Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supplementary Information

Monoalkylation of amines with light electrophiles using a flow microreactor system

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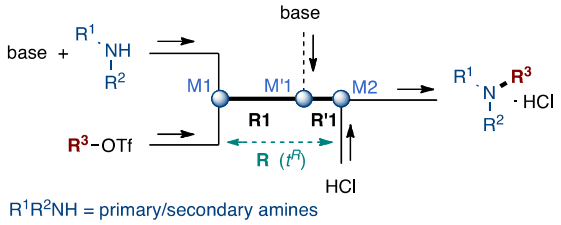
General remarks:

^{1}H NMR spectra were obtained on a Bruker 300. In all measurements $CDCl_3$ was used as solvent unless otherwise noted. Chemical shifts δ 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 stell (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.

(1) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859–1862.
(2) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064–71.

Experimental procedures:



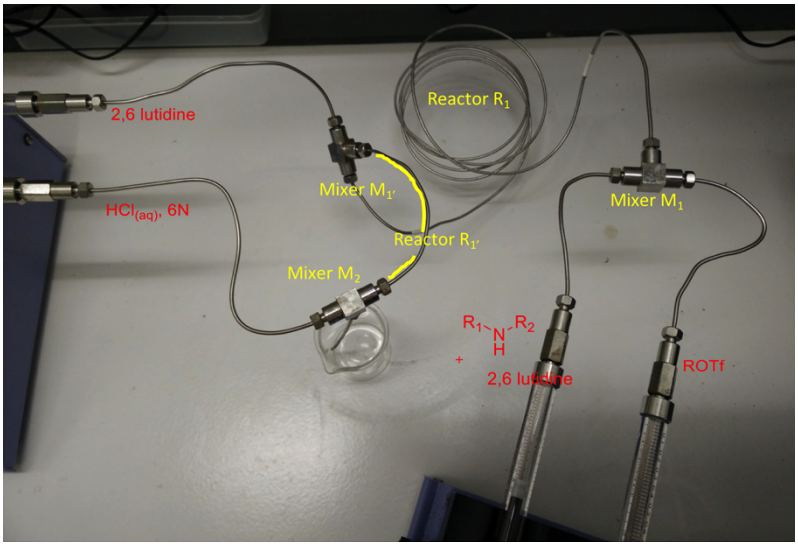
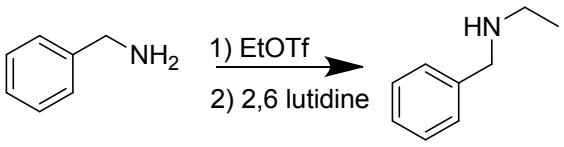


Figure S1: Flow microreactor system for the alkylation of amines: general depiction (up); picture of the system used for alkylation with ROTf (R = Et, Pr, allyl and propargyl; Table 2, entries 1-14)

	Material	$Ø_{in}$ (mm)	Length (cm)	V_{in}(µL)
M1	Stainless Steel	0.5	-	0.57
M'1	Stainless Steel	0.5	-	0.57
M2	Stainless Steel	1	-	2.1
R1	Stainless Steel	0.762	47	220
R'1	Stainless Steel	0.508	12	23
M, M'	PEEK	0.15	-	0.058
R	PEEK	0.5	24	47.1
R'	PEEK	0.5	3	5.9

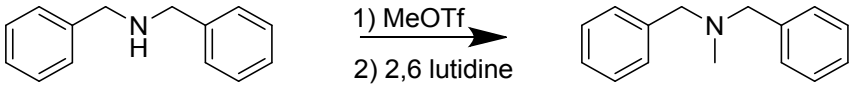
Table S1: Features of the micromixers and -reactor used for the alkylation of amines (R > Me, Stainless steel; R = Me, PEEK)

Typical procedure for ethylation of benzylamine



(all syringes were filled with the reagents and the corresponding quantity of $MeNO_2$ 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 $MeNO_2$. Syringe 2 (S2, 1 mL) was filled with EtOTf (164 µL, 1.2 mmol) in $MeNO_2$. Syringe 3 (S3, 1 mL) was filled with 2,6-lutidine (74.1 µL, 0.6 mmol) and $MeNO_2$. 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 CH_2Cl_2 (×3) and the combined organic layers were dried on $MgSO_4$, filtrated and evaporated under vacuum. The crude product was analyzed by ^1H NMR.

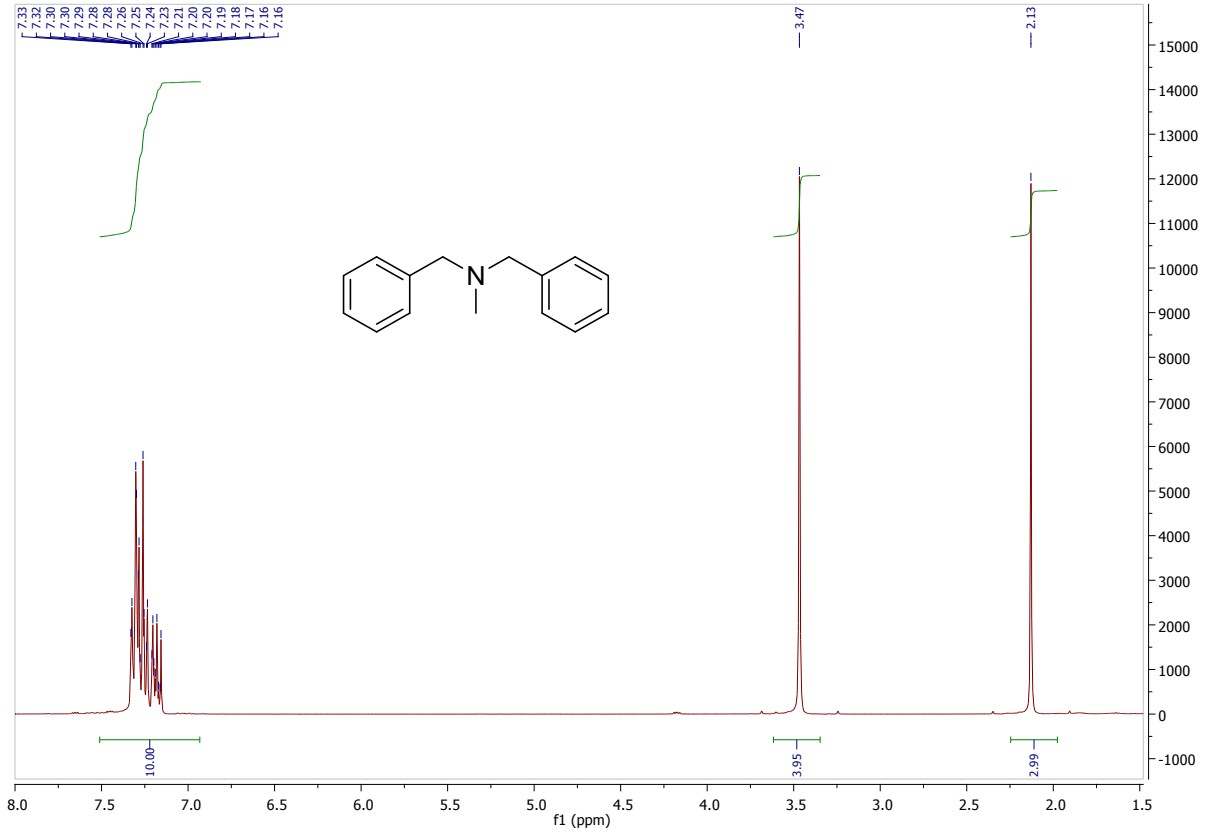
Typical procedure for methylation of dibenzylamine

