Efficient Phosphine-Mediated Formal C(sp^3)-C(sp^3) Coupling Reactions of Alkyl Halides in Batch and Flow

Uyen P. N. Tran,[a] Katharina J. Hock,[a,b] Christopher P. Gordon,[c,*] Rene M. Koenigs[b,*] and Thanh V. Nguyen[a,*]

School of Chemistry, University of New South Wales, Sydney, Australia. Email: t.v.nguyen@unsw.edu.au

Institute of Organic Chemistry, RWTH Aachen University, Aachen, Germany. Email: rene.koenigs@rwth-aachen.de

School of Science and Health, Western Sydney University, Campelltown, Australia. Email: c.gordon@westernsydney.edu.au

Supporting Information

Table of Contents

General Methods

Reactions, unless otherwise stated, were conducted under a positive pressure of argon in oven-dried glassware. Toluene, CH_2Cl_2, tetrahydrofuran (THF), and acetonitrile were dried with an SPS apparatus. Commercially available reagents were used as purchased unless otherwise noted. Polymer supported triphenylphosphine (CAS # 39319-11-4, catalogue # 93093) was purchased from Sigma-Alrich and used as is. Analytical thin layer chromatography was performed using aluminium plates precoated with silica gel 60 F_{254} (0.2 mm). Flash chromatography employed 230-400 mesh silica gel. Solvents used for chromatography are quoted as volume/volume ratios.

NMR spectroscopy was performed at 298 K using an Avance III HD 400 (400.1 MHz, ^{1}H; 100.6 MHz, ^{13}C, 376.5 MHz, ^{19}F) or an Avance III 300 (300 MHz, ^{1}H; 75 MHz, ^{13}C; 282.5 MHz, ^{19}F). Data is expressed in parts per million (ppm) downfield shift from tetramethylsilane with residual solvent as an internal reference (δ 7.26 ppm for chloroform, 5.27 ppm for dichloromethane, 1.94 ppm for acetonitrile, and 2.09 ppm for the toluene methyl group) and is reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J in Hz) and integration (number of protons). ^{13}C NMR spectra were recorded at 298 K with complete proton decoupling. Data is expressed in parts per million (ppm) downfield shift relative to the internal reference (δ 77.2 ppm for the central peak of deuterated chloroform).

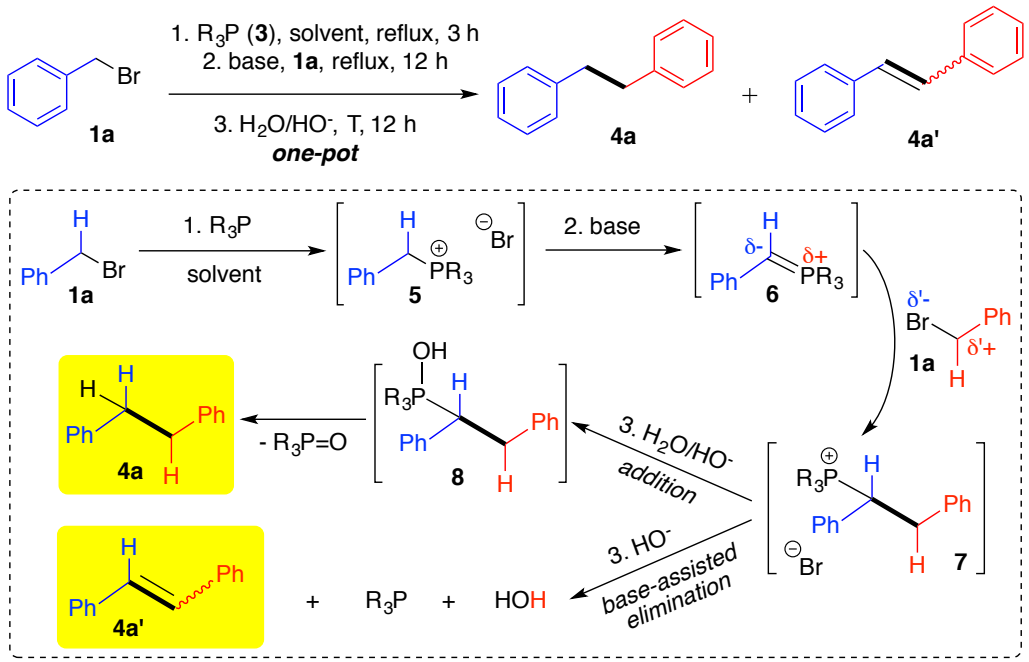
Infrared spectra were obtained on a ThermoNicolet Avatar 370 FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). HRMS were performed at the Bioanalytical Mass Spectrometry Facility within the Mark Wainwright Analytical Centre at the University of New South Wales on an Orbitrap LTQ XL (Thermo Fisher Scientific, San Jose, CA, USA) ion trap mass spectrometer. LCMS and GCMS analyses were carried out on Shimadzu LCMS-2010 EV and GCMS-QP2010 Ultra, respectively.

Microwave reactions were carried out in 35 mL microwave vials on CEM Discover – SP W/ACTIVENT 909155 or 30 mL vials on Anton Paar Monowave 300.

Phosphine Auxiliary Screening and Optimization of the C(sp^3)-C(sp^3) Coupling Reaction

General procedure for Table 1: A mixture of benzylbromide (1.0 mmol) and phosphine **3** (1.0 mmol) was taken up in dry solvent (3 mL) in a reaction flask loaded with a stirrer bar under argon atmosphere. The reaction mixture was heated to the indicated temperature then cooled to room temperature. A 2 mL solution of benzylbromide (1.0 mmol) and base (1.0 mmol) was subsequently added. The reaction mixture was heated to the indicated temperature again then cooled to room temperature. An aqueous solution of NaOH (indicated molar concentration, 1 mL) was then added and the reaction mixture was heated to the indicated temperature again then cooled to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic phases was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The products were purified from the residues by column chromatography (silica-gel, 100% hexanes → hexane/EtOAc = 95/5).

Table 1: Phosphine auxiliary screening and optimization of the reaction[a]



Entry	R_3P (3)	base/solvent	[OH^-]/T	Yield[b] (%) 4a/4a'
1	Cy_3P	KHMDS/THF	2 M/70 °C	21/trace
2[c]	$Cy_3P{\cdot}HBF_4$	KHMDS/THF	2 M/70 °C	30/trace
3	$^tBu_3P$	KHMDS/THF	2 M/70 °C	58/11
4[c]	$^tBu_3P{\cdot}HBF_4$	KHMDS/THF	2 M/70 °C	56/12
5	$^nBu_3P$	KHMDS/THF	2 M/70 °C	15/trace
6	**Ph_3P**	**KHMDS/THF**	**2 M/70 °C**	**60/12**
7	*o*-Tol_3P	KHMDS/THF	2 M/70 °C	49/n.d.
8	p-Tol_3P	KHMDS/THF	2 M/70 °C	57/n.d.
9	(1-naphthyl)$_3P$	KHMDS/THF	2 M/70 °C	40/32

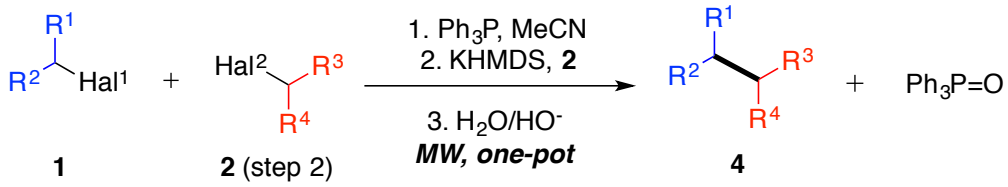
10	(2-furyl)$_3$P	KHMDS/THF	2 M/70 °C	64/15
11	(2,4,6-MeO$_3$Ph)$_3$P	KHMDS/THF	2 M/70 °C	51/n.d.
12	(C$_6$F$_5$)$_3$P	KHMDS/THF	2 M/70 °C	trace/n.d.
13	Ph$_3$P	LDA/THF	2 M/70 °C	58/18
14	Ph$_3$P	KO^{t}Bu/THF	2 M/70 °C	34/14
15	Ph$_3$P	KHMDS/Tol	2 M/70 °C	49/trace
16	**Ph$_3$P**	**KHMDS/MeCN**	**2 M/70 °C**	**66/trace**
17[d]	**Ph$_3$P-resin**	**KHMDS/MeCN**	**2 M/70 °C**	**65/5**
18	Ph$_3$P	KHMDS/MeCN	1 M/70 °C	54/trace
19	Ph$_3$P	KHMDS/MeCN	5 M/70 °C	51/20
20	Ph$_3$P	KHMDS/MeCN	2 M/rt	12/trace
21	Ph$_3$P	KHMDS/MeCN	2 M/100 °C	84/trace
22[e]	**Ph$_3$P**	**KHMDS/MeCN**	**2 M/150 °C**	**94/trace**
23[d,e]	**Ph$_3$P-resin**	**KHMDS/MeCN**	**2 M/150 °C**	**89/trace**

[a] Reaction conditions: halide **1a** (1.0 mmol) and phosphine **3** (1.0 mmol) in THF (3 mL), followed by the addition of **1a** (1.0 mmol) and base (1.0 mmol), finally aq. NaOH (1 mL) with conventional heating; [b] Overall yield of isolated product; [c] Phosphonium tetrafluoroborate was deprotonated with 1 equiv of base in step 1; [d] Ph$_3$P on polymer support (~3 mmol/g) was used; [e] All steps were carried out in MW reactor (reaction time: step 1 = 2 h at 150 °C, step 2 = 3 h at 150 °C, step 3 = 1 h at 100 °C).

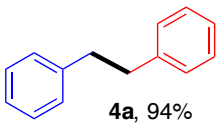
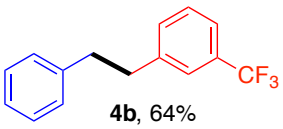
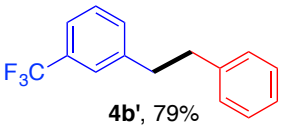
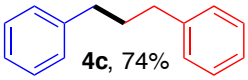
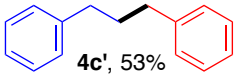
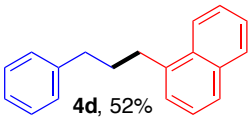
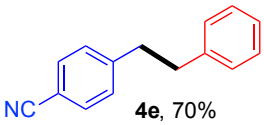
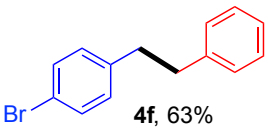
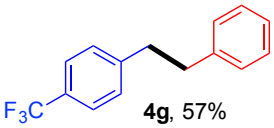
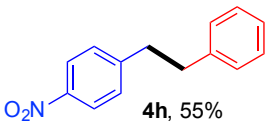
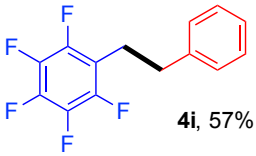
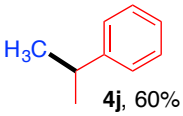
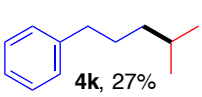
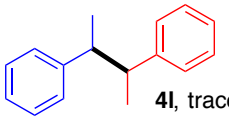
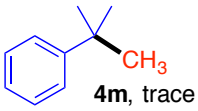
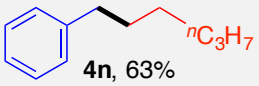
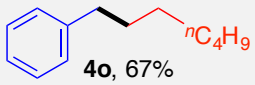
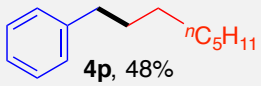
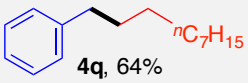
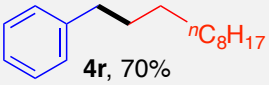
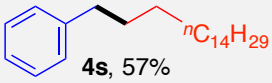
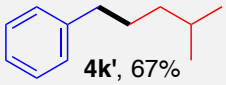
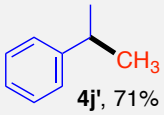
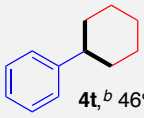
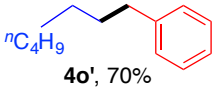
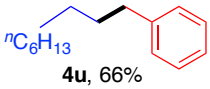
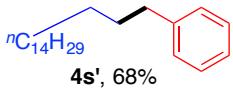
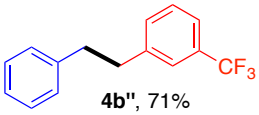
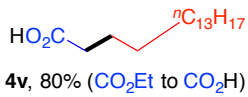
Substrate Scope under Microwave-Assisted Conditions

General procedure for Table 2: A mixture of halide **1** (1.0 mmol) and triphenylphosphine (1.0 mmol) was taken up in dry acetonitrile (3 mL) in a microwave vial loaded with a stirrer bar. The reaction mixture was heated to 150 °C in microwave reactor (ramp-up time 2 min, holding time 120 min) then cooled to room temperature. A 2 mL solution of halide **2** (1.0 mmol) and KHMDS (1.0 mmol) was subsequently added to the reaction vial. The reaction mixture was heated to 150 °C again (ramp-up time 2 min, holding time 180 min) then cooled to room temperature. An aqueous solution of NaOH (2 M, 1 mL, 2 mmol) was then added and the reaction mixture was heated to 100 °C (ramp-up time 2 min, holding time 60 min) before cooled to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic phases was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified from the residues by column chromatography (silica-gel, 100% hexanes → hexane/EtOAc = 95/5).

Table 2: Substrate scope under microwave-assisted conditions[a]

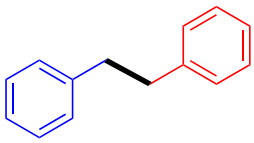


1 **2** (step 2) **4**

Hal^1 = Br Hal^2 = Br	 **4a**, 94%	 **4b**, 64%	 **4b'**, 79%
	 **4c**, 74%	 **4c'**, 53%	 **4d**, 52%
	 **4e**, 70%	 **4f**, 63%	 **4g**, 57%
	 **4h**, 55%	 **4i**, 57%	 **4j**, 60%
	 **4k**, 27%	 **4l**, trace	 **4m**, trace
Hal^1 = Br Hal^2 = I	 **4n**, 63%	 **4o**, 67%	 **4p**, 48%
	 **4q**, 64%	 **4r**, 70%	 **4s**, 57%
	 **4k'**, 67%	 **4j'**, 71%	 **4t**,[b] 46%[10]
Hal^1 = I Hal^2 = Br	 **4o'**, 70%	 **4u**, 66%	 **4s'**, 68%
Hal^1 = Br Hal^2 = OMs	 **4b''**, 71%	Hal^1 = Br Hal^2 = OTs	 **4v**, 80% (CO_2Et to CO_2H)

[a] Reaction conditions: halide **1** (1.0 mmol) and Ph_3P (1.0 mmol) in MeCN (3 mL), followed by the addition of **2** (1.0 mmol) and KHMDS (1.0 mmol), finally aq. NaOH (2 M, 1 mL). All steps were carried out in MW reactor (reaction time: step 1 = 2 h at 150 °C, step 2 = 3 h at 150 °C, step 3 = 1 h at 100 °C); [b] From benzyl bromide and 1,5-diiodopentane.

Characterization Data of C(sp^3)-C(sp^3) Coupled Products (Table 2)



4a[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.26 (4H, m, Ar*H*), 7.21-7.17 (6H, m, Ar-*H*), 2.95 (4H, s, ArCH_2) ppm.

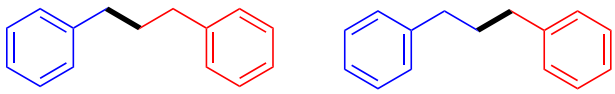
^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 128.5 (2C), 128.4 (2C), 126.0, 38.0 ppm.

4b[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.05 (m, 9H, ArH), 2.91–2.81 (m, 4H, $2CH_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.6, 141.1, 132.0, 131.9, 128.7, 128.5 (4C), 126.2, 125.2, 124.4, 122.8, 37.7, 37.6 ppm.

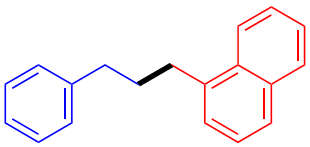
^{19}F NMR (282.5 MHz, $CDCl_3$): δ = -62.61 (d, J = 53.7 Hz) ppm.



4c[3]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.33 (m, 4H), 7.26 (d, J = 7.1 Hz, 6H, Ar-H), 2.67 (t, J = 8.1 Hz, 4H, Ar-CH_2), 2.03 (quintet, J = 7.3 Hz, 2H, Ar-CH_2-C*H*$_2$-CH_2-Ar) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.4, 128.6 (2C), 128.4 (2C), 125.9, 35.6, 33.1 ppm.

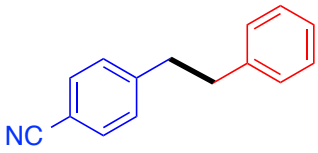


4d[4]

[1] W. Kerr, R. Mudd, J. Brown, *Chem. Eur. J.* **2016**, *22*, 4738 – 4742
[2] G. Molander, C. Yun, *Tetrahedron,* **2002**, *58*, 1465-1470
[3] K. Huihui, J. Caputo, Z. Melchor, A. Olivares, A. Spiewak, K. Johnson, T. DiBenedetto, S. Kim, L. Ackerman, D. Weix**,** *J. Am. Chem. Soc.* **2016**, *138* , 5016–5019.
[4] W. Guo, Z. Wang, *Tetrahedron* **2013**, *69*, 9580-9585

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01-7.98 (m, 1H), 7.89-7.86 (m, 1H), 7.74 (d, J=8.0 Hz, 1H), 7.54-7.40 (m, 3H), 7.37-7.02 (m, 6H), 3.14 (t, J = 7.9 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 2.18-2.10 (m, 2H) ppm.

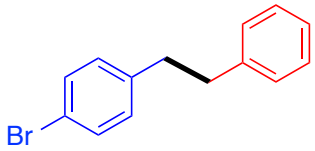
^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.2, 138.5, 133.9, 132.2, 128.8, 128.5 (2C), 128.3 (2C), 126.6, 125.9, 125.8, 125.7, 125.5, 125.4, 123.8, 35.9, 32.6, 32.3 ppm.



4e[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 – 7.54 (m, 2H, Ar*H*), 7.39 – 7.21 (m, 5H, Ar*H*), 7.19 – 7.12 (m, 2H, Ar*H*), 3.06 – 2.92 (m, 4H, Ar-CH_2) ppm.

