Decarboxylative Reissert Type Trifluoro- and Trichloro-Methylation of Quinoline Derivatives in Batch and Continuous Flow

M. Therkelsen, M. T. Rasmussen and A. T. Lindhardt*\textsuperscript{a},

Department of Engineering, Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Finlandsgade 22, 8200 Aarhus N. lindhardt@eng.au.dk

Table of Contents:

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Considerations</td>
<td>2</td>
</tr>
<tr>
<td>General Methods</td>
<td>2</td>
</tr>
<tr>
<td>Optimization of the decarboxylative trifluoromethylation of (iso)quinoline</td>
<td>4</td>
</tr>
<tr>
<td>Experimental Details</td>
<td>5</td>
</tr>
<tr>
<td>NMR spectra</td>
<td>15</td>
</tr>
</tbody>
</table>
**General Considerations.** All chemicals were used as received without further purification. Starting materials were made according to literature procedures. Flash chromatography was carried out on activated aluminum oxide, neutral, Brockmann activity I. $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra were recorded at 400, 100 and 378 MHz respectively. Chemical shifts are reported in ppm downfield from TMS ($\delta = 0$) and referenced to the residual solvent peak, using peak pattern abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; sext, sextet; m, multiplet; dd, doublet of doublets; td, triplet of doublets. HRMS was recorded on an LC TOF (ES).

**General Method A:**
Stock solution A: substrate (1.2 M) in DMF. Stock solution B: alkylation agent (2.4 M) in DMF. Stock solution C: trichloroacetic acid (2.88 M) in MeCN. Stock solution D: triethylamine (3.6 M) in MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 1.309 ml/min. Stock solutions C and D were pumped at 1.066 ml/min. Stock solutions A and B were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d. 2.0 mm, length 5 m, reactor volume 15.7 mL) placed in an oil bath heated at 120 °C or 140 °C, providing a retention time of 6 min in the first reactor. Stock solutions C and D were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to another T-connector combining all 4 stock solutions attached by a 1/16 – 1/8 in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d. 2.0 mm, length 5 m, reactor volume 15.7 mL) heated at 40 °C, providing a retention time of 3 min. in the second reactor for an overall retention time of 9 min. The flow reactors were allowed to run for 13.5 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 3 h, corresponding to a turnover of 282.7 mmol of starting isoquinoline.

To the crude reaction mixture was added aqueous NaHCO$_3$ 10% (250 mL). The crude reaction mixture was extracted with Et$_2$O (3 x 250 mL). The combined organic phases were washed with aqueous NaHCO$_3$ 10 % (3 x 250 mL) and brine (250 mL), dried using Na$_2$SO$_4$, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration.

**General Method B:**
Stock solution A: substrate (1.2 M) in DMF. Stock solution B: alkylation agent (2.4 M) in DMF. Stock solution C: trichloroacetic acid (2.4 M) in MeCN. Stock solution D: triethylamine (3 M) in MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.055 ml/min. Stock solutions C and D were pumped at 0.066 ml/min. Stock solutions A and B were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d. 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 120 °C, providing a retention time of 20 min. in the first reactor. Stock solutions C and D were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to another T-connector combining all 4 stock solutions attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d. 0.75 mm, length 5.5 m, reactor volume 2.43 mL) heated at 40 °C, providing a retention time of 10 min. in the second reactor for an overall retention time of 30 min. The flow reactors were allowed to run for 45 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 1 h, corresponding to a turnover of 3.96 mmol of starting isoquinoline.
To the crude reaction mixture was added aqueous NaHCO$_3$ 10 % (25 mL). The crude reaction mixture was extracted with Et$_2$O (3 × 50 mL). The combined organic phases were washed with aqueous NaHCO$_3$ 10 % (3 × 50 mL) and brine (50 mL), dried over Na$_2$SO$_4$, filtered, and solvent was removed under reduced pressure.

The crude product was purified using plug filtration.

**General procedure C:**

Substrate (5 mmol) was dissolved in 20 mL NMP in a 100 mL reaction flask. Methyl trifluoroacetate (1005.8 µL, 10 mmol) was added. The flask was then sealed (caution – use blast shield) and stirred at 150 °C for 19 h. The reaction mixture was extracted with Et$_2$O (3 × 75 mL). The combined organic phases were washed with aqueous NaHCO$_3$ 10 % (3 × 50 mL) and brine (50 mL). The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using alumina as the solid phase, the mobile phase is specified for each individual entry as stated below.
Optimization of the decarboxylative trifluoromethylation of (iso)quinoline.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Starting material</th>
<th>MTFA</th>
<th>Cul</th>
<th>Additive</th>
<th>Solvent/temp</th>
<th>Conv./% (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoquinoline</td>
<td>1.2 eq.</td>
<td>0.3 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>70</td>
</tr>
<tr>
<td>Isoquinoline</td>
<td>1.2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>71</td>
</tr>
<tr>
<td>Isoquinoline</td>
<td>1.2 eq.</td>
<td>0.3 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>75</td>
</tr>
<tr>
<td>Isoquinoline</td>
<td>2 eq.</td>
<td>1 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>100</td>
</tr>
<tr>
<td>Isoquinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>100</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>1 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>100</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>100 (59) ^b</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>100 (53)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>Chlorobenzene/150 °C</td>
<td>89 (40)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>O-Xylene/150 °C</td>
<td>69 (26)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>Sulfolane/150 °C</td>
<td>100 (50)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>100 (65)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/150 °C</td>
<td>100 (64)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/180 °C</td>
<td>100 (35)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>NMP/125 °C</td>
<td>100 (55)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>2 eq.</td>
<td>0 eq.</td>
<td>LiCl 0.5 eq.</td>
<td>DMF/150 °C</td>
<td>100 (56)</td>
</tr>
</tbody>
</table>

^a NMR yield. ^b Isolated yield.
Experimental Details

1-Methylquinolin-1-ium iodide.