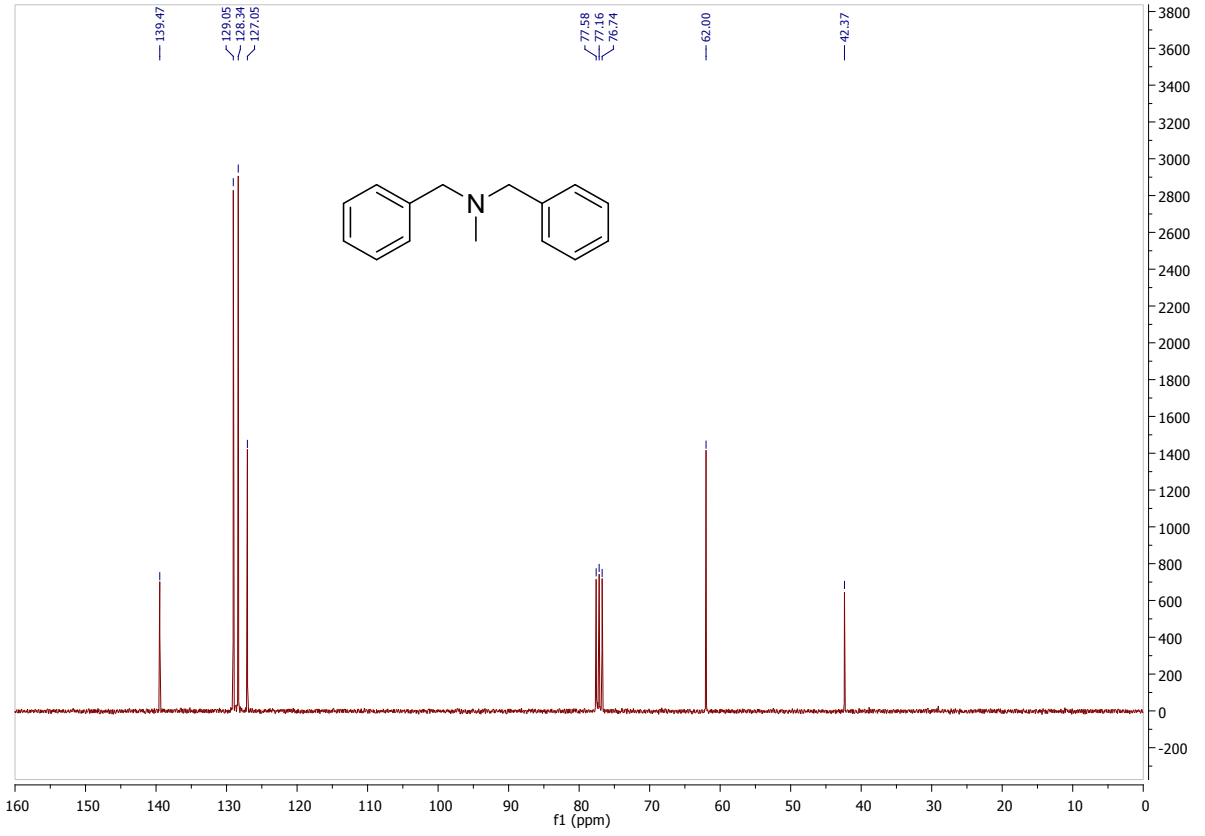


(all syringes were filled with the reagents and the corresponding quantity of $MeNO_2$ to obtain a total volume of 1 mL)Syringe 1 (S1) was filled with dibenzylamine (157 µL, 0.8 mmol), 2,6 lutidine (18.5 µL, 0.2 mmol) and $MeNO_2$. Syringe 2 (S2) was filled with MeOTf (136 µL, 1.2 mmol) and $MeNO_2$. syringe 3 (S3) was filled with 2,6 lutidine (74.1 µL, 0.6 mmol) and $MeNO_2$. 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 CH_2Cl_2 (×3) and the combined organic layers were dried on $MgSO_4$, 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 ($CDCl_3$, 300 MHz), δ: 7.33 – 7.16 (m, 10H), 3.43 (s, 4H), 2.10 (s, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz), δ: 139.5, 129.1, 128.3, 127.1, 62.0, 42.4.

