), 2.67 – 2.50 (m, 2H), 2.18 – 2.07 (m, 1H), 1.98 – 1.89 (m, 2H), 1.89 – 1.80 (m, 2H), 1.65 – 1.55 (m, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 167.7, 150.1, 144.8, 140.4, 128.8 \) (2C), 128.6 (2C), 128.5 (2C), 126.7, 124.3 (2C), 56.4, 46.5, 46.1, 32.1, 30.8, 30.3, 26.3, 24.2; HRMS (ESI): calculated for [M+Na]\(^+\) (C\(_{21}\)H\(_{25}\)N\(_3\)O\(_5\)SNa) m/z: 454.1407, found 454.1411; IR (neat, cm\(^{-1}\)): 3103, 3063, 2974, 2876, 1642, 1529, 1448, 1349, 1162, 855, 699, 608.
4g: 4-Nitro-N-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (57.2 mg, 69%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.29 (d, $J$ = 8.8 Hz, 2H), 7.99 (d, $J$ = 8.8 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 5.86 (bs, 1H), 3.94 (bs, 1H), 3.20 – 3.11 (m, 1H), 2.99 – 2.68 (m, 5H), 1.94 – 1.58 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 168.5, 150.2, 145.8, 140.5, 128.8 (2C), 128.7 (4C), 126.6, 124.1 (2C), 54.1, 46.1, 45.9, 35.1, 31.3, 26.0, 24.0; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{20}$H$_{23}$N$_3$O$_5$SNa) m/z: 440.1251, found 440.1251; IR (neat, cm$^{-1}$): 3104, 2952, 2876, 1629, 1528, 1451, 1348, 1164, 1091, 855, 613.

4h: N-Methyl-2-nitro-N-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:4-7:3) yielded the product (69.0 mg, 80%) as a pale yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.94 – 7.90 (m, 1H), 7.71 – 7.60 (m, 3H), 7.30 – 7.24 (m, 2H), 7.23 – 7.12 (m, 3H), 4.75 (apt, $J$ = 7.4 Hz, 1H), 3.70 – 3.61 (m, 1H), 3.44 – 3.37 (m, 2H), 3.31 – 3.23 (m, 1H), 3.14 (s, 3H), 2.71 – 2.56 (m, 2H), 2.21 – 2.12 (m, 1H), 1.95 – 1.78 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 168.5, 148.3, 140.8, 133.6, 132.7, 131.7, 130.8, 128.6 (2C), 128.5 (2C), 126.4, 124.4, 56.7, 46.6, 46.2, 32.3, 31.1, 31.0, 26.3, 24.2; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{21}$H$_{25}$N$_3$O$_5$SNa) m/z: 454.1407, found 454.1412; IR (neat, cm$^{-1}$): 3064, 3025, 2951, 2875, 1637, 1542, 1440, 1370, 1348, 1161, 937, 851, 729, 700.
4i: N-Methyl-N-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)pyridine-2-sulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (57.0 mg, 74%) as a pale yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.66 – 8.63$ (m, 1H), 7.92 – 7.83 (m, 2H), 7.49 – 7.43 (m, 1H), 7.31 – 7.24 (m, 2H), 7.21 – 7.12 (m, 3H), 4.81 (dd, $J = 8.0$, 6.8 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.45 – 3.32 (m, 2H), 3.30 – 3.22 (m, 1H), 3.04 (s, 3H), 2.67 – 2.52 (m, 2H), 2.20 – 2.09 (m, 1H), 1.98 – 1.77 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 168.2$, 157.2, 150.1, 141.0, 137.9, 128.6 (2C), 128.6 (2C), 126.7, 126.3, 122.8, 56.9, 46.6, 46.1, 32.3, 30.9, 30.8, 26.3, 24.4; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{20}$H$_{25}$N$_3$O$_3$SNa) m/z: 410.1509, found 410.1507; IR (neat, cm$^{-1}$): 3025, 2951, 2874, 1640, 1577, 1449, 1428, 1340, 1172, 1083, 937, 778, 744, 700, 589.

4j: N-Methyl-N-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)naphthalene-2-sulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (60.8 mg, 70%) as a pale yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.29$ (d, $J = 1.6$ Hz, 1H), 7.97 – 7.89 (m, 3H), 7.69 – 7.59 (m, 3H), 7.28 – 7.15 (m, 3H), 7.05 – 7.00 (m, 2H), 4.66 (dd, $J = 9.0$, 6.1 Hz, 1H), 3.76 – 3.67 (m, 1H), 3.42 – 3.33 (m, 1H), 3.31 – 3.20 (m, 2H), 3.01 (s, 3H), 2.63 – 2.53 (m, 1H), 2.52 – 2.42 (m, 1H), 2.17 – 2.05 (m, 1H), 1.94 – 1.82 (m, 2H), 1.81 – 1.70 (m, 2H), 1.54 – 1.44 (m, 1H); $^{13}$C NMR (175 MHz, CDCl$_3$): $\delta = 167.7$, 140.8, 136.2, 135.1, 132.4, 129.6, 129.3, 129.0, 128.7 (2C), 128.7 (3C), 128.2, 127.8, 126.5, 122.7, 56.5, 46.7, 46.2, 32.4, 30.8, 29.8, 26.4, 24.3; HRMS (ESI): calculated for [M+H]$^+$ (C$_{25}$H$_{29}$N$_2$O$_3$S) m/z: 437.1893, found 437.1892; IR (neat, cm$^{-1}$): 3058, 3025, 2969, 2876, 1642, 1447, 1336, 1159, 933, 751, 702, 651.
4k: 2-(1H-Indol-1-yl)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

![Chemical structure](image)

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (51.4 mg, 77%) as a pale yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.63$ (d, $J = 7.7$ Hz, 1H), 7.34 – 7.25 (m, 3H), 7.25 – 7.17 (m, 3H), 7.17 – 7.08 (m, 3H), 6.55 (d, $J = 3.3$ Hz, 1H), 4.97 – 4.92 (m, 1H), 3.58 – 3.39 (m, 2H), 3.28 – 3.20 (m, 1H), 2.88 – 2.79 (m, 1H), 2.65 – 2.52 (m, 3H), 2.43 – 2.31 (m, 1H), 1.87 – 1.66 (m, 4H); $^{13}$C NMR (175 MHz, CDCl$_3$): $\delta = 167.9$, 140.9, 136.1, 128.7, 128.7 (2C), 128.6 (2C), 126.4, 126.3, 121.8, 121.3, 119.9, 109.1, 102.7, 56.3, 46.5, 46.3, 33.8, 32.0, 26.2, 21.4; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{22}$H$_{24}$N$_2$ONa) m/z: 355.1781, found 355.1780; IR (neat, cm$^{-1}$): 3026, 2969, 2875, 1645, 1456, 1400, 1308, 1192, 700.

4l: Methyl 8-(((N,4-dimethylphenyl)sulfonamido)-9-oxo-9-(pyrrolidin-1-yl)nonanoate

![Chemical structure](image)

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:1) yielded the product (55.8 mg, 64%) as a pale yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.63$ (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.3$ Hz, 2H), 4.64 – 4.58 (m, 1H), 3.86 – 3.76 (m, 1H), 3.67 (s, 3H), 3.50 – 3.31 (m, 2H), 3.30 – 3.24 (m, 1H), 2.91 (s, 3H), 2.42 (s, 3H), 2.28 (t, $J = 7.6$ Hz, 2H), 2.01 – 1.91 (m, 2H), 1.88 – 1.79 (m, 2H), 1.79 – 1.69 (m, 1H), 1.63 – 1.52 (m, 2H), 1.33 – 1.11 (m, 7H); $^{13}$C NMR (175 MHz, CDCl$_3$): $\delta = 174.2$, 168.3, 143.5, 136.4, 129.6 (2C), 127.2 (2C), 56.9, 51.5, 46.6, 45.9, 34.1, 30.3, 28.9 (2C), 28.2, 26.3, 26.0, 24.9, 24.2, 21.6; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{22}$H$_{34}$N$_2$O$_5$SNa) m/z: 461.2081, found 461.2079; IR (neat, cm$^{-1}$): 2931, 2860, 1734, 1641, 1437, 1335, 1154, 1088, 815, 713, 652.
4m: \(N\{(1,10\text{-Dioxo-1-(pyrrolidin-1-yl)undecan-2-yl}-N,4\text{-dimethylbenzenesulfonamide}}

\[
\begin{align*}
\text{The product was prepared according to general procedure E. Purification by column chromatography on silica} \\
\text{gel (EtOAc: heptane = 1:1) yielded the product (60.0 mg, 69\%) as a pale yellow liquid.}
\end{align*}
\]

\[^1H\text{ NMR (400 MHz, CDCl}_3\text{):} \] \(\delta = 7.63 \,(d, \, J = 8.3 \text{ Hz, 2H}), \, 7.28 \,(d, \, J = 8.3 \text{ Hz, 2H}), \, 4.62 \,(dd, \, J = 8.2, \, 6.2 \text{ Hz, 1H}), \, 3.85 \,-\, 3.77 \,(m, \, 1H), \, 3.51 \,-\, 3.24 \,(m, \, 3H), \, 2.91 \,(s, \, 3H), \, 2.42 \,(s, \, 3H), \, 2.40 \,(t, \, J = 7.4 \text{ Hz, 2H}), \, 2.13 \,(s, \, 3H), \, 2.00 \,-\, 1.92 \,(m, \, 2H), \, 1.88 \,-\, 1.79 \,(m, \, 2H), \, 1.79 \,-\, 1.69 \,(m, \, 1H), \, 1.60 \,-\, 1.48 \,(m, \, 2H), \, 1.32 \,-\, 1.12 \,(m, \, 9H); \]^13C\text{ NMR (175 MHz, CDCl}_3\text{):} \] \(\delta = 209.3 \, , \, 168.4 \, , \, 143.5 \, , \, 136.4 \, , \, 129.7 \,(2C) \, , \, 127.3 \,(2C) \, , \, 56.9 \, , \, 46.7 \, , \, 46.0 \, , \, 43.8 \, , \, 30.4 \, , \, 30.0 \, , \, 29.3 \, , \, 29.2 \, , \, 28.3 \, , \, 26.3 \, , \, 26.2 \, , \, 24.3 \, , \, 23.9 \, , \, 21.7; \) \text{HRMS (ESI): calculated for } [\text{M+Na}]^+ \,(C_{23}H_{36}N_2O_4SNa) \text{ m/z: 459.2288, found 459.2289; IR (neat, cm}^{-1}\text{:} \) 2928, 2855, 1711, 1640, 1598, 1441, 1334, 1154, 1088, 911, 814, 730, 651.

