SUPPLEMENTARY MATERIAL

Synthesis of Non-Symmetrical & Axially-Chiral Dibenzo[1,3]diazepines: Direct Pd/CPhos-Catalysed Arylation of bis-Anilinomethylenes

Tim Wezeman[^a], Yuling Hu[^a], John McMurtrie[^c] Stefan Bräse[^a,b] Kye-Simeon Masters[^c]

[^a] T. Wezeman, Y. Hu, Prof. Dr. S. Bräse, Institute of Organic Chemistry (IOC), Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany), E-mail: braese@kit.edu

[^b] Prof. Dr. S. Bräse, Institute of Toxicology and Genetics (ITG), Karlsruhe Institute of Technology (KIT), Eggenstein-Leopoldshafen (Germany)

[^c] Prof. Dr. J. McMurtrie, Dr. K.-S. Masters,* Chemistry, Physics and Mechanical Engineering, Queensland University of Technology (QUT), GPO Box 2434, Brisbane, Queensland, 4001 (Australia), E-mail: kye.masters@qut.edu.au
Experimental Details and $^1$H/$^{13}$C-NMR Spectra

General

All chemicals and solvents were obtained from Aldrich and were used as supplied without further purification, unless otherwise noted. Column chromatography was performed on Davisil (LC60A, 40-63µm Grace). NMR data were recorded on a Varian Infinity-Plus 400 spectrometer ($^1$H at 400 MHz; $^{13}$C at 100 MHz), and resonances are reported in terms of chemical shift ($\delta$) in parts per million (ppm) referenced to the solvent peak; coupling constants ($J$) are given in Hertz (Hz) and the number of protons per signal as $n$H. Splitting is reported as br. = broad, s = singlet, d = doublet, dd = doublet of doublets and m = multiplet.

General procedure for acetylation of anilines.

Aniline (1.0 equiv.) is dissolved in dry THF (4 mL per mmol aniline) under argon before acetic anhydride (2 equiv.) is added slowly. The reaction mixture is stirred at room temperature until completion is observed by TLC. The reaction is poured on ice-cold water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. If needed, purification was by flash chromatography (SiO$_2$, hexanes:ethyl acetate mixes) to afford the $N$-acetyl aniline.
1: \(N\)-(3,5-Dimethylphenyl)acetamide:

\[
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{NH} \\
\text{O}
\end{array}
\]

Isolated as a colourless crystalline solid, 1.63 g, 100% yield,

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.16 (s, 1H), 7.12 (s, 2H), 6.75 (s, 1H), 2.29 (s, 6H), 2.15 (s, 3H).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 168.35, 138.82, 126.20, 117.76, 24.81, 21.50.

HRMS (+EI): calculated for \([C_{10}H_{13}NONa]^+\): 186.0889; found: 186.0831.

2a: \(N\)-(3,5-Dimethylphenyl)-\(N\)-((methylthio)methyl)acetamide

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

\(N\)-(3,5-Dimethylphenyl)acetamide (1.58 g, 9.66 mmol, 1.0 equiv.) was dissolved in dry DMF (25 ml) at 0 °C under argon. Fresh sodium hydride (60% in mineral oil, 1.16 g, 28.98 mmol, 3.0 equiv.) was added in portions of 100 mg and the suspension was stirred at room temperature for 1 hour before the reaction mixture was cooled to –5 °C. Chloromethyl methyl sulfide (1.32 mL, 14.50 mmol, 1.5 equiv. \textit{Caution: very smelly compound}) was added dropwise over 30 minutes with vigorous stirring (Note: faster addition led to poorer results). After the addition was complete the reaction mixture was allowed to slowly reach room temperature while stirring overnight. The reaction was quenched with brine (10 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated. Purification by flash chromatography (SiO\(_2\), hexanes:ethyl acetate gradient from 9:1 to 5:1) afforded the \(N\)-(3,5-dimethylphenyl)-\(N\)-((methylthio)methyl)acetamide as yellow oil (1.79 g, 8.03 mmol, 83% yield).

