Supplementary Information

Monoalkylation of amines with light electrophiles using a flow microreactor system

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General remarks:

$^1$H NMR spectra were obtained on a Bruker 300. In all measurements CDCl$_3$ was used as solvent unless otherwise noted. Chemical shifts $\delta$ are given in ppm relative to TMS as internal standard. Coupling constants $J$ are measured in Hz. Microflow reactions were performed with Harvard Apparatus syringe pumps (Pump 11 Elite) equipped with Hamilton gastight syringes (1 mL). Peek (P-885) and stainless steel (U-428) T-shaped micromixers with swept volume respectively of 29 nL and 570 nL were manufactured by IDEX Health & Science. Peek (1532) and stainless steel (U-137) microtubes with inner diameter respectively of 500 µm and 762 µm and fittings (PTFE and stainless steel) were also purchased from IDEX Health & Science. All chemicals were used as provided without further purification. Propyl, Allyl and propargyl triflate were freshly prepared according to the literature.$^{1,2}$ The conversion of amine into products was measured by $^1$H NMR spectra directly from the crude product for benzylamine and aniline derivatives.

Experimental procedures:

![Flow microreactor system for the alkylation of amines: general depiction (up); picture of the system used for alkylation with ROTf (R = Et, Pr, allyl and propargyl; Table 2, entries 1-14)](image)

**Figure S1:** Flow microreactor system for the alkylation of amines: general depiction (up); picture of the system used for alkylation with ROTf (R = Et, Pr, allyl and propargyl; Table 2, entries 1-14)

<table>
<thead>
<tr>
<th>Material</th>
<th>Ø (mm)</th>
<th>Length (cm)</th>
<th>V (µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Stainless Steel</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>M’1</td>
<td>Stainless Steel</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>M2</td>
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<td>-</td>
</tr>
<tr>
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</tr>
<tr>
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<tr>
<td>M, M’</td>
<td>PEEK</td>
<td>0.15</td>
<td>-</td>
</tr>
<tr>
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<td>PEEK</td>
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</tr>
<tr>
<td>R’</td>
<td>PEEK</td>
<td>0.5</td>
<td>3</td>
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</tbody>
</table>

**Table S1:** Features of the micromixers and -reactor used for the alkylation of amines (R > Me, Stainless steel; R = Me, PEEK)
Typical procedure for ethylation of benzylamine

(all syringes were filled with the reagents and the corresponding quantity of MeNO₂ to obtain a total volume of 1 mL). Syringe 1 (S1, 1 mL) was filled with benzylamine (88 µL, 0.8 mmol), 2,6-lutidine (18.5 µL, 0.2 mmol) in MeNO₂. Syringe 2 (S2, 1 mL) was filled with EtOTf (164 µL, 1.2 mmol) in MeNO₂. Syringe 3 (S3, 1 mL) was filled with 2,6-lutidine (74.1 µL, 0.6 mmol) and MeNO₂. Syringe (S4, 1 mL) contained a solution of aq. HCl 6 N. Micromixers (M) and microreactors (R) were immersed in a hot bath at 80 °C. Solutions in S1 and S2 were introduced into M1 (V = 570 nL, Ø = 0.5 mm) (flow rate = 707 µL/min) and passed through R1 (V = 220 µL). The resulting solution was reacted with 2,6-lutidine (S3) in M’1 (V = 570 nL, Ø = 0.5 mm) (flow rate = 707 µL/min) and passed through trough R’1 (V = 23 µL) and finally the reaction was quenched by HCl (S4) in M2 (flow rate = 707 µL/min) and collected in a flask. Volatiles were evaporated under vacuum and a few drops of a solution of aq. NaOH 2 N until pH > 9 was reached. The solution was extracted with CH₂Cl₂ (×3) and the combined organic layers were dried on MgSO₄, filtrated and evaporated under vacuum. The crude product was analyzed by ¹H NMR.

Typical procedure for methylation of dibenzylamine

(all syringes were filled with the reagents and the corresponding quantity of MeNO₂ to obtain a total volume of 1 mL). Syringe 1 (S1) was filled with dibenzylamine (157 µL, 0.8 mmol), 2,6-lutidine (18.5 µL, 0.2 mmol) and MeNO₂. Syringe 2 (S2) was filled with MeOTf (136 µL, 1.2 mmol) and MeNO₂. Syringe 3 (S3) was filled with 2,6-lutidine (74.1 µL, 0.6 mmol) and MeNO₂. Syringe (S4) contained a solution of aq. HCl 6 N. Micromixers (M) and microreactors (R) were immersed in a hot bath at 80 °C. Solution in S1 and S2 were introduced into M (V = 58 nL, Ø = 0.15 mm) (flow rate = 1414 µL/min) and passed through R (V = 47.1 µL) for 1 s. The resulting solution was reacted with 2,6-lutidine (S3) in M’ (V = 58 nL, Ø = 0.15 mm) (flow rate = 1414 µL/min) and passed through trough R’ (V = 5.9 µL) and finally the reaction was quenched by HCl (S4) in M2 (flow rate = 1414 µL/min) and collected in a flask. Volatiles were evaporated under vacuum and a few drops of a solution of aq. NaOH 2 N until pH > 9 was reached. The solution was extracted with CH₂Cl₂ (×3) and the combined organic layers were dried on MgSO₄, filtrated and evaporated under vacuum. The crude product was purified by column chromatography with a solution of Cyclohexane and AcOEt (99/1) to give ¹₀ (74 mg, 84%).
NMR data and spectra

*N*-Methyldibenzylamine (data consistent with literature)³

$^1$H NMR (CDCl₃, 300 MHz), $\delta$: 7.33 – 7.16 (m, 10H), 3.43 (s, 4H), 2.10 (s, 3H).