4n: \(N\{(7\text{-Cyano-1-oxo-1-(pyrrolidin-1-yl)hexan-2-yl}-N,4\text{-dimethylbenzenesulfonamide}}

\[
\begin{align*}
\text{The product was prepared according to general procedure E. Purification by column chromatography on silica} \\
\text{gel (EtOAc: heptane = 1:9-7:3) yielded the product (32.5 mg, 47\%) as a pale yellow liquid.}
\end{align*}
\]

\[^1H\text{ NMR (400 MHz, CDCl}_3\text{):} \] \(\delta = 7.65 \,(d, \, J = 8.2 \text{ Hz, 2H}), \, 7.31 \,(d, \, J = 8.2 \text{ Hz, 2H}), \, 4.62 \,(dd, \, J = 8.9, \, 6.1 \text{ Hz, 1H}), \, 3.85 \,-\, 3.77 \,(m, \, 1H), \, 3.51 \,-\, 3.28 \,(m, \, 3H), \, 2.87 \,(s, \, 3H), \, 2.43 \,(s, \, 3H), \, 2.28 \,(t, \, J = 7.1 \text{ Hz, 2H}), \, 2.01 \,-\, 1.93 \,(m, \, 2H), \, 1.89 \,-\, 1.76 \,(m, \, 3H), \, 1.72 \,-\, 1.49 \,(m, \, 3H), \, 1.39 \,-\, 1.31 \,(m, \, 2H); \]^13C\text{ NMR (100 MHz, CDCl}_3\text{):} \] \(\delta = 167.6 \, , \, 143.8 \, , \, 136.3 \, , \, 129.9 \,(2C) \, , \, 127.3 \,(2C) \, , \, 119.5 \, , \, 56.9 \, , \, 46.8 \, , \, 46.2 \, , \, 30.4 \, , \, 27.3 \, , \, 26.3 \, , \, 25.4 \, , \, 25.2 \, , \, 24.2 \, , \, 21.7 \, , \, 17.1; \) \text{HRMS (ESI): calculated for } [\text{M+Na}]^+ \,(C_{19}H_{27}N_3O_3SNa) \text{ m/z: 400.1665, found 400.1672; IR (neat, cm}^{-1}\text{:} \) 2950, 2875, 2246, 1641, 1444, 1334, 1156, 1088, 816, 714, 653.
4o: N-(6-Chloro-1-oxo-1-(pyrrolidin-1-yl)hexan-2-yl)-N,4-dimethylbenzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:1) yielded the product (51.2 mg, 66%) as a pale yellow liquid.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 7.65 (d, J = 8.4 \text{ Hz, } 2\text{H}), 7.30 (d, J = 8.4 \text{ Hz, } 2\text{H}), 4.63 (dd, J = 8.8, 6.1 \text{ Hz, } 1\text{H}), 3.87 – 3.78 (m, 1\text{H}), 3.52 – 3.27 (m, 5\text{H}), 2.89 (s, 3\text{H}), 2.42 (s, 3\text{H}), 2.02 – 1.92 (m, 2\text{H}), 1.88 – 1.60 (m, 5\text{H}), 1.40 – 1.21 (m, 3\text{H}); \]

\[ ^13C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta = 167.9, 143.7, 136.3, 129.8 (2\text{C}), 127.3 (2\text{C}), 57.0, 46.8, 46.1, 44.6, 32.2, 30.4, 27.4, 26.3, 24.3, 23.6, 21.7; \]

\[ \text{HRMS (ESI): calculated for [M+Na]^+ (C}_{18}\text{H}_{27}\text{ClN}_{2}\text{O}_{3}\text{SNa) m/z: 409.1323, found 409.1330; IR (neat, cm}^{-1}\text{): 2951, 2873, 1640, 1441, 1334, 1154, 1088, 929, 912, 815, 713, 652.} \]

4p: N,4-Dimethyl-N-(1-oxo-1-(pyrrolidin-1-yl)undec-10-en-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:19-2:3) yielded the product (39.6 mg, 47%) as a pale yellow liquid.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 7.64 (d, J = 8.3 \text{ Hz, } 2\text{H}), 7.28 (d, J = 8.3 \text{ Hz, } 2\text{H}), 5.86 – 5.75 (m, 1\text{H}), 5.03 – 4.91 (m, 2\text{H}), 4.62 (dd, J = 8.0, 6.0 \text{ Hz, } 1\text{H}), 3.86 – 3.78 (m, 1\text{H}), 3.50 – 3.25 (m, 3\text{H}), 2.92 (s, 3\text{H}), 2.42 (s, 3\text{H}), 2.07 – 1.92 (m, 4\text{H}), 1.88 – 1.69 (m, 3\text{H}), 1.40 – 1.12 (m, 11\text{H}); \]

\[ ^13C \text{ NMR (175 MHz, CDCl}_3\text{): } \delta = 168.5, 143.5, 139.2, 136.5, 129.7 (2\text{C}), 127.3 (2\text{C}), 114.4, 57.0, 46.7, 46.0, 33.9, 30.4, 29.4, 29.3, 29.1, 29.0, 28.3, 26.3, 26.2, 24.3, 21.7; \]

\[ \text{HRMS (ESI): calculated for [M+Na]^+ (C}_{23}\text{H}_{36}\text{N}_{2}\text{O}_{3}\text{SNa) m/z: 443.2339, found 443.2336; IR (neat, cm}^{-1}\text{): 3070, 2925, 2855, 1643, 1441, 1338, 1160, 1088, 910, 815, 713, 652.} \]
4q: *N*-Methyl-4-nitro-*N*-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:3) yielded the product (60.0 mg, 72%) as a pale yellow solid.

^1^H NMR (400 MHz, CDCl3): δ = 8.25 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.27 – 7.21 (m, 3H), 7.14 – 7.10 (m, 2H), 4.94 (dd, J = 9.2, 6.2 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.33 – 3.12 (m, 3H), 3.13 (s, 3H), 2.87 – 2.79 (m, 1H), 2.71 (dd, J = 13.3, 6.2 Hz, 1H), 1.90 – 1.64 (m, 4H); ^13^C NMR (100 MHz, CDCl3): δ = 167.8, 150.1, 145.0, 136.3, 129.4 (2C), 129.0 (2C), 128.5 (2C), 127.4, 124.4 (2C), 58.4, 46.6, 45.9, 36.1, 31.1, 26.2, 24.3; HRMS (ESI): calculated for [M+Na]^+ (C_{20}H_{23}N_{3}O_{5}SNa) m/z: 440.1244, found 440.1251; IR (neat cm^-1): 3104, 3063, 3029, 2876, 1640, 1528, 1447, 1347, 1162, 942, 853, 738, 699, 609.

4r: *N*,*N*-Dimethyl-2-((*N*-methyl-4-nitrophenyl)sulfonamido)-4-phenylbutanamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:5 – 1:2) yielded the product (60.4 mg, 74%) as a pale yellow liquid.

^1^H NMR (400 MHz, CDCl3): δ = 8.31 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.28 – 7.22 (m, 1H), 7.16 – 7.10 (m, 2H), 4.83 (apt, J = 7.5 Hz, 1H), 3.01 (s, 3H), 2.99 (s, 3H), 2.86 (s, 3H), 2.67 – 2.58 (m, 1H), 2.57 – 2.48 (m, 1H), 2.17 – 2.07 (m, 1H), 1.63 – 1.53 (m, 1H); ^13^C NMR (100 MHz, CDCl3): δ = 169.3, 150.2, 144.7, 140.3, 128.8 (2C), 128.7 (2C), 128.5 (2C), 126.7, 124.3 (2C), 54.4, 37.3, 36.0, 32.1, 30.7, 30.5; HRMS (ESI): calculated for [M+Na]^+ (C_{19}H_{23}N_{3}O_{5}SNa) m/z: 428.1251, found 428.1248; IR (neat cm^-1): 3103, 3061, 3026, 2933, 2866, 1645, 1528, 1346, 1161, 932, 854, 736, 697, 606.
4s: N,4-dimethyl-N-(1-morpholino-1-oxohexan-2-yl)benzenesulfonamide

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (10–50% EtOAc in heptane) yielded the product (28.4 mg, 44% (59% brsm)) as a pale yellow liquid.

1H NMR (400 MHz, CDCl₃): δ = 7.66 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 4.79 (dd, J = 9.3, 5.3 Hz, 1H), 3.89 – 3.79 (m, 1H), 3.74 – 3.55 (m, 6H), 3.52 – 3.40 (m, 1H), 2.83 (s, 3H), 2.43 (s, 3H), 1.98 – 1.89 (m, 2H), 1.87 – 1.75 (m, 1H), 1.28 – 1.09 (m, 3H), 0.86 (t, J = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl₃): δ = 168.3, 143.8, 136.2, 129.8 (2C), 127.4 (2C), 67.1 (2C), 54.6, 46.4, 42.6, 30.3, 30.1, 21.7, 19.6, 13.8; HRMS (ESI): calculated for [M+Na]+ (C₁₇H₂₆N₂NaO₄S) m/z: 377.1505, found 377.1502; IR (neat, cm⁻¹): = 2960, 2925, 2856, 1649, 1453, 1337, 1163, 1115, 934, 816.

5a: N-(tert-butoxycarbonyl)-O-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)-L-threonine

The product was prepared according to general procedure E using N-(tert-Butoxycarbonyl)-L-threonine methyl ester (commercially available) as a nucleophile. Product isolated as the free carboxylic Acid. Purification by flash column chromatography (EtOAc: heptane = 1:2-5:1) as a yellow oil (72.0 mg, 83%, 1:1.1 d.r. determined by crude 1H NMR).