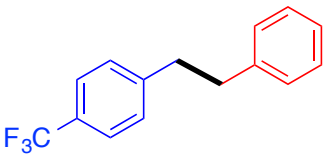
^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.3, 140.6, 132.2, 129.4, 128.8, 128.5, 128.5, 128.2, 126.3, 119.1, 109.9, 37.9, 37.2 ppm.



4f[6]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.41 (m, 2H, Ar*H*), 7.37 – 7.16 (m, 5H, Ar*H*), 7.12 – 7.05 (m, 2H, Ar*H*), 2.93 (s, 2H, Ar-CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.3, 140.7, 131.4, 130.3, 128.5 (2C), 128.4 (2C), 126.1, 119.7, 37.7, 37.3 ppm.



4g[7]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 – 7.51 (m, 2H, Ar*H*), 7.39 – 7.21 (m, 5H, Ar*H*), 7.21 – 7.15 (m, 2H, Ar*H*), 3.15 – 2.83 (m, 4H, Ar-CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.77, 141.05, 128.81 (2C), 128.45 (2C), 126.17, 125.26 (q, *J* = 3.8 Hz), 37.67, 37.52 ppm.

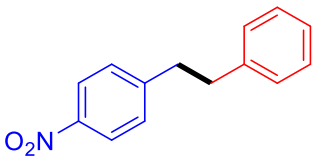
---

[5] Shen, Z.-L., Goh, K. K. K., Yang, Y.-S., Lai, Y.-C., Wong, C. H. A., Cheong, H.-L. and Loh, T.-P. *Angew. Chem. Int. Ed*. **2011**, *50*, 511–514.

[6] T. Di Franco; N.Boutin; X. Hu, *Synthesis* **2013**, 45, 2949-2958

[7] P. J. Rushworth, D. G. Hulcoop, D. J. Fox, *J. Org. Chem.* **2013**, *78*, 9517-9521.

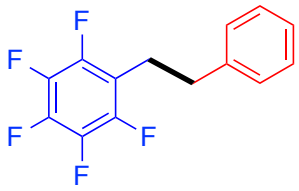
^{19}F NMR (377 MHz, $CDCl_3$): δ = -62.28 ppm.



4h[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16-8.13 (m, 2H, ArH), 7.33-7.28 (m, 4H, ArH), 7.26-7.22 (m, 1H, ArH), 7.17-7.15 (m, 2H, ArH), 3.04-3.08 (m, 2H, CH_2), 2.97-3.00 (m, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.4, 146.5, 140.5, 129.4 (2C), 128.5 (2C), 128.4 (2C), 126.3, 123.6 (2C), 37.7, 37.2.

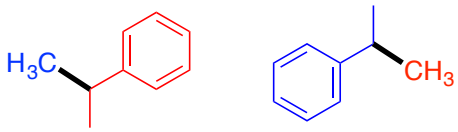


4i[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.16 (m, 5H, Ar*H*), 3.30 – 2.73 (m, 4H, Ar-CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.04, 128.56 (2C), 128.32 (2C), 126.55, 35.36, 24.46 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -144.31 (dd, *J* = 22.1, 8.4 Hz), -157.55 (d, *J* = 21.1 Hz), -162.75 – -162.98 (m) ppm.



4j[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.23 (m, 5H, ArH), 3.01-3.95 (m, 1H, CH), 1.36-1.33 (m, 6H, 2CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.9, 128.4 (2C), 126.5 (2C), 125.8, 34.2, 24.1 (2C) ppm

---

[8] J. Angelique; G. Eduardo; Z. Jieping, *J. Org. Chem.* **2002**, 3163-3164

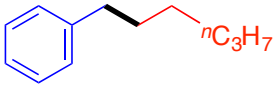
[9] S. Xu, G. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4669-4672

[10] K. Takahiro; K. Chikako; K. Chizuru, *Tetrahedron* **2012**, *68*, 1492 -1501

4k[11]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23-7.09 (m, 5H, ArH), 2.51 (t, J = 7.7 Hz, 2H, Ar-CH_2), 1.59-1.45 (m, 3H, $ArCH_2$-C*H*$_2$), 1.19-1.12 (m, 2H, CH_2-C*H*-$(CH_3)_2$), 0.80 (d, 6H, J = 6.6 Hz, $2CH_3$) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143, 128.4 (2C), 128.2 (2C), 125.6, 38.7, 36.3, 29.4, 27.9, 22.6 (2C) ppm.



4n[12]

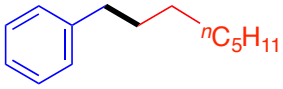
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20-7.09 (m, 5H, Ar-H), 2.53 (t, J= 7.6 Hz, 2H, CH_2-Ar), 1.59-1.51 (m, 2H, $ArCH_2$-C*H*$_2$), 1.26-1.18 (m, 6H, $3CH_2$), 0.81 (t, J= 7.1 Hz, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = δ 143.0, 128.4 (2C), 128.2 (2C), 125.6, 36.0, 31.8, 31.5, 29.1, 22.7, 14.1 ppm.

4o[13]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22-7.06 (m, 5H, Ar-H), 2.52 (t, J = 7.8 Hz, 2H, Ar-CH_2), 1.56-1.51 (quint, J = 7.5 Hz, 2H, Ar-CH_2-C*H*$_2$), 1.26-1.18 (m, 8H, $4CH_2$), 0.81 (t, J = 7.0 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.0, 128.4 (2C), 128.2 (2C), 125.6, 36.0, 31.9, 31.6, 29.3, 29.2, 22.7, 14.1 ppm.

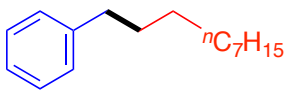


4p[14]

[11] D. Burns, J. Miller, Ho-Kit Chan, and Michael O. Delaney, *J. Am. Chem. Soc.* **1997**, *119*, 2125-2133
[12] C.Yang, Z. Zhang, Y. Liu, L. Liu, *Angew. Chem. Int. Ed*. **2011**, *50*, 3905-3907
[13] L. McCann, H. Hunter, J. Clyburne, M. Organ, *Angew. Chem. Int. Ed*. **2012**, *51*, 7024-7027
[14] K. Nakata, C. Feng, Y. Kobayashi, *Tetrahedron Lett.* **2014,** *55*, 5774–5777

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22-7.06 (m, 5H, Ar-H), 2.52 (t, J = 7.5 Hz, 2 H, CH_2-Ar), 1.64 (quint, J = 7.6 Hz, 2 H, Ar-CH_2-C*H*$_2$), 1.33–1.29 (m, 10 H), 0.91 (t, J = 7.0 Hz, 3H, CH_3) ppm.

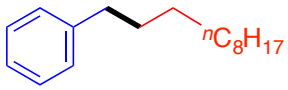
^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 128.4 (2C), 128.2 (2C), 125.6, 36.0, 31.9, 31.5, 29.5, 29.4, 29.3, 22.7, 14.2 ppm.



4q[15]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.17 (m, 5H, ArH), 2.63 (t, J = 7.5 Hz, 2H, CH_2-Ar), 1.64 (quint, J = 7.4 Hz, 2H, Ar-CH_2-C*H*$_2$), 1.30-1.26 (m, 14H, 7CH_2), 0.91 (t, J = 7.0 Hz, 3H, CH_3) ppm.

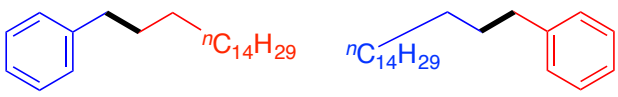
^{13}C NMR (76 MHz, $CDCl_3$): δ = 143.1, 128.4(2C), 128.2 (2C), 125.5, 36.0, 31.9, 31.5, 29.7, 29.63, 29.61, 29.5, 29.4, 22.7, 14.1 ppm.



4r[16]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.20 (m, 5H, ArH), 2.64 (t, J = 7.5Hz, 2H, Ar-CH_2), 1.65 (quint, J = 7.3 Hz, 2H, Ar-CH_2-C*H*$_2$), 1.41-1.30 (m, 16H, 8CH_2), 0.89 (t, J=7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 143.0, 128.4 (2C), 128.2 (2C), 125.5, 36.0 (C_1), 31.9 (C_9), 31.5 (C_2), 29.68, 29.64, 29.61, 29.5, 29.4 (2C), 22.7, 14.1 ppm

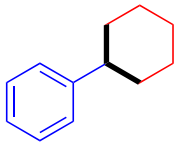


4s[17,18]

[15] M. Tobisu, T. Takahira, T. Morioka, N. Chatani, *J. Am. Chem. Soc.* **2016**, *138*, 6711–6714
[16] A. Link, C. Fischer, C. Sparr, *Angew. Chem. Int. Ed.* **2015**, *54*, 12163-12166
[17] AIST- Integrated Spectral Database System of Organic Compounds. (Data obtained from the National Institute of Advanced Industrial Science and Technology (Japan))
[18] E. Emary; Morgan, *J. Am. Oil Chem. Soc.* **1978,** 55, 593-595

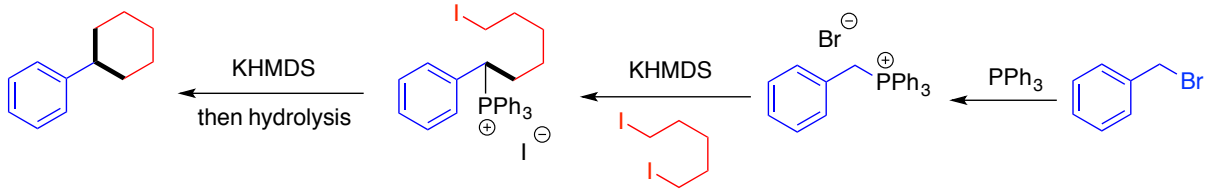
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22-7.09 (m, 5H, ArH), 2.53 (t, J= 7.5 Hz, 2H, Ar-CH_2), 1.54 (quint, J = 7.3 Hz, 2H, Ar-CH_2-CH_2), 1.25-1.18 (m, 28H, 14CH_2), 0.81 (t, J = 6.5 Hz, 3H, CH_3)

^{13}C NMR (75 MHz, $CDCl_3$): 143.0, 128.4 (2C), 128.2 (2C), 125.5, 36.0, 31.9, 31.5, 29.7 (9C), 29.6, 29.5, 29.4, 22.7, 14.1 ppm



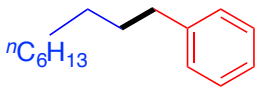
4t[19]

This compound was produced according to the general procedure with benzylbromide as halide **1** and 1,5-diiodopentane as halide **2**. Two molar equivalents of KHMDS were used to facililate the second ylide formation and the cyclization of the six-membered ring. Presumably, the reaction proceeded through intermediates depicted below:



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.22 (m, 5H, ArH), 2.59-2.53 (m, 1H, Ar-C*H*), 1.96-1.80 (m, 5H, 5CH_2), 1.55-1.30 (m, 5H, 5CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.1, 128.3 (2C), 126.9 (2C), 125.8, 44.7, 34.5(2C), 27.0 (2C), 26.2 ppm



4u[20]

^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.24 (m, 5H, ArH), 2.70 (t, J = 7.7 Hz, 2H, Ar-CH_2), 1.71 (quint, J = 7.1 Hz, 2H, Ar-CH_2-CH_2), 1.45-1.36 (m, 10H, 5CH_2), 1.00-0.97 (t, J = 7.0 Hz, 3H, CH_3) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 143.0, 128.5 (2C), 128.3 (2C), 125.6, 36.1, 32.0, 31.6, 29.7, 29.6, 29.4 (2C), 22.8, 14.2 ppm

---

[19] C. Indranil, O. Martin, *Org. Lett.* **2016**, *18*, 2463-2466

[20] P. Tuhin, A. Soumitra, Akanksha, M. Debabrata, *Chem. Commun.* **2013**, *49*, 69-71

4v[21]

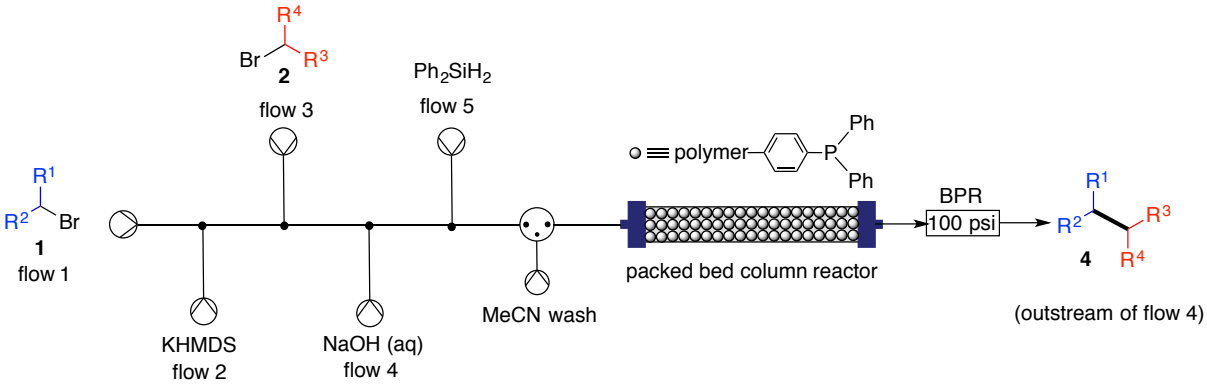
This compound was produced according to the general procedure with ethyl bromoacetate as halide **1** and pentadecyl tosylate as halide **2**. The ethyl ester group was hydrolyzed under the reaction conditions.

^{1}H NMR (400 MHz, $CDCl_3$): 3.69 (s, 1H, HO-CO), 2.32 (t, J = 7.5 Hz, 2H, CO-CH_2), 1.66-1.59 (m, 2H, $COCH_2$-CH_2), 1.33-1.27 (m, 27H, 13(CH_2)-CH_3), 0.9 (t, J = 6.6 Hz, 3H, CH_2-CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): 174.4, 51.4, 34.1, 31.9, 29.7 (5C), 29.6, 29.5, 29.4, 29.3, 29.2, 25.0, 22.7, 14.1 ppm.

[21] E. Bengsch, B. Perly, C. Deleuze, A. Valero., *J. Magn. Reson.* **1986**, *68*, 1-13

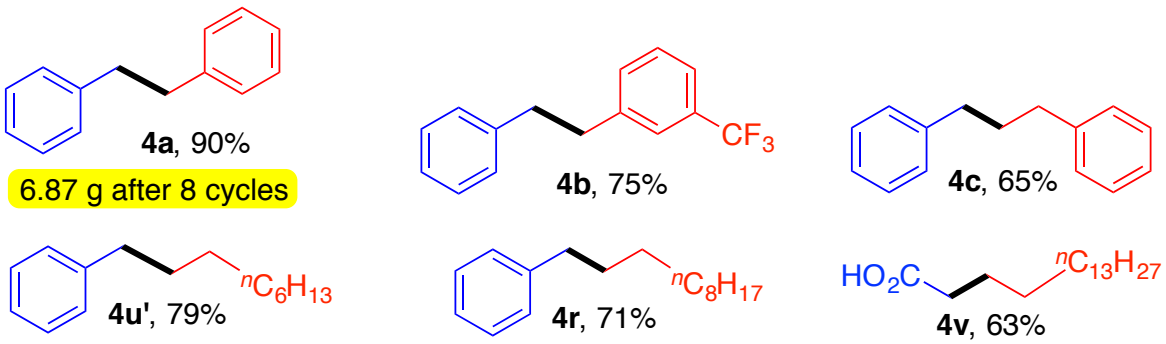
General Settings for C(sp^3)-C(sp^3) Coupling Reactions in Flow



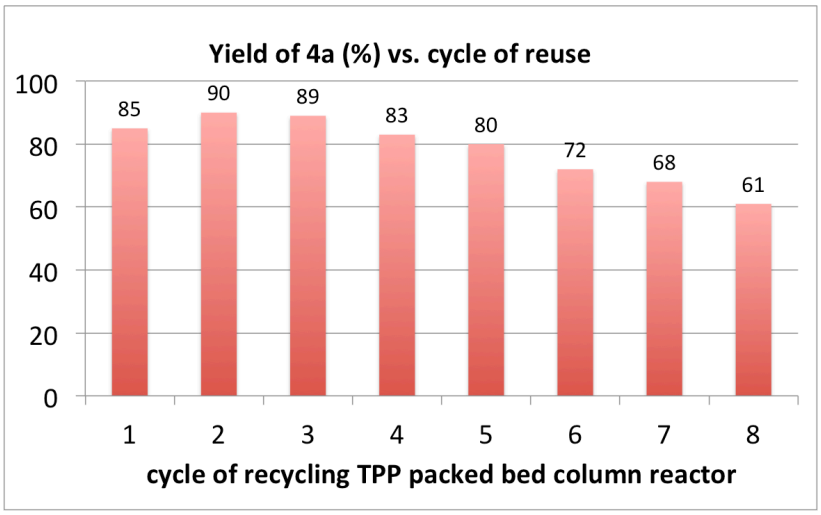
Typical reactions and conditions: i) Pump 1: alkyl bromide **1** (2.4 equiv.) in acetonitrile (0.08 M), 0.3 mL/min, column T = 120 °C, 5 h; ii) Pump 2: 1.0 M KHMDS (5.0 equiv.), THF, 0.3 mL/min, column T = 20 °C, 50 min; iii) Pump 3: alkyl bromide **2** (2.4 equiv.) in acetonitrile (0.08 M), 0.3 mL/min, column T = 120 °C, 5 h; iv) Pump 4: 2.0 M $NaOH_{(aq)}$, 0.3 mL/min, column T = 20 °C, 4 h; v) Pump 5 (optional for regeneration of TPP-resin): Ph_2SiH_2 (2.4 equiv.) in acetonitrile (0.08 M), 0.3 mL/min, column T = 120 °C, 5 h. Yields based on molar amount of Ph_3P on TPP-resin used (3 mmol on 1 g).

TPP-resin: triphenylphosphine, styrene polymer-bound, 100-200 mesh, ~3.0 mmol/g loading, 2% cross-linked with divinylbenzene. This resin was purchased from Sigma-Alrich and used as is. For **4a**, 2 g of TPP-resin was used; for other flow setups, 1 g TPP-resin was used.

