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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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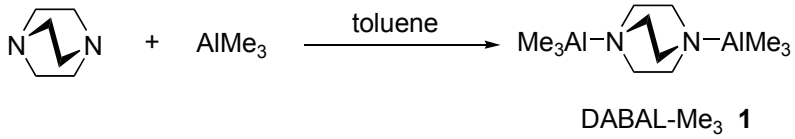
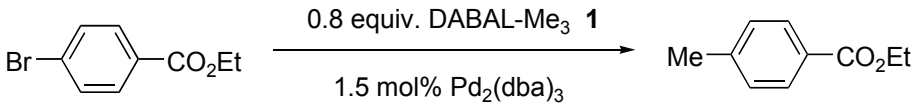
PALLADIUM-CATALYZED CROSS-COUPLING USING AN AIR-STABLE TRIMETHYLALUMINUM SOURCE. PREPARATION OF ETHYL 4-METHYLBENZOATE

A.



DABAL-Me_3 **1**

B.



2

Submitted by Andrej Vinogradov and Simon Woodward.[1]
Checked by Denise Rageot and Andreas Pfaltz.

1. Procedure

Caution! Trialkylaluminum compounds are pyrophoric and must not be allowed to come into contact with air or moisture. These compounds should only be handled by individuals trained in their proper and safe use.

A. [m-(1,4-Diazabicyclo[2.2.2]octane-kN1:kN4)]hexamethyldialuminum DABAL-Me_3 (**1**) (Note 1). A 250-mL, three-necked, round-bottomed flask is equipped with an egg-shaped, teflon-coated, magnetic stir bar (*ca*. 25 mm), a glass stopper, a reflux condenser and a 100-mL pressure-equalizing dropping funnel (Note 2). The reflux condenser is fitted at the top with a two-tap Schlenk adaptor connected to a bubbler and an argon/vacuum manifold (Note 3). A modest flow of argon is applied as judged by the exit bubbler (1-2 bubbles per second) and the reaction is kept under argon during the entire procedure. The glass stopper is removed and dry DABCO (5.40 g, 48.1 mmol, 1.00 equiv) (Note 4) is added in one portion using a powder funnel (Note 5). The open joint is sealed with a rubber septum and dry deoxygenated toluene (30 mL) (Note 6) is added via syringe. The solution is stirred for 10 min until all DABCO has dissolved (Note 7) and the rubber septum is replaced by a 0–150 °C thermometer in a gas-tight adaptor. The dropping funnel is charged with 2 M

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trimethylaluminum in toluene (47.0 mL, 94.0 mmol, 1.95 equiv) (Note 8) using a syringe. The trimethylaluminum solution is then added to the DABCO solution over 25 min at room temperature (Note 9) causing the formation of a white precipitate after *ca.* 10 min. Residual trimethylaluminum in the dropping funnel is rinsed with additional dry deoxygenated toluene (3 mL) (Note 6). The solution is stirred for 30 min at room temperature before DABAL-Me_3 (**1**) is allowed to settle for ca. 10 min. The dropping funnel is replaced by a rubber septum (Note 10, 11) and the toluene is removed by cannular filtration (Note 12). The colorless DABAL-Me_3 (**1**) is washed by injection of dry deoxygenated diethyl ether (40 mL) (Note 13), brief stirring and removal of the solvent by cannular filtration. This procedure is repeated twice (2 x 40 mL of dry deoxygenated diethyl ether). The product is dried under high vacuum (0.05 mmHg) at room temperature to afford DABAL-Me_3 (**1**) (9.97 g, 38.9 mmol, 81%) (Notes 14, 15) as a colorless solid.

B. Ethyl 4-methylbenzoate (**2**). A 500-mL, two-necked, round-bottomed flask is equipped with an egg-shaped, teflon-coated, magnetic stir bar (*ca*. 25 mm), a rubber septum and a reflux condenser fitted at the top with a two-tap Schlenk adaptor connected to a bubbler and an argon manifold (Note 2, 4). The flow of argon is reduced to a modest level as judged by the exit bubbler (1-2 bubbles per second), the rubber septum is removed and solid $Pd_2(dba)_3$ (550 mg, 0.600 mmol, 1.50 mol%) (Note 16) and X-Phos (573 mg, 1.20 mmol, 3.00 mol%) (Note 17) are added. The joint is sealed again with the rubber septum and dry THF (200 mL) (Note 18) and ethyl 4-bromobenzoate (9.16 g, 40.0 mmol, 1.00 equiv) (Note 19) are added by syringe. The joint is opened again to add DABAL-Me_3 (**1**) (8.31 g, 32.4 mmol, 0.801 equiv) using a powder funnel. The open socket is sealed with a glass stopper and the dark purple reaction mixture is heated at reflux for 4 h in an oil bath (90 °C). Completion of the reaction can by confirmed by working up an aliquot (1 mL) of the reaction mixture, as described below, and recording its ^{1}H NMR spectrum (Note 20). The argon flow is slightly increased (3-4 bubbles per second), heating is stopped and the reaction mixture is allowed to cool to room temperature over an hour. The flask is further cooled in an ice bath for 15 min and the reaction is quenched by cautious, portionwise, addition of 2 M aqueous HCl (160 mL) (Note 21). The resulting biphasic mixture is transferred into a separatory funnel (1 L) with diethyl ether (2 x 100 mL) (Note 22). The layers are separated, retained separately and the aqueous fraction is re-extracted with diethyl ether