1H NMR (600 MHz, CDCl₃) Diastereoisomers present: δ = 7.32 – 7.29 (m, 2H), 7.19 – 7.17 (m, 3H), 5.56 (d, J = 8.4 Hz, 0.5H, d1), 5.26 (d, J = 8.4 Hz, 0.5H, d2), 5.06 – 5.04 (m, 0.5H, d1), 4.99 – 4.98 (m, 0.5H, d2), 4.87 (bs, 0.5H, d1), 4.68 (bs, 0.5H, d2), 4.43 – 4.42 (m, 0.5H, d2), 4.29 (bs, 0.5H), 4.22 (m, J = 6.0 Hz, 0.5H), 4.09 (d, J = 9.0 Hz, 0.5H, d1), 3.53 – 3.47 (m, 1H), 3.41 – 3.29 (m, 2H), 3.13 – 3.06 (m, 1H), 2.90 – 2.84 (m, 1H), 2.74 – 2.67 (m, 1H),
2.24 – 2.17 (m, 1H), 2.02 – 1.76 (m, 5H), 1.47 (bs, 4.5H), 1.46 (bs, 4.5H), 1.28 (d, J= 6.6 Hz, 1.5H), 1.25 (d, J= 6.6 Hz, 1.5H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ = 172.4 (d1), 172.1 (d2), 169.1 (d1), 169.0 (d2), 156.5 (d1), 156.4 (d2), 140.4 (d1), 140.3 (d2), 128.8 (d1) (2C), 128.8 (d2) (2C), 128.7 (d1) (2C), 128.6 (d2) (2C), 126.6, 80.0 (d1), 79.8 (d2), 73.2 (d1), 72.0 (d2), 68.5 (d1), 68.0 (d2), 60.2 (d1), 69.4 (d2), 46.5 , 45.9, 32.1 (d1), 32.0 (d2), 31.6 (d1), 31.4 (d2), 28.5 (d1) (3C), 28.5 (d2) (3C), 26.2 (d1), 26.2 (d2), 23.9 (d1), 23.9 (d2), 19.5 (d1), 18.6 (d2);

HRMS (ESI): calculated for [M+Na]$^+$ (C$_{23}$H$_{34}$N$_2$O$_6$Na) m/z: 457.2315 found [M+Na]$^+$: 457.2299; IR (neat, cm$^{-1}$): 3359, 2975, 2931, 2882, 1745, 1712, 1635, 1496, 1453.

5b: 2-(((3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:2-7:1) as a yellow oil (87.4mg, 92%, d.r 1:1, determined by crude $^1$H NMR).

$^1$H NMR (600 MHz, CDCl$_3$): Diastereoisomers are present δ = 7.28 – 7.26 (m, 2H), 7.24 – 7.23 (m, 1H), 7.20 – 7.17 (m, 2H), 5.77 (d, J = 3.8 Hz, 0.5H, d1), 5.67 (d, J = 3.5 Hz, 0.5H, d2), 4.57 – 4.54 (m, 1H), 4.40 – 4.38 (m, 0.5H, d1), 4.26 – 4.23 (m, 1.5H), 4.18 – 4.16 (m, 0.5H, d2), 4.09 – 4.07 (m, 0.5H, d1), 4.05 – 3.98 (m, 2H), 3.85 – 3.79 (m, 1.5H), 3.53 – 3.49 (m, 0.5H, d1), 3.47 – 3.30 (m, 3H), 2.87 – 2.81 (m, 1H), 2.77 – 2.74 (m, 0.5H, d1), 2.71 – 2.67 (m, 0.5H, d2), 2.16 – 2.05 (m, 1.5H), 1.99 – 1.96 (m, 0.5H, d1), 1.91 – 1.85 (m, 2H), 1.83 – 1.78 (m, 2H), 1.59 (bs, 1.5H, d1), 1.55 (bs, 1.5H, d2), 1.45 (bs, 1.5H, d1), 1.44 (bs, 1.5H, d2), 1.35 (bs, 4.5H), 1.31(bs, 1.5H, d1); $^{13}$C NMR (151 MHz, CDCl$_3$): δ = 169.9 (d1), 169.5 (d2), 141.8 (d1), 141.5 (d2), 128.7, 128.6, 128.5, 128.5, 128.4, 126.2 (d1), 126.1 (d2), 113.0 (d1), 113.0 (d2), 109.8 (d1), 109.6 (d2), 104.5 (d1), 103.7 (d2), 82.0, 80.3, 78.9, 78.4, 78.1, 77.6, 76.7, 76.5, 75.5, 75.4, 65.7, 65.0, 46.7, 46.3, 45.9, 45.9, 33.6, 33.3, 31.9, 31.6, 27.1, 27.1, 27.0, 27.0, 26.7, 26.5, 26.5, 26.4, 26.4, 25.6, 25.2, 23.9, 23.8; HRMS (ESI): calculated for [M+Na]$^+$ (C$_{26}$H$_{37}$NO$_7$Na) m/z: 498.2468 found [M+Na]$^+$: 498.2460; IR (neat, cm$^{-1}$): 2982, 2933, 2875, 1635, 1631, 1452.
5c: Methyl N-(tert-butoxycarbonyl)-S-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)-L-cysteinate

The product was prepared according to general procedure E. Purification by flash column chromatography (EtOAc: heptane = 1:1-4:1) as a yellow oil (78.3mg, 87%, d.r. 1:1, determined by crude $^1$H NMR).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.29 - 7.25$ (m, 2H), 7.20 - 7.15 (m, 3H), 5.33 (bs, 1H), 4.57 (bs, 0.5H, d1), 4.39 (bs, 0.5H, d2), 3.73 (s, 1.5H, d1), 3.72 (s, 1.5H, d2), 3.64 - 3.58 (m, 3H), 3.20 - 3.17 (m, 1H), 2.77 - 2.63 (m, 2H), 2.39 - 2.33 (m, 1H), 2.04 - 2.00 (m, 1H), 1.99 - 2.65 (m, 4H), 1.45 (s, 4.5H, d1), 1.43 (s, 4.5H, d2); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 171.5$, 169.0 (d1), 168.7 (d2), 155.3 (d1), 155.2 (d2), 140.9 (d1), 140.9 (d2), 128.5 (C2), 128.4 (C2), 126.1, 80.0, 53.7 (d1), 53.3 (d2), 52.5, 46.2, 46.2, 46.1, 46.0, 33.2, 33.1, 33.0, 30.9 (d1), 30.3 (d2), 28.3, 26.0, 24.3 (d1), 24.3 (d2), 24.4 (d2); HRMS (ESI): calculated for [M+Na]$^+$ (C$_{23}$H$_{34}$N$_2$O$_5$SNa) m/z: 473.2086 found [M+Na]$^+$: 473.2080; IR (neat, cm$^{-1}$): 3289, 2973, 2929, 2875, 1745, 1711, 1435.

5d: Methyl N-{1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl}-N-tosylglycinate

The product was prepared according to general procedure E. Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (58.0 mg, 63%) as a pale yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.66$ (d, $J = 8.3$ Hz, 2H), 7.32 - 7.21 (m, 4H), 7.21 - 7.16 (m, 1H), 7.04 (d, $J = 8.3$ Hz, 2H), 4.39 (d, $J = 18.3$ Hz, 1H), 4.39 - 4.34 (m, 1H), 4.17 (d, $J = 18.3$ Hz, 1H), 3.71 (s, 3H), 3.54 - 3.45 (m, 1H), 3.38 - 3.22 (m, 2H), 3.02 - 2.93 (m, 1H), 2.66 - 2.57 (m, 1H), 2.53 - 2.44 (m, 1H), 2.43 (s, 3H), 2.12 - 2.01 (m, 1H), 1.90 - 1.74 (m, 4H), 1.62 - 1.51 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 170.5$, 167.4, 144.0, 140.7, 137.0, 129.8 (2C), 128.6 (2C), 128.6 (2C), 127.8 (2C), 126.4, 55.7, 52.3, 46.2, 46.1, 45.3, 31.9, 30.9, 26.2, 24.2, 21.7; HRMS
(ESI): calculated for [M+Na]+ (C_{24}H_{30}N_{2}O_{5}SNa) m/z: 481.1768, found 481.1758; IR (neat, cm\(^{-1}\)): 2951, 2876, 2251, 1756, 1638, 1598, 1447, 1341, 1206, 1156, 1093, 909, 813, 727, 700, 654.

6: 2-Amino-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

![structure](image)

To 32 mg (0.077 mmol) 4h in 0.5 mL MeCN 25.3 mg (0.23 mmol) thiophenol and 42.4 mg (0.31 mmol) freshly ground K_{2}CO_{3} was added. The mixture was heated to 50 °C for 40 h. Then, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc: 99% MeOH, 1% NH\(_{4}\)OH = 9:1) to yield amine 6 (16.6 mg, 93%) as a pale yellow liquid.

\(^1\)H NMR (400 MHz, CDCl\(_{3}\)): \(\delta = 7.31 – 7.25 \text{ (m, 2H)}\), \(7.23 – 7.16 \text{ (m, 3H)}\), \(3.54 – 3.37 \text{ (m, 3H)}\), \(3.34 – 3.26 \text{ (m, 1H)}\), \(3.19 – 3.10 \text{ (m, 1H)}\), \(2.86 – 2.67 \text{ (m, 2H)}\), \(1.96 – 1.74 \text{ (m, 6H)}\), \(1.71 \text{ (br, 2H)}\); \(^{13}\)C NMR (100 MHz, CDCl\(_{3}\)): \(\delta = 174.1\), 141.7, 128.7 (2C), 128.6 (2C), 126.1, 52.4, 46.1, 46.0, 36.9, 32.2, 26.2, 24.2; HRMS (ESI): calculated for [M+H]+ (C\(_{14}\)H\(_{21}\)N\(_{2}\)O) m/z: 233.1648, found 233.1647; IR (neat, cm\(^{-1}\)): 3363, 3060, 3025, 2950, 2873, 1631, 1449, 1370, 1342, 752, 701.