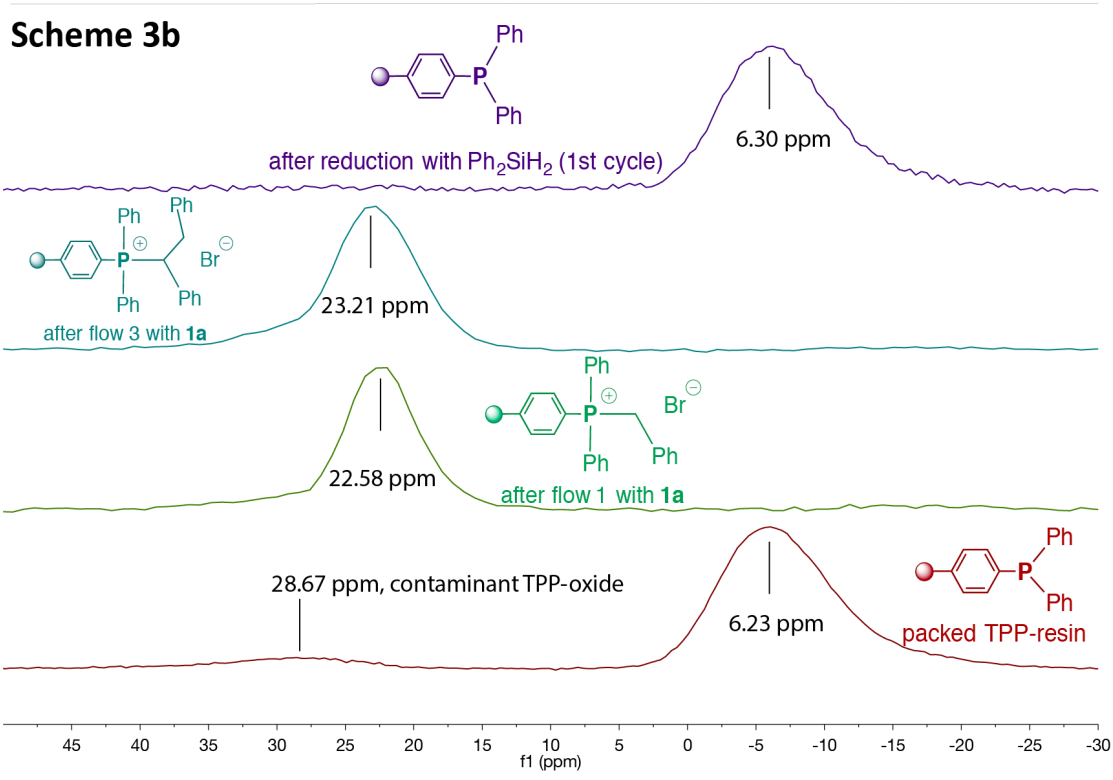
Equipment: Pumps = Little Things Factory GmbH Mr. Q continuous syringe pump; Column = Omnifit®, L × I.D. 100 mm × 10 mm, bed volume 5.6 mL, fixed ends; Heat block for column = FRX volcano; Pressure regulator = Upchurch Scientific™ 100 psi.



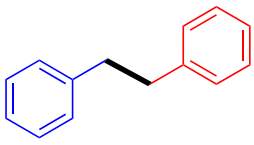
Recyclability of TPP-resin and Solid State ^{31}P NMR Studies



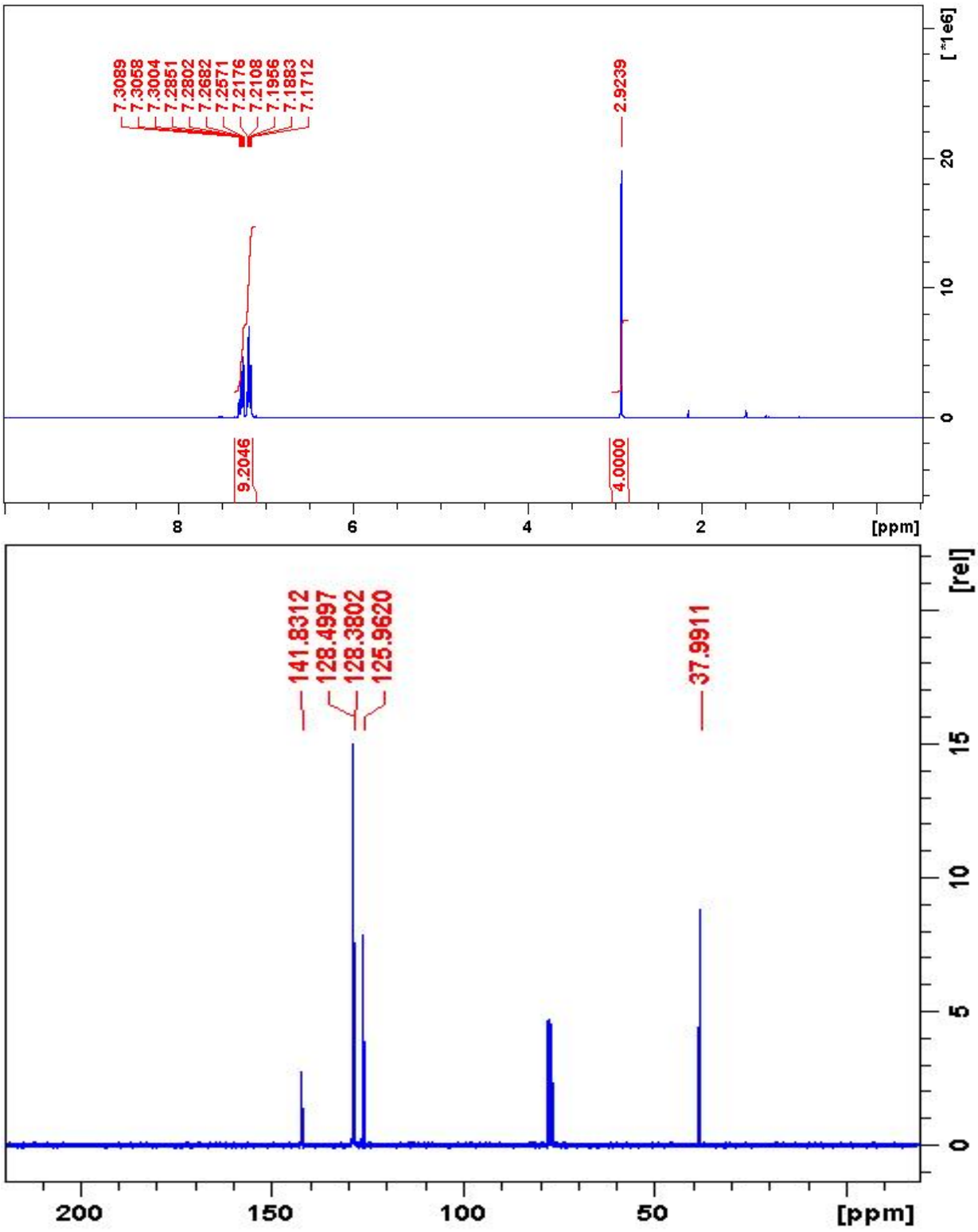
We carried out solid-state ^{31}P NMR (121.4 MHz, 25 °C) studies of TPP-resin on a Bruker Avance III 700 MHz Solid State NMR spectrometer after each step of the homocoupling reaction of **1a** to **4a**. We could not obtain a solid state ^{31}P NMR spectrum for the polymer-bound phosphonium ylide intermediate due to the unstable nature of this species. The presence of these phosphine, phosphine oxide and phosphonium salts intermediates in the reaction was confirmed by the characteristic solid-state ^{31}P NMR signals.



NMR Spectra of C(sp^3)-C(sp^3) Coupled Products

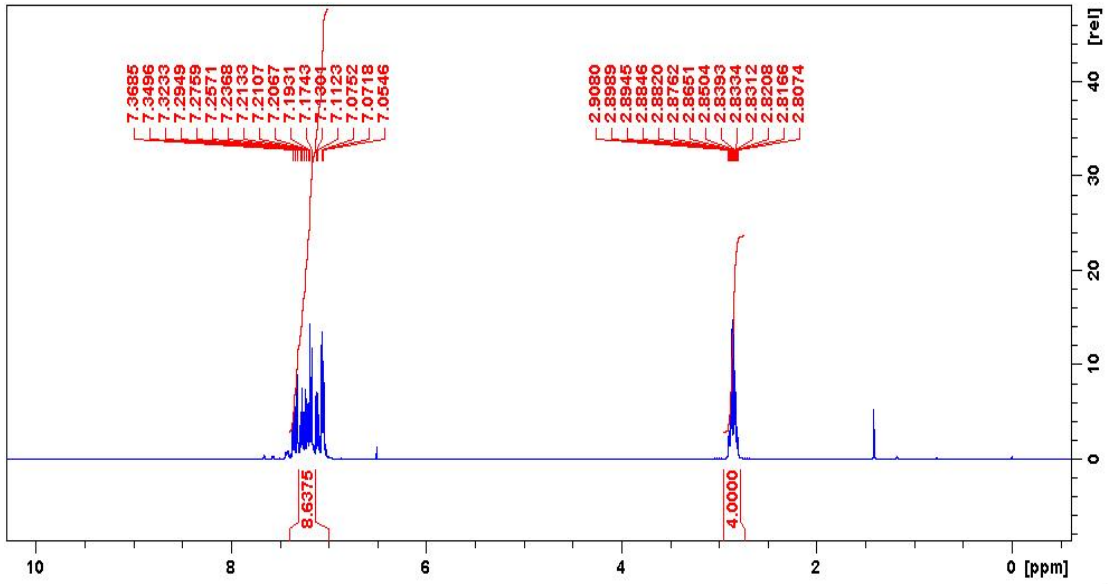


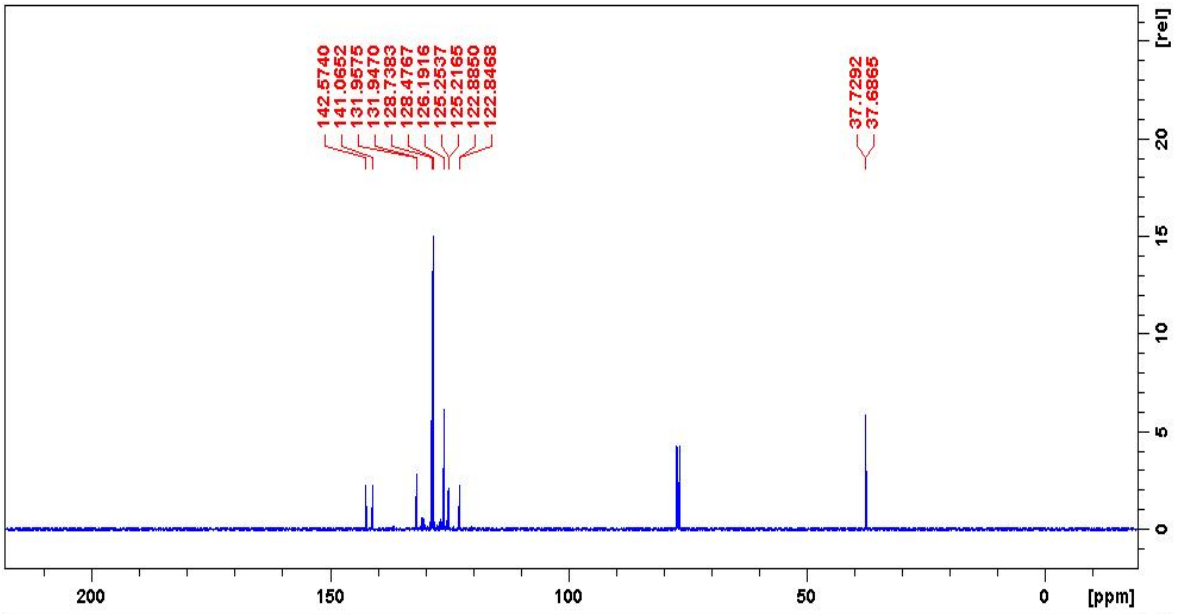
4a

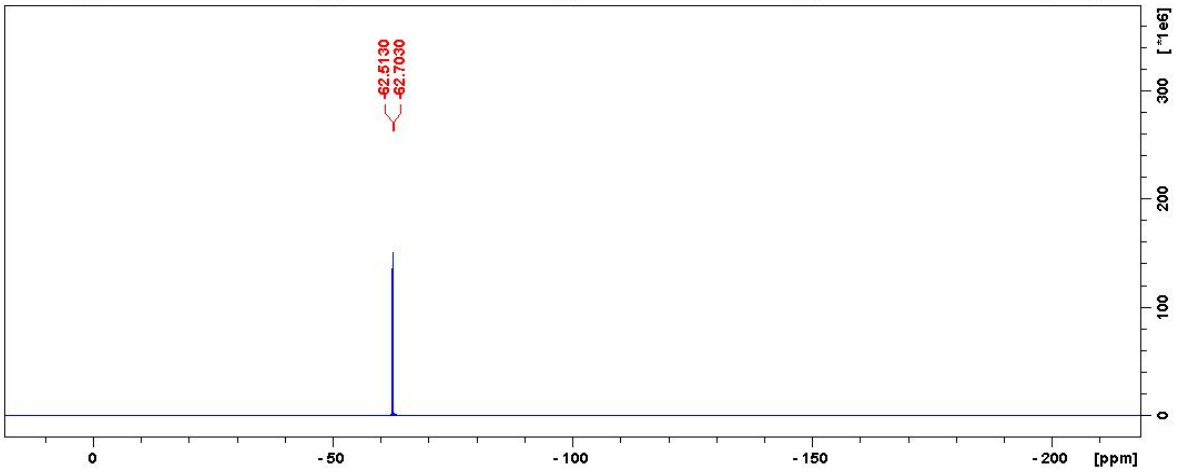


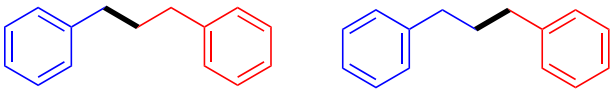

CF3
F3C

4b

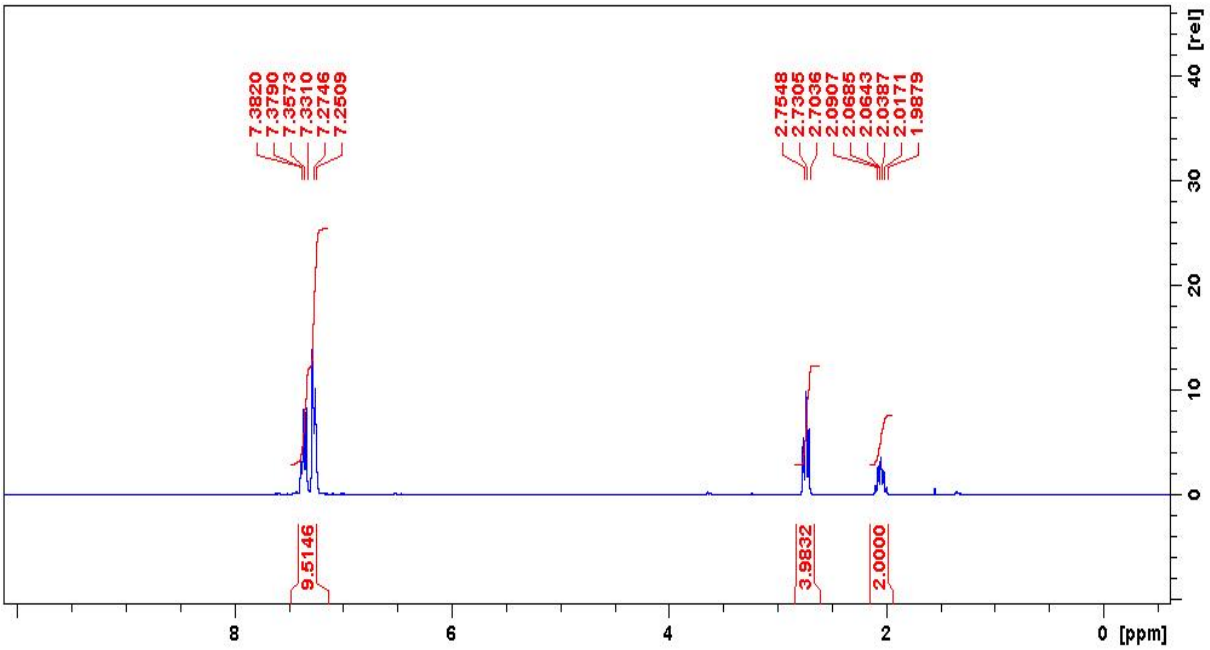

7.3685
7.3496
7.3233
7.2949
7.2759
7.2571
7.2368
7.2133
7.2107
7.2067
7.1931
7.1743
7.1391
7.1123
7.0752
7.0718
7.0546
2.9080
2.8989
2.8945
2.8846
2.8820
2.8762
2.8651
2.8504
2.8393
2.8334
2.8312
2.8208
2.8166
2.8074
8.6375
4.0000
[rel]
[ppm]

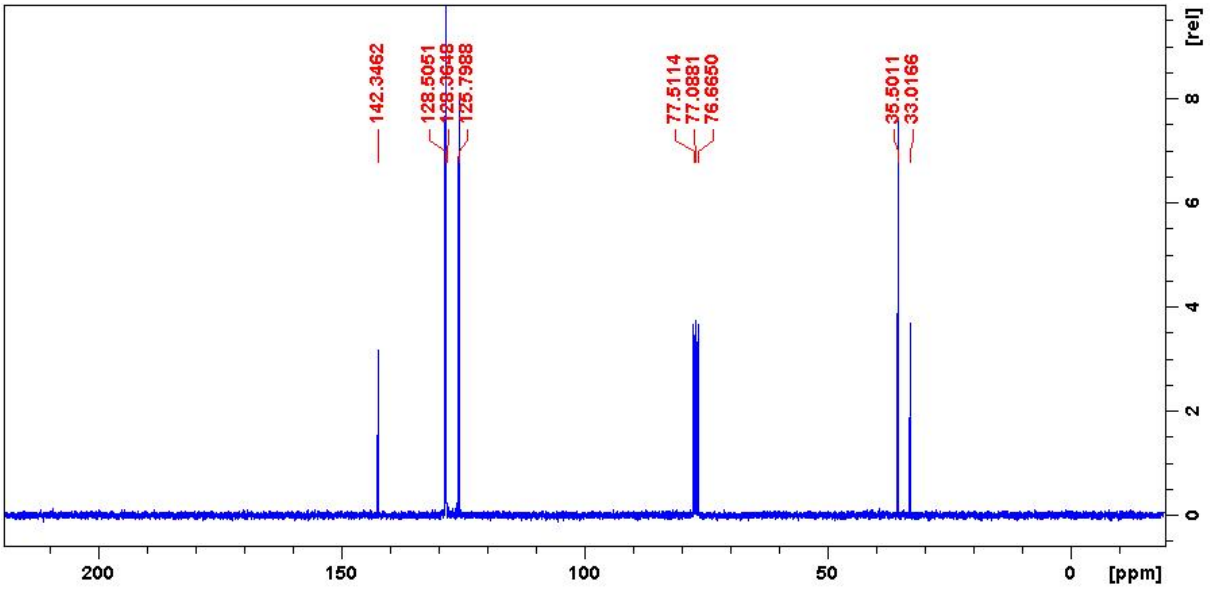

142.5740
141.0652
131.9575
131.9470
128.7383
128.4767
126.1916
125.2537
125.2165
122.8850
122.8468
37.7292
37.6865
[rel]
[ppm]