TLC (hexanes:ethyl acetate 2:1) \(R_f = 0.44\)

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.00 (s, 1H), 6.86 (s, 2H), 4.81 (s, 2H), 2.34 (s, 6H), 2.17 (s, 3H), 1.87 (s, 3H).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 170.79, 141.75, 139.37, 129.91, 125.85, 52.43, 22.62, 21.18, 15.40.

HRMS (+EI): calculated for \([C_{12}H_{17}NOSNa]^+\): 246.0923; found: 246.0919.

2b: \(N\)-((Methylthio)methyl)-\(N\)-phenylacetamide

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{Me} \\
\text{O}
\end{array}
\]
N-Phenylacetamide (2.03 g, 15.0 mmol, 1.0 equiv.) was dissolved in dry DMF (30 mL) at 0 °C under argon. Sodium hydride (60% in mineral oil, 1.80 g, 45.0 mmol, 3.0 equiv.) was added in portions of 100 mg and the suspension was stirred at room temperature for 1 hour before the reaction mixture was cooled to −5 °C; chloromethyl methyl sulfide (1.89 mL, 22.6 mmol, 1.5 equiv. Caution: very smelly compound) was added dropwise over 30 minutes under vigorous stirring (Note: faster addition led to poorer results). After the addition was complete the reaction mixture was allowed to slowly reach room temperature while stirring overnight. The reaction was quenched with brine (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate and concentrated. Purification by flash chromatography (SiO₂, hexanes:ethyl acetate gradient from 7:1 to 3:1) afforded the N-((methylthio)methyl)-N-phenylacetamide as yellow to orange oil that crystallized at −20 °C (2.37 g, 12.1 mmol, 81% yield).

TLC (hexanes:ethyl acetate 2:1) Rᵣ = 0.37

I H NMR (400 MHz, Chloroform-d) δ 7.49 – 7.33 (m, 3H), 7.28 – 7.20 (m, 2H), 4.83 (s, 2H), 2.15 (s, 3H), 1.85 (s, 3H).

C NMR (101 MHz, Chloroform-d) δ 170.87, 142.02, 129.84, 128.59, 128.52, 52.66, 22.84, 15.50.

HRMS (+EI): calculated for [C₁₀H₁₃NOSNa]⁺: 218.0610; found: 218.0602.

3a: N-(2-Iodophenyl)acetamide

Iodoaniline (480 mg, 2.19 mmol, 1.0 equiv.) was charged in a round bottom flask with triethylamine (0.67 mL, 4.82 mmol, 2.2 equiv.) and acetic anhydride (0.146 mL, 2.63 mmol, 1.2 equiv.) and stirred at room temperature for 2 days. Progress is followed by TLC. Once the reaction is complete the reaction is poured on ice-cold water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. Purification was done by flash chromatography (SiO₂, hexanes:ethyl acetate 9:1 to 3:1) to afford N-(2-iodophenyl)acetamide in 80% yield as white powder (460 mg, 1.76 mmol).

I H NMR (400 MHz, Chloroform-d) δ 8.18 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.37 – 7.28 (m, 1H), 6.83 (t, J = 7.6 Hz, 1H), 2.23 (s, 3H).

C NMR (101 MHz, Chloroform-d) δ 168.36, 138.89, 138.32, 129.40, 126.14, 122.23, 90.12, 24.97.

3b: N-(2-Bromo-3-methylphenyl)acetamide:
The aniline was synthesized according to ACIE 2010, 49, 7257-7260.

Yielded the product as an off-white solid 440 mg, 80%.

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.16 (d, \(J = 8.1\) Hz, 1H), 7.71 (bs, 1H), 7.21 (t, \(J = 7.9\) Hz, 1H), 7.00 (d, \(J = 6.9\) Hz, 1H), 2.42 (s, 3H), 2.24 (s, 3H).