Stock solution A: quinoline (1.2 M) in 20% DMF/MeCN. Stock solution B: Mel (2.4 M) in 20% DMF/MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.184 ml/min and combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d. 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 120 °C, providing a retention time of 6 min. The flow reactor was allowed to run for 9 minutes (1.5 times the retention time) before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 1 h, corresponding to 13.25 mmol of starting quinoline. Excess Mel and solvents were removed by freeze-drying to give the title compound as a yellow solid. (3.43 g, 97%); mp 133.1-135.9 °C. \(^1\)H NMR (400MHz, CD\(_2\)CN) δ 9.23 (d, J = 6.0 Hz, 1H) 9.13 (d, J = 8.4 Hz, 1H) 8.39 (dd, J = 8.4, 1.6 Hz, 2H) 8.25 (td, J = 8.4, 1.2 Hz, 1H) 8.03 (t, J = 7.2 Hz, 2H) 4.6 (s, 3H); \(^3\)C NMR (100 MHz, CD\(_2\)CN) δ 150.6, 148.3, 139.6, 136.6, 131.3, 131.0, 130.4, 122.6, 119.6, 46.8; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{10}\)H\(_{10}\)N: 144.0808; found: 144.0807. Obtained melting point and NMR-data fits with literature values.

1-Propylquinolin-1-ium iodide.

Stock solution A: quinoline (1.2 M) in 10% DMF/MeCN. Stock solution B: propyl iodide (2.4 M) in 10% DMF/MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.074 ml/min and combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d. 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 150 °C, providing a retention time of 15 min. The flow reactor was allowed to run for 22.5 minutes (1.5 times the retention time) before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 42.29 min, corresponding to 3.76 mmol of starting quinoline. Excess propyl iodide and solvents were removed by freeze-drying to give a yellow solid. This was triturated using toluene to give the title compound as a yellow solid. (0.87 g, 77%); mp 128.5-130 °C. \(^1\)H NMR (400 MHz, CD\(_3\)SOCD\(_3\)) δ 9.60 (d, J = 4.4 Hz, 1H), 9.32 (d, J = 8.0 Hz, 1H), 8.67 (d, J = 8.8 Hz, 1H), 8.51 (d, J = 7.8 Hz, 1H), 8.28 (t, J = 7.2 Hz, 1H), 8.21 (t, J = 6.4 Hz, 1H), 8.06 (t, J = 7.6 Hz, 1H), 5.05 (t, J = 6.8 Hz, 2H), 2.00 (m, 2H), 0.97 (t, J = 6.8 Hz, 3H); \(^3\)C NMR (100 MHz, CD\(_3\)SOCD\(_3\)) δ 149.6, 147.3, 137.4, 135.6, 130.7, 129.9, 129.7, 122.1, 119.0, 58.5, 22.9, 10.6; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{12}\)H\(_{14}\)N: 172.1121; found: 172.1122. Obtained melting point is within 10 degrees of literature value.

1-Allylquinolin-1-ium 4-methylbenzenesulfonate.

Stock solution A: quinoline (1.2 M) in DMF. Stock solution B: allyl tosylate (2.4 M) in DMF. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.055 ml/min and combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d. 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 120 °C, providing a retention time of 20 min. The flow reactor was allowed to run for 30 minutes (1.5 times the retention time) before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 60 min, corresponding to 3.96 mmol of
starting quinoline. Excess solvents were removed by freeze-drying to give an orange solid. This was triturated using toluene to give the title compound as an orange solid. (0.92 g, 69%, average of 2 runs); mp 88.1-90.0 °C. \(^1\)H NMR (400 MHz, CD\(_3\)SOCD\(_3\)) \(\delta\) 9.58 (d, \(J = 4.8\) Hz, 1H), 9.33 (d, \(J = 8.0\) Hz, 1H), 8.57-8.46 (m, 2H), 8.30-8.15 (m, 2H), 8.04 (t, \(J = 7.6\) Hz, 1H), 7.49 (d, \(J = 7.6\) Hz, 2H), 7.09 (d, \(J = 7.2\) Hz, 2H), 6.30-6.13 (m, 1H), 5.75 (d, \(J = 3.6\) Hz, 2H), 5.39 (d, \(J = 10.4\) Hz, 1H), 5.32 (d, \(J = 17.2\) Hz, 1H), 2.26 (s, 3H). \(^{13}\)C NMR (100 MHz, CD\(_3\)SOCD\(_3\)) \(\delta\) 150.2, 148.1, 145.9, 137.9, 137.7, 135.8, 131.6, 130.9, 130.1, 129.9, 128.3, 125.7, 122.6, 120.7, 119.5, 59.3, 21.0; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{12}\)H\(_{13}\)N: 170.0964; found: 170.0964.

Unidentified impurity at 2.55 ppm (triplet) with a corresponding carbon signal at 34.6 ppm.

### 1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (2).

The compound was obtained using general procedure C with quinoline (591.0 µL, 5.0 mmol) as substrate. The crude product was purified by flash chromatography eluting with 50% toluene in pentane to give the title compound as a green oil (539.4 mg, 51%). \(^1\)H NMR (400 MHz, CD\(_3\)CN) \(\delta\) (ppm): 7.18 (td, \(J = 8.0, 1.5\) Hz, 1H), 7.02 (dd, \(J = 7.4, 1.4\) Hz, 1H), 6.74 (d, \(J = 9.7\) Hz, 1H), 6.70 (t, \(J = 7.4\) Hz, 1H), 6.65 (d, \(J = 8.2\) Hz, 1H), 5.67 (dd, \(J = 9.7, 5.9\) Hz, 1H), 4.68 (pent, \(J = 6.8\) Hz, 1H), 3.06 (s, 3H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN) \(\delta\) (ppm): 144.8, 131.3, 130.8, 128.3, 126.4 (q, \(J = 290\) Hz), 121.7, 118.5, 115.6, 112.1, 61.6 (q, \(J = 29\) Hz), 39.3. \(^{19}\)F NMR (378 MHz, CD\(_3\)CN) \(\delta\) (ppm): -77.8. HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{11}\)H\(_{12}\)F\(_3\)N: 214.0838; found: 214.0834.

### 1-methylquinolin-1-ium 2,2,2-trifluoroacetate (3).

Quinoline (4 mmol, 1 equiv) and methyl trifluoroacetate (16 mmol, 4 equiv) were dissolved in 10 mL methanol in a 100 mL sealed reaction flask (caution – use blast shield). The reaction mixture was stirred at 85 °C for 2 days. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and a brown solid was isolated. The solid was washed 3 times with diethyl ether (20 mL) and dried under reduced pressure to give the title compound as brown needles (0.87 g, 85%).: mp 100.8-103.1 °C. \(^1\)H NMR (400 MHz, CD\(_3\)CN) \(\delta\) 9.40 (d, \(J = 5.6\) Hz, 1H), 9.12 (d, \(J = 8.4\) Hz, 1H), 8.38 (t, \(J = 8.8\) Hz, 2H), 8.28 (t, \(J = 7.6\) Hz, 1H), 8.01 (dd, \(J = 6.0\) Hz, 2H), 4.62 (s, 3H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN) \(\delta\) 160.0 (q, \(J = 93\) Hz), 151.2, 148.6, 139.9, 136.8, 131.5, 131.1, 130.7, 122.9, 120.3, 118.8 (q, \(J = 297\) Hz), 46.4. \(^{19}\)F NMR (378 MHz, CD\(_3\)CN) \(\delta\) -75.2. HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{10}\)H\(_{10}\)F\(_3\)N: 144.0808; found: 144.0807.