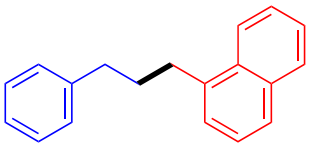

-62.5130
-62.7030
[*1e6]
[ppm]



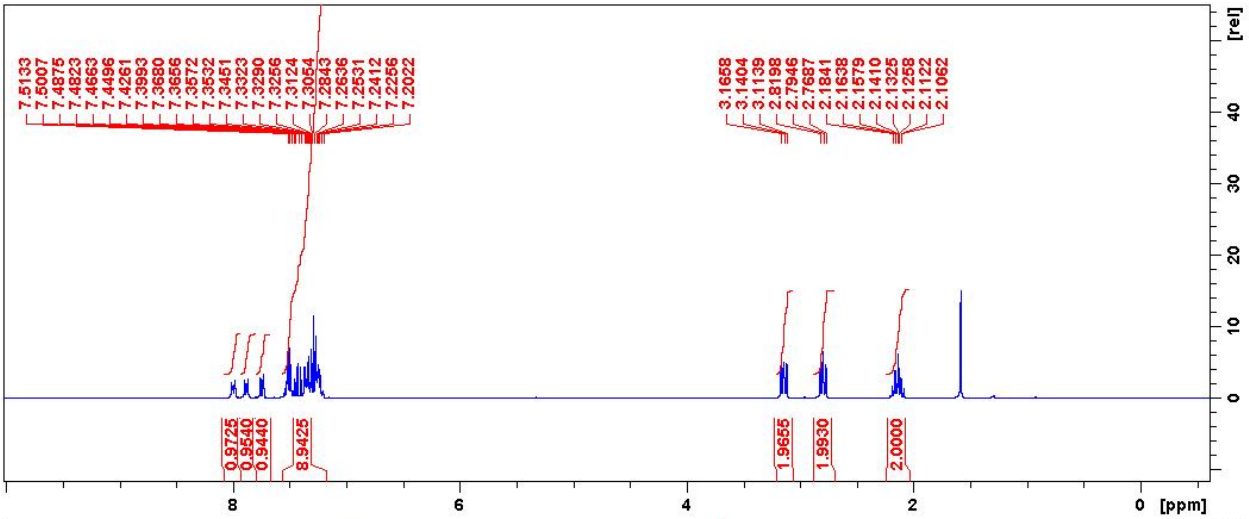
4c

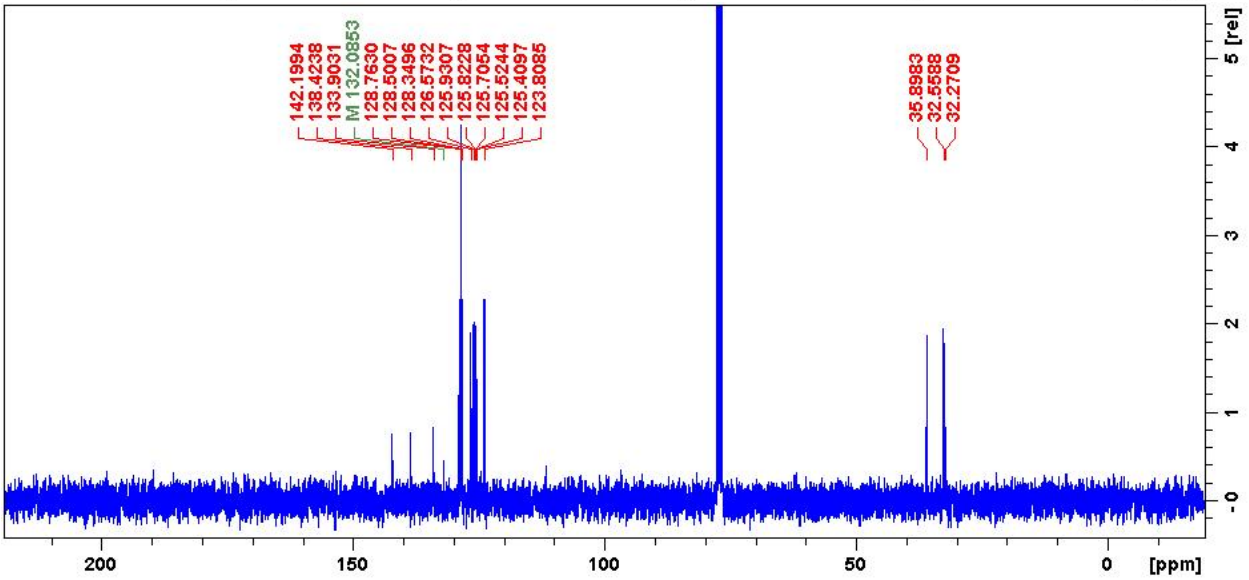

7.3820
7.3790
7.3573
7.3310
7.2746
7.2509
2.7548
2.7305
2.7036
2.0907
2.0685
2.0643
2.0387
2.0171
1.9879
9.5146
3.9832
2.0000
[rel]
[ppm]

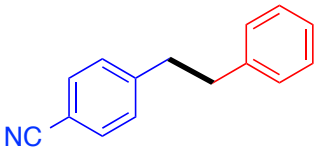

142.3462
128.5051
128.3648
125.7988
77.5114
77.0881
76.6650
35.5011
33.0166
[rel]
[ppm]



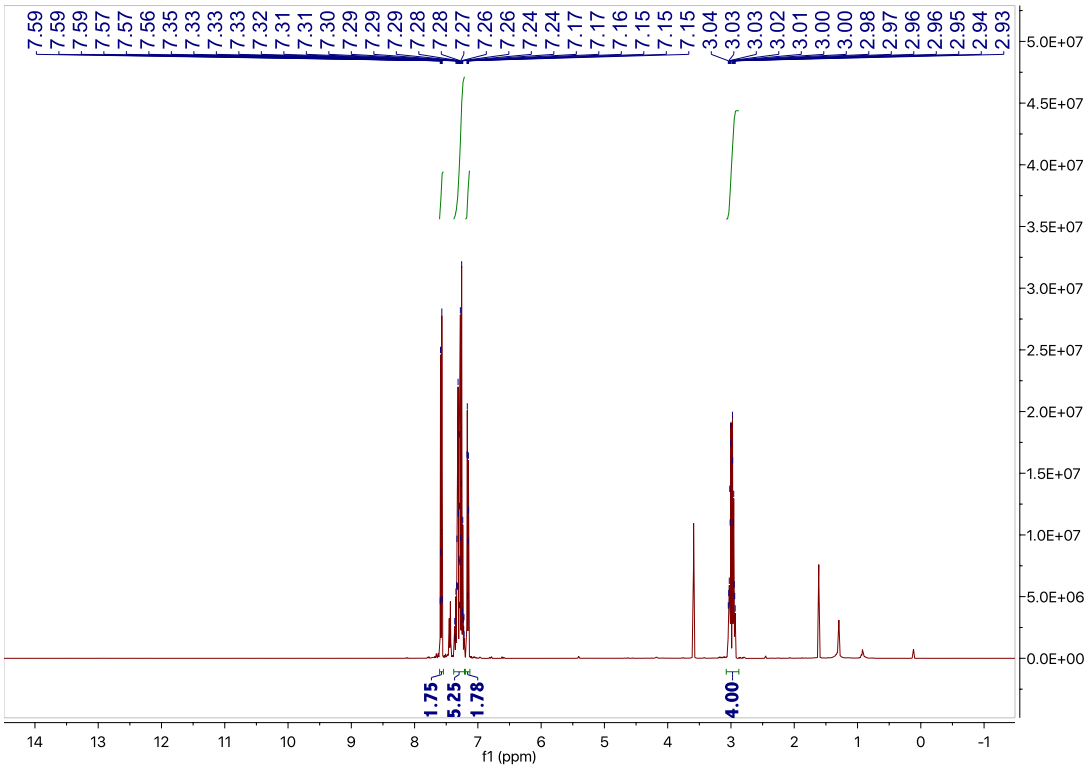
4d

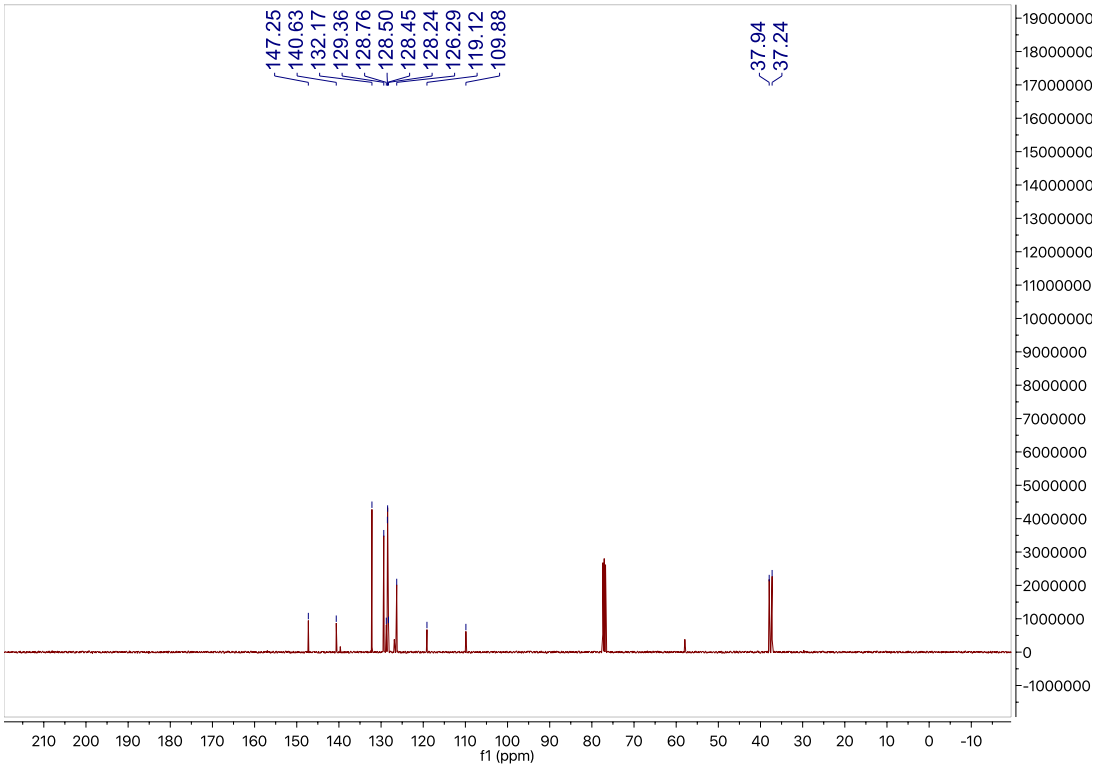

7.5133
7.5007
7.4875
7.4823
7.4663
7.4496
7.4261
7.3993
7.3680
7.3656
7.3572
7.3532
7.3451
7.3323
7.3290
7.3256
7.3124
7.3054
7.2843
7.2636
7.2531
7.2412
7.2256
7.2022
3.1658
3.1404
3.1139
2.8198
2.7946
2.7687
2.1841
2.1638
2.1579
2.1410
2.1325
2.1258
2.1122
2.1062
0.9725
0.9540
0.9440
8.9425
1.9655
1.9930
2.0000
[rel]
[ppm]

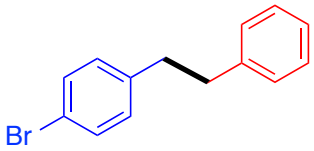

142.1994
138.4238
133.9031
M 132.0853
128.7630
128.5007
128.3496
126.5732
125.9307
125.8228
125.7054
125.5244
125.4097
123.8085
35.8983
32.5588
32.2709
[rel]
[ppm]


NC

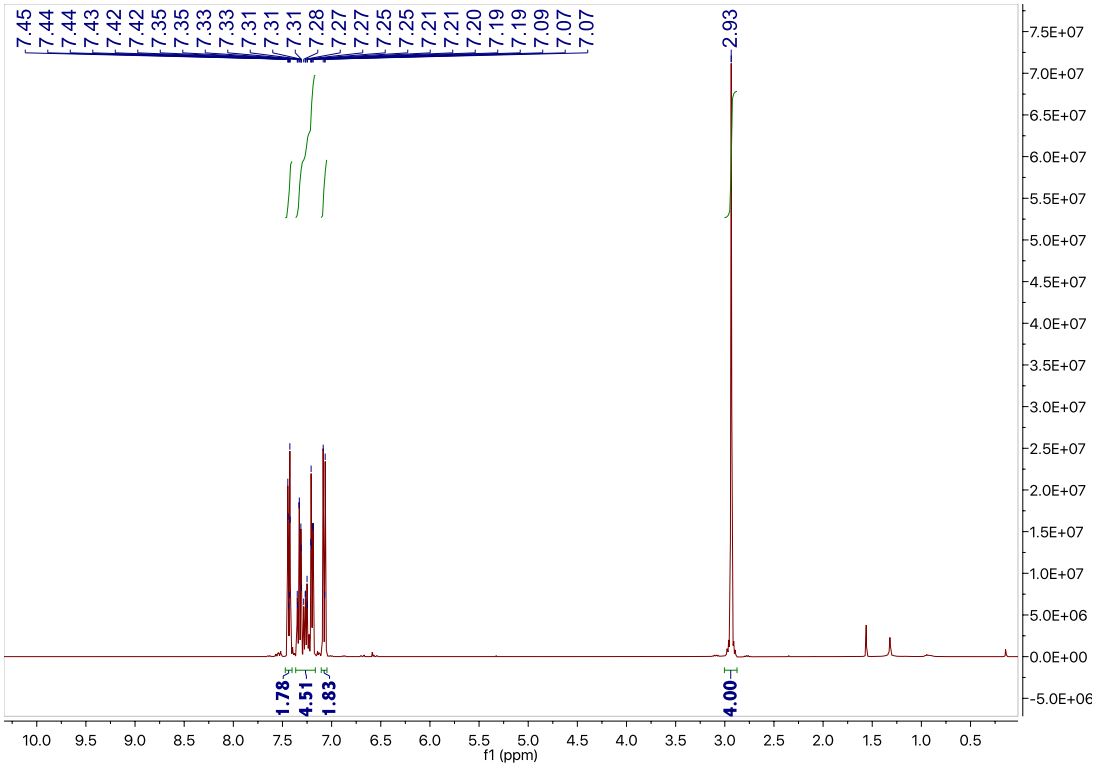
4e

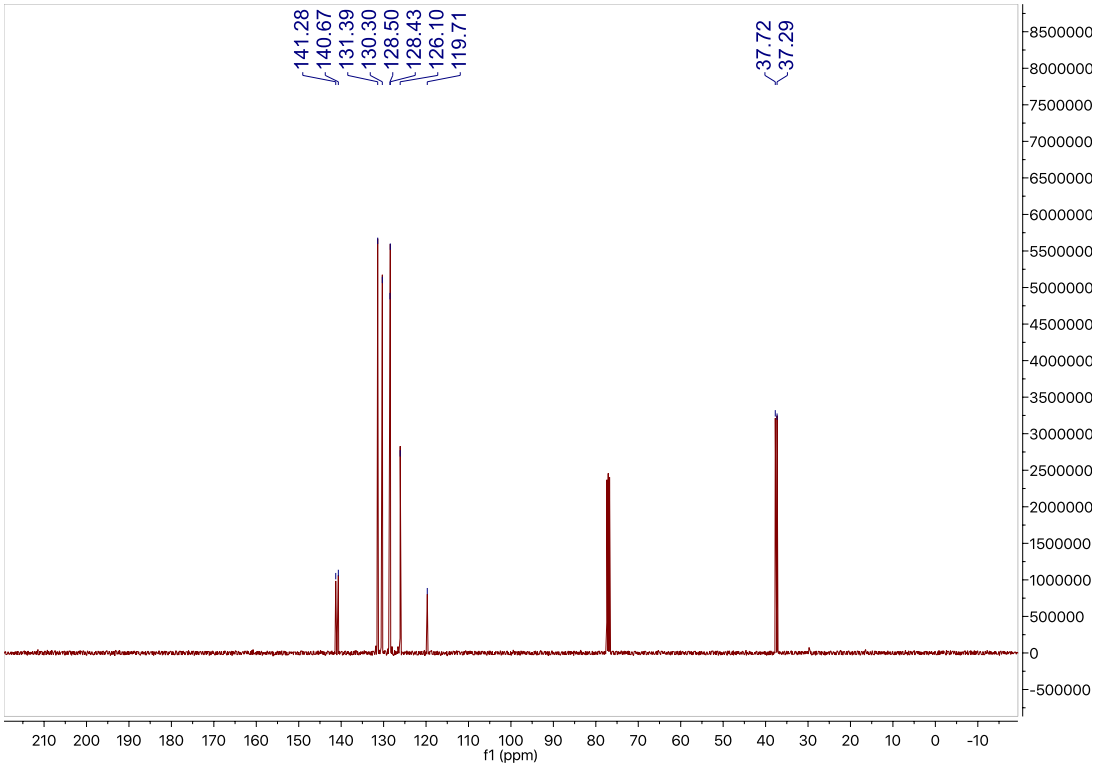

7.59
7.59
7.59
7.57
7.57
7.56
7.35
7.33
7.33
7.33
7.32
7.31
7.31
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.26
7.26
7.24
7.24
7.17
7.17
7.16
7.15
7.15
7.15
3.04
3.03
3.03
3.02
3.01
3.00
3.00
2.98
2.97
2.96
2.96
2.95
2.94
2.93
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
1.75
5.25
1.78
4.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

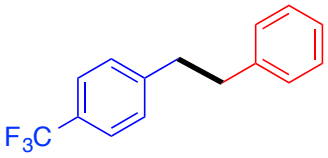

147.25
140.63
132.17
129.36
128.76
128.50
128.45
128.24
126.29
119.12
109.88
37.94
37.24
19000000
18000000
17000000
16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Br