\(^{13}\)C NMR (101 MHz, c\text{dcl}_3) \(\delta\) 168.36, 138.45, 135.82, 127.61, 126.24, 119.54, 116.27, 25.00, 23.94.

HRMS (+EI): calculated for [C\(_9\)H\(_{10}\)BrNONa]\(^+\): 249.9838; found: 249.9836.

4a: \(N\)-(3,5-Dimethylphenyl)-N-((N-(2-iodophenyl)acetamido)methyl)acetamide

\[\text{N-(3,5-Dimethylphenyl)-N-((methylthio)methyl)acetamide (112 mg, 0.5 mmol, 1.0 equiv.) was dissolved in 2.0 ml dry DCM at room temperature under argon. Sulfuryl chloride (0.5 mmol, 1.0 equiv., 0.5 ml, 1M solution in DCM) was added and the solution was stirred for 2h at room temperature before the solvent was removed under reduced pressure. Meanwhile a solution of N-(2-iodophenyl)acetamide (123.5 mg, 0.48 mmol, 0.95 equiv.) and dry potassium tert-butoxide (56 mg, 0.5 mmol, 1.0 equiv.) in dry DMF was prepared and stirred under argon at room temperature for 1 h. The freshly prepared N-(chloromethyl)-N-(3,5-dimethylphenyl)acetamide was dissolved in 1 mL dry DMF and added dropwise to the reaction mixture. After the addition was complete the reaction stirred at room temperature for 20 minutes. The reaction was quenched with brine (5 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL) and concentrated. Purification by HPLC with a C\text{18} column with 40% THF in water afforded the} \(N\)-(3,5-dimethylphenyl)-N-((N-(2-iodophenyl)acetamido)methyl)acetamide as a colorless oil (71.1 mg, 0.163 mmol, 33% yield)

**Major isomer (rotamer):** \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.91 (d, \(J = 7.3\) Hz, 1H), 7.38 (t, \(J = 7.1\) Hz, 1H), 7.09 (t, \(J = 7.0\) Hz, 2H), 6.94 (s, 1H), 6.61 (s, 2H), 5.96 (d, \(J = 12.8\) Hz, 1H), 5.13 (d, \(J = 12.9\) Hz, 1H), 2.28 (s, 6H), 1.76 (s, 3H), 1.72 (s, 3H).

**Minor isomer (rotamer):** \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.86 (d, \(J = 7.6\) Hz, 1H), 7.22 (t, \(J = 7.2\) Hz, 1H), 6.99 (t, \(J = 7.4\) Hz, 2H), 6.74 (d, \(J = 7.2\) Hz, 1H), 6.49 (s, 2H), 5.67 (d, \(J = 14.1\) Hz, 1H), 5.26 (d, \(J = 14.2\) Hz, 1H), 2.22 (s, 6H), 1.84 (s, 3H), 1.73 (s, 3H).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 171.18, 170.32, 144.04, 142.13, 140.03, 139.75, 139.68, 139.11, 130.45, 130.21, 130.02, 129.63, 129.28, 128.85, 125.52, 125.43, 100.91, 59.67, 22.81, 22.61, 21.18, 21.08.

HRMS (+EI): calculated for [C\(_{19}\)H\(_{21}\)IN\(_2\)O\(_2\)Na]\(^+\): 459.0540; found: 459.0539.