### 2,3-Dimethyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (5).

The compound was obtained using general procedure C with 3-methylisoquinoline (999.8 mg, 4.9 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a pale red solid (646.1 mg, 58%); mp 85.7 - 87.2 °C. \(^1\)H NMR (400 MHz, CD\(_3\)CN) \(\delta\) (ppm): 7.21 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.10-7.03 (m, 2H), 6.91 (d, \(J = 7.6\) Hz, 1H), 5.32 (s, 1H), 5.02 (q, \(J = 8.0\) Hz, 1H), 3.11 (s, 3H), 2.02 (s, 3H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN) \(\delta\) (ppm): 144.0, 136.1, 129.9, 128.7, 127.3 (q, \(J = 290\) Hz), 124.9, 123.1, 120.6, 98.2, 65.3 (q, \(J = 29\) Hz), 39.4, 20.0. \(^{19}\)F NMR (378 MHz, CD\(_3\)CN) \(\delta\) (ppm): -76.9. HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{12}\)H\(_{13}\)F\(_3\)N: 228.0995; found: 228.0987.
5-Bromo-2-methyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (6).

The compound was obtained using general procedure C with 5-bromoisoquinoline (1040.3 mg, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a red oil (938.1 mg, 64 %). $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ (ppm): 7.51 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 7.00 (t, $J = 7.8$ Hz, 1H), 6.43 (dd, $d = 7.5$, 1.1 Hz, 1H), 5.59 (d, $J = 7.5$ Hz, 1H), 5.09 (q, $J = 7.7$ Hz, 1H), 3.10 (s, 3H). $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) δ (ppm): 139.50, 134.25, 133.97, 128.92, 126.83 (q, $J = 290$ Hz), 126.67, 121.88, 118.85, 96.04, 63.03 (q, $J = 29$ Hz), 42.50. $^{19}$F NMR (378 MHz, CD$_3$CN) δ (ppm): -76.80. HRMS (ESI-TOF) m/z: [M + H$^+$] calculated for C$_{12}$H$_{13}$BrF$_3$N: 291.9943; found: 291.9971.

6-Methoxy-1-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (7).

The compound was obtained using general procedure C with 6-methoxyquinoline (689.8 µL, 5.0 mmol) as substrate. In this reaction 3 equivalents of methyl trifluoroacetate (150 mL, 14.9 mmol) were used. The crude product was purified by flash chromatography with 10% DCM in toluene to give the title compound as a green solid (750.3 mg, 62 %); mp 47.0 – 48.9 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.77 (dd, $J = 8.7, 2.9$ Hz, 1H), 6.65 (d, $J = 9.7$ Hz, 1H), 6.62 (d, $J = 2.9$ Hz, 1H), 6.54 (d, $J = 8.7$ Hz, 1H), 5.67 (dd, $J = 9.7, 5.8$ Hz, 1H), 4.44 (pent, $J = 6.7$ Hz, 1H), 3.76 (s, 3H), 3.05 (s, 3H). $^{13}$C NMR (100 MHz, CD$_2$CN) δ 152.9, 139.0, 131.1, 126.5 (q, $J = 290$ Hz), 122.6, 116.8, 115.9, 114.0, 112.9, 61.5 (q, $J = 29$ Hz), 56.2, 39.3. $^{19}$F NMR (378 MHz, CD$_3$CN) δ -76.9. HRMS (ESI-TOF) m/z: [M + H$^+$] calculated for C$_{12}$H$_{13}$F$_3$NO: 244.0944; found: 244.0943.

1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinolin-6-yl 4-methylbenzenesulfonate (8).

The compound was obtained using general procedure C with quinolin-6-yl 4-methylbenzenesulfonate (1393.8 mg, 4.7 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a brownish red solid (400.1 mg, 22 %); mp 120.0 – 125.8 °C. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ (ppm): 7.69 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 6.75 (dd, $J = 8.8$, 2.8 Hz, 1H), 6.68 (d, $J = 2.8$ Hz, 1H), 6.59 (d, $J = 9.8$ Hz, 1H), 6.50 (d, $J = 8.9$ Hz, 1H), 5.70 (dd, $J = 9.8, 5.8$ Hz, 1H), 4.68 (pent, $J = 6.7$ Hz, 1H), 3.01 (s, 3H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz, CD$_2$CN) δ (ppm): 147.0, 143.6, 141.7, 133.1, 130.9, 130.3, 129.3, 126.0 (q, $J = 259$ Hz), 124.0, 122.2, 121.8, 117.3, 112.5, 61.6, 61.5, 21.7. $^{19}$F NMR (378 MHz, CD$_3$CN) δ (ppm): -77.8 HRMS (ESI-TOF) m/z: [M + H$^+$] calculated for C$_{18}$H$_{17}$F$_3$SO$_3$N: 384.0876; found: 384.0879.

1,4-Dimethyl-2-(trifluoromethyl)-1,2-dihydroquinoline (9).

The compound was obtained using general procedure C with lepidine (661.0 µL, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a green oil (723.0 mg, 64 %). $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ (ppm): 7.22-7.17 (m, 2H), 6.74 (d, $J = 7.5$ Hz, 1H), 6.65 (d, $J = 8.1$ Hz, 1H), 5.54 (d, $J = 6.0$ Hz, 1H), 4.58 (pent, $J = 6.9$ Hz, 1H), 3.05 (s, 3H), 2.09 (s, 3H). $^{13}$C NMR (100 MHz, CD$_2$CN) δ (ppm): 144.8, 136.7, 126.6 (q, $J = 290$ Hz), 125.1, 122.9, 118.2, 113.0, 112.1, 61.5
(q, J = 29 Hz), 39.4, 18.9. $^{19}$F NMR (378 MHz, CD$_3$CN) δ (ppm): -77.4. HRMS (ESI-TOF) m/z: [M + H$^+$] calculated for C$_{12}$H$_{13}$F$_3$N: 228.0995; found: 228.0991.