(3 x 150 mL). The organic layers are combined, dried over $MgSO_4$ (30 g) and filtered though a plug of activated charcoal (5 g) (Note 23) layered on the top of SiO_2 (50 g) (Note 24). The plug is further washed with diethyl ether (1 L). Removal of the solvent by rotatory evaporation (25 °C, 150 mmHg) affords the crude product as a clear brown oil in quantitative yield. Short-path distillation under reduced pressure (118–120 °C at 0.1 mmHg) gives the product **2** (6.11 g, 37.2 mmol, 93%) as a colorless oil (Note 25).

2. Notes

1. DABAL-Me_3 (**1**) is available from Aldrich (Catalog No. 682101) which may alternatively be used as received in part B. The preparation of **1** presented here requires the use of *pyrophoric* $AlMe_3$ solutions; the synthesis should be conducted in a fumehood.

2. The glassware was dried in a >120 °C oven overnight, assembled hot and a brisk flow of argon was applied until residual air had been swept out of the apparatus and through the dropping funnel (*ca.* 5 min).

3. A two-tap Schlenk adaptor connected to a bubbler and an argon/vacuum manifold is illustrated in Yu, J.; Truc. V.; Riebel, P.; Hierl, E.; Mudryk, B., *Org. Synth.* **2008**, *85*, 64-71.

4. 1,4-Diazabicyclo[2.2.2]octane (DABCO) was purchased from Aldrich (98% grade). This slightly hygroscopic amine was sublimed (60–90 °C at 0.1 mm Hg) in a Kugelrohr distillation apparatus by cooling the collecting flask with dry ice. The checkers stored the freshly sublimed DABCO in a desiccator over P_2O_5 overnight.

5. The flow of argon should be moderate to facilitate addition without blowing the solid out of the addition funnel.

6. The submitters purchased toluene (> 99%) from Fisher Scientific. The solvent was dried over sodium overnight and deoxygenated by aerating with argon for 10 min. Alternatively, toluene can be distilled from sodium-benzophenone under argon. The checkers purchased toluene (>99%, over 4 Å molecular sieves from Fluka. It was deoxygenated by aerating with argon for 15 min and used without further drying.

7. The submitters warmed the mixture at 40 °C until the DABCO was completely dissolved. If necessary, to facilitate final dissolution of DABCO, submitters reported the possibility to add an additional quantity of toluene (5 mL). The checkers did not observe any need to help the dissolution of DABCO; it completely dissolved upon stirring.

8. Trimethylaluminum solutions in toluene were purchased from Aldrich (2 M) and used as received. Such solutions should be treated as *pyrophoric* and transferred by syringe under an argon atmosphere. Re-use of a 20 mL syringe proved to be the most effective method.

9. The temperature remained at <30 °C during addition. The submitters added the trimethylaluminum solution over 15 min and observed a *ca.* 20-30 °C rise in the temperature of the reaction mixture and formation of a white precipitate after 5-10 min. If the internal temperature rises above *ca.* 60 °C, the submitters reported the possibility to control the temperature by using a water bath.

10. Occasionally, slight smoking at the end of the addition funnel could be seen but ceased readily. To maximize safety, the discarded dropping funnel was opened and placed at the back of the fumehood overnight.

11. The set-up should be left under a slight positive pressure of argon to avoid ingress of air.

12. The cannular filtration was conducted under an argon atmosphere using Teflon tubing (800 mm x 2 mm). One side of the tubing was covered with filter paper, secured with a Teflon band, and fitted to the reaction flask with a rubber septum. The cannular filtration is described in detail in ref. 2. To the collected solvents and washings was added dropwise *iso*-propanol (*ca*. 5 mL) before storing them at the rear of the fumehood overnight and later subjected to appropriate disposal.