4b: \(N\)-(2-Bromo-3-methylphenyl)-N-((N-(3,5-dimethylphenyl)acetamido)methyl)acetamide
N-(3,5-Dimethylphenyl)-N-((methylthio)methyl)acetamide (223 mg, 1.0 mmol, 1.0 equiv.) was dissolved in 2 ml dry DCM at room temperature under argon. Sulfuryl chloride (1.0 mmol, 1.0 equiv., 1.0 ml, 1M solution in DCM) was added and the solution was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. A mixture of N-(2-bromo-3-methylphenyl)acetamide (228 mg, 1.0 mmol, 1.0 equiv.) and dry potassium tert-butoxide (112 mg, 1.0 mmol, 1.0 equiv.) in dry DMF was prepared and stirred under argon at –20 °C for 1 h. The freshly prepared N-(chloromethyl)-N-(3,5-dimethylphenyl)acetamide was dissolved in 1 mL dry DMF and added dropwise to the reaction mixture. After the addition was complete the reaction was allowed to stir at room temperature for 20 minutes. The reaction was quenched with brine (5 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL) and concentrated. Purification by preparative TLC (Neutral aluminium oxide) afforded the N-(2-bromo-3-methylphenyl)-N-((N-(3,5-dimethylphenyl)acetamido)methyl)acetamide as clear oil (150 mg, 0.371 mmol, 37% yield).

Major isomer: $^1$H NMR (400 MHz, Chloroform-d) δ 7.29 – 7.19 (m, 2H), 6.94 (m, 2H), 6.59 (s, 2H), 5.97 (d, $J = 13.0$ Hz, 1H), 5.15 (d, $J = 13.0$ Hz, 1H), 2.44 (s, 3H), 2.28 (s, 6H), 1.77 (s, 3H), 1.73 (s, 3H).

Minor isomer: $^1$H NMR (400 MHz, Chloroform-d) δ 7.18 – 7.06 (m, 2H), 6.74 (s, 2H), 6.49 (s, 2H), 5.68 (d, $J = 14.1$ Hz, 1H), 5.26 (d, $J = 14.1$ Hz, 1H), 2.41 (s, 3H), 2.24 (s, 6H), 1.83 (s, 3H), 1.69 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 170.72, 139.18, 130.93, 129.75, 128.41, 127.70, 125.60, 117.70, 110.14, 59.47, 23.92, 22.79, 22.58, 21.34.

HRMS (+EI): calculated for [C$_{20}$H$_{23}$BrN$_2$O$_2$Na]$: 427.0815; found: 427.0811.

4c: N-(2-Iodophenyl)-N-((N-phenylacetamido)methyl)acetamide

N-((Methylthio)methyl)-N-phenylacetamide (97.6 mg, 0.5 mmol, 1.0 equiv.) was dissolved in 2 ml dry DCM at room temperature under argon. Sulfuryl chloride (0.5 mmol, 1.0 equiv., 0.5 ml, 1M solution in DCM) was added and the solution was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. Meanwhile a solution of N-(2-iodophenyl)acetamide (130.0 mg, 0.5 mmol, 1.0 equiv.) and dry potassium tert-butoxide (112.2 mg, 1.0 mmol, 2.0 equiv.) in dry DMF was prepared and stirred under argon at room temperature for 1 h. The freshly prepared N-(chloromethyl)-N-phenylacetamide was dissolved in 1 mL dry DMF and added dropwise to the reaction mixture. After the addition was complete the reaction was allowed to stir at room temperature for 10 minutes. The reaction was quenched with brine (5 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL) and concentrated. Purification by HPLC with a C$_{18}$ column with 40% THF in Water afforded the N-(2-iodophenyl)-N-((N-phenylacetamido)methyl)acetamide as white foam (96 mg, 0.24 mmol, 47% yield).

$^1$H NMR (400 MHz, Chloroform-d) δ 7.88 (d, $J = 7.4$ Hz, 1H), 7.45 – 7.23 (m, 4H), 7.12 – 6.99 (m, 4H), 5.92 (d, $J = 12.9$ Hz, 1H), 5.68 (d, $J = 14.2$ Hz, traces of the minor isomer, 1H), 5.28 (d, $J = 14.2$ Hz, traces of the minor isomer, 1H), 5.19 (d, $J = 12.9$ Hz, 1H), 1.75 (s, 3H), 1.68 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 170.97, 139.18, 130.93, 129.75, 128.41, 127.70, 125.60, 117.70, 110.14, 59.47, 23.92, 22.79, 22.58, 21.34.
140.08, 139.71, 138.76, 130.19, 130.09, 129.99, 129.49, 129.37, 129.10, 128.93, 128.67, 128.55, 128.04, 127.90, 126.14, 123.56, 122.79, 119.69, 100.68, 99.42, 90.75, 63.43, 59.57, 53.50, 29.60, 24.60, 24.37, 22.77, 22.66, 21.66.