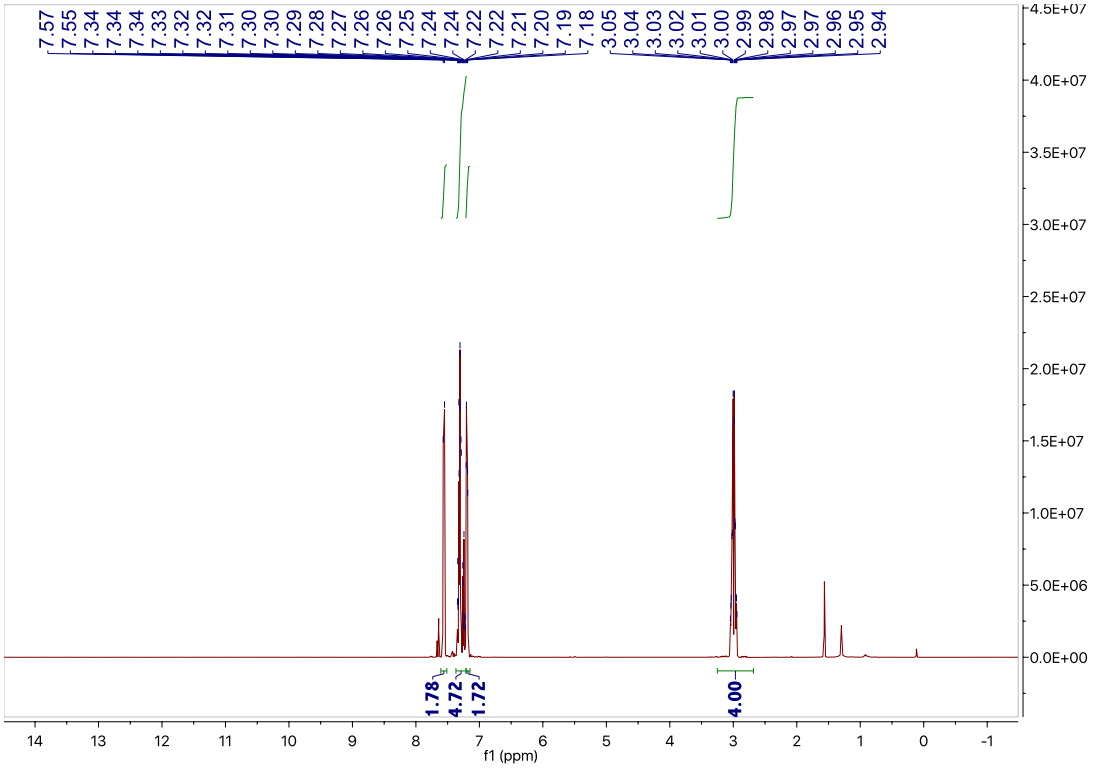
4f

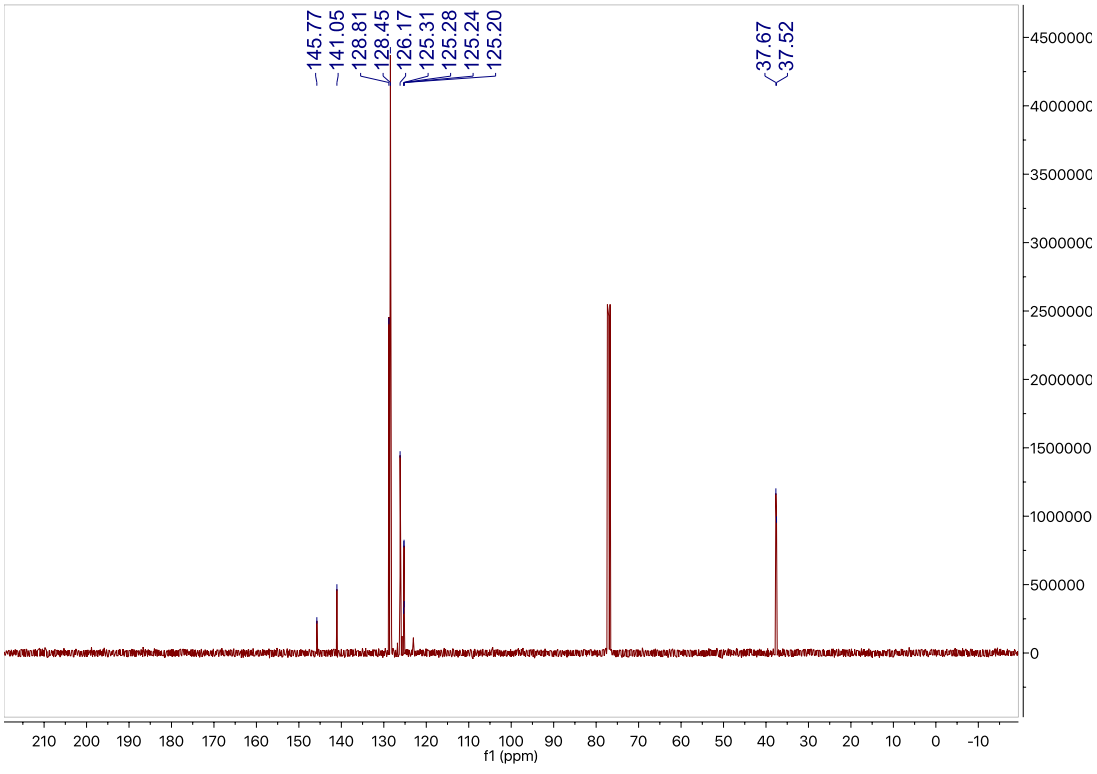

7.45
7.44
7.44
7.43
7.42
7.42
7.35
7.35
7.33
7.33
7.31
7.31
7.31
7.28
7.27
7.27
7.25
7.25
7.21
7.21
7.20
7.19
7.19
7.09
7.07
7.07
2.93
1.78
4.51
1.83
4.00
f1 (ppm)

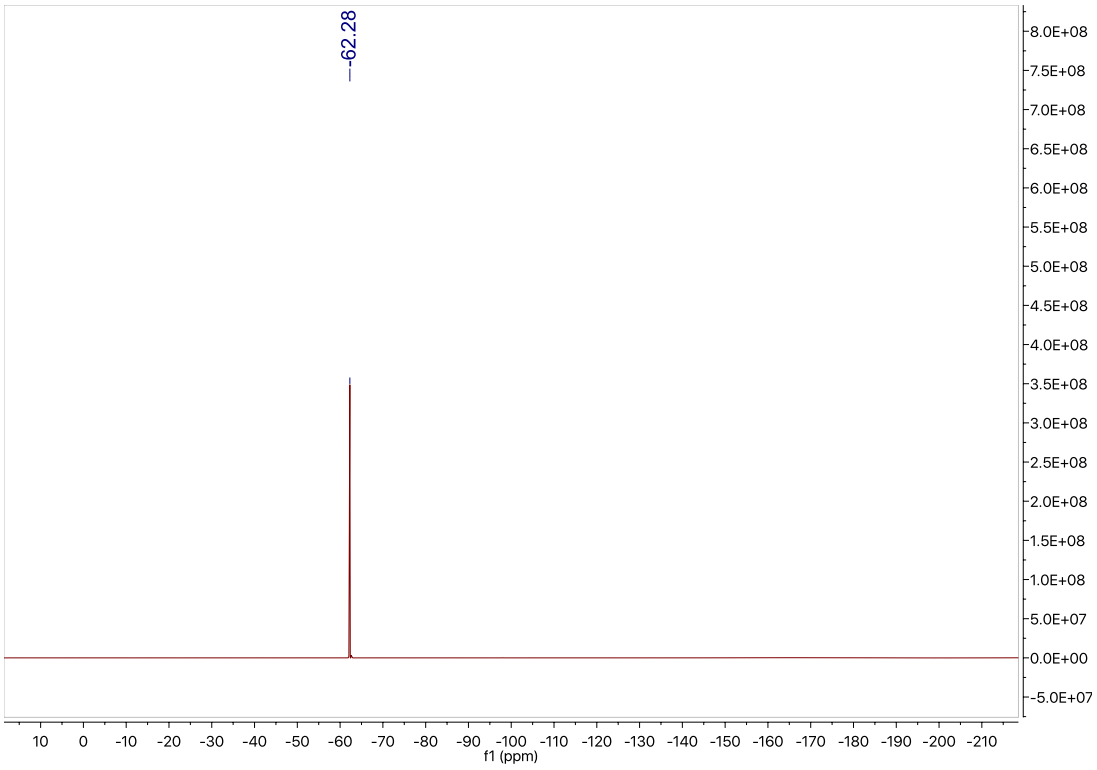

141.28
140.67
131.39
130.30
128.50
128.43
126.10
119.71
37.72
37.29
f1 (ppm)

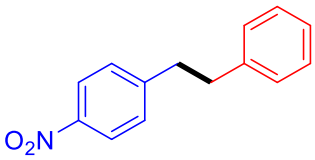

F3C

4g

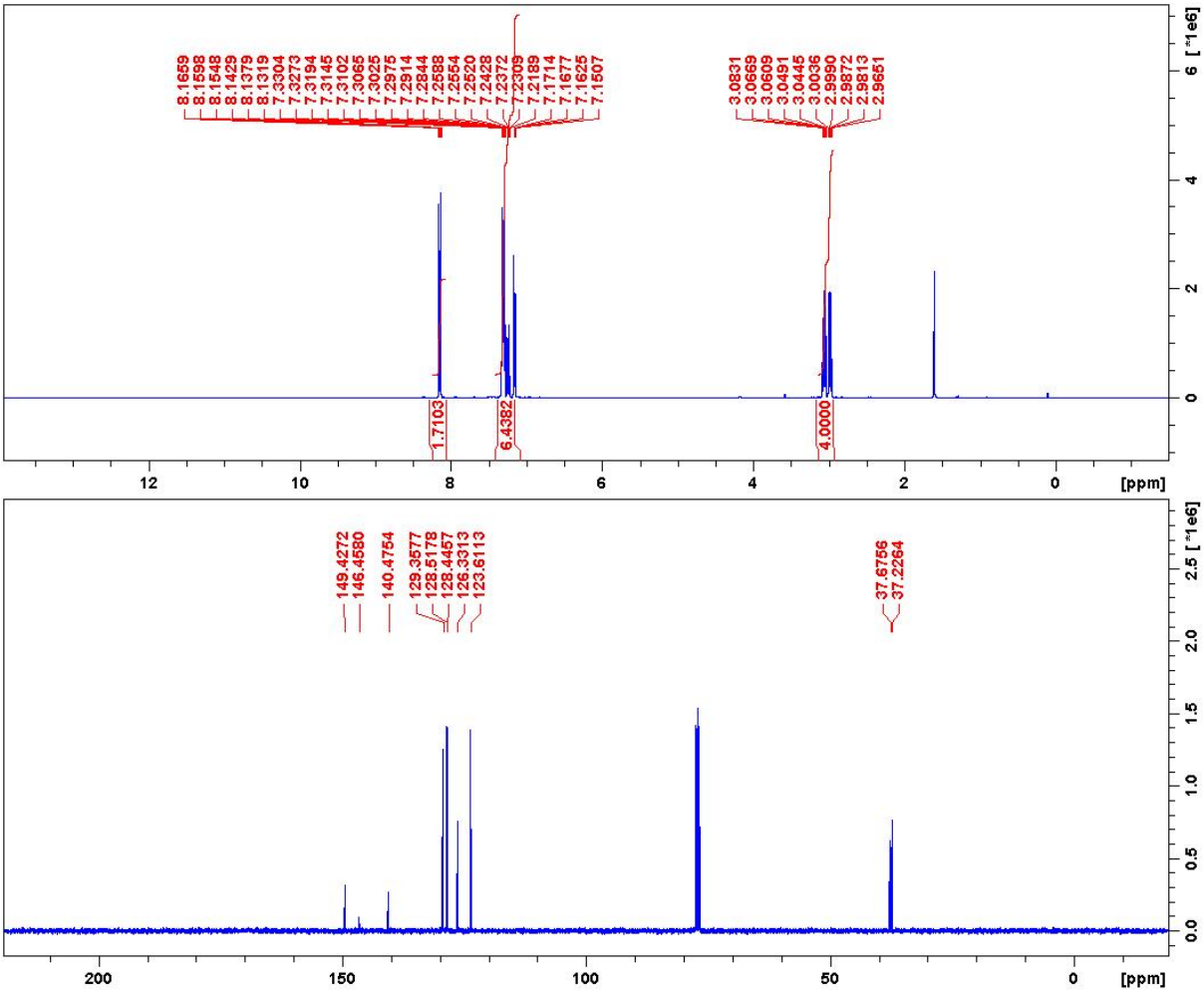

7.57
7.55
7.34
7.34
7.34
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.28
7.27
7.26
7.26
7.25
7.24
7.24
7.22
7.22
7.21
7.20
7.19
7.18
3.05
3.04
3.03
3.02
3.01
3.00
2.99
2.98
2.97
2.97
2.96
2.95
2.94
1.78
4.72
1.72
4.00
f1 (ppm)

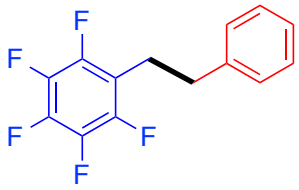

145.77
141.05
128.81
128.45
126.17
125.31
125.28
125.24
125.20
37.67
37.52
f1 (ppm)


-62.28
8.0E+08
7.5E+08
7.0E+08
6.5E+08
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