13. The submitters purchased diethyl ether (>99%) from Sigma-Aldrich. The solvent was distilled from sodium-benzophenone under an argon atmosphere and collected by syringe. The checkers used diethyl ether (VWR, HPLC grade) dried and degassed using a Pure-Solve^{TM} system.

14. The submitters obtained 9.20-10.0 g (74-81%) of DABAL-Me_3 (**1**). When carried out at half of the scale reported in the procedure, the checkers obtained 4.87 g (79%) of **1**.

15. Combustion of neat DABAL-Me_3 (**1**) can be induced by water, aqueous acids and other strong proton sources. It should be regarded as incompatible with strong oxidizing agents. Samples can be stored in air-tight containers under argon or nitrogen at room temperature (storage lifetime under these conditions is at least one year). The compound can be handled in air (15 min to 4 h, depending on the moisture content of the laboratory air). Longer exposure results in slow controlled decomposition to aluminum hydroxides/oxides. Unwanted samples of DABAL-Me_3 (**1**) can be disposed of by cautious, slow hydrolysis with alcohols or for small amounts even

ice/ice-water mixtures. The reagent should be considered as harmful by ingestion and strongly irritating to the eyes and mucous membranes. DABAL-Me_3 (**1**) has the following properties: mp 230 °C (dec., in air chars from 160 °C); it is soluble in THF, CH_2Cl_2, C_6H_6 and $CHCl_3$, but only sparingly soluble in Et_2O or in toluene at room temperature. Its physical properties are as follows: ^{1}H NMR (400 MHz, C_6D_6, 25 °C) δ: –0.64 (s, 18 H), 1.97 (s, 12 H) ppm; ^{13}C NMR (101 MHz, C_6D_6, 25 °C) δ: –9.8, 43.6 ppm. NMR samples need to be prepared in dry, non-protic solvents. Recrystallization of **1** from dry benzene under argon (crude **1** (1.00 g) dissolved in hot C_6H_6 (8-10 mL) provides 0.55-0.60 g of colorless rhomboidal crystals (unit cell parameters and X-ray structure identical to literature values[5]).

16. $Pd_2(dba)_3$ (dba = dibenzylideneacetone) was purchased from Alpha Aesar by the submitters and used as received. The checkers obtained $Pd_2(dba)_3$ from Sigma-Aldrich and used it without further purification. Literature preparations of this compound are available in ref. 3.

17. X-Phos was purchased from Alfa Aesar by the submitters and used as received. The checkers obtained X-Phos (97%) from Sigma-Aldrich.

18. The submitters obtained tetrahydrofuran (THF, >99%) from Sigma-Aldrich and distilled it from sodium-benzophenone under an argon atmosphere. The checkers used tetrahydrofuran (VWR, HPLC-grade) dried using a Pure-Solve™ system.

19. Ethyl 4-bromobenzoate (Aldrich, 98%) was dried overnight using activated 4Å molecular sieves before use.

20. Complete consumption of ethyl 4-bromobenzoate is easily identified by the absence of the two apparent doublets of the phenylene group in its ^{1}H NMR spectrum. Its physical properties are as follows: ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 1.42 (t, J = 7.1 Hz, 3 H), 4.40 (q, J = 7.1 Hz, 2 H), 7.60 (app. d, J = 8.5 Hz, 2 H), 7.92 (app. d, J = 8.5 Hz, 2 H) ppm. Alternatively, the submitters reported that GC analysis can be used to confirm completion of the reaction: 15 m factorFOUR column, column flow: He, 1.5 mL·min^{-1}, run isothermally at 120 °C, t_R = 2.75 min (**2**), t_R = 4.95 min (ethyl 4-bromobenzoate).

21. The quenching procedure releases methane. Care should be taken to add the acid at such rate that excessive foaming is avoided. If the flask is re-stoppered the rate of the hydrolysis reaction can be judged by the rate of out-gassing from the exit bubbler. Typically, addition of the 2 M HCl over 10-15 min is required.

22. The submitters purchased diethyl ether (>99%) from Sigma-Aldrich and used it as supplied. The checkers obtained diethyl ether (>99%) from J. T. Baker and used it as received.

23. The checkers purchased activated charcoal from Fluka.

24. Silica gel 60 (220 240 mesh) supplied by Fluka was used as received. The SiO_2 was slurried up in diethyl ether, before layering it with activated charcoal and filtering the organic phase.