HRMS (+EI): calculated for \([\text{C}_{17}\text{H}_{17}\text{IN}_{2}\text{O}_{2}\text{Na}]^{+}\): 431.0227; found: 431.0227.

4d: \(\text{N-}(2\text{-Bromo-3-methylphenyl})\text{-}\text{N-}((\text{N-phenylacetamido})\text{methyl})\text{acetamide}\)

\[
\text{N-}((\text{Methylthio})\text{methyl})\text{-}\text{N-}\text{phenylacetamide} (97.6 \text{ mg, 0.5 mmol, 1.0 equiv.}) \text{ was dissolved in 2 mL dry DCM at room temperature under argon. Sulfuryl chloride (0.5 mmol, 1.0 equiv., 0.5 mL, 1M solution in DCM) was added and the solution was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. Meanwhile a solution of } \text{N-}(2\text{-bromo-3-methylphenyl})\text{acetamide (114 mg, 0.5 mmol, 1.0 equiv.) and dry potassium tert-butoxide (112.2 mg, 1.0 mmol, 2.0 equiv.) in dry DMF was prepared and stirred under argon at room temperature for 1 h. The freshly prepared } \text{N-}(\text{chloromethyl})\text{-N-phenylacetamide was dissolved in 1 mL dry DMF and added dropwise to the reaction mixture. After the addition was complete the reaction was allowed to stir at room temperature for 10 minutes. The reaction was quenched with brine (5 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL) and concentrated. Purification by HPLC with a C18 column with 30% THF in water afforded the } \text{N-}(2\text{-bromo-3-methylphenyl})\text{-N-}((\text{N-phenylacetamido})\text{methyl})\text{acetamide as white crystals (76.1 mg, 0.20 mmol, 41% yield).}
\]

\(^1\text{H NMR (400 MHz, Chloroform-}d\text{)} \delta 8.19 – 8.06 (m, minor isomer, 1H), 7.78 (s, minor isomer, 1H), 7.50 – 7.43 (m, minor isomer, 1H), 7.45 – 7.29 (m, 3H), 7.29 – 7.16 (m, 2H), 7.16 – 7.02 (m, 2H), 6.94 (d, J = 5.8 Hz, 1H), 6.60 (d, J = 7.4 Hz, 1H), 5.94 (d, J = 12.9 Hz, minor isomer, 1H), 5.74 (d, J = 14.2 Hz, 1H), 5.28 (t, J = 13.9 Hz, minor isomer, 1H), 2.43 (s, 3H), 1.77 (s, 3H), 1.71 (s, 3H).

\(^13\text{C NMR (101 MHz, Chloroform-}d\text{)} \delta 171.04, 170.82, 142.28, 141.11, 140.47, 130.93, 129.54, 128.25, 128.10, 128.04, 127.70, 126.72, 59.32, 23.86, 22.76, 22.45.

HRMS (+EI): calculated for \([\text{C}_{18}\text{H}_{19}\text{BrN}_{2}\text{O}_{2}\text{Na}]^{+}\): 397.0522; found: 397.0512.