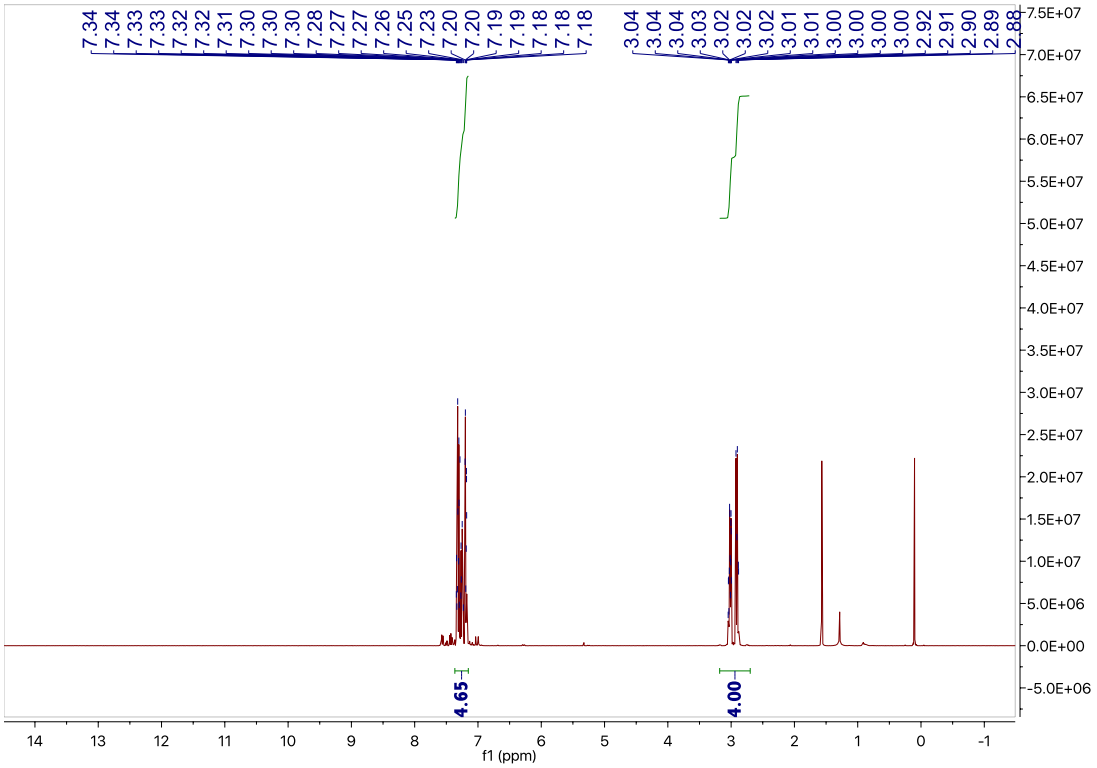

O2N

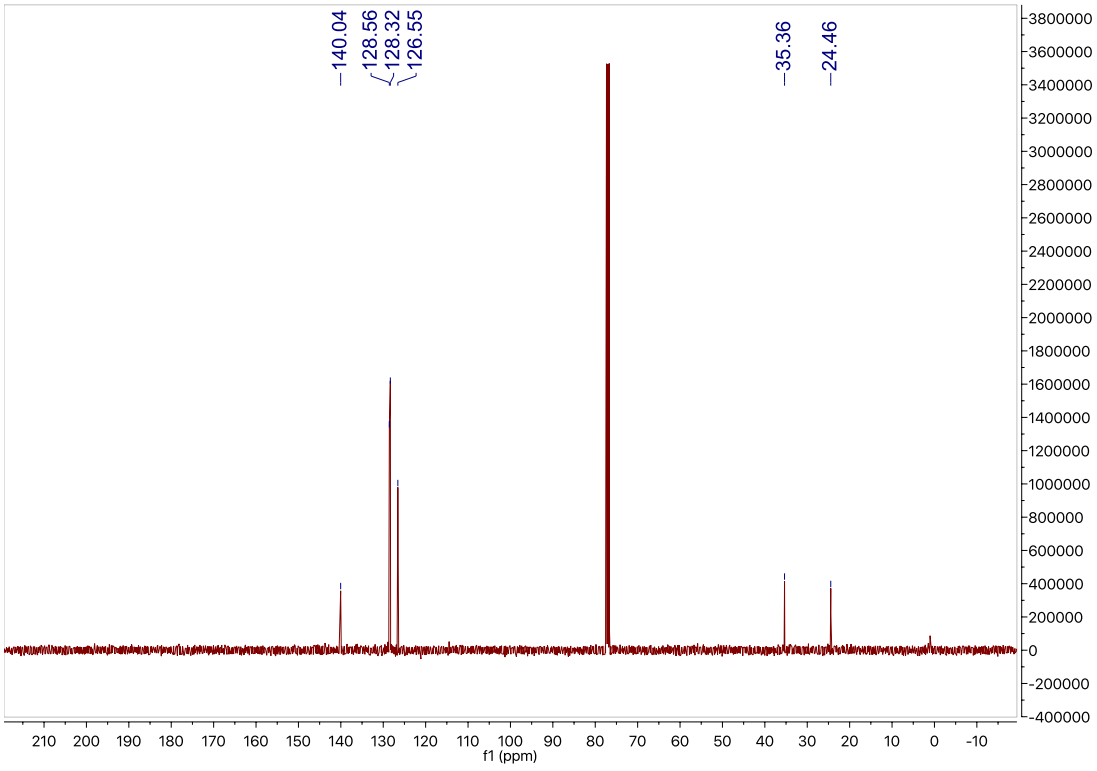
4h

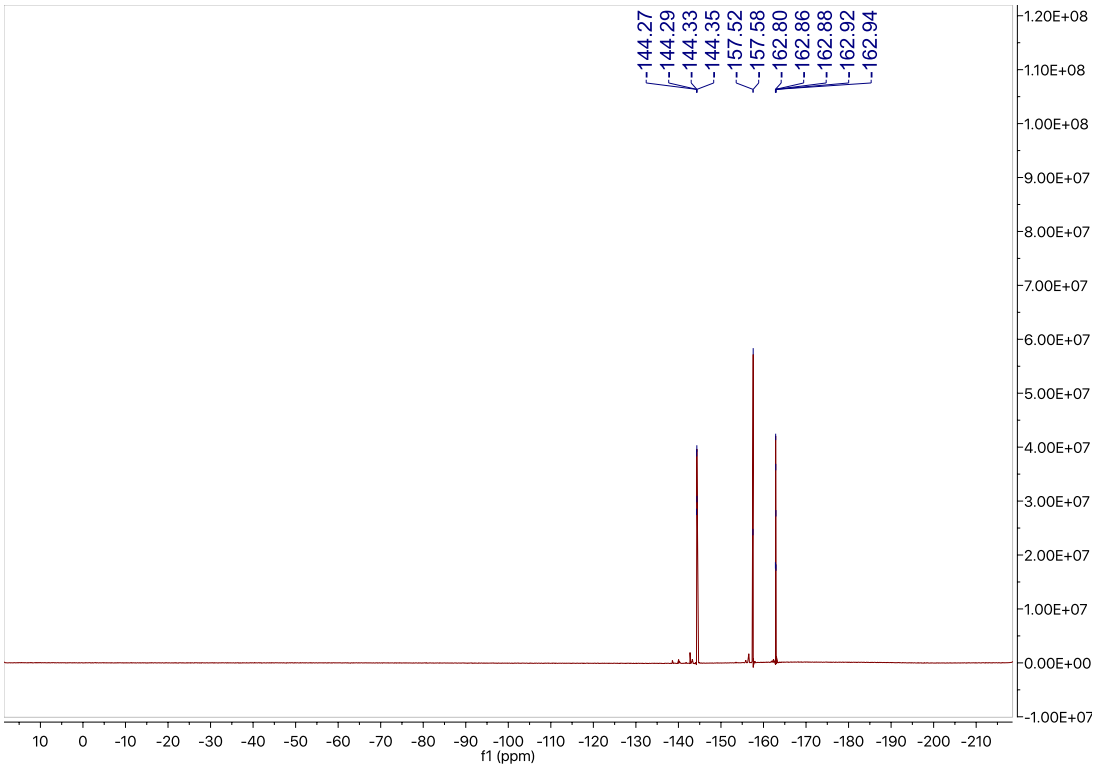

8.1659
8.1598
8.1548
8.1429
8.1379
8.1319
7.3304
7.3273
7.3194
7.3145
7.3102
7.3065
7.3025
7.2975
7.2914
7.2844
7.2588
7.2554
7.2520
7.2428
7.2372
7.2309
7.2189
7.1714
7.1677
7.1625
7.1507
3.0831
3.0669
3.0609
3.0491
3.0445
3.0036
2.9990
2.9872
2.9813
2.9651
1.7103
6.4382
4.0000
[ppm]
149.4272
146.4580
140.4754
129.3577
128.5178
128.4457
126.3313
123.6113
37.6756
37.2264
[ppm]

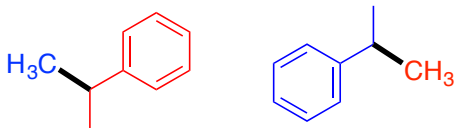

F
F
F
F
F

4i

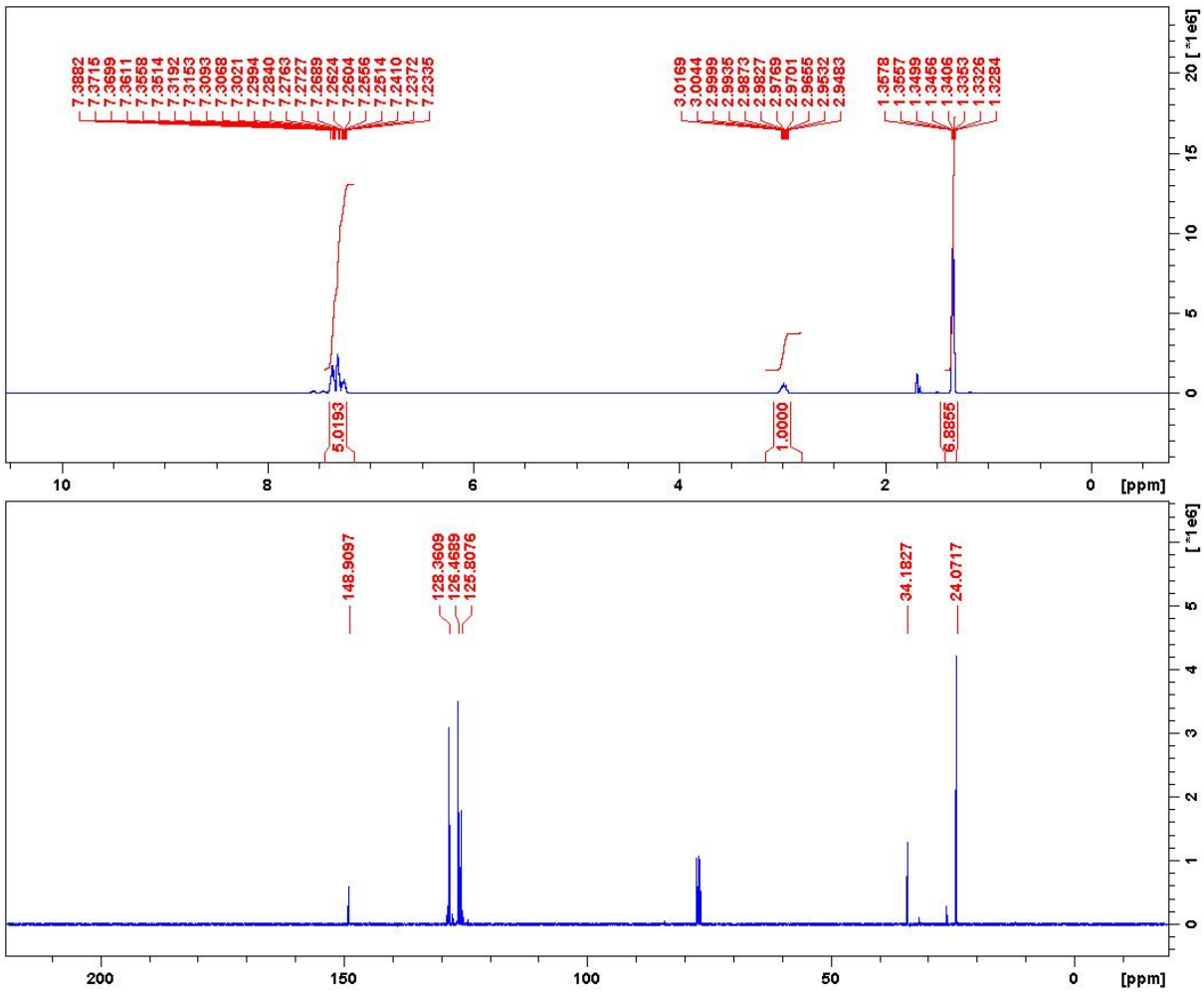

7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.30
7.28
7.27
7.27
7.26
7.25
7.23
7.20
7.20
7.19
7.19
7.18
7.18
7.18
3.04
3.04
3.04
3.03
3.02
3.02
3.01
3.01
3.00
3.00
3.00
3.00
2.92
2.91
2.90
2.89
2.88
4.65
4.00
f1 (ppm)


140.04
128.56
128.32
126.55
35.36
24.46
f1 (ppm)

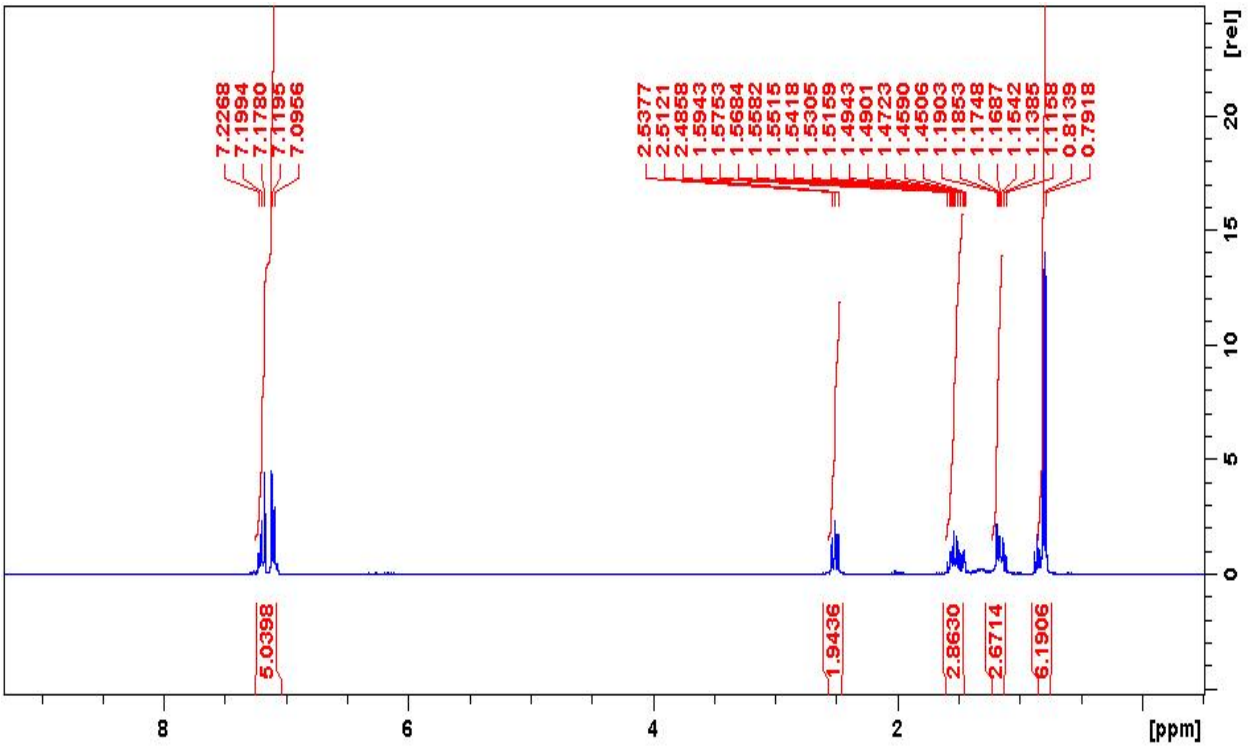

-144.27
-144.29
-144.33
-144.35
-157.52
-157.58
-162.80
-162.86
-162.88
-162.92
-162.94
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

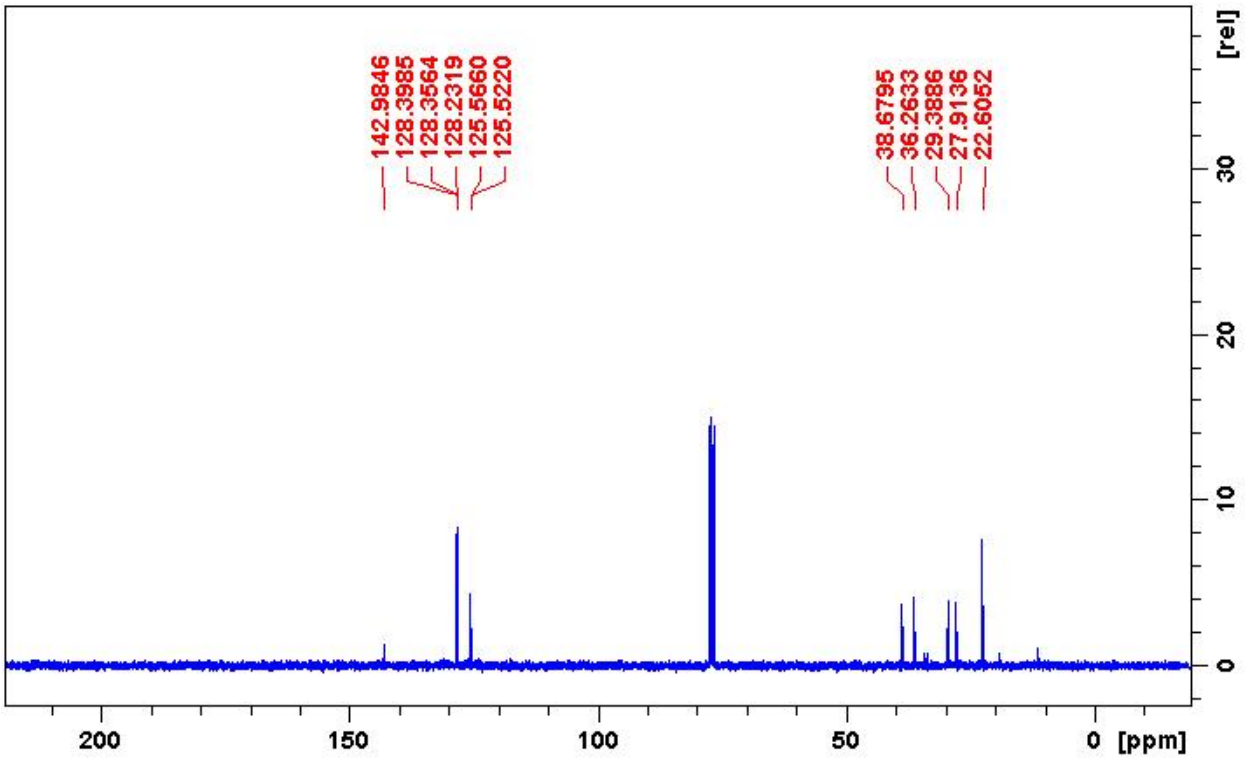

H3C
CH3

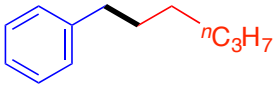
4j


7.3882
7.3715
7.3699
7.3611
7.3558
7.3514
7.3192
7.3153
7.3093
7.3068
7.3021
7.2994
7.2840
7.2763
7.2727
7.2689
7.2624
7.2604
7.2556
7.2514
7.2410
7.2372
7.2335
3.0169
3.0044
2.9999
2.9935
2.9873
2.9827
2.9769
2.9701
2.9655
2.9532
2.9483
1.3578
1.3557
1.3499
1.3456
1.3406
1.3353
1.3326
1.3284
5.0193
1.0000
6.8855
10
8
6
4
2
0
[ppm]
20 [*1e6]
15
10
5
0
148.9097
128.3609
126.4689
125.8076
34.1827
24.0717
200
150
100
50
0
[ppm]
[*1e6]
5
4
3
2
1
0

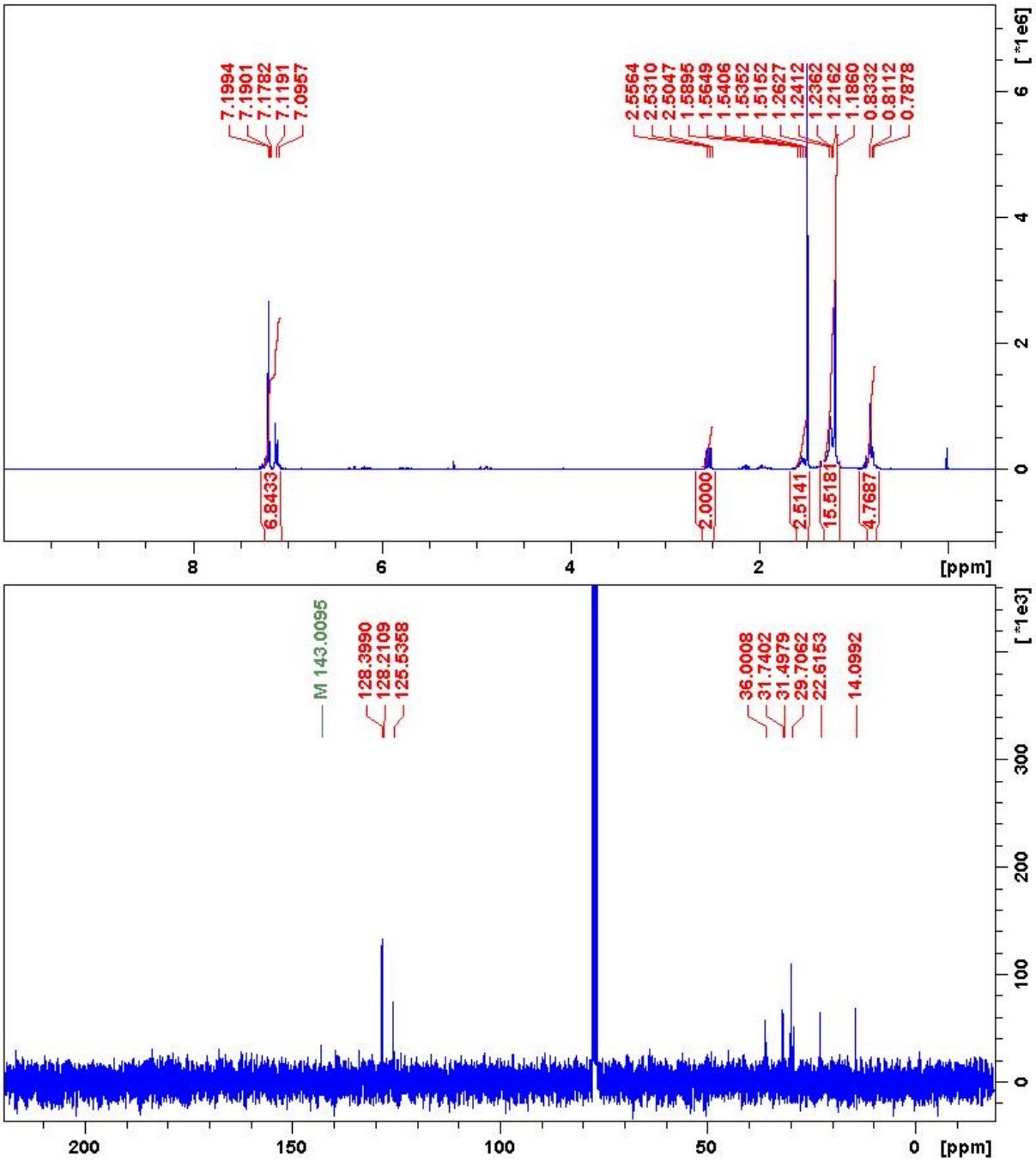
4k


7.2268
7.1994
7.1780
7.1195
7.0956
2.5377
2.5121
2.4858
1.5943
1.5753
1.5684
1.5582
1.5515
1.5418
1.5305
1.5159
1.4943
1.4901
1.4723
1.4590
1.4506
1.1903
1.1853
1.1748
1.1687
1.1542
1.1385
1.1158
0.8139
0.7918
5.0398
1.9436
2.8630
2.6714
6.1906
[rel]
[ppm]