25. The submitters obtained 5.98-6.31 g (91-96%) of **2**. When carried out at half of the scale reported in the procedure the checkers obtained 2.95 g (90%) of **2**. The compound has literature properties[4] and is stable indefinitely. Its physical properties are as follows: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 1.38 (t, J = 7.1 Hz, 3 H), 2.40 (s, 3 H), 4.36 (q, J = 7.1 Hz, 2 H), 7.22 (app. d, J = 8.3 Hz, 2 H), 7.94 (app. d, J = 8.3 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ: 14.4, 21.7, 60.8, 127.9, 129.1, 129.7, 143.5, 166.8; Anal. calcd. for $C_{10}H_{12}O_2$: C, 73.15%; H, 7.37%; found: 72.90%; H, 7.38%. The purity of the compound was checked by GC analysis; Rtx-1701 column (30 m x 0.25 mm x 0.25 μm), 60 kPa He, 100 °C, 2 min isotherm, 7 °C·min^{-1}, 250 °C, 10 min isotherm, t_R = 13.6 min (**2**), t_R = 16.5 (ethyl 4-bromobenzoate).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory": National Academy Press: Washington. DC. 1995.

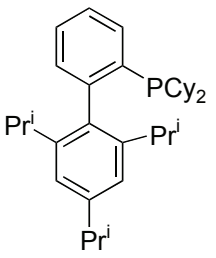
3. Discussion

The abnormally high air stability of the DABCO *bis*-$AlMe_3$ adduct (**1**) was first noted by Bradley in the early 1990s.[5] However, synthetic applications of the material only recently became popular – especially since the commercialization of this reagent. Originally prepared in Et_2O, the combination of pyrophoric trimethylaluminium and a very low flash point of ether is less desirable on large scales for safety reasons, even though somewhat higher yields can be realized. The toluene-based procedure described here is effective and safe at scales up to at least 10 g. In combination with $Pd_2(dba)_3$ and Buchwald's X-Phos,[6] DABAL-Me_3 (**1**) is effective for the methylation of aryl halides ArX (X = Cl, Br, I) and triflates

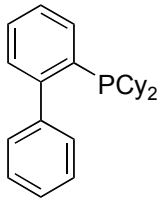
(X = OTf).[7] A wide range of other functional groups is tolerated under these reaction conditions (F, CF_3, vinyl, CO_2R, CN, CHO, OTs, NO_2, OMe, and OAc) (Table 1). Complete conversion is attained within 4 h at THF reflux (with 0.8 equiv of DABAL-Me_3), avoiding the often problematic post-reaction chromatographic separation of residual halide starting materials.

Chemoselective methylation (>95% selectivity) of C-Br over C-Cl bonds can be attained through use of Cy-JohnPhos.[8] Aside from C(sp^2)-X (X = Cl, Br, I, OTf), benzylic halides can be used in Pd^0/X-Phos couplings (e.g., $PhCH_2Br$ is methylated in 72% yield). One limitation of the methylation procedure is its present inability to tolerate the methylation of electron deficient heterocycles (e.g. halopyridines and isoquinolines; entries 34-35, Table 1). The low yields of methylated products isolated in these cases are believed to be due to competing Chichibabin-type processes. Additionally, enolizable substrates capable of self-condensation are not always tolerated (entry 26, Table 1). The use of 0.8 equiv of DABAL-Me_3 per coupled C-X, together with Pd^0/X-Phos makes for a highly robust procedure. In small-scale reactions (0.25 mmol) the procedure can be carried out in undried THF under standard reflux conditions in air – the DABAL-Me_3 (**1**) acting simultaneously as a drying agent. However, the slower rates of heating in large-scale reactions (such as that presented here) slows the solvent drying/deoxygenation process too much, leading to non-reproducibility. Couplings with DABAL-Et_3 allow ethylation procedures in >85% yield without any issues associated with β-elimination. The ethyl analogue is not stable in air and is best prepared in situ from DABCO and $AlEt_3$.

In addition to the cross-coupling procedure illustrated here, DABAL-Me_3 (**1**) has found application in a wide range of transformations including: 1,2-additions to aldehydes[9] and enones,[10] 1,4-additions to enones,[11] methylation of allylic electrophiles[12] and direct conversion of esters to amides.[13]



X-Phos

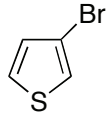
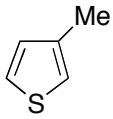
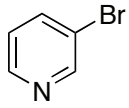
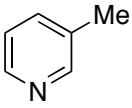
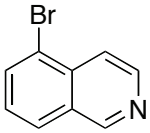
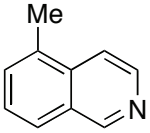
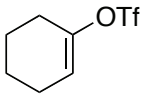
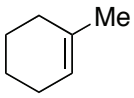
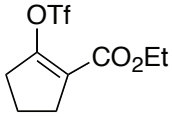
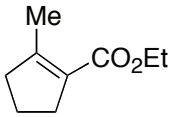