**General procedure for cyclization via direct arylation.**

Aryl halide (0.1 mmol, 1.0 equiv.), potassium carbonate (27.6 mg, 0.20 mmol, 2 equiv.), palladium acetate (2.2 mg, 0.01 mmol, 0.10 equiv.) and CPhos (4.3 mg, 0.01 mmol, 0.1.0 equiv.) were charged in a round bottom flask fitted with a condenser or in a sealed vial. The setup was purged with argon three times before 2 mL anhydrous DMA was added. The reaction mixture was stirred at elevated temperatures for noted times until GCMS confirmed full conversion of the starting material. The DMA was evaporated under reduced pressure or by gently blowing nitrogen into the flask and the crude was filtered over a short column (SiO\(_2\)) with ethyl acetate. Purification of the cyclized product was done by flash column chromatography or preparative thin layer chromatography (SiO\(_2\), hexanes:ethyl acetate mixtures) unless noted otherwise.
7a: 1,1’-(1,3-Dimethyl-5H-dibenzo[d,f][1,3]diazepine-5,7(6H)-diyl)bis(ethan-1-one)

Stirred at 145 °C for 1 h, purified by flash column chromatography (SiO2, hexanes:ethyl acetate mixtures) and subsequently HPLC with a C18 column with 30% THF in water. Isolated 28 mg; 78% yield.

\[ \text{H NMR (400 MHz, Chloroform-}d\text{)} \delta 7.50 – 7.38 (m, 3H), 7.38 – 7.29 (m, 1H), 7.18 (s, 1H), 6.98 (s, 1H), 5.78 (dd, J = 45.1, 11.5 Hz, 2H), 2.36 (s, 6H), 1.63 (s, 3H), 1.60 (s, 3H). \]

\[ \text{C NMR (101 MHz, Chloroform-}d\text{)} \delta 171.09, 170.91, 139.71, 138.93, 138.90, 136.99, 136.45, 133.61, 132.79, 130.53, 129.63, 129.29, 128.88, 126.98, 63.13, 22.97, 22.72, 21.23, 20.36. \]


7b: 1,1’-(1-Methyl-5H-dibenzo[d,f][1,3]diazepine-5,7(6H)-diyl)bis(ethan-1-one)

Stirred for 1 h at 145 °C; isolated 7 mg as colourless solids; 39% yield.

\[ \text{H NMR (400 MHz, Chloroform-}d\text{)} \delta 7.50 – 7.41 (m, 3H), 7.40 – 7.31 (m, 3H), 7.20 – 7.15 (m, 1H), 5.80 (dd, J = 46.8, 11.6 Hz, 2H), 2.42 – 2.39 (m, 3H), 1.64 (s, 3H), 1.60 (s, 3H). \]

\[ \text{C NMR (101 MHz, Chloroform-}d\text{)} \delta 170.97, 170.80, 136.86, 132.04, 130.54, 129.93, 129.58, 129.36, 128.93, 126.43, 63.23, 23.00, 22.78, 20.51. \]


7c: 1,1’-(5H-Dibenzo[d,f][1,3]diazepine-5,7(6H)-diyl)bis(ethan-1-one)

Stirred for 1 h at 145 °C; isolated 8 mg as slightly reddish solid; 29% yield.

\[ \text{H NMR (400 MHz, Chloroform-}d\text{)} \delta 7.55 – 7.44 (m, 6H), 7.35 (t, J = 1.0 Hz, 1H), 7.34 – 7.32 (m, 1H), 5.94 (s, 2H), 1.58 (s, 6H). \]

\[ \text{C NMR (101 MHz, Chloroform-}d\text{)} \delta 171.12, 138.65, 138.23, 130.08, 129.88, 129.32, 128.29, 64.04, 22.96. \]


7d: (S)-1,1’-(1,3,11-Trimethyl-5H-dibenzo[d,f][1,3]diazepine-5,7(6H)-diyl)bis(ethan-1-one)
From 4d (40.2 mg, 0.100 mmol). Stirred at 145 °C for 2 h; isolated as a white solid, 11.3 mg, 0.035 mmol, 35% yield.

$^1$H NMR (600 MHz, Chloroform-d) δ 7.38 – 7.37 (m, 2H), 7.20 – 7.19 (m, 2H), 7.01 (s, 1H), 5.69 (s, 2H), 2.41 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.21 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H).

$^{13}$C NMR (150 MHz, Chloroform-d) δ 171.00, 164.69, 138.82, 138.64, 137.77, 137.30, 136.23, 133.04, 131.22, 129.30, 126.57, 125.93, 62.17, 22.63, 22.57, 21.11, 19.37, 19.25.