142.9846
128.3985
128.3564
128.2319
125.5660
125.5220
38.6795
36.2633
29.3886
27.9136
22.6052
[rel]
[ppm]

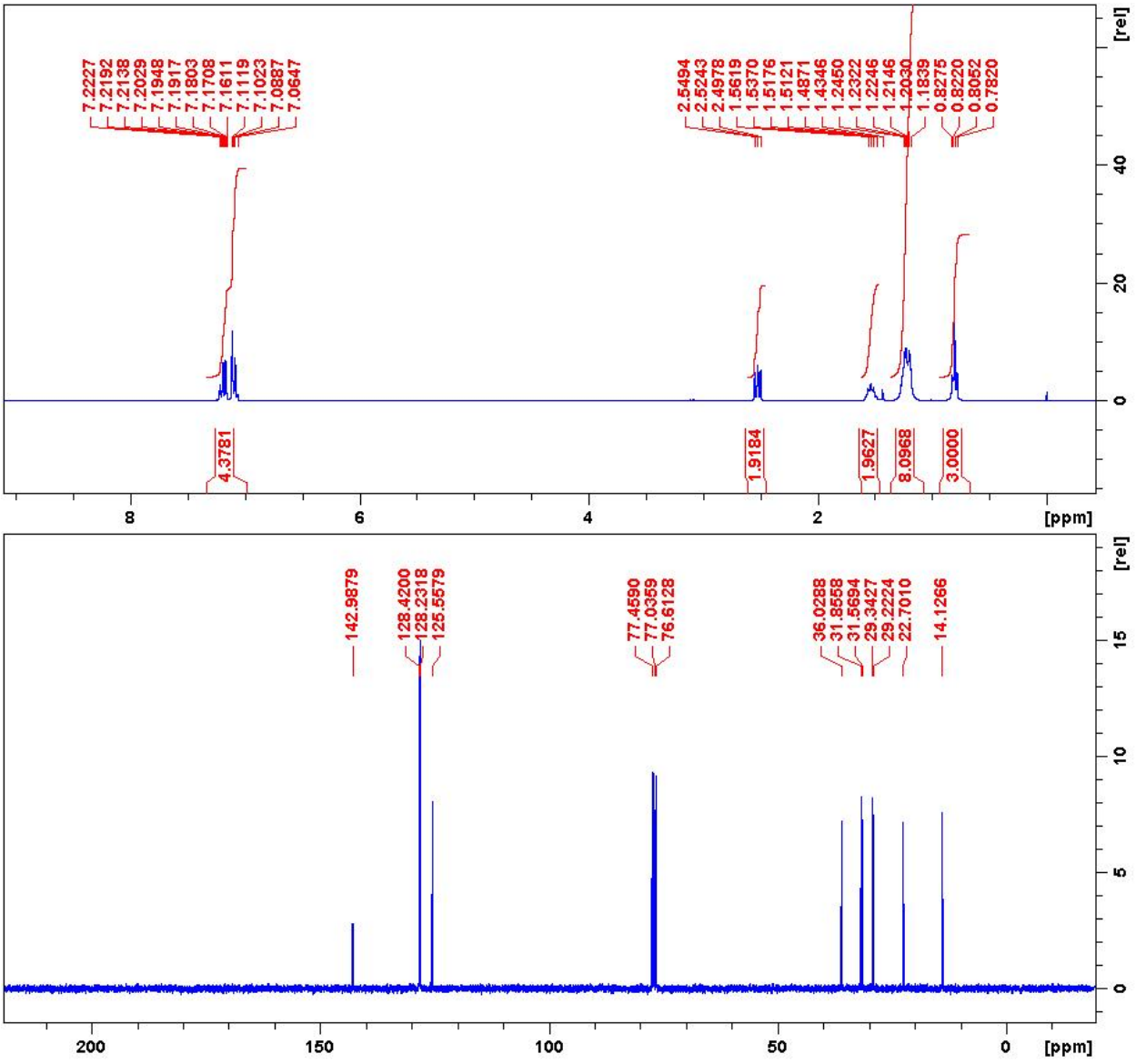

nC3H7

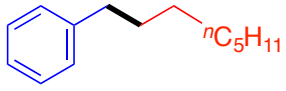
4n


7.1994
7.1901
7.1782
7.1191
7.0957
2.5564
2.5310
2.5047
1.5895
1.5649
1.5406
1.5352
1.5152
1.2627
1.2412
1.2362
1.2162
1.1860
0.8332
0.8112
0.7878
6.8433
2.0000
2.5141
15.5181
4.7687
[*1e6]
[ppm]
M 143.0095
128.3990
128.2109
125.5358
36.0008
31.7402
31.4979
29.7062
22.6153
14.0992
[*1e3]
[ppm]

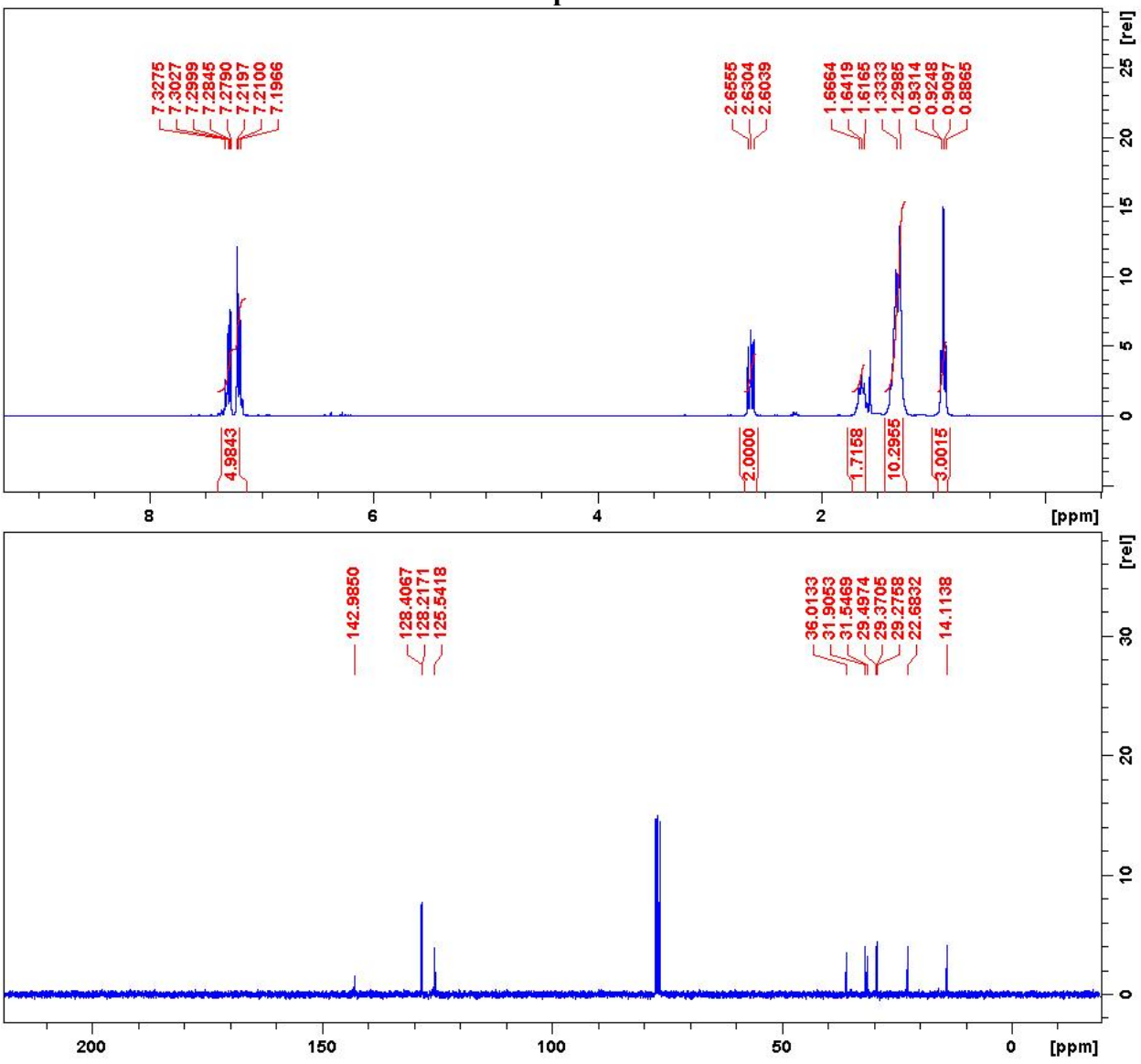

^{n}C$_4$H$_9$
^{n}C$_4$H$_9$

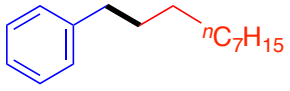
4o


7.2227
7.2192
7.2138
7.2029
7.1948
7.1917
7.1803
7.1708
7.1611
7.1119
7.1023
7.0887
7.0647
2.5494
2.5243
2.4978
1.5619
1.5370
1.5176
1.5121
1.4871
1.4346
1.2450
1.2322
1.2246
1.2146
1.2030
1.1839
0.8275
0.8220
0.8052
0.7820
4.3781
1.9184
1.9627
8.0968
3.0000
[rel]
[ppm]
142.9879
128.4200
128.2318
125.5579
77.4590
77.0359
76.6128
36.0288
31.8558
31.5694
29.3427
29.2224
22.7010
14.1266
[rel]
[ppm]

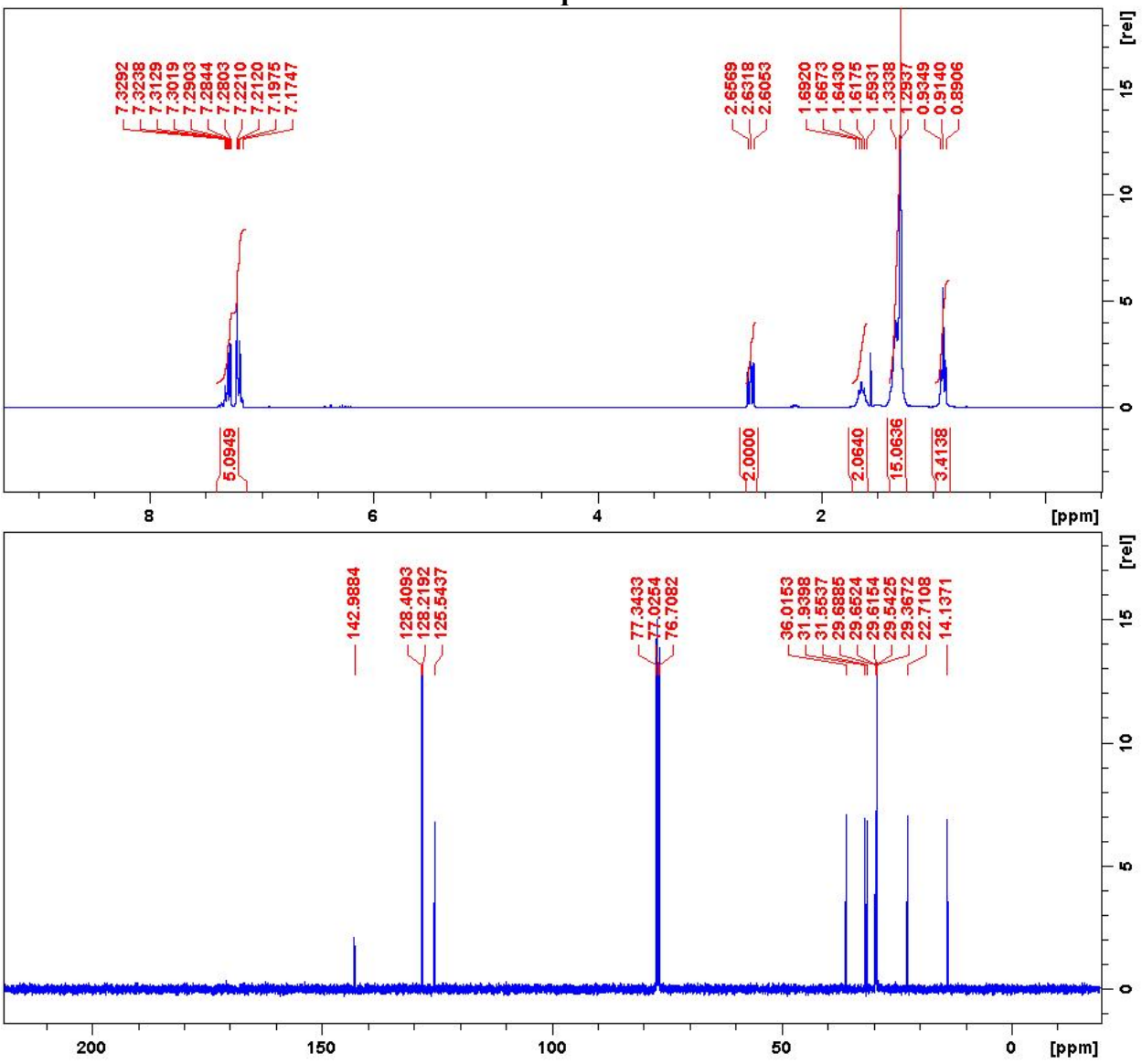

nC5H11

4p

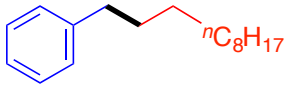

7.3275
7.3027
7.2999
7.2845
7.2790
7.2197
7.2100
7.1966
2.6555
2.6304
2.6039
1.6664
1.6419
1.6165
1.3333
1.2985
0.9314
0.9248
0.9097
0.8865
4.9843
2.0000
1.7158
10.2965
3.0015
[rel]
[ppm]
142.9850
128.4067
128.2171
125.5418
36.0133
31.9053
31.5469
29.4974
29.3705
29.2758
22.6832
14.1138
[rel]
[ppm]


$^{n}C_7H_{15}$

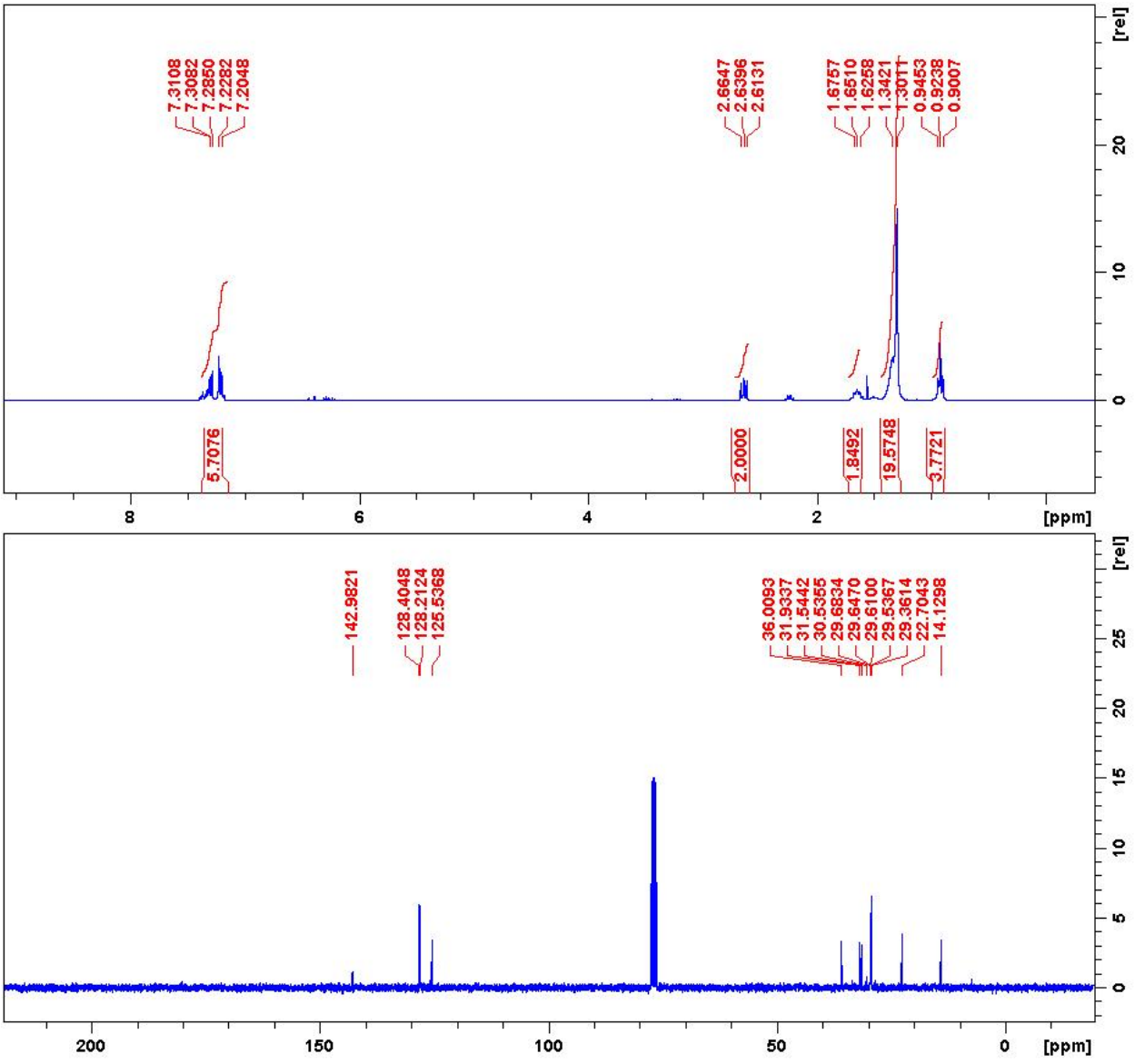
4q

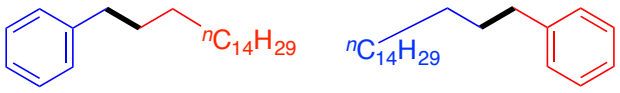

7.3292
7.3238
7.3129
7.3019
7.2903
7.2844
7.2803
7.2210
7.2120
7.1975
7.1747
2.6569
2.6318
2.6053
1.6920
1.6673
1.6430
1.6175
1.5931
1.3338
1.2937
0.9349
0.9140
0.8906
5.0949
2.0000
2.0640
15.0636
3.4138
[rel]
[ppm]