5-Methyl-6-(trifluoromethyl)-5,6-dihydrophenanthridine (10).

The compound was obtained using general procedure C with phenanthridine (896.1 mg, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with pentane to give the title compound as a white solid (856.1 mg, 65%); mp 58.2 - 59.5 °C. $^1$H NMR (400 MHz, CD$_3$CN) δ (ppm): 7.91 (d, J = 7.9, 1H), 7.83 (dd, J = 7.8, 1.3 Hz, 1H), 7.49 (td, J = 7.8, 2.1 Hz, 1H), 7.39-7.28 (m, 3H), 6.89 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.07 (q, J = 7.7 Hz, 1H), 3.19 (s, 3H). $^{13}$C NMR (100 MHz, CD$_3$CN) δ (ppm): 144.4, 133.0, 130.7, 130.5, 129.4, 128.2, 127.2 (q, J = 290 Hz), 127.0, 124.1, 123.6, 122.3, 119.4, 113.7, 64.1 (q, J = 29 Hz), 39.6. $^{19}$F NMR (378 MHz, CD$_3$CN) δ (ppm): -74.2. HRMS (ESI-TOF) m/z: [M + H$^+$] calculated for C$_{13}$H$_{13}$F$_3$N: 264.0995; found: 264.0994.

1-Methyl-2-(trifluoromethyl)-1,2-dihydro-1,10-phenanthroline (11).

The compound was obtained using general procedure C with phenanthroline (901.1 mg, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with 10% DCM in toluene to give the title compound as a yellow solid (589.1 mg, 56%); mp 69.7 - 70.7 °C. $^1$H NMR (400 MHz, CD$_3$CN) δ (ppm): 148.7, 142.1, 141.9, 137.3, 131.0, 130.8, 127.6, 126.3 (q, J = 285 Hz), 123.3, 122.1, 120.5, 115.9, 63.7 (q, J = 30 Hz), 47.3. $^{19}$F NMR (378 MHz, CD$_3$CN) δ (ppm): -74.9. HRMS (ESI-TOF) m/z: [M + H$^+$] calculated for C$_{24}$H$_{25}$F$_{3}$N: 265.0947; found: 265.0952.

7-Chloro-1-methyl-2-(trifluoromethyl)-2,3-dihydroquinolin-4-one (13).

The compound was obtained using general procedure C with 7-chloro-4-(N,N-dimethylamino)quinoline (1040.9 mg, 5.0 mmol) as substrate. The product was purified by flash chromatography with 0-50% EtOAc in toluene to give the title compound as a brown solid (637.0 mg, 56%); mp 76.3 - 79.9 °C. $^1$H NMR (400 MHz, CD$_3$CN) δ (ppm): 7.70 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 1.7 Hz, 1H), 6.76 (dd, J = 8.4, 1.8 Hz, 1H), 4.41-4.30 (m, 1H), 3.25 (dd, J = 17.5, 7.7 Hz, 1H), 3.14 (s, 3H), 2.76 (dd, J = 17.5, 1.5 Hz, 1H). $^{13}$C NMR (100 MHz, CD$_3$CN) δ (ppm): 190.3, 151.1, 142.6, 129.2, 127.6 (q, J = 288 Hz), 118.5, 118.4, 113.8, 61.7 (q, J = 29 Hz), 40.1, 35.0. $^{19}$F NMR (378 MHz, CD$_3$CN) δ (ppm): -74.1. HRMS (ESI-TOF) m/z: [M + H$^+$] calculated for C$_{11}$H$_{10}$ClF$_3$NO: 264.0398; found: 264.0399.

1-Methyl-2-(trichloromethyl)-1,2-dihydroquinoline (14)$^3$.

The compound was obtained using general method B and purified using plug filtration with 10% DCM in toluene to give the title compound as a brown solid (0.86 g, 83%, average of 2 runs); mp 67.9-69.7 °C. $^1$H NMR (400MHz, CD$_3$CN) δ 7.28-7.21 (m, 1H), 7.07 (dd, J = 7.6, 1.2 Hz, 1H), 6.88 (d, J = 10.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.73 (td, J = 7.6, 1.2 Hz, 1H), 6.02 (dd, J = 9.6, 5.6 Hz, 1H), 4.94 (d, J = 6.0 Hz, 1H), 3.38 (s, 3H). $^{13}$C NMR (100 MHz,
CD$_3$CN) $\delta$ 145.4, 131.1, 130.5, 128.0, 122.6, 118.7, 118.0, 113.6, 106.7, 76.4, 44.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{12}$H$_{13}$Cl$_3$N: 261.9952; found: 261.9945. Obtained melting point and NMR-data fits with reported values.

1,4-Dimethyl-2-(trichloromethyl)-1,2-dihydroquinoline (15). The compound was obtained using general method B and purified using plug filtration with 10% DCM in toluene to give the title compound as a brown oil (0.94 g, 86%, average of 2 runs). $^1$H NMR (400MHz, CD$_3$SOCD$_3$) $\delta$ 7.24-7.17 (m, 2H), 6.80 – 6.70 (m, 2H), 5.84 (dd, $J = 6.0, 1.2$ Hz, 1H), 5.03 (d, $J = 6.0$ Hz, 1H), 3.33 (s, 3H), 2.12 (s, 3H). $^{13}$C NMR (100 MHz, CD$_3$SOCD$_3$) $\delta$ 144.0, 135.0, 129.2, 123.6, 122.3, 117.2, 114.7, 112.5, 106.3, 74.4, 43.2, 18.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{12}$H$_{13}$Cl$_3$N: 276.0108; found: 276.0101. Obtained NMR-data fits with reported values.

1-Propyl-2-(trichloromethyl)-1,2-dihydroquinoline and 1-propyl-4-(trichloromethyl)-1,4-dihydroquinoline (16 + 17). The compounds was obtained using general method B and purified using plug filtration 10% toluene in pentane to give 16 and 17 as an inseparable mixture (0.96 g, 84%, average of 2 runs) brown oil.

1-propyl-2-(trichloromethyl)-1,2-dihydroquinoline (16): $^1$H NMR (400MHz, CD$_3$CN) $\delta$ inter alia 7.19-7.15 (m, 1H) 7.08 (dd, $J = 7.2, 1.2$ Hz, 1H) 6.93 (d, $J = 8.4$ Hz, 1H) 6.87 (d, $J = 9.6$ Hz, 1H) 6.03 (d, $J = 9.6, 6.0$ Hz, 1H) 4.19-4.10 (m, 1H) 0.79 (t, $J = 7.2$, 3H).