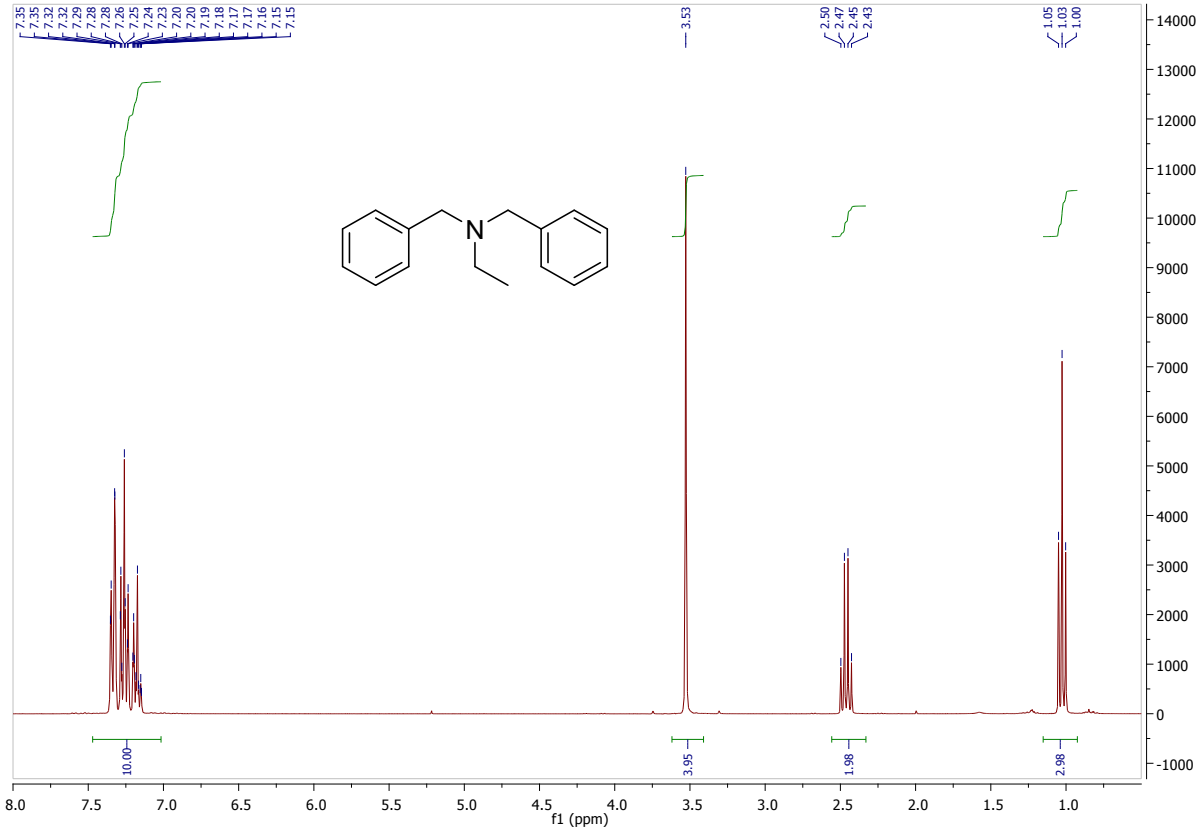


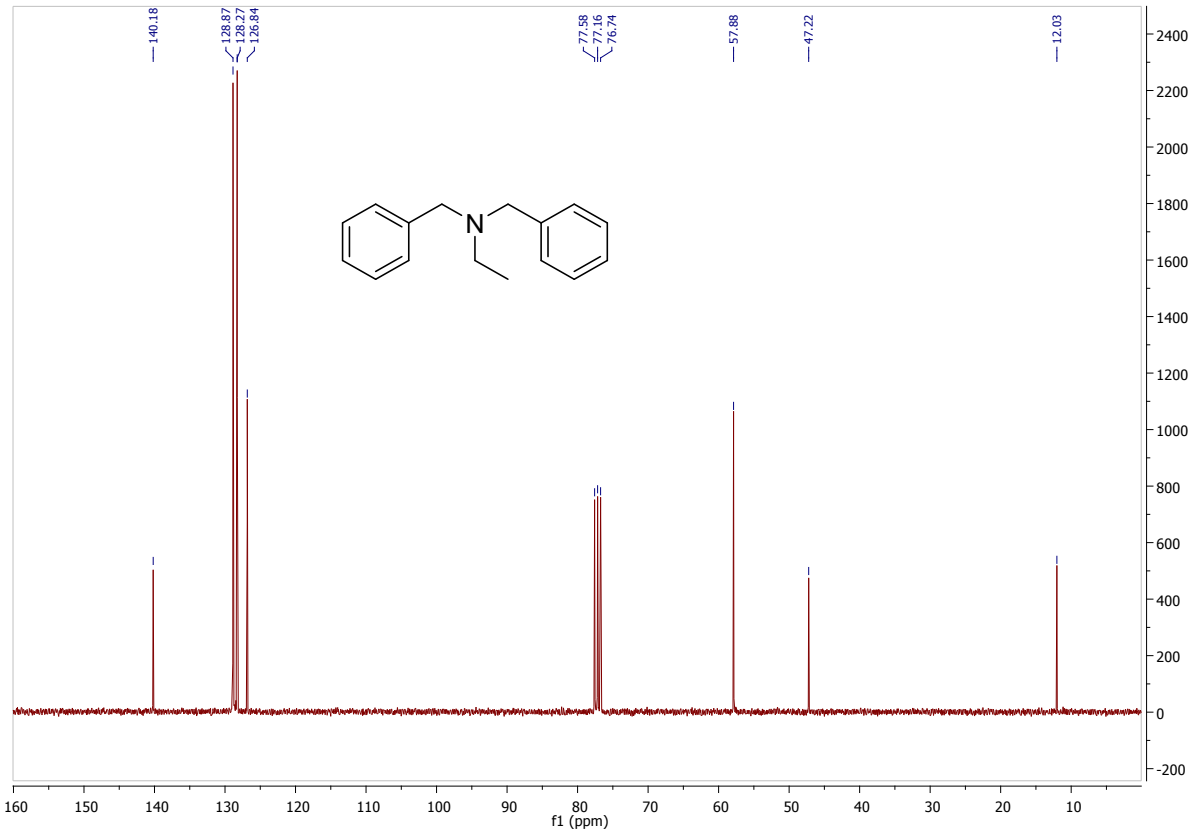


N-Ethyldibenzylamine (data consistent with literature)[4]

^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.35 – 7.15 (m, 10H), 3.48 (s, 4H), 2.42 (q, J = 7.1, 2H), 0.98 (t, J = 7.1, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 140.2, 128.9, 128.3, 126.8, 57.9, 47.2, 12.0.

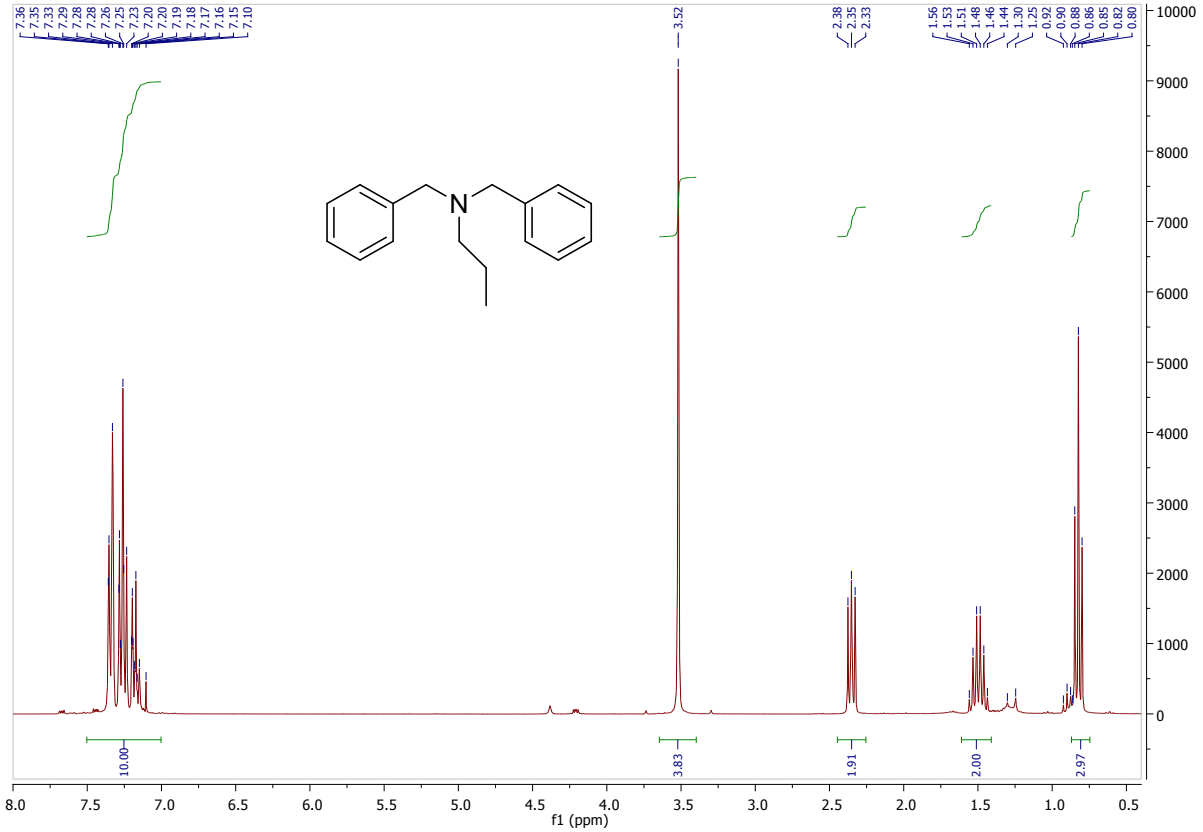


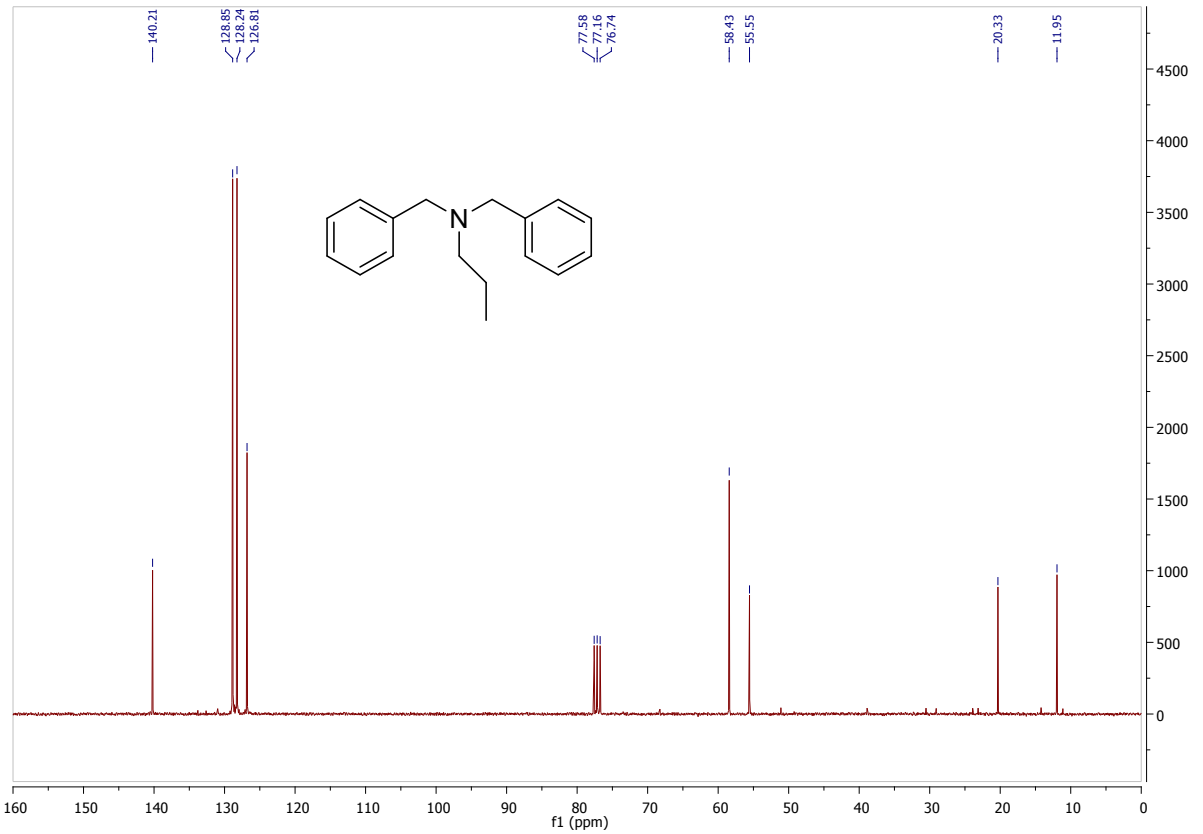


N-Propyldibenzylamine (data consistent with literature)[5]