142.9884
128.4093
128.2192
125.5437
77.3433
77.0254
76.7082
36.0153
31.9398
31.5537
29.6885
29.6524
29.6154
29.5425
29.3672
22.7108
14.1371
[rel]
[ppm]

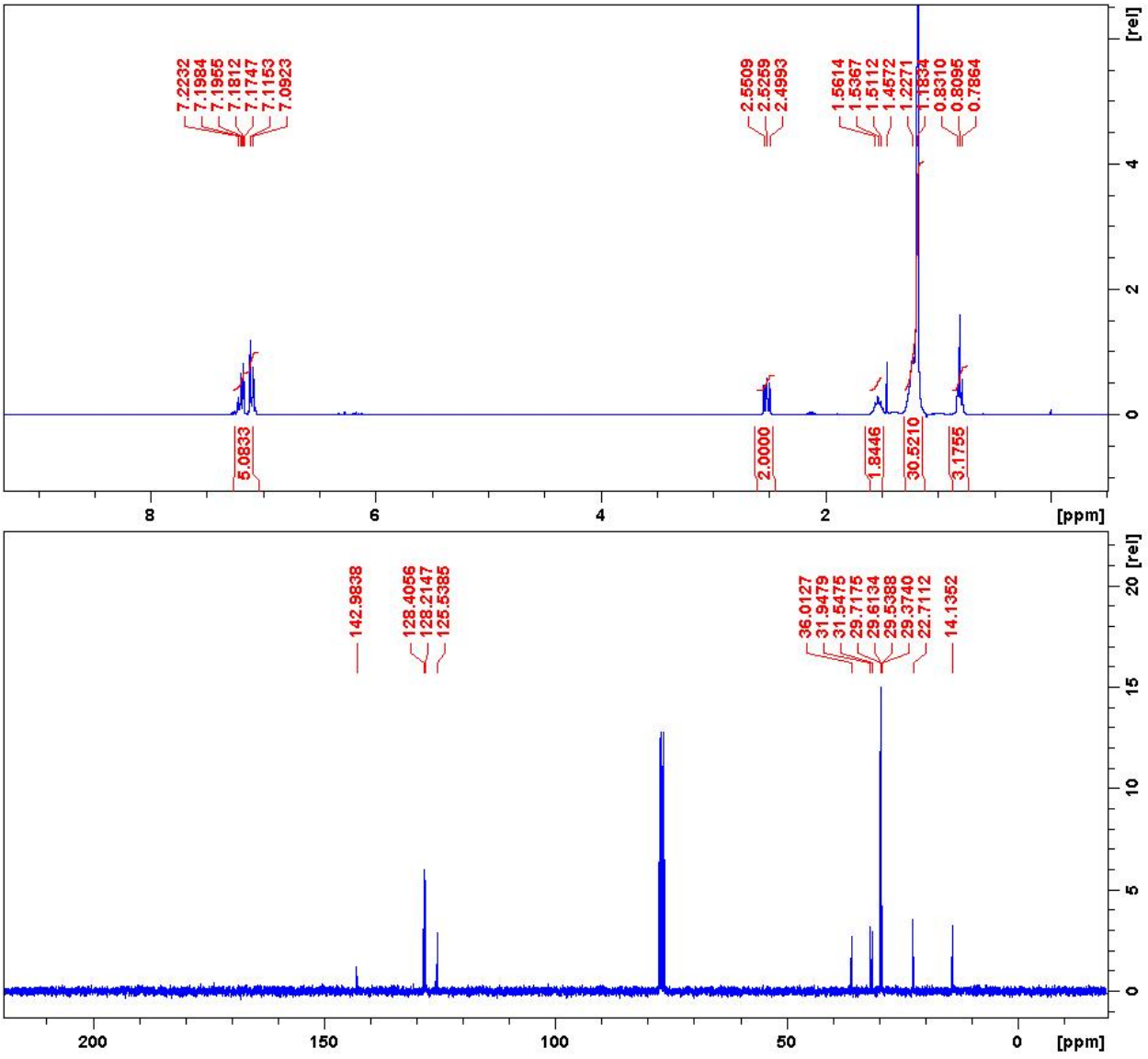

$^{n}C_8H_{17}$

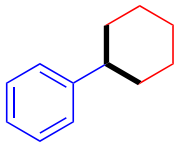
4r


7.3108
7.3082
7.2850
7.2282
7.2048
2.6647
2.6396
2.6131
1.6757
1.6510
1.6258
1.3421
1.3011
0.9453
0.9238
0.9007
5.7076
2.0000
1.8492
19.5748
3.7721
[rel]
[ppm]
142.9821
128.4048
128.2124
125.5368
36.0093
31.9337
31.5442
30.5355
29.6834
29.6470
29.6100
29.5367
29.3614
22.7043
14.1298
[rel]
[ppm]

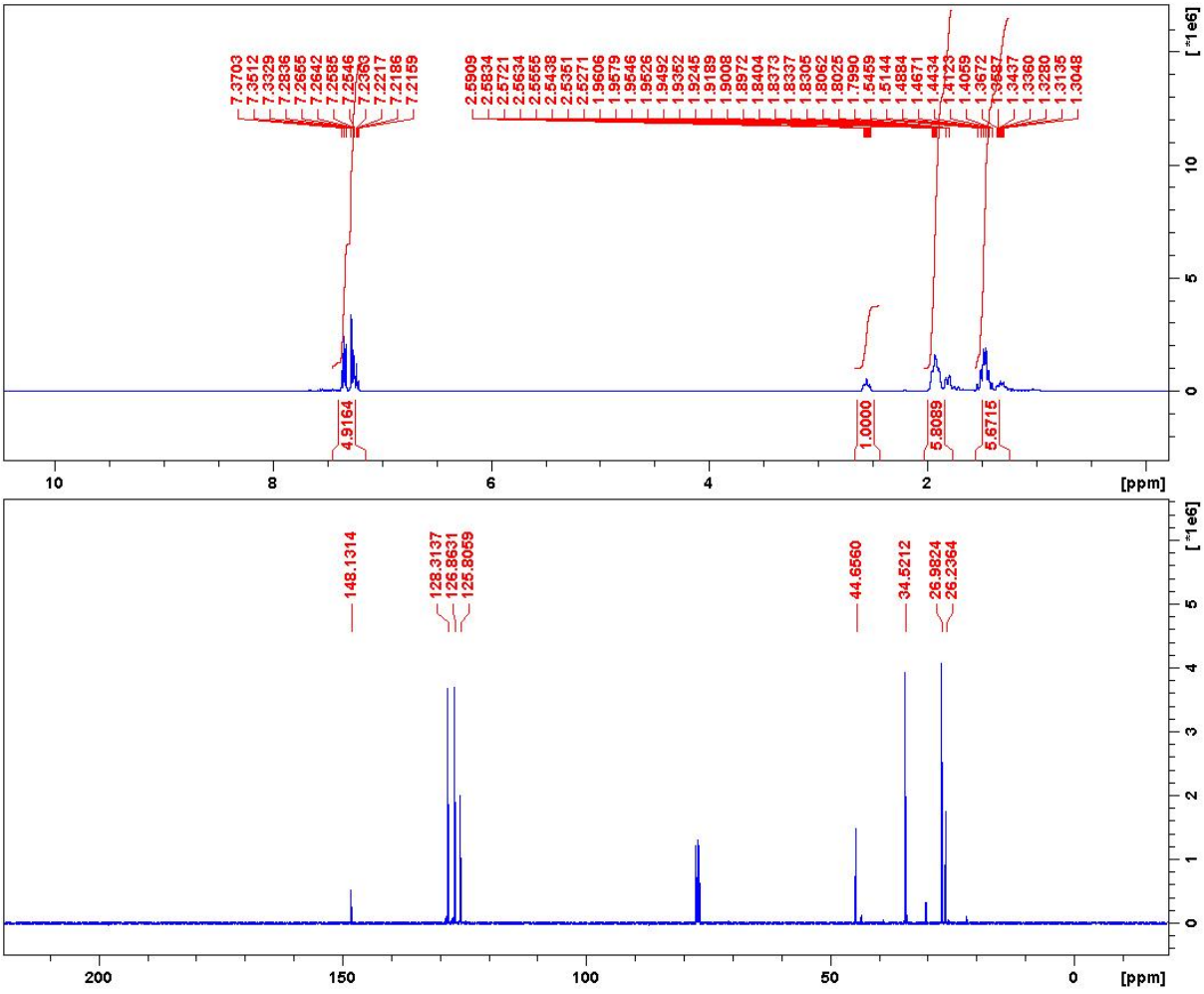

nC14H29
nC14H29

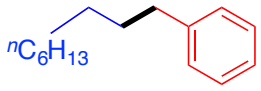
4s


7.2232
7.1984
7.1955
7.1812
7.1747
7.1153
7.0923
2.5509
2.5259
2.4993
1.5614
1.5367
1.5112
1.4572
1.2271
1.1834
0.8310
0.8095
0.7864
5.0833
2.0000
1.8446
30.5210
3.1755
[rel]
[ppm]
142.9838
128.4056
128.2147
125.5385
36.0127
31.9479
31.5475
29.7175
29.6134
29.5388
29.3740
22.7112
14.1352
[rel]
[ppm]

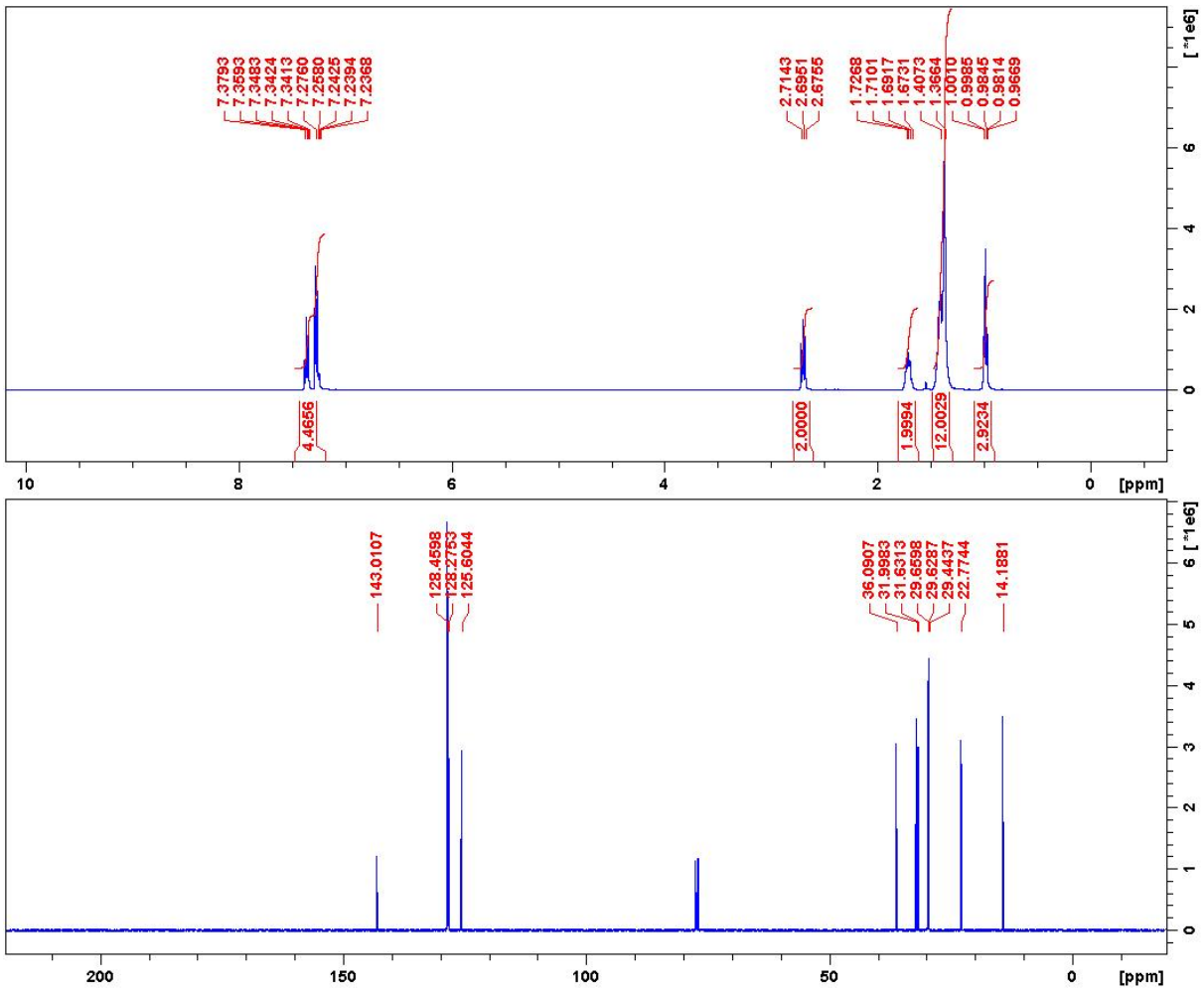


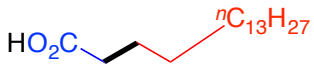
4t


7.3703
7.3512
7.3329
7.2836
7.2655
7.2642
7.2585
7.2546
7.2363
7.2217
7.2186
7.2159
2.5909
2.5834
2.5721
2.5634
2.5555
2.5438
2.5351
2.5271
1.9606
1.9579
1.9546
1.9526
1.9492
1.9352
1.9245
1.9189
1.9008
1.8972
1.8404
1.8373
1.8337
1.8305
1.8062
1.8025
1.7990
1.5459
1.5144
1.4884
1.4671
1.4434
1.4123
1.4059
1.3672
1.3587
1.3437
1.3360
1.3280
1.3135
1.3048
4.9164
1.0000
5.8089
5.6715
[*1e6]
[ppm]
148.1314
128.3137
126.8631
125.8059
44.6560
34.5212
26.9824
26.2364
[*1e6]
[ppm]

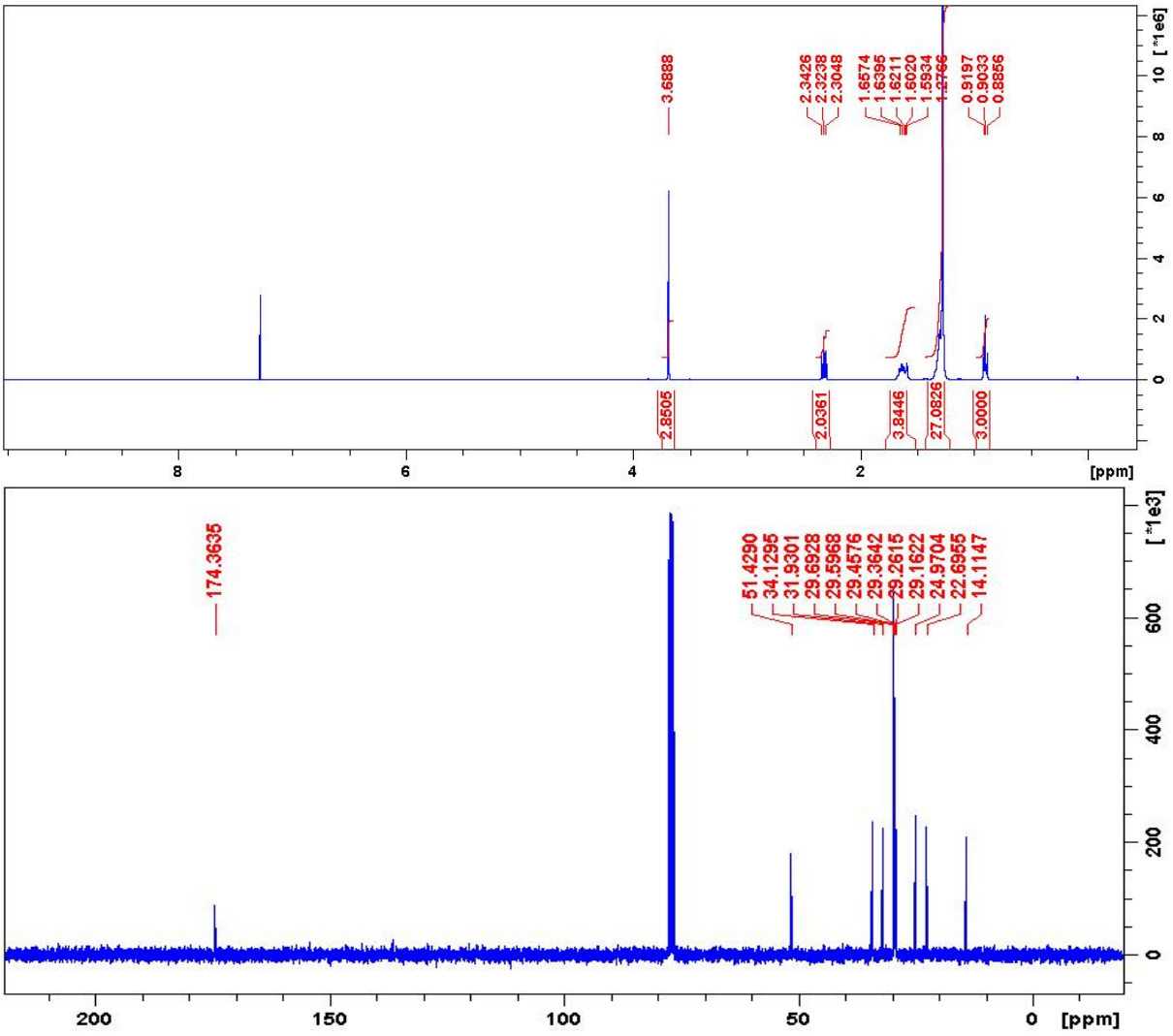

nC6H13

4u


7.3793
7.3593
7.3483
7.3424
7.3413
7.2760
7.2580
7.2425
7.2394
7.2368
2.7143
2.6951
2.6755
1.7268
1.7101
1.6917
1.6731
1.4073
1.3664
1.0010
0.9985
0.9845
0.9814
0.9669
4.4656
2.0000
1.9994
12.0029
2.9234
[*1e6]
[ppm]
143.0107
128.4598
128.2763
125.6044
36.0907
31.9983
31.6313
29.6598
29.6287
29.4437
22.7744
14.1881
6 [*1e6]
[ppm]


HO2C
nC13H27

4v


3.6888
2.3426
2.3238
2.3048
1.6574
1.6395
1.6211
1.6020
1.5934
1.2766
0.9197
0.9033
0.8856
2.8505
2.0361
3.8446
27.0826
3.0000
[ppm]
174.3635
51.4290
34.1295
31.9301
29.6928
29.5968
29.4576
29.3642
29.2615
29.1622
24.9704
22.6955
14.1147
[ppm]