1-propyl-4-(trichloromethyl)-1,4-dihydroquinoline (17): $^1$H NMR (400MHz, CD$_3$CN) $\delta$ inter alia 7.49 (dd, $J = 7.6, 1.6$ Hz, 1H) 7.35-7.30 (m, 1H) 6.61 (d, $J = 7.6$ Hz, 1H) 4.53 (d, $J = 5.6$ Hz, 1H) 3.77-3.68 (m, 1H) 0.94 (t, $J = 7.2$, 3H).

Both isomers: $^{13}$C NMR (100 MHz, CD$_3$CN) $\delta$ 143.6, 137.1, 133.9, 131.4, 130.1, 129.7, 128.4, 124.3, 121.2, 118.9, 118.1, 115.9, 113.2, 106.8, 93.6, 75.1, 59.4, 57.3, 52.7, 22.2, 21.0, 11.6, 11.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{12}$H$_{13}$Cl$_3$N: 290.0265; found: 290.0263.

7-Chloro-4-(cyclopentyl)-2-(trichloromethyl)-1,2-dihydroquinoline (18). The compound was obtained using general method B (run at half concentration) and purified using plug filtration with 10% DCM in toluene to give the title compound as a white solid (0.28 g, 37%, average of 2 runs); mp 145.2-147.6 °C. $^1$H NMR (400MHz, CD$_3$Cl$_3$) $\delta$ 7.41 (d, $J = 8.4$ Hz, 1H), 6.72 (dd, $J = 8.4, 2.0$ Hz, 1H), 6.65 (d, $J = 2.0$ Hz, 1H), 5.04 (d, $J = 6.0$ Hz, 1H), 4.76 (d, $J = 6.4$ Hz, 1H), 4.74 – 4.69 (m, 1H), 3.37 (s, 3H), 2.00 – 1.85 (m, 4H), 1.84 – 1.72 (m, 2H), 1.70 – 1.50 (m, 2H). $^{13}$C NMR (100 MHz, CD$_3$Cl$_3$CO) $\delta$ 152.3, 147.1, 135.8, 124.2, 118.9, 117.8, 113.1, 108.0, 91.0, 79.9, 77.0, 43.9, 33.4, 33.2, 24.81, 24.78; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{16}$H$_{28}$Cl$_5$NO: 380.0137; found: 380.0134.
2-Methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (19). The compound was obtained using general method B and purified using plug filtration with 10% toluene in pentane to give the title compound as a white solid. (0.91 g, 88%); mp 76.8-80.4 °C. $^1$H NMR (400MHz, CD$_2$CN) δ 7.40 (d, $J = 7.6$ Hz, 1H), 7.30 (td, $J = 7.6$, 1.2 Hz, 1H), 7.18 (td, $J = 7.6$, 1.2 Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 6.37 (dd, $J = 7.2$, 1.2 Hz, 1H), 5.61 (d, $J = 7.2$ Hz, 1H), 5.27 (s, 1H), 3.27 (s, 3H). $^{13}$C NMR (100 MHz, CD$_2$CN) δ 136.7, 135.5, 131.7, 129.8, 125.4, 124.2, 121.6, 107.8, 101.4, 77.7, 45.5; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{11}$H$_{11}$Cl$_3$N: 261.9949; found: 261.9956.

2-Methyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (20). The compound was obtained using general method B and purified using plug filtration with 50% DCM in toluene to give the title compound as a dark red solid (1.06 g, 87%, average of 2 runs); mp 128.2-129.8 °C. $^1$H NMR (400MHz, CD$_2$CN) δ 8.02 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.66 (d, $J = 7.6$ Hz, 1H), 7.26 (t, $J = 8.0$, 1H), 6.70 (dd, $J = 7.6$, 1.2 Hz, 1H), 6.27 (d, $J = 7.6$ Hz, 1H), 5.43 (s, 1H), 3.37 (s, 3H). $^{13}$C NMR (100 MHz, CD$_2$CN) δ 143.6, 142.1, 137.7, 130.6, 126.9, 124.4, 123.3, 105.8, 95.3, 77.1, 45.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{11}$H$_{10}$Cl$_3$N$_2$: 306.9802; found: 306.9801.

2-Propyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (21). The compound was obtained using general method B and purified using plug filtration with 10% Toluene in pentane to give the title compound as a purple solid (0.84 g, 73%, average of 2 runs); mp 59.4-61.6 °C. $^1$H NMR (400MHz, CD$_2$CN) δ 7.42 (d, $J = 7.6$ Hz, 1H), 7.31 (td, $J = 7.6$, 1.2 Hz, 1H), 7.18 (td, $J = 7.6$, 1.2 Hz, 1H), 7.10 (d, $J = 8.0$ Hz, 1H), 6.40 (dd, $J = 7.2$, 1.2 Hz, 1H), 5.64 (d, $J = 7.2$ Hz, 1H), 5.32 (s, 1H), 3.50 (t, $J = 7.2$ Hz, 2H), 1.47 (sext, $J = 7.2$ Hz, 2H), 0.73 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CD$_2$CN) δ 135.9, 135.7, 131.5, 129.8, 125.5, 124.3, 122.1, 107.3, 102.3, 76.4, 59.9, 24.2, 11.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{13}$H$_{14}$Cl$_3$N: 290.0265; found: 290.0267.

Ethyl 2-(1-(trichloromethyl)isoquinolin-2(1H)-yl)acetate (22). The compound was obtained using general method B and purified using plug filtration with toluene to give the title compound as a light brown solid (0.67 g, 50%); mp 94.6-96.9 °C. $^1$H NMR (400MHz, CD$_2$CN) δ 7.41 (d, $J = 7.6$ Hz, 1H), 7.33 (td, $J = 7.6$, 1.2 Hz, 1H), 7.21 (td, $J = 7.6$, 1.2 Hz, 1H), 7.12 (d, $J = 7.6$ Hz, 1H), 6.28 (d, $J = 7.2$ Hz, 1H), 5.70 (d, $J = 7.2$ Hz, 1H), 5.35 (s, 1H), 4.38 (d, $J = 18.0$ Hz, 1H), 4.18 (d, $J = 18.0$ Hz, 1H), 4.11 - 3.92 (m, 2H), 1.07 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CD$_2$CN) δ 171.1, 135.7, 135.3, 131.6, 129.8, 125.8, 124.6, 123.0, 106.8, 103.6, 76.2, 61.7, 59.0, 14.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for C$_{16}$H$_{15}$Cl$_3$NO$_2$: 334.0163; found: 334.0165.