7a: 2-(Methylamino)-2-(4-nitrophenyl)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one

![structure](image)

The product was prepared according to general procedure F from amide 4f (63 mg, 0.15 mmol). Purification by column chromatography on silica gel (EtOAc: heptane = 1:1) yielded the product (24.0 mg, 45%) as a pale yellow liquid.

\(^1\)H NMR (400 MHz, CDCl\(_{3}\)): \(\delta = 8.21 \text{ (d, } J = 9.0 \text{ Hz, 2H)}\), \(7.57 \text{ (d, } J = 9.0 \text{ Hz, 2H)}\), \(7.25 – 7.20 \text{ (m, 2H)}\), \(7.19 – 7.13 \text{ (m, 1H)}\), \(7.12 – 7.06 \text{ (m, 2H)}\), \(3.53 \text{ (bs, 2H)}\), \(3.20 \text{ (bs, 1H)}\), \(2.70 \text{ (bs, 1H)}\), \(2.62 – 2.53 \text{ (m, 1H)}\), \(2.42 – 2.33 \text{ (m, 2H)}\), \(2.28 \text{ (s, 3H)}\), \(2.17 – 1.88 \text{ (br, 1H)}\) \(1.74 – 1.49 \text{ (m, 5H)}\); \(^{13}\)C NMR (150 MHz, CDCl\(_{3}\)): \(\delta = 170.6\), 150.0, 147.0, 141.7, 128.6 (2C), 128.4 (2C), 127.3 (2C), 126.1, 123.8 (2C), 68.5, 47.9, 46.6, 35.4, 29.4, 29.2, 26.8, 23.2; HRMS
(ESI): calculated for [M+H]+ (C21H26N3O3) m/z: 368.1969, found 368.1971; IR (neat, cm\(^{-1}\)): 2946, 2876, 2798, 1625, 1603, 1519, 1401, 1346, 1109, 854.

7b: 2-(Methylamino)-2-(4-nitrophenyl)-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one

\[
\text{O}^+ - \text{N} - \text{O} \\
\text{O}^+ - \text{N} - \text{NH} \\
\text{O}^+ - \text{N} - \text{NH}
\]

The product was prepared according to general procedure F from amide 4r (417.5 mg, 1 mmol). Purification by column chromatography on silica gel (EtOAc: heptane = 3:2) yielded the product (159.0 mg, 45%) as a pale yellow solid.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.10\) (d, \(J = 9.0\) Hz, 2H), 7.31 – 7.24 (m, 2H), 7.14 – 7.11 (m, 1H), 7.11 – 7.06 (m, 2H), 6.52 (d, \(J = 9.0\) Hz, 2H), 3.71 (d, \(J = 14.3\) Hz, 1H), 3.67 – 3.62 (m, 1H), 3.60 – 3.49 (m, 2H), 3.24 (d, \(J = 14.3\) Hz, 1H), 2.50 (s, 3H), 2.44 – 2.36 (m, 1H), 1.79 – 1.62 (m, 3H), 1.61 – 1.52 (m, 2H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta = 169.8, 149.8, 146.7, 135.9, 130.4\) (2C), 128.1 (2C), 127.2 (2C), 126.8, 123.3 (2C), 69.5, 47.6, 46.4, 41.1, 30.1

HRMS (ESI): calculated for [M+H]+ (C20H24N3O3) m/z: 354.1812, found 354.1816; IR (neat, cm\(^{-1}\)): 3028, 2947, 2875, 2802, 1629, 1599, 1518, 1398, 1345, 1107, 850, 705.

7c: N,N-Dimethyl-2-(methylamino)-2-(4-nitrophenyl)-4-phenylbutanamide

\[
\text{O}^+ - \text{N} - \text{O} \\
\text{O}^+ - \text{N} - \text{NH} \\
\text{O}^+ - \text{N} - \text{NH}
\]

The product was prepared according to general procedure F from amide 4q (39 mg, 0.096 mmol). Purification by column chromatography on silica gel (EtOAc: heptane = 1:2) yielded the product (17.0 mg, 51%) as a colourless liquid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.23\) (d, \(J = 9.0\) Hz, 2H), 7.53 (d, \(J = 9.0\) Hz, 2H), 7.26 – 7.20 (m, 2H), 7.19 – 7.13 (m, 1H), 7.10–7.04 (m, 2H), 2.91 (bs, 3H), 2.74 (bs, 3H), 2.65 – 2.53 (m, 1H), 2.39 – 2.26 (m, 2H), 2.30 (s, 3H), 2.25 – 2.12 (m, 1H), 1.97 (bs, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 171.7, 150.4, 146.9, 141.6, 128.6\) (2C), 128.4 (2C), 126.8 (2C), 126.1, 123.9 (2C), 68.5, 37.6, 36.5, 29.5 (2C), 29.4; HRMS (ESI): calculated for [M+H]+ (C19H23N3O3) m/z: 354.1812, found 354.1816; IR (neat, cm\(^{-1}\)): 2995, 2876, 2798, 1625, 1603, 1519, 1401, 1346, 1109, 854.

HRMS (ESI): calculated for [M+H]+ (C20H24N3O3) m/z: 354.1812, found 354.1816; IR (neat, cm\(^{-1}\)): 2995, 2876, 2798, 1625, 1603, 1519, 1401, 1346, 1109, 854.
m/z: 342.1813, found 342.1813. **IR (neat, cm⁻¹):** 2928, 2857, 1666, 1634, 1601, 1518, 1385, 1345, 1256, 1091, 855, 701, 659.
NMR Spectra

$^1$H NMR
CDCl$_3$
700 MHz

$^{13}$C NMR
CDCl$_3$
176 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
176 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR
CDCl$_3$
600 MHz

$^{13}C$ NMR
CDCl$_3$
151 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR
CDCl$_3$
600 MHz

$^{13}C$ NMR
CDCl$_3$
151 MHz
$^{1}$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR  
CDCl$_3$  
600 MHz

$^{13}C$ NMR  
CDCl$_3$  
151 MHz

1db
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR
CDCl$_3$
600 MHz

$^{13}C$ NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR
CDCl$_3$
600 MHz

1f

$^{13}C$ NMR
CDCl$_3$
151 MHz

1f
$\text{H NMR}$

$\text{CDCl}_3$

$600 \text{ MHz}$

$\text{13C NMR}$

$\text{CDCl}_3$

$151 \text{ MHz}$
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR
CDCl$_3$
400 MHz

$^{13}C$ NMR
CDCl$_3$
100 MHz
$^1$H NMR  
CDCl$_3$,  
600 MHz

$^{13}$C NMR  
CDCl$_3$,  
151 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz
$^1\text{H NMR}$
$\text{CDCl}_3$
$600\text{ MHz}$

$^1\text{C NMR}$
$\text{CDCl}_3$
$151\text{ MHz}$

2e
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR
CDCl$_3$
600 MHz

$^{13}C$ NMR
CDCl$_3$
151 MHz
$^{1}{H}$ NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^1$H NMR  
CDCl$_3$  
400 MHz

$^{13}$C NMR  
CDCl$_3$  
100 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz

2l
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz
$^{1}H$ NMR
CDCl$_3$
400 MHz

$^{13}C$ NMR
CDCl$_3$
100 MHz
$^1$H NMR  
CDCl$_3$  
600 MHz

$^{13}$C NMR  
CDCl$_3$  
151 MHz
**$^1$H NMR**  
CDCl$_3$  
600 MHz

**$^{13}$C NMR**  
CDCl$_3$  
151 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR
$CDCl_{3}$
$600$ MHz

$^{13}C$ NMR
$CDCl_{3}$
$151$ MHz

[Diagram showing NMR spectra]
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$\text{H NMR}$

$\text{CDCl}_3$

$600 \text{ MHz}$

$\text{C NMR}$

$\text{CDCl}_3$

$151 \text{ MHz}$
$^{1}$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz
$^{1}H$ NMR 
$CDCl_{3}$
600 MHz

$^{13}C$ NMR 
$CDCl_{3}$
151 MHz
$^{1}$H NMR  
CDCl$_3$  
600 MHz

$^{13}$C NMR  
CDCl$_3$  
151 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
151 MHz


$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz

3o
$^{1}H$ NMR
CDCl$_3$
400 MHz

$^{13}C$ NMR
CDCl$_3$
100 MHz
^1H NMR
CDCl\textsubscript{3}
400 MHz

\[
\begin{array}{c}
\text{4d}
\end{array}
\]

^13C NMR
CDCl\textsubscript{3}
100 MHz

\[
\begin{array}{c}
\text{4d}
\end{array}
\]
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz
$^{1}H$ NMR  
CDCl$_3$  
400 MHz

$^{13}C$ NMR  
CDCl$_3$  
100 MHz
$\text{H NMR}$

$\text{CDCl}_3$

$400 \text{ MHz}$

$\text{C NMR}$

$\text{CDCl}_3$

$100 \text{ MHz}$

$\text{H}_2\text{O}$
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz
$^1\text{H NMR}$

CDCl$_3$

400 MHz

$^{13}\text{C NMR}$

CDCl$_3$

175 MHz
$\text{H NMR} \quad \text{CDCl}_3 \quad 400 \text{ MHz}$

$\text{C NMR} \quad \text{CDCl}_3 \quad 175 \text{ MHz}$
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
175 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
175 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
175 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
100 MHz
$^{1}H$ NMR  
CDCl$_3$  
600 MHz

$^{13}$C NMR  
CDCl$_3$  
151 MHz
$^1$H NMR
CDCl$_3$
600 MHz

$^1$C NMR
CDCl$_3$
176 MHz
$^1\text{H NMR}$

CDCl$_3$

400 MHz

$^{13}\text{C NMR}$

CDCl$_3$

100 MHz
$^1$H NMR
CDCl$_3$
400 MHz

$^{13}$C NMR
CDCl$_3$
150 MHz
$\text{NMR}$

$\text{CDCl}_3$

$400 \text{ MHz}$

$\text{H NMR}$

$\text{CDCl}_3$

$100 \text{ MHz}$

$\text{C NMR}$

$\text{CDCl}_3$

$100 \text{ MHz}$
References

[1] Peng, B.; Geerdink, D.; Farès, C.; Maulide, N. Chemoselective Intermolecular α-Arylation of Amides. *Angew. Chem. Int. Ed.* **2014**, *53*, 5462–5466.