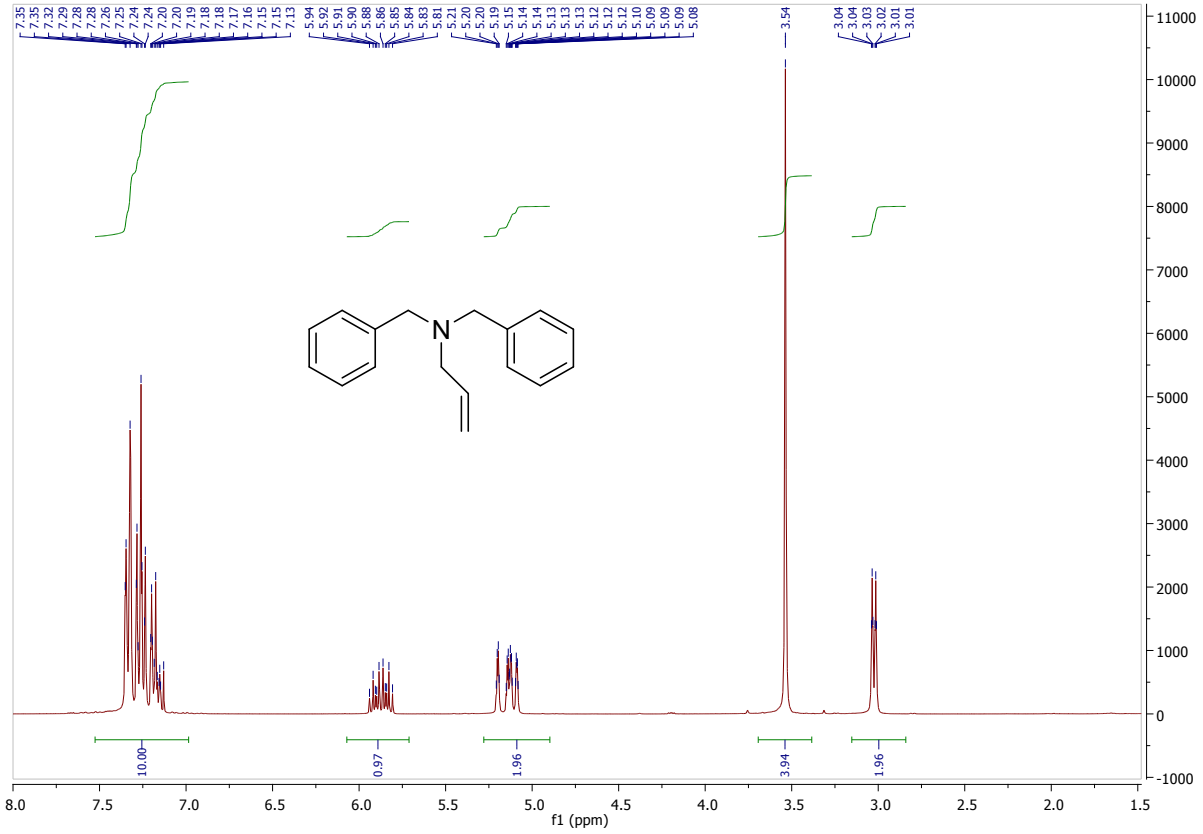
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.40 – 6.88 (m, 10H), 3.44, (s, 4H), 2.28 (dd, J = 7.4, <0.5 , 2H), 1.42 (s, J = 7.4, 2H), 0.75 (t, J = 7.4, 3H).

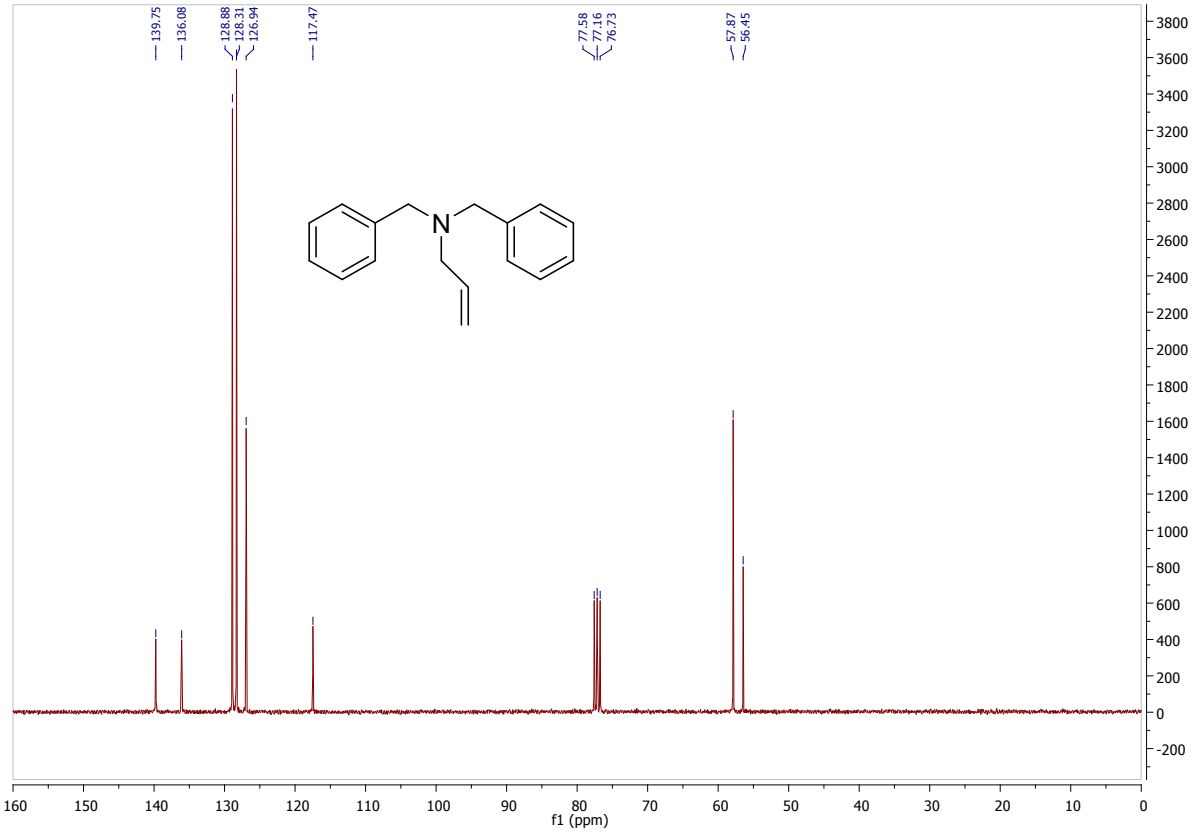
^{13}C NMR ($CDCl_3$, 75 MHz), δ: 140.2, 128.9, 128.2, 126.8, 58.4, 55.6, 20.3, 12.0.