HRMS (+EI): calculated for [C$_{20}$H$_{22}$N$_2$O$_2$Na$^+$]: 345.1590; found: 345.1589.

9a: N-((2-Iodophenoxy)methyl)-N-phenylacetamide

$\text{N-(phenyl)acetamide (100 mg, 0.74 mmol, 1.0 equiv.) and dry potassium tert-butoxide (87.4 mg, 0.74 mmol, 1.0 equiv.) are charged in a 10 mL round bottom flask with 2 ml dry dimethylacetamide at } -20 \text{ °C under argon. 1-(Chloromethoxy)-2-iodobenzene (198.6 mg, 0.74 mmol, 1.0 equiv.) was added and the reaction was stirred to room temperature overnight before the solvent was removed under reduced pressure. The product was purified by preparative TLC (SiO$_2$) and isolated as colorless oil (95.8 mg, 0.26 mmol, 35% yield).}$

$^1$H NMR (400 MHz, Chloroform-d) δ 7.75 (dd, $J = 7.8$, 1.1 Hz, 1H), 7.47 – 7.34 (m, 3H), 7.31 (d, $J = 7.1$ Hz, 2H), 7.25 (t, $J = 9.6$ Hz, 1H), 7.03 (t, $J = 12.1$ Hz, 1H), 6.73 (td, $J = 7.7$, 1.0 Hz, 1H), 5.66 (s, 2H), 1.90 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 171.48, 155.47, 141.35, 139.71, 129.81, 129.63, 128.76, 128.70, 123.48, 113.87, 87.08, 75.44, 23.03.

HRMS (+EI): calculated for [C$_{15}$H$_{14}$INO$_2$Na$^+$]: 389.9961; found: 389.9956.

9b: N-(3,5-Dimethylphenyl)-N-((2-iodophenoxy)methyl)acetamide

$\text{N-(3,5-dimethylphenyl)acetamide (100 mg, 0.61 mmol, 1.0 equiv.) and dry potassium tert-butoxide (72 mg, 0.61 mmol, 1.0 equiv.) are charged in a 10 mL round bottom flask with 2 ml dry dimethylacetamide at } -20 \text{ °C under argon. 1-(Chloromethoxy)-2-iodobenzene (165 mg, 0.61 mmol, 1.0 equiv.) was added and the reaction}$
was stirred to room temperature overnight before the solvent was removed under reduced pressure. The product was purified by preparative TLC (SiO₂) and isolated as a colorless oil (112 mg, 0.283 mmol, 47% yield).

\[ \text{HM NMR (400 MHz, Chloroform-d):} \delta 7.77 (dd, J = 7.8, 1.5 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.08 – 7.03 (m, 1H), 7.01 (s, 1H), 6.92 (s, 2H), 6.73 (td, J = 7.6, 1.3 Hz, 1H), 5.64 (s, 2H), 2.34 (s, 6H), 1.89 (d, J = 13.0 Hz, 3H). \]

\[ \text{CC NMR (101 MHz, Chloroform-d):} \delta 171.64, 155.47, 141.11, 139.74, 139.54, 130.28, 129.64, 126.38, 123.39, 113.86, 87.02, 75.25, 22.98, 21.32. \]

HRMS (+EI): calculated for \([\text{C}_17\text{H}_{18}\text{INO}_2\text{Na}]^+\): 418.0274; found: 418.0273.