S10
2-Allyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (23).\(^5\)

The compound was obtained using general method B and purified using plug filtration with toluene to give the title compound as a purple solid (1.06 g, 93%, average of 2 runs); mp 32.7-35.8 °C. \(^1\)H NMR (400MHz, CD\(_3\)CN) \(\delta\) 7.41 (d, \(J = 7.6\) Hz, 1H), 7.32 (td, \(J = 7.6, 1.2\) Hz, 1H), 7.19 (td, \(J = 7.6, 1.2\) Hz, 1H), 7.12 (d, \(J = 7.6\) Hz, 1H), 6.41 (dd, \(J = 7.2, 1.2\) Hz, 1H), 5.84 – 5.70 (m, 1H), 5.68 (d, \(J = 7.2\) Hz, 1H), 5.28 (s, 1H), 5.08 – 4.95 (m, 2H), 4.26-4.09 (m, 2H). \(^13\)C NMR (100 MHz, CD\(_3\)CN) \(\delta\) 135.1, 134.53, 134.48, 130.8, 129.5, 129.2, 125.1, 124.1, 121.6, 116.8, 102.8, 75.8, 60.1; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{13}\)H\(_{16}\)Cl\(_3\): 288.0108; found: 288.0108.

2-Allyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (23) – Scaleup. The compound was obtained using general method A. Product was collected for three hours and purified using plug filtration with toluene to give the title compound as a purple solid (72.7 g, 89%); mp 33.8-36.3 °C; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{13}\)H\(_{16}\)Cl\(_3\): 288.0108; found: 288.0109. Obtained NMR-data fits with reported values.

2-Allyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (24).

The compound was obtained using general method B and purified using plug filtration with 25% DCM in toluene to give the title compound as an orange solid (0.92 g, 76%, average of 2 runs); mp 101-102.9 °C. \(^1\)H NMR (400MHz, CD\(_3\)CN) \(\delta\) 8.04 (dd, \(J = 8.0, 1.2\) Hz, 1H), 7.68 (d, \(J = 7.6\) Hz, 1H), 7.30 (t, \(J = 8.0\) Hz, 1H), 6.72 (dd, \(J = 7.6, 1.2\) Hz, 1H), 6.34 (d, \(J = 7.6\) Hz, 1H), 5.87 – 5.71 (m, 1H), 5.44 (s, 1H), 5.14 – 5.00 (m, 2H), 4.36 – 4.15 (m, 2H). \(^13\)C NMR (100 MHz, CD\(_3\)CN) \(\delta\) 143.9, 140.9, 137.5, 135.1, 130.7, 126.9, 124.9, 123.8, 118.1, 106.7, 96.7, 75.2, 60.5. HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{13}\)H\(_{22}\)Cl\(_4\)N: 332.9959; found: 332.9960.

6,7-Dimethoxy-2-methyl-1-(trichloromethyl)-1,2,3,4-tetrahydroisoquinoline (25).

The compound was obtained using general method B and purified using plug filtration with 50% DCM in pentane to give the title compound as a white solid (0.98 g, 76%, average of 2 runs); mp 107.8-110.2 °C. \(^1\)H NMR (400MHz, CD\(_3\)CN) \(\delta\) 7.08 (s, 1H), 6.78 (s, 1H), 4.39 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.31-3.26 (m, 1H), 3.20 – 3.09 (m, 1H), 2.76 (s, 3H), 2.65 – 2.53 (m, 1H), 2.46 – 2.33 (m, 1H). \(^13\)C NMR (100 MHz, CD\(_3\)CN) \(\delta\) 150.3, 147.4, 133.0, 122.9, 117.1, 112.0, 108.5, 79.8, 56.6, 56.3, 53.4, 48.1, 29.8; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{13}\)H\(_{13}\)Cl\(_3\)NO\(_2\): 324.0319; found: 324.0325.

6,7-Dimethoxy-2-methyl-1-(trichloromethyl)-1,2,3,4-tetrahydroisoquinoline (25). Stock solution A: isoquinoline (1.2 M) in DMF. Stock solution B: alkylation agent (2.4 M) in DMF. Stock solution C: trichloroacetic acid (2.88 M) in MeCN. Stock solution D: triethylamine (3.6 M) in MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.393 ml/min. Stock solutions C and D were pumped at 0.393 ml/min. Stock solutions A and B were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached by a 1/16 – 1/8 in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d. 2.0 mm, length 5 m, reactor volume 15.7 ml) placed in an oil bath heated at 120 °C, providing a retention time of 20 min. in the first reactor. Stock solutions C and D were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to another T-connector combining all 4 stock solutions.
attached by a 1/16 – 1/8 in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d. 2.0 mm, length 5 m, reactor volume 15.7 mL) heated to 40 °C providing a retention time of 10 min. in the second reactor for an overall retention time of 30 min. The flow reactor was allowed to run for 45 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 5 h, corresponding to the turnover of 141.56 mmol of starting isoquinoline.

To the crude reaction mixture was added aqueous NaHCO₃ 10 % (250 mL). The crude reaction mixture was extracted with diethyl ether (3 × 250 mL). The combined organic phases were washed with aqueous NaHCO₃ 10% (3 × 250 mL) and brine (250 mL), dried using Na₂SO₄, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 50% DCM in toluene to give the title compound as a white solid (38.83 g, 85%).

NaHCO₃ extracted with 141.56 mmol of starting isoquinoline. Collection was continued for 5 h, corresponding to the turnover of 30 min. in the second reactor for an overall retention time of 30 min. The flow reactor was allowed to run for 45 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 5 h, corresponding to the turnover of 141.56 mmol of starting isoquinoline.

To the crude reaction mixture was added aqueous NaHCO₃ 10 % (250 mL). The crude reaction mixture was extracted with diethyl ether (3 × 250 mL). The combined organic phases were washed with aqueous NaHCO₃ 10% (3 × 250 mL) and brine (250 mL), dried using Na₂SO₄, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 50% DCM in toluene to give the title compound as a white solid (38.83 g, 85%).

NaHCO₃ extracted with 141.56 mmol of starting isoquinoline. Collection was continued for 5 h, corresponding to the turnover of 30 min. in the second reactor for an overall retention time of 30 min. The flow reactor was allowed to run for 45 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 5 h, corresponding to the turnover of 141.56 mmol of starting isoquinoline.