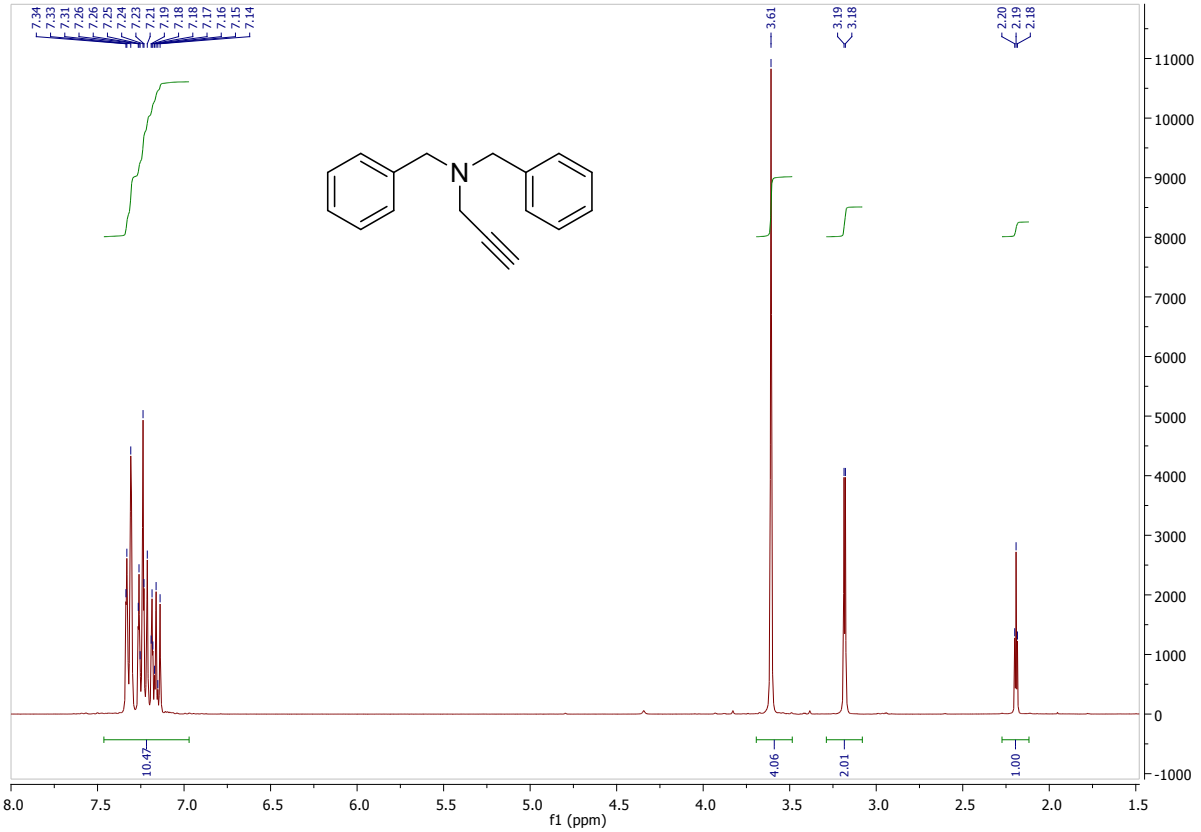


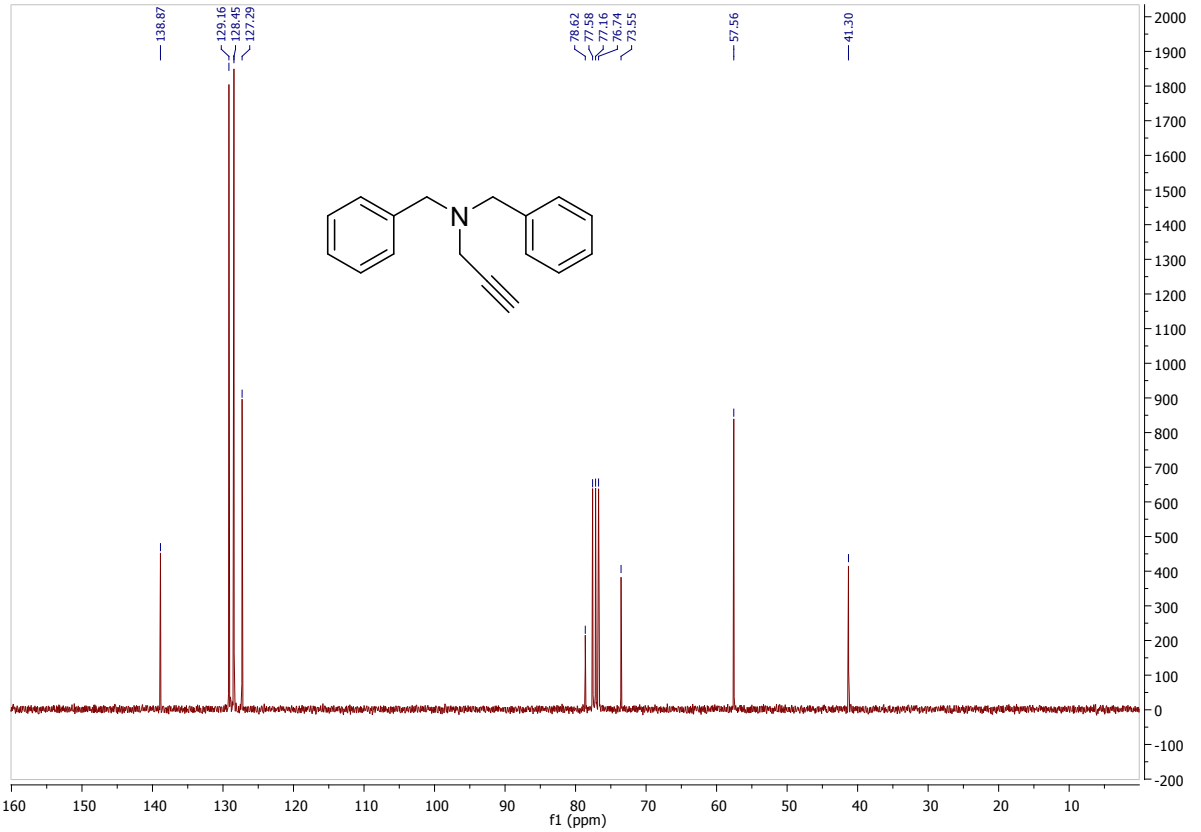
N-Allyldibenzylamine (data consistent with literature)[6]
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.53 – 6.99 (m, 10H), 5.87 (ddt, *J* = 16.5, 10.2, 6.3, 1H), 5.28 – 4.90 (m, 2H), 3.54 (s, 4H), 3.02 (dt, *J* = 6.2, 1.2 Hz, 2H).
^{13}C NMR ($CDCl_3$, 75 MHz), δ: 139.8, 136.1, 128.9, 128.3, 126.9, 117.5, 57.9, 56.45.