[2] Zhou, X.; Zhang, G.; Gao, B.; Huang, H. Palladium-Catalyzed Hydrocarbonylative C–N Coupling of Alkenes with Amides. *Org. Lett.*, **2018**, *20*, 2208–2212.

[3] Tona, V.; de la Torre, A.; Padmanaban, M.; Ruider, S.; González, L.; Maulide, N. Chemo- and Stereoselective Transition-Metal-Free Amination of Amides with Azides. *J. Am. Chem. Soc.* **2014**, *138*, 8348–8351.

[4] Zhang, F. et al. Cu-Catalyzed Cascades to Carbocycles: Union of Diaryliodonium Salts with Alkenes or Alkynes Exploiting Remote Carbocations. *J. Am. Chem. Soc.* **2014**, *136*, 8851–8854.

[5] de la Torre, A.; Kaiser, D.; Maulide, N. Flexible and Chemoselective Oxidation of Amides to α-Keto Amides and α-Hydroxy Amides. *J. Am. Chem. Soc.* **2017**, *139*, 6578–6581.

[6] Zultanski, S. L.; Zhao, J.; Stahl S. S. Practical Synthesis of Amides via Copper/ABNO-Catalyzed Aerobic Oxidative Coupling of Alcohols and Amines. *J. Am. Chem. Soc.* **2016**, *138*, 6416–6419.

[7] Feldman, K. S.; Folda, T. S. Studies on the Synthesis of the Alkaloid (−)-Gilbertine via Indolidene Chemistry. *J. Org. Chem.* **2016**, *81*, 4566–4575.

[8] Saidykhan, A.; Bowen, R. D.; Gallagher, R. T.; Martin, W. H. C. Intramolecular NC Rearrangements Involving Sulfonamide Protecting Groups. *Tetrahedron Lett.* **2015**, *56*, 66–68.

[9] Gioiello, A.; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R. Building a Sulfonamide Library by Eco-Friendly Flow Synthesis. *ACS Comb. Sci.* **2013**, *15*, 235–239.

[10] Chow, S. Y.; Stevens, M. Y.; Odell, L. R. Sulfonyl Azides as Precursors in Ligand-Free Palladium-Catalyzed Synthesis of Sulfonyl Carbamates and Sulfonyl Ureas and Synthesis of Sulfonamides. *J. Org. Chem.* **2016**, *81*, 2681–2691.

[11] Brockway, A. J.; Cosner, C. C.; Volkov, O. A.; Phillips, M. A.; De Brabander, J. K. Improved Synthesis of MDL 73811 – A Potent AdoMetDC Inhibitor and Anti-Trypanosomal Compound. *Synthesis* **2016**, *48*: 2065–2068.

[12] Liang, R.; Li, S.; Wang, R.; Lu, L.; Li, F. N-Methylation of Amines with Methanol Catalyzed by a Cp*Ir Complex Bearing a Functional 2,2′-Bibenzimidazole Ligand. *Org. Lett.* **2017**, *19*, 5790–5793.

[13] Wright, S. W.; Hallstrom, K. N. A Convenient Preparation of Heteroaryl Sulfonamides and Sulfonyl Fluorides from Heteroaryl Thiols. *J. Org. Chem.* **2006**, *71*, 1080–1084.
X-ray Analysis

The X-ray intensity data were measured on Bruker X8 APEX2 diffractometer equipped with multilayer monochromator, Mo Kα INCOATEC micro focus sealed tube and Cryoflex cooling device. The structure was solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted at calculated positions and refined with riding model. The following software was used: Bruker SAINT software package<sup>b</sup> using a narrow-frame algorithm for frame integration, SADABS<sup>c</sup> for absorption correction, OLEX2<sup>d</sup> for structure solution, refinement, molecular diagrams and graphical user-interface, Shexle<sup>ε</sup> for refinement and graphical user-interface SHELXS-2015<sup>f</sup> for structure solution, SHELXL-2015<sup>g</sup> for refinement, PLATON<sup>h</sup> for symmetry check. Experimental data and CCDC-Codes Experimental data and CCDC-Code (Available online: http://www.ccdc.cam.ac.uk/conts/retrieving.html) can be found in Table S1. Crystal data, data collection parameters, and structure refinement details are given in Tables S2 and S3. Crystal structure is visualized in Figure S1.

**Table S1** Experimental parameter and CCDC-Code.

| Sample | Machine | Source | Temp. | Detector Distance | Time/Frame | #Frames | Frame width | CCDC  |
|--------|---------|--------|-------|-------------------|------------|---------|-------------|-------|
| 7c     | X8      | Mo     | 100   | 35                | 4          | 1073    | 0.500       | 1898975 |

<sup>a</sup> Bruker SAINT v8.38B Copyright © 2005-2019 Bruker AXS
<sup>b</sup> Sheldrick, G. M. (1996). SADABS. University of Göttingen, Germany.
<sup>c</sup> Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H., OLEX2, (2009), J. Appl. Cryst. 42, 339-341
<sup>d</sup> C. B. Huebschle, G. M. Sheldrick and B. Dittrich, ShelXle: a Qt graphical user interface for SHELXL, J. Appl. Cryst., 44, (2011) 1281-1284
<sup>e</sup> Sheldrick, G. M. (2015). SHELXS v 2016/4 University of Göttingen, Germany.
<sup>f</sup> Sheldrick, G. M. (2015). SHELXL v 2016/4 University of Göttingen, Germany.
<sup>g</sup> A. L. Spek, Acta Cryst. 2009, D65, 148-155.
2-(Methylamino)-2-(4-nitrophenyl)-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one 7b

Figure S1 Crystal structure, drawn with 50% displacement ellipsoid. The bond precision for C-C single bonds is 0.0048Å. The chiral orientation could not be determined (visualized R).

Table S2 Sample and crystal data.

| Chemical formula | C20H23N3O3 | Crystal system | orthorhombic |
|------------------|-------------|----------------|--------------|
| Formula weight [g/mol] | 353.41 | Space group | P2₁2₁2₁ |
| Temperature [K] | 100 | Z | 4 |
| Measurement method | \( f \) and \( w \) scans | Volume [Å³] | 1819.4(2) |
| Radiation (Wavelength [Å]) | MoKα (\( \lambda = 0.71073 \)) | Unit cell dimensions [Å] and [°] | 6.3111(4), 90 |
| Crystal size / [mm³] | 0.35 \times 0.18 \times 0.07 | 9.3707(5), 90 |
| Crystal habit | clear colourless plate | 30.764(3), 90 |
| Density (calculated) / [g/cm³] | 1.29 | Absorption coefficient / [mm⁻¹] | 0.088 |
| Abs. correction Tmin | 0.97 | Abs. correction Tmax | 0.994 |
| Abs. correction type | multiscan | F(000) [e⁻] | 752 |
Table S3 Data collection and structure refinement.

| Index ranges          | -7 ≤ h ≤ 7, -11 ≤ k ≤ 11, -36 ≤ l ≤ 37 | Theta range for data collection [°] | 4.544 to 50.68 |
|-----------------------|----------------------------------------|-------------------------------------|-----------------|
| Reflections number    | 13667                                   | Data / restraints / parameters      | 3331/0/239      |
| Refinement method     | Least squares                          | Final R indices                     | all data        |
| Function minimized    | Σ w(Fo^2 - Fc^2)^2                     | R1 = 0.0572, wR2 = 0.1099           |
| Goodness-of-fit on F^2| 1.063                                   | I>2σ(I)                             | R1 = 0.0460, wR2 = 0.1023 |
| Largest diff. peak and hole [e Å^3] | 0.29/-0.21                              | Weighting scheme                    | w=1/[σ^2(Fo^2)+(0.0264P)^2 +0.7427P] |
|                       |                                        |                                     | where P=(Fo^2+2Fc^2)/3  |
Computational details

The conformational space of all flexible molecules has been initially searched using the OPLS_2005 force field and the systematic Monte Carlo conformers search routine implemented in MACROMODEL 11.5.

To consider the flexibility of the complexes composed of individual fragments (e.g. the complex of a cation with the negatively charged TfO⁻ counterion), the electrostatic potential of the ions has been studied applying natural bond orbital (NBO) population analysis. The reciprocal positions of the fragments have been determined based on the calculated NBO charges. The obtained complexes have been used to restrict further the conformational search and obtain the set of complexes that will be reoptimized using density functional theory (DFT) methods.

Accordingly, the structures located at force field level have then been subjected to B3LYP-D3/def2-SVP (using def2-ECP for iodine atom) geometry optimization. The “Ultrafine” integration grid has been applied. The nature of all stationary points (minima and transition states) was verified through the computation of the vibrational frequencies. The thermal corrections to the Gibbs free energy were combined with the single point energies calculated at the DLPNO-CCSD(T)/def2-TZVP (using “TightPNO” settings) to yield DLPNO-CCSD(T)//DFT Gibbs free energies (”G_{298}”) at 298.15 K. All energies are reported in kcal mol⁻¹.

The density-based solvation model SMD was applied to consider solvent (DCM) effects for both geometries and energies. Solvation factors (for the Gibbs free energies at the DLPNO-CCSD(T)//DFT level of theory) have been calculated by single point energies in gas phase of the optimized geometries in solution. Free energies in solution have been corrected to a reference state of 1 mol l⁻¹ at 298.15 K through addition of RTln(24.46) = +7.925 kJ mol⁻¹ to the gas phase (1 atm) free energies.

The DFT calculations have been performed with the Gaussian09 program package. The ORCA 4.0.1 software was applied for the DLPNO-CCSD(T) computations.

References

(1) Banks, J. L.; Beard, H. S.; Cao, Y.; Cho, A. E.; Damm, W.; Farid, R.; Felts, A. K.; Halgren, T. A.; Mainz, D. T.; Maple, J. R.; Murphy, R.; Philipp, D. M.; Repasky, M. P.; Zhang, L. Y.; Berne, B. J.; Friesner, R. A.; Gallicchio, E.; Levy, R. M. J. Comput. Chem. 2005, 26 (16), 1752–1780.