To the crude reaction mixture was added aqueous NaHCO₃ 10 % (250 mL). The crude reaction mixture was extracted with diethyl ether (3 × 250 mL). The combined organic phases were washed with aqueous NaHCO₃ 10% (3 × 250 mL) and brine (250 mL), dried using Na₂SO₄, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 50% DCM in toluene to give the title compound as a white solid (38.83 g, 85%).

3-methyl-4-(trichloromethyl)-3,4-dihydroquinazoline (26).

The compound was obtained using general method B and purified using plug filtration with ethyl acetate to give title compound as a white solid (0.23 g, 22%); mp 118.4-120.3 °C.

1H NMR (400 MHz, CD₂SOCD₃) δ 7.47 (s, 1H), 7.42 – 7.30 (m, 2H), 7.18 (td, J = 7.2, 1.2 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 5.64 (s, 1H), 3.42 (s, 3H). 13C NMR (100 MHz, CD₂SOCD₃) δ 149.9, 143.3, 130.1, 129.6, 124.0, 117.3, 104.7, 72.1, 41.8; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C₁₄H₁₅Cl₂N₂: 262.9904; found: 262.9907.

TOCSY confirmed the structure given.

5-Methyl-6-(trichloromethyl)-5,6-dihydrophenanthridine (27).³

The compound was obtained using general method B and purified using plug filtration with toluene to give the title compound as a white solid (1.06 g, 86%, average of 2 runs); mp 73.1-75.9 °C. 1H NMR (400 MHz, CD₂CN) δ 7.94 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 7.6, 1.6 Hz, 1H), 7.59 (dd, J = 8.0, 1.2 Hz, 1H), 7.51 (td, J = 7.6, 1.2 Hz, 1H), 7.38 (td, J = 7.6, 1.2 Hz, 1H), 7.36-7.31 (m, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.90 (td, J = 7.6, 1.2 Hz, 1H) 5.35 (s, 1H), 3.46 (s, 3H). 13C NMR (100 MHz, CD₂CN) δ 144.1, 133.6, 131.7, 130.4, 130.2, 127.8, 127.4, 123.7, 123.5, 123.4, 119.5, 115.1, 106.6, 78.3, 44.0; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C₁₅H₁₃Cl₂N: 312.0108; found: 312.0110. Obtained melting point and NMR-data fits with reported values.

5-Bromo-2-methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (28).

5-Bromoisoquinoline (1.06 g., 5.1 mmol) and Mel (0.623 µL, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 mL, 12.5 mmol) and trichloroacetic acid (1.63 g., 10 mmol) were added. The reaction mixture was heated at 40 °C for 1 h. To the crude reaction mixture was added aqueous NaHCO₃ 10% (25 mL). The crude reaction mixture was extracted with Et₂O (3 × 50 mL). The combined organic phases were washed with aqueous NaHCO₃ 10% (3 × 50 mL) and brine (50 mL), dried using Na₂SO₄, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 10% DCM in toluene to give the title compound as a dark purple oil (1.61 g, 94%); 1H NMR (400MHz, CD₂CN) δ 7.57 (dd, J = 8.0, 1.2 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H),
7.07 (t, J = 7.6 Hz, 1H), 6.53 (dd, J = 7.2, 1.2 Hz, 1H), 5.85 (d, J = 7.2 Hz, 1H), 5.31 (s, 1H), 3.31 (s, 3H). 13C NMR (100 MHz, CD3CN) δ 139.0, 134.8, 133.7, 131.5, 126.2, 123.0, 118.8, 106.6, 99.6, 77.4, 45.5; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C11H10BrCl3N: 339.9057; found: 339.9052.

2,3-Dimethyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (29).

3-Methylisoquinoline (366.5 mg, 2.56 mmol) and Mel (311 µL, 5 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (0.87 mL, 6.25 mmol) and trichloroacetic acid (817 mg, 5 mmol) were added. The reaction mixture was heated at 40 °C for 2 h. To the crude reaction mixture was added aqueous NaHCO3 10% (25 mL). The crude reaction mixture was purified using using Na2SO4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with toluene to give the title compound as a brown solid (0.97 g, 72%); mp 46.5-49.0 °C. 1H NMR (400MHz, CD3CN) δ 7.37 (d, J = 7.6 Hz, 1H), 7.27 (td, J = 7.6, 1.2 Hz, 1H), 7.11 (td, J = 7.6, 1.2 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 5.54 (s, 1H), 5.20 (s, 1H), 3.28 (s, 3H), 2.08 (s, 3H). 13C NMR (100 MHz, CD3CN) δ 143.4, 136.5, 131.2, 129.7, 124.5, 123.5, 122.0, 107.4, 101.9, 79.7, 43.1, 20.4; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C12H13Cl3N: 276.0108; found: 276.0107.

2-Methyl-1-(trichloromethyl)-1,2-dihydrophthalazine (30).

Phthalazine (664 mg, 5 mmol) and Mel (623 µL, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 mL, 12.5 mmol) and trichloroacetic acid (2.45 g, 15 mmol) were added. The reaction mixture was heated at 40 °C for 1 h. To the crude reaction mixture was added aqueous NaHCO3 (25 mL). The crude reaction mixture was purified using plug filtration with 50% DCM in toluene to give the title compound as a colorless solid (1.25 g, 95%); mp 101.1-103.4 °C. 1H NMR (400MHz, CD3CN) δ 7.56 – 7.46 (m, 3H), 7.43 (s, 1H), 7.37 – 7.28 (m, 1H), 5.52 (s, 1H), 3.54 (s, 3H). 13C NMR (100 MHz, CD3CN) δ 134.9, 131.2, 130.6, 130.3, 128.0, 124.8, 122.4, 105.8, 74.7, 47.6; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C12H13Cl3N: 262.9902; found: 262.9902.

2-Benzyl-1-(trichloromethyl)-1,2-dihydrophthalazine (31).

Phthalazine (665 mg, 5.1 mmol) and benzyl bromide (1.2 mL, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 mL, 12.5 mmol) and trichloroacetic acid (1.63 g, 10 mmol) were added. The reaction mixture was heated at 40 °C for 1 h. To the crude reaction mixture was added aqueous NaHCO3 10% (25 mL). The crude reaction mixture was purified using plug filtration with DCM to give the title compound as a brown solid (1.48 g, 87%); mp 98.2-
100.2 °C; \(^1\)H NMR (400MHz, CD\(_3\)CN) δ 7.61 – 7.39 (m, 4H), 7.39 – 7.28 (m, 1H), 7.26 – 7.14 (m, 3H), 7.14 – 7.03 (m, 2H), 5.67 (s, 1H), 5.11 (d, \(J = 15.6\) Hz, 1H), 5.01 (d, \(J = 15.6\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN) δ 139.9, 136.5, 131.0, 130.69, 130.65, 129.4, 128.4, 128.2, 127.9, 125.0, 122.8, 105.9, 73.5, 63.6; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{16}\)H\(_{14}\)Cl\(_3\)N\(_2\): 339.0217; found: 339.0219.