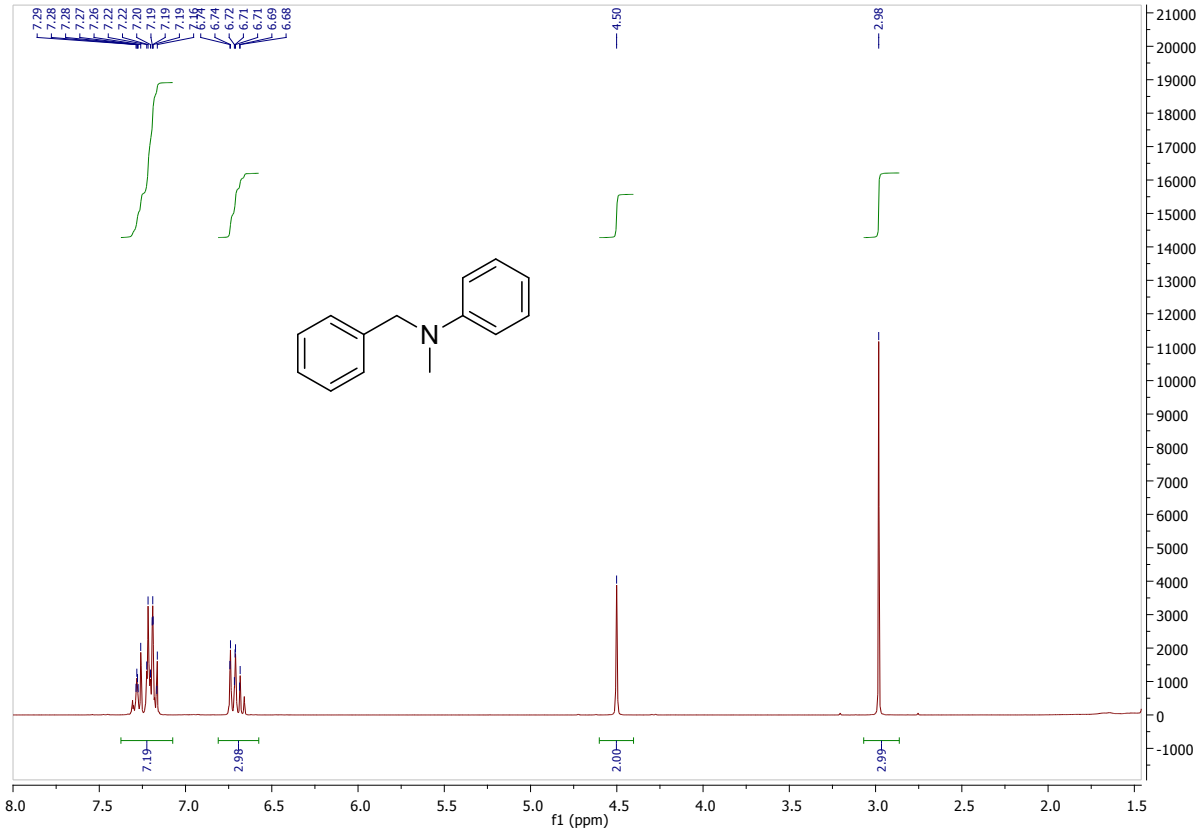


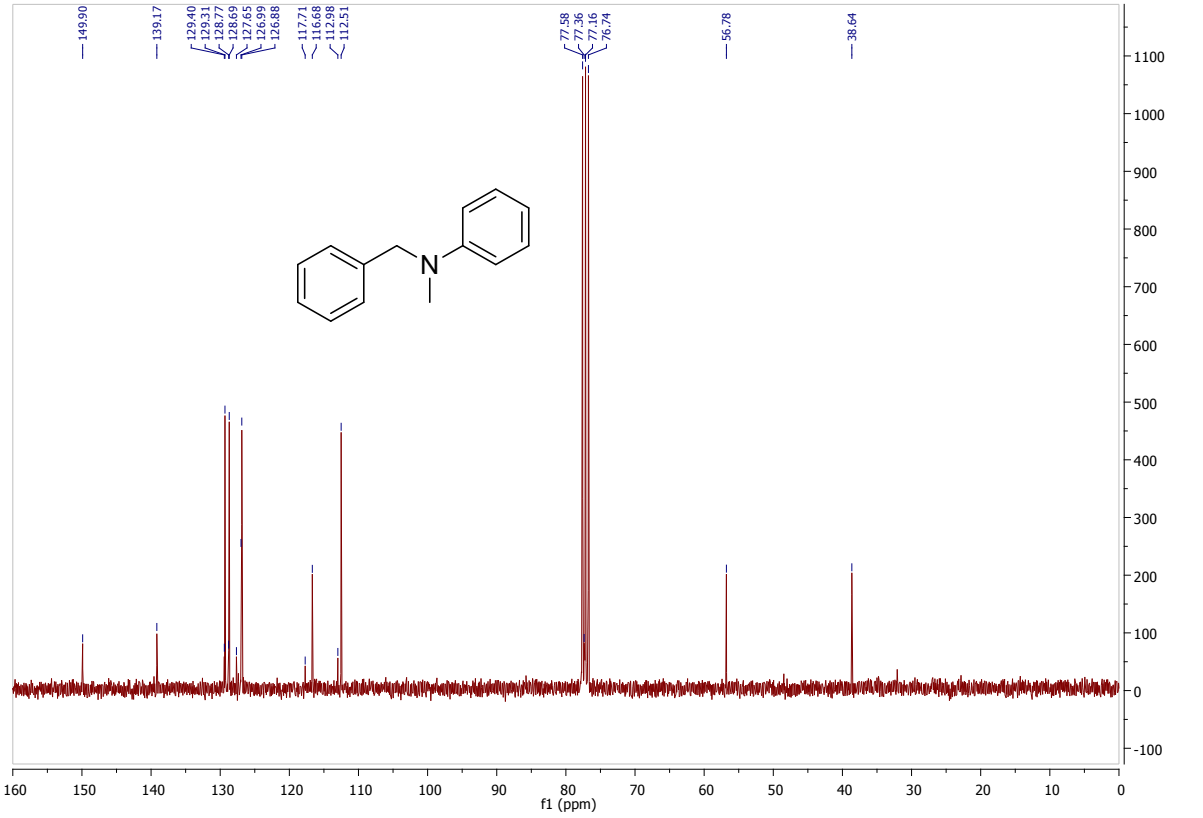
N-Propargyldibenzylamine (data consistent with literature)[7]
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.34 – 7.14 (m, 10H), 3.61 (s, 4H), 3.18 (d, J = 2.4, 2H), 2.19 (t, J = 2.4, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz), δ: 138.9, 129.2, 128.5, 127.3, 78.6, 73.6, 41.3.