**12a: \(N-((2\text{-Bromophenyl})\text{thio})\text{methyl})-N\text{-phenylacetamide}**

\[ \text{N-(phenyl)-N-((methylthio)methyl)acetamide (97.5 mg, 0.5 mmol, 1 equiv.) was dissolved in 2 ml dry DCM at room temperature under argon. Sulfuryl chloride (0.5 mmol, 1 equiv., 0.5 ml, 1M solution in DCM) was added and the solution was stirred for 10 min at room temperature before the solvent was removed under reduced pressure. Meanwhile a mixture of 2-bromobenzenethiol (94 mg, 0.5 mmol, 1.0 equiv.) and dry potassium tert-butoxide (56 mg, 0.5 mmol, 1 equiv.) in dry dimethylacetamide at –20 °C was prepared and stirred under argon for 10 min. The freshly prepared \(N-(\text{chloromethyl})-N-(\text{phenyl})\text{acetamide} \) was dissolved in 1 mL dry DMA and added dropwise to the reaction mixture. After the addition was complete the reaction was stirred to room temperature overnight before the solvent was removed under reduced pressure. The reaction was quenched with brine (5 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 10 mL) and concentrated. Purification by flash chromatography (SiO₂, hexanes:ethyl acetate gradient from 9:1 to 4:1) afforded the \(N-((2\text{-bromophenyl})\text{thio})\text{methyl})-N\text{-phenylacetamide} \) as colorless oil (75 mg, 0.22 mmol, 45% yield).**

\[ \text{HM NMR (400 MHz, Chloroform-d):} \delta 7.51 (dd, J = 8.0, 0.9 Hz, 1H), 7.45 (dd, J = 7.9, 1.4 Hz, 1H), 7.42 – 7.31 (m, 3H), 7.23 – 7.14 (m, 3H), 7.03 (td, J = 7.9, 1.2 Hz, 1H), 5.25 (s, 2H), 1.83 (s, 3H). \]

\[ \text{CC NMR (101 MHz, Chloroform-d):} \delta 170.78, 141.54, 133.22, 131.18, 129.85, 128.65, 128.55, 127.90, 52.33, 22.86. \]

**12b: \(N-(3,5\text{-Dimethylphenyl})-N-((2\text{-iodophenyl})\text{thio})\text{methyl)acetamide}**

\[ \text{N-(3,5-Dimethylphenyl)-N-((methylthio)methyl)acetamide (112 mg, 0.5 mmol, 1 equiv.) was dissolved in 2 ml dry DCM at room temperature under argon. Sulfuryl chloride (0.5 mmol, 1 equiv., 0.5 ml, 1M solution in DCM) was added and the solution was stirred for 10 min at room temperature before the solvent was removed under} \]
reduced pressure. Meanwhile a mixture of 2-bromobenzenethiol (94 mg, 0.5 mmol, 1.0 equiv.) and dry potassium tert-butoxide (56 mg, 0.5 mmol, 1 equiv.) in dry dimethylacetamide at –20 °C was prepared and stirred under argon for 10 min. The freshly prepared N-(chloromethyl)-N-(3,5-dimethylphenyl)acetamide was dissolved in 1 mL dry DMA and added dropwise to the reaction mixture. After the addition was complete the reaction was stirred to room temperature overnight before the solvent was removed under reduced pressure. The reaction was quenched with brine (5 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 10 mL) and concentrated. Purification by flash chromatography (SiO₂, hexanes:ethyl acetate gradient from 9:1 to 4:1) afforded the N-(3,5-dimethylphenyl)-N-((2-iodophenyl)thio)methyl)acetamide as colorless oil (84 mg, 0.23 mmol, 46% yield).

¹H NMR (400 MHz, Chloroform-d) δ 7.51 (dd, J = 8.0, 1.0 Hz, 1H), 7.46 (dd, J = 7.9, 1.4 Hz, 1H), 7.19 (td, J = 7.8, 1.3 Hz, 1H), 7.02 (td, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 6.73 (s, 2H), 5.21 (s, 2H), 2.28 (s, 6H), 1.83 (s, 3H).

¹³C NMR (101 MHz, Chloroform-d) δ 170.84, 144.05, 141.45, 140.68, 139.54, 136.02, 133.14, 132.38, 131.41, 130.79, 130.18, 128.69, 127.88, 127.80, 126.80, 126.01, 122.09, 52.35, 22.79, 21.31.