(2) MacroModel, Schrödinger, LLC, New York, NY, 2018.

(3) Becke, A. J. Chem. Phys. 1993, 98, 5648–5652.

(4) Lee, C.; Yang, W.; Parr, R. G. Phys. Rev. B 1988, 37 (2), 785–789.

(5) Vosko, S. H.; Wilk, L.; Nusair, M. Can. J. Phys. 1980, 58 (8), 1200–1211.

(6) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. J. Phys. Chem. 1994, 98 (45), 11623–11627.

(7) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. J. Chem. Phys. 2010, 132 (15), 154104.

(8) Weigend, F.; Ahlrichs, R. Phys. Chem. Chem. Phys. 2005, 7 (18), 3297–3305.

(9) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M. J. Chem. Phys. 2003, 119 (21), 11113–11123.

(10) Riplinger, C.; Neese, F. J. Chem. Phys. 2013, 138 (3), 34106.

(11) Riplinger, C.; Sandhoefer, B.; Hansen, A.; Neese, F. J. Chem. Phys. 2013, 139 (13), 134101.

(12) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. J. Phys. Chem. B 2009, 113 (18), 6378–6396.
The mechanism of the transformation from $C(I)$ to $D$

In order to check whether the transformation from $C(I)$ to $D$ is concerted or stepwise (through addition/elimination mechanism), we have performed a relaxed potential energy surface scan starting from the intermediate $C(I)$ and leading to the product $D$. The results are presented in Figure S2 below.

The distance $C_1-O_1$ was gradually decreased with the step of 0.025 Å, while all other structural parameters were fully optimized at each step. One can see that going via conformational change ($C(I)_a$, $C(I)_b$ and $C(I)_c$) and overcoming a barrier with the transition state $TS_{C(I)-D}$ the product $D$ is obtained without any additional intermediate (this intermediate would be necessary for the addition/elimination mechanism). Thus, we can conclude that the $C(I)\rightarrow D$ step is concerted and has the single transition state $TS_{C(I)-D}$.

Figure S2 The relaxed potential energy surface scan for the reaction $C(I)\rightarrow D$ (B3LYP-D3-SMD/def2-SVP, ultrafine integration grid)
Coordinates of the most stable \( \Delta G_{298, \text{DCM}} \) conformations as computed at the DLPNO-CCSD(T)/def2-TZVP//B3LYP-D3/def2-SVP level of theory

|  | \( C \) | \( H \) | \( O \) |
|---|---|---|---|
| \( A \) | -4.89487 | 0.14582 | 0.04982 |
| \( H \) | -4.96668 | -0.77164 | -0.55449 |
| \( H \) | -5.35520 | -0.06874 | 1.03195 |
| \( C \) | -3.47167 | 0.60635 | 0.17602 |
| \( H \) | -3.29346 | 1.64385 | 0.46649 |
| \( C \) | -2.42106 | -0.20945 | -0.02189 |
| \( N \) | -2.42234 | -1.56175 | -0.19281 |
| \( C \) | -2.96723 | -2.46471 | 0.83883 |
| \( H \) | -4.01074 | -2.74923 | 0.60979 |
| \( H \) | -2.96452 | -1.97190 | 1.82351 |
| \( C \) | -1.45707 | -2.25511 | -1.07024 |
| \( H \) | -1.66366 | -2.03059 | -2.13012 |
| \( H \) | -0.42567 | -1.94233 | -0.85366 |
| \( C \) | -1.66954 | -3.73192 | -0.72248 |
| \( H \) | -0.77413 | -4.33639 | -0.92993 |
| \( H \) | -2.50721 | -4.15168 | -1.30534 |
| \( C \) | -2.03793 | -3.68044 | 0.76607 |
| \( H \) | -1.13171 | -3.49073 | 1.36498 |
| \( H \) | -2.51332 | -4.60133 | 1.13630 |
| \( O \) | -1.06411 | 0.25974 | -0.01657 |
| \( N \) | -0.87340 | 1.61005 | -0.01388 |
| \( C \) | -0.73929 | 2.22057 | -1.22227 |
| \( C \) | -0.64702 | 2.18687 | 1.19832 |
| \( C \) | -0.46761 | 3.58541 | -1.21050 |

\( \Delta G_{298, \text{DCM}} \) \( \approx \sum_{\text{conf}} \text{Conformation Energy} \) for \( A \) and \( B \) are:

|  | \( A \) | \( B \) |
|---|---|---|
| \( C \) | -0.37255 | 5.5084 |
| \( H \) | -0.19818 | 4.04266 |
| \( C \) | -0.29712 | 4.25341 |
| \( H \) | -0.36738 | 4.10443 |
| \( H \) | -0.07698 | 5.32324 |

\( \Delta G_{298, \text{DCM}} \) for \( \text{TS}_{A-B} \):

|  | \( \text{TS}_{A-B} \) |
|---|---|
| \( C \) | 4.93060 |
| \( H \) | 6.01564 |
| \( H \) | 4.72056 |
| \( C \) | 4.16772 |
| \( H \) | 4.59762 |
| \( C \) | 2.98282 |
**Lutidine**

| Element | X | Y | Z |
|---------|---|---|---|
| N       | -0.00001 | -0.94113 | 0.00004 |
| C       | 1.16140 | -0.26855 | 0.00554 |
| C       | -1.16141 | -0.26853 | -0.00550 |
| C       | 1.20296 | 1.13532 | 0.00719 |
| C       | -1.20295 | 1.13533 | -0.00718 |
| C       | -2.16232 | 1.65775 | -0.01245 |
| C       | 0.00001 | 1.84276 | -0.26855 |
| C       | 1.20296 | 1.13532 | -0.26853 |
| C       | -2.39043 | 1.84953 | 0.80146 |
| C       | 2.50687 | 1.65103 | -0.95330 |
| C       | 2.32223 | -0.47990 | 0.12028 |
| C       | -2.42027 | -1.09675 | 0.00296 |
| C       | -2.39042 | -1.84943 | -0.80159 |
| C       | -2.50690 | -1.65111 | 0.95320 |
| C       | -3.32225 | -0.47989 | -0.12028 |
| C       | 3.01903 | -0.10396 | 0.22960 |
| H       | -0.25914 | 3.48141 | -0.96147 |
| H       | 0.38532 | 2.48516 | -1.89957 |
| C       | -0.50991 | 1.92151 | -0.10459 |
| H       | 0.33781 | 1.85860 | 0.57832 |
| C       | -1.69217 | 1.22059 | 0.30733 |
| N       | -2.39354 | 0.14519 | 0.15415 |
| C       | -2.03580 | -1.03750 | -0.66360 |
| H       | -1.36399 | -1.67328 | -0.06884 |
| H       | -1.50655 | -0.72856 | -1.57149 |

**TS\(_{B'-C(O)}\)**

| Element | X | Y | Z |
|---------|---|---|---|
| C       | -0.46586 | 2.81540 | -1.28414 |
| H       | -0.25914 | 3.48141 | -0.96147 |
| H       | 0.38532 | 2.48516 | -1.89957 |
| C       | -0.50991 | 1.92151 | -0.10459 |
| H       | 0.33781 | 1.85860 | 0.57832 |
| C       | -1.69217 | 1.22059 | 0.30733 |
| N       | -2.39354 | 0.14519 | 0.15415 |
| C       | -2.03580 | -1.03750 | -0.66360 |
| H       | -1.36399 | -1.67328 | -0.06884 |
| H       | -1.50655 | -0.72856 | -1.57149 |

**C(O)**

| Element | X | Y | Z |
|---------|---|---|---|
| C       | 0.34927 | 2.36617 | 1.50419 |
| H       | 0.79278 | 3.31601 | 1.17114 |
| H       | -0.61775 | 2.57475 | 1.98521 |
| C       | 0.14733 | 1.47590 | 0.29281 |
| H       | -0.53379 | 1.95172 | -0.42509 |
| C       | 1.45131 | 1.23135 | -0.48158 |
| N       | 2.25028 | 0.19108 | -0.16383 |
| C       | 3.50051 | 0.00358 | -0.92151 |
| H       | 4.16488 | 0.86949 | -0.75592 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| H | 3.29087 | -0.04457 | -2.00070 | H | 1.43100 | 2.86151 | 0.06903 |
| C | 2.14222 | -0.76844 | 0.95233 | H | 0.07680 | 3.88968 | 0.63441 |
| H | 1.75893 | -0.28760 | 1.86105 | C | -0.95140 | 1.29758 | -1.10036 |
| H | 1.45610 | -1.59177 | 0.69396 | H | -0.78264 | 0.21722 | -1.11599 |
| C | 3.57571 | -1.28431 | 1.10082 | H | -2.03056 | 1.50747 | -1.14684 |
| H | 3.61270 | -2.27098 | 1.58535 | C | -0.17133 | 2.05757 | -2.17443 |
| H | 4.16662 | -0.58039 | 1.71102 | H | -0.72065 | 2.09677 | -3.12577 |
| C | 4.08598 | -1.28839 | -0.34521 | H | 0.79532 | 1.55922 | -2.34051 |
| H | 3.68052 | -2.16100 | -0.88387 | C | 0.05598 | 3.43920 | -1.54392 |
| H | 5.18237 | -1.32034 | -0.42437 | H | -0.86058 | 4.04867 | -1.60762 |
| O | 1.74018 | 2.04849 | -1.35277 | H | 0.87502 | 4.00042 | -2.01538 |
| S | -1.22538 | -0.74560 | -0.24270 | O | -0.10468 | 1.76070 | 2.46854 |
| O | -1.16475 | -2.07936 | 0.32682 | H | 0.66664 | -1.10804 | 1.68901 |
| O | -0.48661 | 0.24559 | 0.79014 | C | -2.71188 | -1.93408 | -0.36910 |
| O | -0.84263 | -0.45171 | -1.61610 | C | -3.73408 | -2.37431 | -1.22674 |
| C | -2.98835 | -0.12822 | -0.02293 | C | -4.91964 | -1.64712 | -1.30368 |
| F | -3.41276 | -0.41505 | 1.19735 | C | -5.05473 | -0.49651 | -0.52739 |
| F | -3.01207 | 1.18852 | -0.20726 | C | -3.99540 | -0.10899 | 0.30673 |
| F | -3.76153 | -0.71915 | -0.92151 | N | -2.85522 | -0.82239 | 0.37685 |
| H | 1.02348 | 1.89799 | 2.23663 | H | -5.72863 | -1.96988 | -1.96445 |
| H | -3.58896 | -3.27754 | -1.82298 |   |   |   |   |