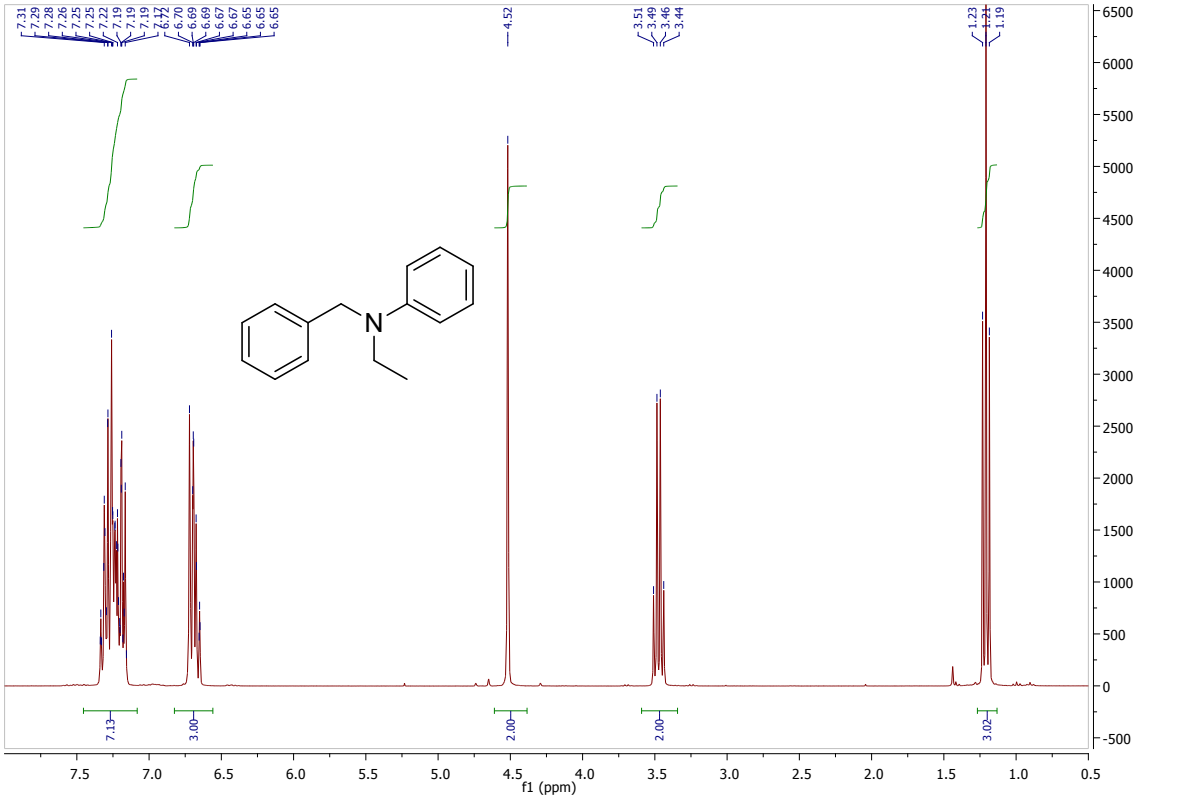


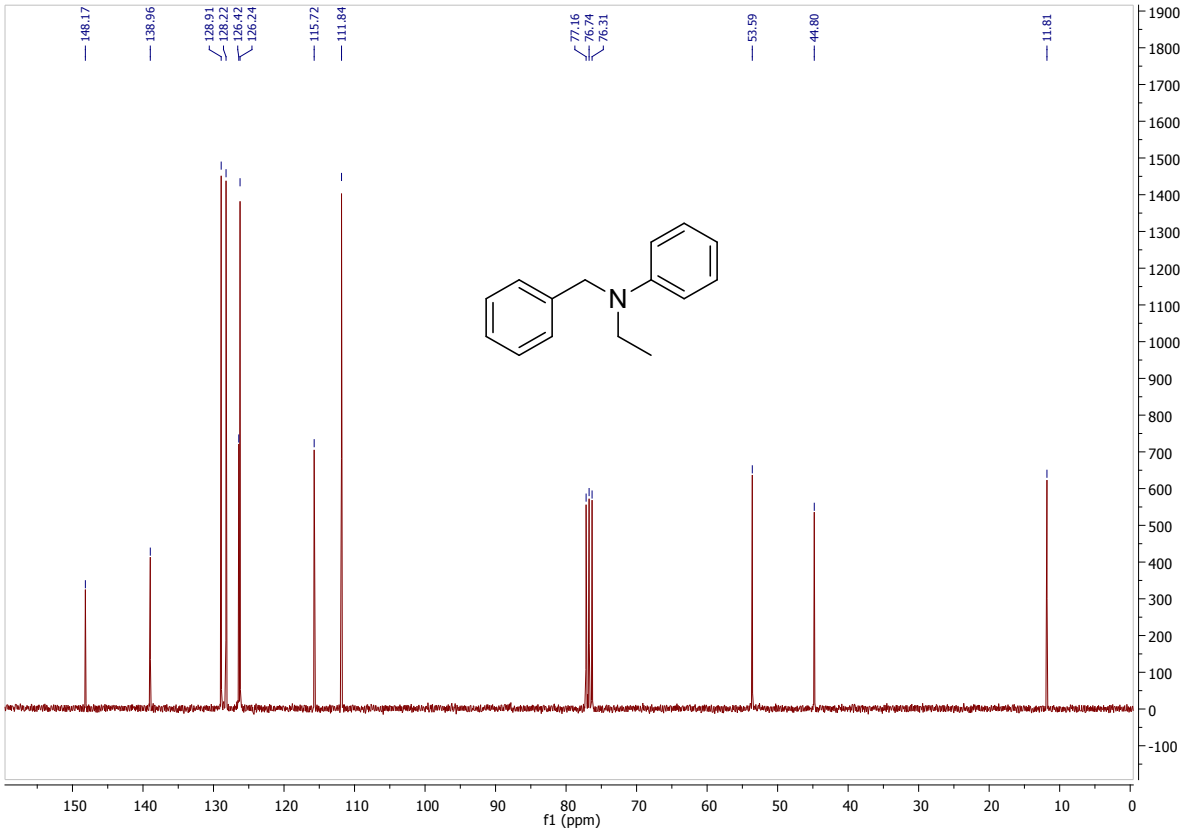
N-Methyl-*N*-benzylaniline (data consistent with literature)[8]
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.32 – 7.02 (m, 7H), 6.75 – 6.52 (m, 3H), 4.44 (s, 2H), 2.92 (s, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz), δ: 149.9, 139.17, 129.2, 128.6, 126.9, 126.8, 116.6, 112.4, 56.7, 38.6.





N-Ethyl-*N*-benzylaniline (data consistent with literature)[9]
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 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), δ: 148.2, 139.0, 128.9, 128.2, 126.4, 126.2, 115.7, 111.8, 53.6, 44.8, 11.8.



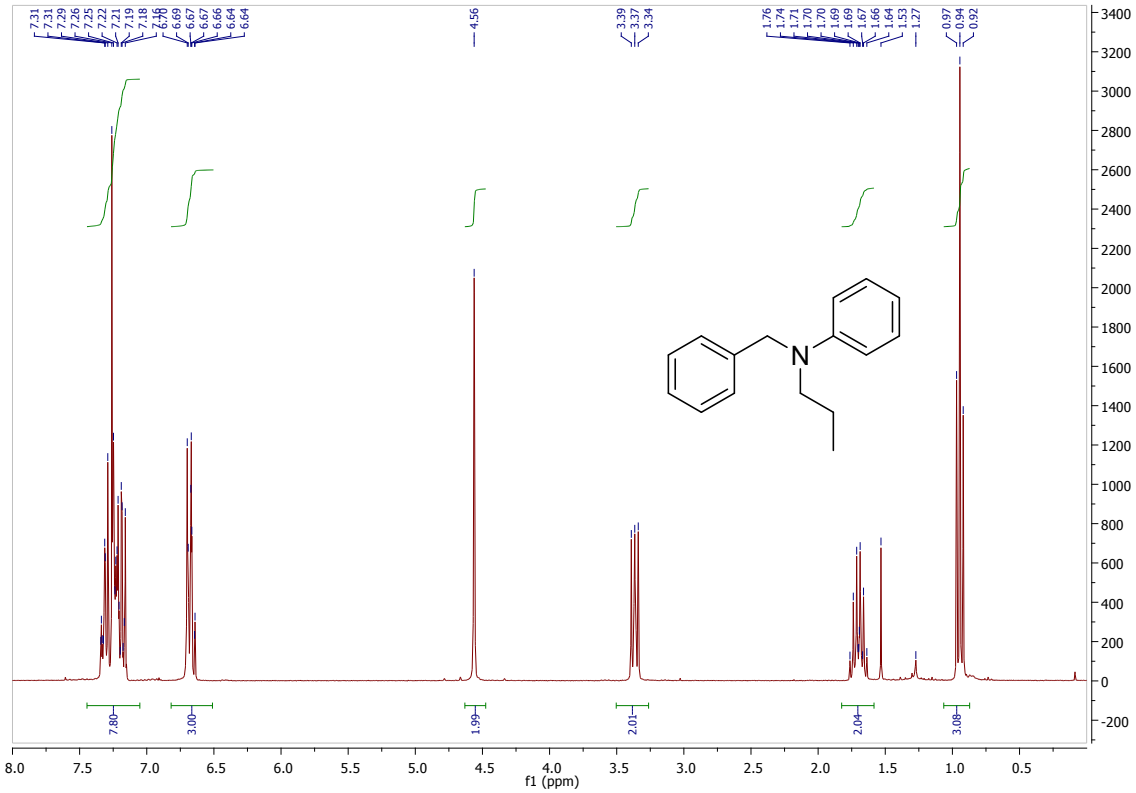


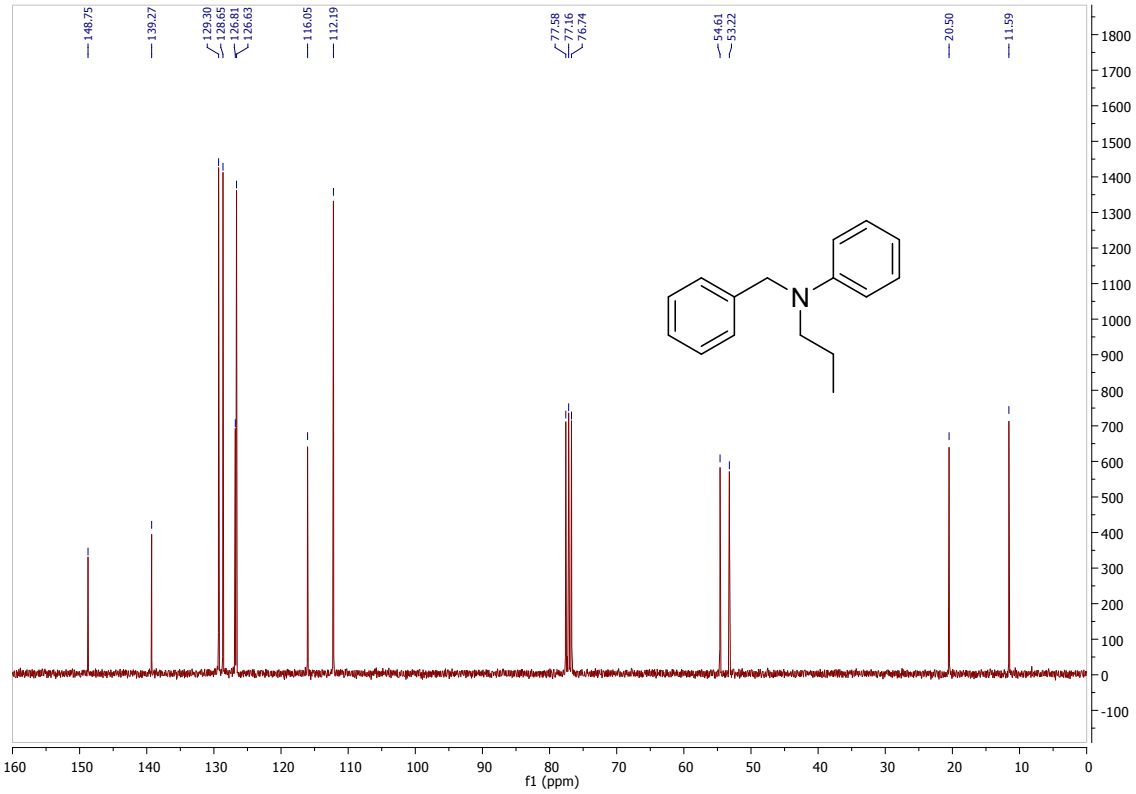
N-Propyl-*N*-benzylaniline

^{1}H NMR ($CDCl_3$, 300 MHz), δ: 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), δ: 148.8, 139.3, 129.3, 128.7, 126.8, 126.6, 116.1, 112.2, 54.6, 53.2, 20.5, 11.6.