$^{13}$C NMR (CDCl₃, 75 MHz), $\delta$: 139.5, 129.1, 128.3, 127.1, 62.0, 42.4.
N-Ethylbenzylamine (data consistent with literature)\textsuperscript{4}

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz), \(\delta\): 7.35 – 7.15 (m, 10H), 3.48 (s, 4H), 2.42 (q, \(J = 7.1\), 2H), 0.98 (t, \(J = 7.1\), 3H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz), \(\delta\): 140.2, 128.9, 128.3, 126.8, 57.9, 47.2, 12.0.
N-Propyldibenzylamine (data consistent with literature)\textsuperscript{5}

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz), \(\delta\): 7.40 – 6.88 (m, 10H), 3.44 (s, 4H), 2.28 (dd, \(J = 7.4, <0.5, 2H\)), 1.42 (s, \(J = 7.4, 2H\)), 0.75 (t, \(J = 7.4, 3H\)).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz), \(\delta\): 140.2, 128.9, 128.2, 126.8, 58.4, 55.6, 20.3, 12.0.
N-allyldibenzylamine (data consistent with literature)\(^6\)

\(^1\)H NMR (CDCl\(_3\), 300 MHz), \(\delta\): 7.53 – 6.99 (m, 10H), 5.87 (ddt, \(J = 16.5, 10.2, 6.3, 1\)H), 5.28 – 4.90 (m, 2H), 3.54 (s, 4H), 3.02 (dt, \(J = 6.2, 1.2\) Hz, 2H).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz), \(\delta\): 139.8, 136.1, 128.9, 128.3, 126.9, 117.5, 57.9, 56.45.
N-Propargyldibenzylamine (data consistent with literature)\textsuperscript{7}

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz), \(\delta\): 7.34 – 7.14 (m, 10H), 3.61 (s, 4H), 3.18 (d, \(J = 2.4\), 2H), 2.19 (t, \(J = 2.4\), 1H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz), \(\delta\): 138.9, 129.2, 128.5, 127.3, 78.6, 73.6, 41.3.
$N$-Methyl-$N$-benzylaniline (data consistent with literature)$^8$

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 7.32 – 7.02 (m, 7H), 6.75 – 6.52 (m, 3H), 4.44 (s, 2H), 2.92 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 149.9, 139.17, 129.2, 128.6, 126.9, 126.8, 116.6, 112.4, 56.7, 38.6.
$N$-Ethyl-$N$-benzylaniline (data consistent with literature)\(^9\)

$^1$H NMR (CDCl\(_3\), 300 MHz), \(\delta\): 7.35 – 6.98 (m, 7H), 6.72 – 6.45 (m, 3H), 4.41 (s, 2H), 3.37 (q, \(J = 7.1\) Hz, 2H), 1.10 (t, \(J = 7.1\) Hz, 3H).

$^{13}$C NMR (CDCl\(_3\), 75 MHz), \(\delta\): 148.2, 139.0, 128.9, 128.2, 126.4, 126.2, 115.7, 111.8, 53.6, 44.8, 11.8.

\[\text{Diagram of } N\text{-Ethyl-N-benzylaniline}\]

\[\text{NMR Spectra of } N\text{-Ethyl-N-benzylaniline}\]
**N-Propyl-N-benzylaniline**

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 7.36 – 6.96 (m, 7H), 6.73 – 6.42 (m, 3H), 4.47 (s, 2H), 3.28 (dd, $J = 7.4, 2H$), 1.61 (s, $J = 7.4, 2H$), 0.86 (t, $J = 7.4, 3H$).

$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 148.8, 139.3, 129.3, 128.7, 126.8, 126.6, 116.1, 112.2, 54.6, 53.2, 20.5, 11.6.

HRMS (ESI) $m$/z [M+H]$^+$ caleld for C$_{16}$H$_{19}$N 226.1596, found 226.1596
N-Allyl-N-benzylaniline (data consistent with literature)\textsuperscript{10}

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 7.40 – 6.89 (m, 7H), 6.73 – 6.52 (m, 3H), 5.88 – 5.75 (m, 1H), 5.22 – 5.05 (m, 2H), 4.47 (s, 2H), 3.94 (m, 2H). $^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 149.1, 139.1, 133.8, 129.3, 128.7, 127.0, 126.7, 116.7, 116.5, 112.5, 54.1, 53.19.