**TS_{\text{B}^\text{C(L)}}**

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | -0.17297 | -0.97986 | 2.37802 | O | 2.99131 | 0.91513 | -1.37883 |
| H | 0.20423 | -0.87758 | 3.40984 | S | 2.45993 | 0.03325 | -0.31779 |
| H | -0.83348 | -1.85733 | 2.37267 | O | 2.33607 | 0.65541 | 1.02242 |
| C | -0.99173 | 0.21344 | 2.06763 | O | 1.30882 | -0.81685 | -0.71705 |
| H | -1.95743 | 0.34366 | 2.55382 | C | 3.81605 | -1.23029 | -0.06116 |
| C | -0.49629 | 1.35195 | 1.33799 | F | 3.45966 | -2.11341 | 0.88327 |
| N | -0.41315 | 1.87248 | 0.15540 | F | 4.95329 | -0.64299 | 0.32686 |
| C | 0.36998 | 3.11025 | -0.08305 | F | 4.06125 | -1.90607 | -1.18979 |

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C  -1.42507 -2.70559  -0.26053  H  0.79448  -0.59656  -2.68431
H   -0.54812 -2.04475  -0.31399  C  -1.87176  -2.11438  0.82608
H   -1.37623 -3.24321   0.70132  C  -2.91572  -2.95555  1.23765
H   -1.34797 -3.45544  -1.06100  C  -4.18480  -2.79404  0.68655
C   -4.10373  1.13668  1.14840  C  -4.38451  -1.79069  -0.25789
H   -5.03982  1.67571  0.94587  C  -3.30905  -0.97168  -0.63356
H   -4.08477  0.89248  2.22366  N  -2.08526  -1.14981  -0.09535
H   -3.26555  1.82242  0.94800  H  -5.00992  -3.44243  0.99222
             H  -2.72097  -3.72742  1.98445

TS_{C(O)-C(L)}
C   0.09274  -1.05081  -1.97069  O  1.78051  0.72199  -0.85819
H   0.48446  -2.01555  -1.62965  S  2.68624  0.47929  0.34008
H  -0.85219  -1.19795  -2.51151  O  3.76032  1.46817  0.44384
C  -0.11031  -0.10659  -0.84237  O  1.95009  0.11489  1.56607
H   0.11704  -0.37434  0.17639  C  3.54219  -1.11344  -0.14753
C  -0.67478  1.26216  -1.15748  F  2.63840  -2.08991  -0.31675
N  -1.03295  2.03573  -0.11507  F  4.39386  -1.48861  0.80662
C  -1.51540  3.40287  -0.34989  F  4.21321  -0.95865  -1.28800
H  -2.54506  3.37072  -0.75104  C  -0.49909  -2.27434  1.42489
H  -0.88730  3.90293  -1.10152  H  0.25569  -2.51689  0.66181
C  -0.94978  1.71385  1.31946  H  -0.16272  -1.35396  1.92646
H  -1.39203  0.73008  1.52659  H  -0.49669  -3.08279  2.16808
H  0.10321  1.68640  1.63982  C  -3.51718  0.13986  -1.62262
C  -1.72301  2.86033  1.97864  H  -2.75878  0.13051  -2.41601
H  -1.39601  3.03858  3.01330  H  -4.51302  0.07189  -2.08096
H  -2.80015  2.62342  1.99777  H  -3.43843  1.11634  -1.11881
C  -1.46171  4.04472  1.03920
H  -0.45505  4.45594  1.22170  C(L)
H  -2.18882  4.86203  1.15148  C  -0.80713  -0.01624  1.86063
O  -0.77110  1.61995  -2.32973  H  -1.65996  -0.00934  2.54877

S149
|    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|
| H  | -0.34041 | -1.00784 | 1.90432 | O  | 2.58777 | -1.13292 | 1.95670 |
| C  | -1.18336 | 0.27228 | 0.39826 | O  | 1.50466 | -1.48288 | -0.27293 |
| H  | -0.42125 | -0.24141 | -0.18648 | C  | 3.98352 | -0.62177 | -0.23670 |
| C  | -2.56445 | -0.26330 | -0.02798 | F  | 3.88406 | -0.13809 | -1.48358 |
| N  | -2.69806 | -1.60335 | -0.07941 | F  | 4.46589 | -1.86773 | -0.31279 |
| C  | -3.98532 | -2.18944 | -0.49229 | F  | 4.86978 | 0.12840 | 0.42896 |
| H  | -4.21706 | -1.87308 | -1.52395 | C  | -2.41416 | 2.46166 | 1.96769 |
| H  | -4.80113 | -1.82452 | 0.15029 | H  | -1.76481 | 2.26934 | 2.83434 |
| C  | -1.67138 | -2.63884 | 0.13738 | H  | -3.00706 | 3.35793 | 2.19230 |
| H  | -0.68200 | -2.32008 | -0.21758 | H  | -3.10172 | 1.61907 | 1.83883 |
| H  | -1.58467 | -2.86699 | 1.21434 | C  | -0.00724 | 0.83583 | -2.11089 |
| C  | -2.23895 | -3.84036 | -0.62095 | H  | 0.36587 | 1.25299 | -3.05445 |
| H  | -1.82441 | -4.79342 | -0.26137 | H  | 0.79547 | 0.24292 | -1.65156 |
| H  | -2.00596 | -3.74889 | -1.69541 | H  | -0.84151 | 0.15510 | -2.34202 |
| C  | -3.74967 | -3.70111 | -0.38981 |    |    |    |    |
| H  | -4.00780 | -4.05573 | 0.62187 | 2-Iodopyridine |
| H  | -4.35863 | -4.26614 | -1.11048 | C  | 0.60298 | -0.00896 | 0.00061 |
| O  | -3.48675 | 0.50399 | -0.30369 | C  | 1.27798 | 1.21941 | 0.00016 |
| H  | -0.04263 | 0.69503 | 2.19584 | C  | 2.67331 | 1.17624 | -0.00003 |
| C  | -1.61029 | 2.72009 | 0.72820 | C  | 3.31947 | -0.06467 | -0.00021 |
| C  | -1.40834 | 4.04002 | 0.32439 | C  | 2.53562 | -1.21955 | -0.00005 |
| C  | -0.70628 | 4.32863 | -0.83934 | N  | 1.19429 | -1.18546 | 0.00020 |
| C  | -0.24735 | 3.27500 | -1.62103 | H  | 3.24792 | 2.10625 | -0.00028 |
| C  | -0.44661 | 1.95633 | -1.21905 | H  | 0.73584 | 2.16583 | 0.00001 |
| N  | -1.07500 | 1.70477 | -0.02161 | H  | 4.40913 | -0.13707 | -0.00053 |
| H  | -0.54213 | 5.36354 | -1.14766 | H  | 3.00023 | -2.21152 | -0.00034 |
| H  | -1.82617 | 4.83771 | 0.93920 | I  | -1.55112 | -0.00453 | -0.00006 |
| H  | 0.26810  | 3.45763 | -2.56414 |    |    |    |    |
| O  | 1.93664  | 0.83581 | 0.54639 |    |    |    |    |
| S  | 2.31483  | -0.59762 | 0.61037 | C  | -0.82065 | 0.73896 | 2.22146 |
|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| H | -0.55336 | 1.38208 | 3.06956 | S | -3.11163 | 0.02132 | -0.50742 |
| H | -1.10251 | 1.34795 | 1.34801 | O | -2.16904 | 1.15771 | -0.69355 |
| C | 0.30346 | -0.14148 | 1.83819 | O | -3.75155 | -0.47493 | -1.74149 |
| H | 1.31836 | 0.04753 | 2.19191 | C | -4.51776 | 0.82402 | 0.43133 |
| C | 0.13341 | -1.35983 | 1.09815 | F | -5.47272 | -0.06665 | 0.72002 |
| N | 0.09897 | -1.86601 | -0.08980 | F | -4.07588 | 1.34713 | 1.58592 |
| C | -0.29061 | -3.27919 | -0.30712 | F | -5.06797 | 1.81019 | -0.28569 |
| H | -1.32268 | -3.39708 | 0.05785 | I | 3.77849 | -0.45945 | 0.39126 |
| H | 0.37221 | -3.94994 | 0.25822 | H | -0.25488 | 2.54973 | -0.17254 |
| C | 0.18041 | -1.10512 | -1.35690 |  |  |  |  |
| H | -0.29530 | -0.12621 | -1.23956 | TS_{C(O)\rightarrow C(I)} |  |  |  |
| H | 1.24251 | -0.96762 | -1.61235 | C | -0.24973 | -0.30221 | 2.41429 |
| C | -0.53460 | -2.02785 | -2.34627 | H | -0.23513 | 0.44396 | 3.21830 |
| H | -0.19938 | -1.85409 | -3.37861 | H | -1.20642 | -0.84195 | 2.42242 |
| H | -1.61902 | -1.84381 | -2.29985 | C | -0.08325 | 0.34080 | 1.08520 |
| C | -0.20020 | -3.43344 | -1.82759 | H | -0.08262 | -0.28964 | 0.20101 |
| H | 0.82492 | -3.71538 | -2.11925 | C | 0.10444 | 1.83986 | 0.97123 |
| H | -0.88663 | -4.20839 | -2.19677 | N | 0.25502 | 2.35096 | -0.26330 |
| O | 0.01578 | -1.88094 | 2.24903 | C | 0.36859 | 3.80605 | -0.44207 |
| H | -1.71198 | 0.13595 | 2.43979 | H | 1.17775 | 4.21011 | 0.18546 |
| C | 2.77210 | 1.34137 | -0.21926 | H | -0.57019 | 4.28690 | -0.11626 |
| C | 3.51027 | 2.32473 | -0.89031 | C | 0.26121 | 1.63571 | -1.54691 |
| C | 2.82246 | 3.46655 | -1.30560 | H | 1.26122 | 1.20607 | -1.73502 |
| C | 1.45161 | 3.57183 | -1.04889 | H | -0.46388 | 0.81420 | -1.56527 |
| C | 0.82028 | 2.52984 | -0.37033 | C | -0.07583 | 2.73915 | -2.55107 |
| N | 1.48270 | 1.43797 | 0.04271 | H | -1.16925 | 2.88148 | -2.57549 |
| H | 3.35521 | 4.26235 | -1.83249 | H | 0.26321 | 2.49722 | -3.56875 |
| H | 4.57657 | 2.19871 | -1.08171 | C | 0.61112 | 3.97084 | -1.94703 |
| H | 0.87746 | 4.44290 | -1.37068 | H | 0.21795 | 4.92410 | -2.32900 |
| O | -2.64510 | -1.02894 | 0.43187 | H | 1.69268 | 3.93994 | -2.16089 |