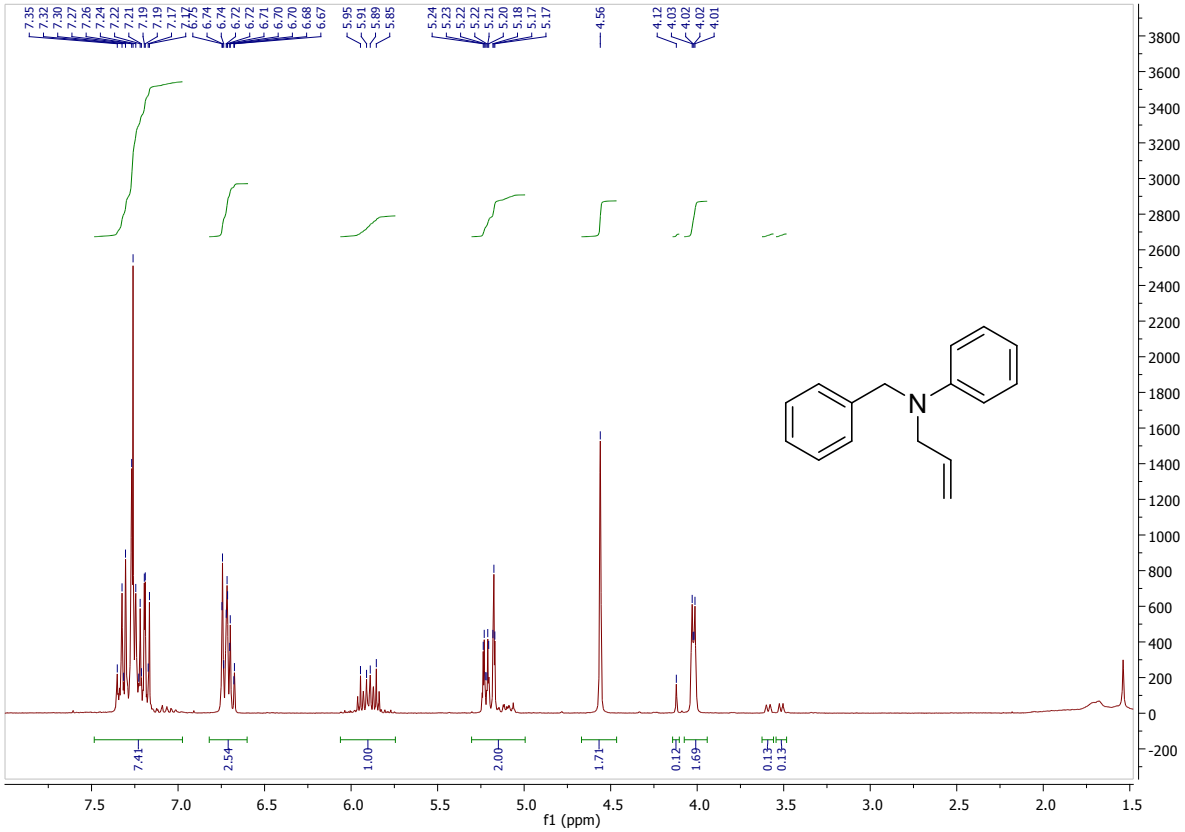
HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N$ 226.1596, found 226.1596

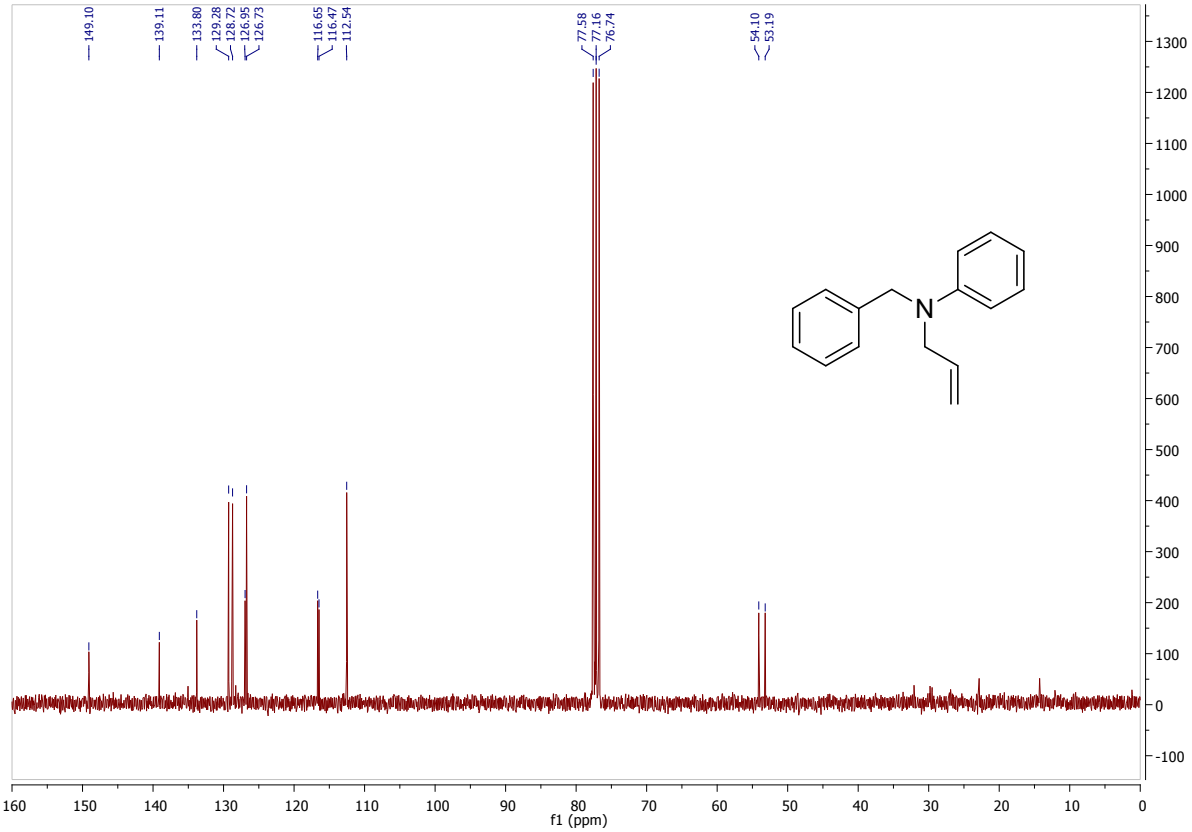




N-Allyl-*N*-benzylaniline (data consistent with literature)[10]

^{1}H NMR ($CDCl_3$, 300 MHz), δ: 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), δ: 149.1, 139.1, 133.8, 129.3, 128.7, 127.0, 126.7, 116.7, 116.5, 112.5, 54.1, 53.19.





(1) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859.
(2) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064.
(3) Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. *J. Org. Chem.* **2007**, *72*, 7551.
(4) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9507.
(5) Tokizane, M.; Sato, K.; Sakami, Y.; Imori, Y.; Matsuo, C.; Ohta, T.; Ito, Y. *Synthesis* **2010**, *2010*, 36.
(6) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354.
(7) Sugiishi, T.; Kimura, A.; Nakamura, H. *J. Am. Chem. Soc.* **2010**, *132*, 5332.
(8) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598.
(9) Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. *Eur. J. Org. Chem.* **2010**, *2010*, 6719.
(10) Gómez-Ayala, S.; Castrillón, J. A.; Palma, A.; Leal, S. M.; Escobar, P.; Bahsas, A. *Bioorg. Med. Chem.* **2010**, *18*, 4721.