1-Methyl-2-(trichloromethyl)-1,2-dihydro-1,10-phenanthroline and 1-methyl-4-(trichloromethyl)-1,4-dihydro-1,10-phenanthroline (32 + 33).

Phenanthridine (901 mg, 5 mmol) and Mel (623 \(\mu\)L, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 ml, 12.5 mmol) and trichloroacetic acid (2.45 g., 15 mmol) was added. The reaction mixture was heated at 40 °C for 2 h. To the crude reaction mixture was added aqueous NaHCO\(_3\) 10% (25 mL). The reaction mixture was cooled to room temperature and triethyl amine (1.74 ml, 12.5 mmol) and trichloroacetic acid (2.45 g., 15 mmol) was added. The crude reaction mixture was extracted with Et\(_2\)O (3 × 50 mL). The combined organic phases were washed with aqueous NaHCO\(_3\) (3 × 50 mL) and brine (50 mL), dried using Na\(_2\)SO\(_4\), filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 10% DCM in toluene pentane to give 32 and 33 as an inseparable mixture (1.22 g, 77%) green solid; mp 114-116 °C.

1-methyl-2-(trichloromethyl)-1,2-dihydro-1,10-phenanthroline (32): \(^1\)HNMR (400MHz, CD\(_3\)CN) δ \textit{inter alia} 8.13 (dd, \(J = 8.4, 1.6\) Hz, 1H) 7.39 (dd, \(J = 8.4, 4.4\) Hz, 1H) 7.36-7.28 (m, 2H), 7.03 (d, \(J = 9.2\) Hz, 1H), 6.15 (dd, \(J = 9.6, 6.0\) Hz, 1H), 4.84 (d, \(J = 6.0\) Hz, 1H), 3.77 (s, 3H)

1-methyl-4-(trichloromethyl)-1,4-dihydro-1,10-phenanthroline (33): \(^1\)HNMR (400MHz, CD\(_3\)CN) δ \textit{inter alia} 8.21 (dd, \(J = 8.4, 1.6\) Hz, 1H), 7.57-7.47 (m, 3H), 6.68 (d, \(J = 6.8\) Hz, 1H), 5.16 (dd, \(J = 7.2, 6.0\) Hz, 1H), 4.66 (d, \(J = 1.6\) Hz, 1H), 3.98 (s, 3H)

Both isomers: \(^{13}\)C NMR (100 MHz, CD\(_3\)CN) δ 148.5, 147.9, 142.4, 141.9, 140.1, 137.5, 137.0, 132.2, 131.0, 130.8, 127.0, 123.8, 122.3, 122.1, 121.1, 120.4, 119.0, 106.2, 97.4, 78.1, 60.2, 50.0, 43.6; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calculated for C\(_{14}\)H\(_{12}\)Cl\(_3\)N\(_2\): 313.0061; found: 313.0062.
NMR-spectra

1-Methylquinolin-1-ium iodide
1-Propylquinolin-1-ium iodide
1-allylquinolin-1-ium 4-methylbenzenesulfonate
1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (2)
1-methylquinolin-1-ium 2,2,2-trifluoroacetate (3)
2,3-Dimethyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (5)
5-Bromo-2-methyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (6)
6-Methoxy-1-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (7)

MeO
N
CF₃

MeO
N
CF₃

1.03
0.99
1.04
1.04
3.33
3.07

0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
11000
12000
13000
14000
15000
16000
17000
18000
19000
20000
21000
22000

0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
11000
12000
13000
14000
15000
16000
17000
18000
19000
20000
21000
22000

11.0 11.5 12.0 12.5 13.0 13.5 14.0 14.5 15.0 15.5 16.0 16.5 17.0 17.5 18.0 18.5 19.0 19.5 20.0 20.5 21.0 21.5 22.0 22.5 23.0
1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinolin-6-yl 4-methylbenzenesulfonate (8)
1,4-Dimethyl-2-(trifluoromethyl)-1,2-dihydroquinoline (9)
5-Methyl-6-(trifluoromethyl)-5,6-dihydrophenanthridine (10)
1-Methyl-2-(trifluoromethyl)-1,2-dihydro-1,10-phenanthroline (11)
7-Chloro-1-methyl-2-(trifluoromethyl)-2,3-dihydroquinolin-4-one (13)
1-Methyl-2-(trichloromethyl)-1,2-dihydroquinoline (14)
1,4-Dimethyl-2-(trichloromethyl)-1,2-dihydroquinoline (15)
1-Propyl-2-(trichloromethyl)-1,2-dihydroquinoline and 1-propyl-4-(trichloromethyl)-1,4-dihydroquinoline (16 + 17)
7-Chloro-4-(cyclopentyloxy)-1-methyl-2-(trichloromethyl)-1,2-dihydroquinoline (18)
2-Methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (19)
2-Methyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (20)
2-Propyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (21)
Ethyl 2-(1-(trichloromethyl)isoquinolin-2(1H)-yl)acetate (22)
2-Allyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (23)
2-Allyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (24)
6,7-Dimethoxy-2-methyl-1-(trichloromethyl)-1,2,3,4-tetrahydroisoquinoline (25)
3-methyl-4-(trichloromethyl)-3,4-dihydroquinazoline (26)
5-Methyl-6-(trichloromethyl)-5,6-dihydrophenanthridine (27)
5-Bromo-2-methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (28)
2,3-Dimethyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (29)

![Chemical structure image]

- Chemical formula: CCl₃
- Molecular weight: 29
2-Methyl-1-(trichloromethyl)-1,2-dihydrophthalazine (30)
2-Benzyl-1-(trichloromethyl)-1,2-dihydrophthalazine (31)
1-Methyl-2-(trichloromethyl)-1,2-dihydro-1,10-phenanthroline and 1-methyl-4-(trichloromethyl)-1,4-dihydro-1,10-phenanthroline (32 + 33)
References
2 Collischonn, C; Chemische Berichte, 1886, 19, 2507.
3 Dubois, M.G; Diaba F; Grellier-Marly, M.C, Synthesis, 1994, 8, 800.