S151
| Atom | X     | Y     | Z     | Atom | X     | Y     | Z     |
|------|-------|-------|-------|------|-------|-------|-------|
| O    | 0.12658 | 2.52853 | 1.99192 | C    | -4.74250 | -0.74938 | 0.80903 |
| H    | 0.53873  | -1.05071 | 2.57466 | H    | -5.07083 | 0.15184  | 0.26129 |
| C    | 2.83241  | -0.77275 | 0.26663 | H    | -4.98509 | -0.59555 | 1.87071 |
| C    | 4.22771  | -0.90217 | 0.29404 | C    | -2.97735 | -2.06396 | -0.25061 |
| C    | 4.95282  | -0.03424 | 1.11009 | H    | -2.21551 | -1.78653 | -0.99328 |
| C    | 4.27023  | 0.92401  | 1.86491 | H    | -2.59258 | -2.91841 | 0.33260 |
| C    | 2.88293  | 0.97980  | 1.76791 | C    | -4.33125 | -2.39219 | -0.88971 |
| N    | 2.18660  | 0.14516  | 0.97798 | H    | -4.39354 | -3.44084 | -1.21465 |
| H    | 6.04206  | -0.11010 | 1.15481 | H    | -4.49092 | -1.75163 | -1.77327 |
| H    | 4.72506  | -1.66435 | -0.30681 | C    | -5.33535 | -2.02818 | 0.21171 |
| H    | 4.79829  | 1.62012  | 2.51900 | H    | -5.36225 | -2.82273 | 0.97620 |
| O    | -2.09583 | 0.74010  | 0.74906 | H    | -6.35952 | -1.88103 | -0.16070 |
| S    | -2.83113 | 0.00066  | -0.35749 | O    | -2.78159 | 0.86214  | 1.92821 |
| O    | -3.65238 | 0.88143  | -1.19315 | H    | -0.83995 | -1.07199 | 3.20126 |
| O    | -1.99652 | -1.01303 | -1.03009 | C    | -0.15173 | 1.66608  | 0.00734 |
| C    | -4.05943 | -1.00595 | 0.63402 | C    | 0.49667  | 2.89675  | 0.05010 |
| F    | -3.41986 | -1.75962 | 1.53609 | C    | 1.11020  | 3.32059  | 1.22589 |
| F    | -4.74749 | -1.81057 | -0.17701 | C    | 1.05887  | 2.49873  | 2.34973 |
| F    | -4.91348 | -0.20916 | 1.27501 | C    | 0.40439  | 1.28466  | 2.26116 |
| H    | 2.29874  | 1.71324  | 2.33002 | N    | -0.18789 | 0.87141  | 1.11505 |
| I    | 1.72324  | -2.12188 | -0.96052 | H    | 1.62548  | 4.28291  | 1.25639 |
| H    | 0.52653  | 3.51220  | -0.84850 | C(l) | H     | 1.52648  | 2.77976  | 3.29372 |
| C    | -0.50948 | -1.39819 | 2.20417 | O    | 2.81895  | 0.85624  | -0.33989 |
| H    | -0.99314 | -2.36324 | 1.99544 | S    | 2.62175  | -0.51478 | 0.17709 |
| H    | 0.57920  | -1.54335 | 2.18813 | O    | 2.69409  | -0.65000 | 1.65345 |
| C    | -0.93033 | -0.42841 | 1.10339 | O    | 1.53023  | -1.28378 | -0.46959 |
| H    | -0.67218 | -0.89343 | 0.14825 | C    | 4.15796  | -1.41648 | -0.39701 |
| C    | -2.42950 | -0.09439 | 1.24216 | F    | 4.14406  | -2.69346 | 0.00816 |
| N    | -3.29259 | -0.93232 | 0.63773 | F    | 5.26333  | -0.83919 | 0.09266 |
|   | X   | Y   | Z   |   | X   | Y   | Z   |
|---|-----|-----|-----|---|-----|-----|-----|
| F | 4.2452 | -1.40792 | -1.73411 | C | 0.50407 | -2.25344 | 0.69298 |
| H | 0.34600 | 0.61052 | 3.10972 | N | 1.17626 | -1.05486 | 0.60047 |
| I | -1.05843 | 1.09451 | -1.80733 | H | 1.68480 | -3.75039 | -2.09640 |
|   |   | 2.88714 | 1.58914 | -2.26858 |
| TS_{C(10-D)} | H | 0.16386 | -4.19378 | -0.11157 |
| C | 1.27371 | 0.77076 | 2.38932 | O | -2.83266 | -2.63108 | -0.13989 |
| H | 2.25717 | 1.18873 | 2.14670 | S | -2.64773 | -1.20134 | 0.16381 |
| H | 0.64298 | 1.56970 | 2.80509 | O | -2.40705 | -0.88466 | 1.60172 |
| C | 0.56334 | 0.15357 | 1.18282 | O | -1.78080 | -0.44446 | -0.77289 |
| H | -0.45695 | -0.11734 | 1.48213 | C | -4.34491 | -0.46756 | -0.13415 |
| C | 0.50055 | 1.05270 | -0.05066 | F | -4.35562 | 0.84676 | 0.14349 |
| N | -0.26542 | 2.11198 | -0.11510 | F | -5.26102 | -1.05833 | 0.63999 |
| C | -0.31774 | 2.94991 | -1.33205 | F | -4.71151 | -0.62217 | -1.41086 |
| H | -0.70566 | 2.33518 | -2.16096 | H | -0.21349 | -2.31998 | 1.51086 |
| H | 0.69232 | 3.29127 | -1.59907 | I | 4.05036 | 0.15848 | 0.05538 |
| C | -1.33236 | 2.46578 | 0.84848 |
| H | -1.83252 | 1.55809 | 1.21037 | D |
| H | -0.89233 | 3.00489 | 1.70223 | C | 1.27143 | -0.77080 | 2.43420 |
| C | -2.24971 | 3.37073 | 0.02140 | H | 0.98569 | -1.51448 | 3.19159 |
| H | -2.81882 | 4.06571 | 0.65488 | H | 2.28335 | -0.97378 | 2.06066 |
| H | -2.96493 | 2.74999 | -0.53902 | C | 0.24818 | -0.80653 | 1.30382 |
| C | -1.28453 | 4.06944 | -0.94467 | H | -0.76734 | -0.58092 | 1.67366 |
| H | -0.74071 | 4.87729 | -0.42751 | C | 0.50249 | 0.08815 | 0.11274 |
| H | -1.78420 | 4.50177 | -1.82307 | N | 0.49352 | 1.36416 | 0.03599 |
| O | 1.26242 | 0.71942 | -1.01423 | C | 0.63004 | 2.09702 | -1.25399 |
| H | 1.39133 | -0.00233 | 3.16291 | H | -0.28518 | 1.88378 | -1.82620 |
| C | 2.06744 | -0.79914 | -0.42057 | H | 1.51370 | 1.72153 | -1.78695 |
| C | 2.21136 | -1.79278 | -1.43796 | C | 0.30307 | 2.29193 | 1.18053 |
| C | 1.54686 | -2.98855 | -1.32487 | H | -0.46399 | 1.89085 | 1.85451 |
| C | 0.69977 | -3.25105 | -0.21571 | H | 1.27124 | 2.37255 | 1.69879 |

S153
|     | x     | y     | z     |
|-----|-------|-------|-------|
| C   | -0.09326 | 3.59410 | 0.48699 |
| H   | 0.12854  | 4.46684 | 1.11633 |
| H   | -1.17060 | 3.56816 | 0.26556 |
| C   | 0.71835  | 3.55832 | -0.81476 |
| H   | 1.76907  | 3.82733 | -0.62303 |
| H   | 0.32292  | 4.23023 | -1.58889 |
| O   | 0.67327  | -0.63464 | -1.00719 |
| H   | 1.25280  | 0.21926 | 2.90820 |
| C   | 0.46264  | -1.93891 | -0.71951 |
| C   | 0.49193  | -2.98933 | -1.61479 |
| C   | 0.23367  | -4.25561 | -1.08690 |
| C   | -0.03896 | -4.42464 | 0.28121 |
| C   | -0.04537 | -3.32398 | 1.11949 |
| N   | 0.21256  | -2.10777 | 0.59222 |
| H   | 0.24061  | -5.12277 | -1.75060 |
| H   | 0.70327  | -2.80949 | -2.66861 |
| H   | -0.24864 | -5.41094 | 0.69587 |
| O   | -2.50958 | 0.74922  | 1.42908 |
| S   | -2.74620 | 0.56711  | -0.02796 |
| O   | -2.59926 | 1.78659  | -0.85026 |
| O   | -2.10677 | -0.65410 | -0.58648 |
| C   | -4.57136 | 0.17534  | -0.12633 |
| F   | -4.94756 | 0.01345  | -1.39823 |
| F   | -5.29255 | 1.16651  | 0.40478 |
| F   | -4.84567 | -0.95065 | 0.54081 |
| H   | -0.24959 | -3.36294 | 2.19040 |
| I   | 4.13480  | 0.37577  | -0.13179 |