Cy-JohnPhos

Table 1. Methylation of aryl and vinyl halides and pseudohalides with DABAL-Me_3 **1**.[a]

Entry	Substrate	Product	Yield [%][b]
1	C_6H_5Br	C_6H_5Me	>99
2	C_6H_5OTf	C_6H_5Me	>99
3	4-MeC_6H_4Br	1,4-$Me_2C_6H_4$	>99
4	4-MeC_6H_4Cl	1,4-$Me_2C_6H_4$	>99
5	4-FC_6H_4Br	4-FC_6H_4Me	>99
6	4-ClC_6H_4Br	4-ClC_6H_4Me	96[c]
7	4-$(CF_3)C_6H_4Br$	4-$(CF_3)C_6H_4Me$	>99
8	4-$tBuC_6H_4Br$	4-$tBuC_6H_4Me$	96
9	4-NCC_6H_4Br	4-NCC_6H_4Me	95
10	4-NCC_6H_4Cl	4-NCC_6H_4Me	95
11	3-NCC_6H_4Br	3-NCC_6H_4Me	95
12	2-NCC_6H_4Br	2-NCC_6H_4Me	96
13	4-$(H_2C{=}CH)C_6H_4Br$	4-$(H_2C{=}CH)C_6H_4Me$	>99
14	4-$(H_2C{=}CH)C_6H_4Cl$	4-$(H_2C{=}CH)C_6H_4Me$	98
15	4-$(MeO)C_6H_4Br$	4-$(MeO)C_6H_4Me$	>99
16	4-$(MeO)C_6H_4Cl$	4-$(MeO)C_6H_4Me$	>99
17	4-$(MeO)C_6H_4OTf$	4-$(MeO)C_6H_4Me$	>99
18	2-$(MeO)C_6H_4Br$	2-$(MeO)C_6H_4Me$	>99
19	4-$(EtO_2C)C_6H_4Br$	4-$(EtO_2C)C_6H_4Me$	99
20	4-$(EtO_2C)C_6H_4Cl$	4-$(EtO_2C)C_6H_4Me$	98
21	4-HOC_6H_4Br	4-HOC_6H_4Me	94[d]
22	4-$(O_2N)C_6H_4Br$	4-$(O_2N)C_6N_4Me$	76
23	4-$(O_2N)C_6H_4Cl$	4-$(O_2N)C_6N_4Me$	81
24	4-$(O_2N)C_6H_4OTf$	4-$(O_2N)C_6N_4Me$	59
25	4-$(HOCH_2)C_6H_4Br$	4-$(HOCH_2)C_6H_4Me$	79
26	4-$(MeOC)C_6H_4Br$	4-$(MeOC)C_6H_4Me$	0[e]
27	4-$(CHO)C_6H_4Br$	4-$(CHO)C_6H_4Me$	88[f]
28	$C_6H_5CH_2Br$	$C_6H_5CH_2Me$	72
29	1-$C_{10}H_7OTf$	1-$C_{10}H_7Me$	>99
30	2-$C_{10}H_7OTf$	2-$C_{10}H_7Me$	98
31	1-$C_{10}H_7Cl$	1-$C_{10}H_7Me$	90
32	2-$C_{10}H_7Cl$	2-$C_{10}H_7Me$	98

Table 1. (continued)

Entry	Substrate	Product	Yield [%][b]
33			90
34			16
35			59
36			>99
37			98

[a] Reactions performed on a 0.25 mmol scale using 1.5mol % $Pd_2(dba)_3$, 3 mol % X-Phos, 0.8 equiv. DABAL-Me_3 (**1**), THF, N_2, 80 °C, 4 h. In all cases quantitative conversions were attained. [b] Yields determined by GC *vs.* internal standard. In reactions run at larger scale the isolated yields were directly comparable and typically within 5% of the GC yields. [c] 1.0 equivalents of DABAL-Me_3 **1** used; using Cy-JohnPhos, <2% dimethylation observed. [d] 1.6 equivalents of DABAL-Me_3 **1** used. [e] Major products are self-aldol derived. [f] 0.5 equivalents of DABAL-Me_3 **1** used.

1. School of Chemistry, The University of Nottingham, NG7 2RD United Kingdom; e-mail simon.woodward@nottingham.ac.uk

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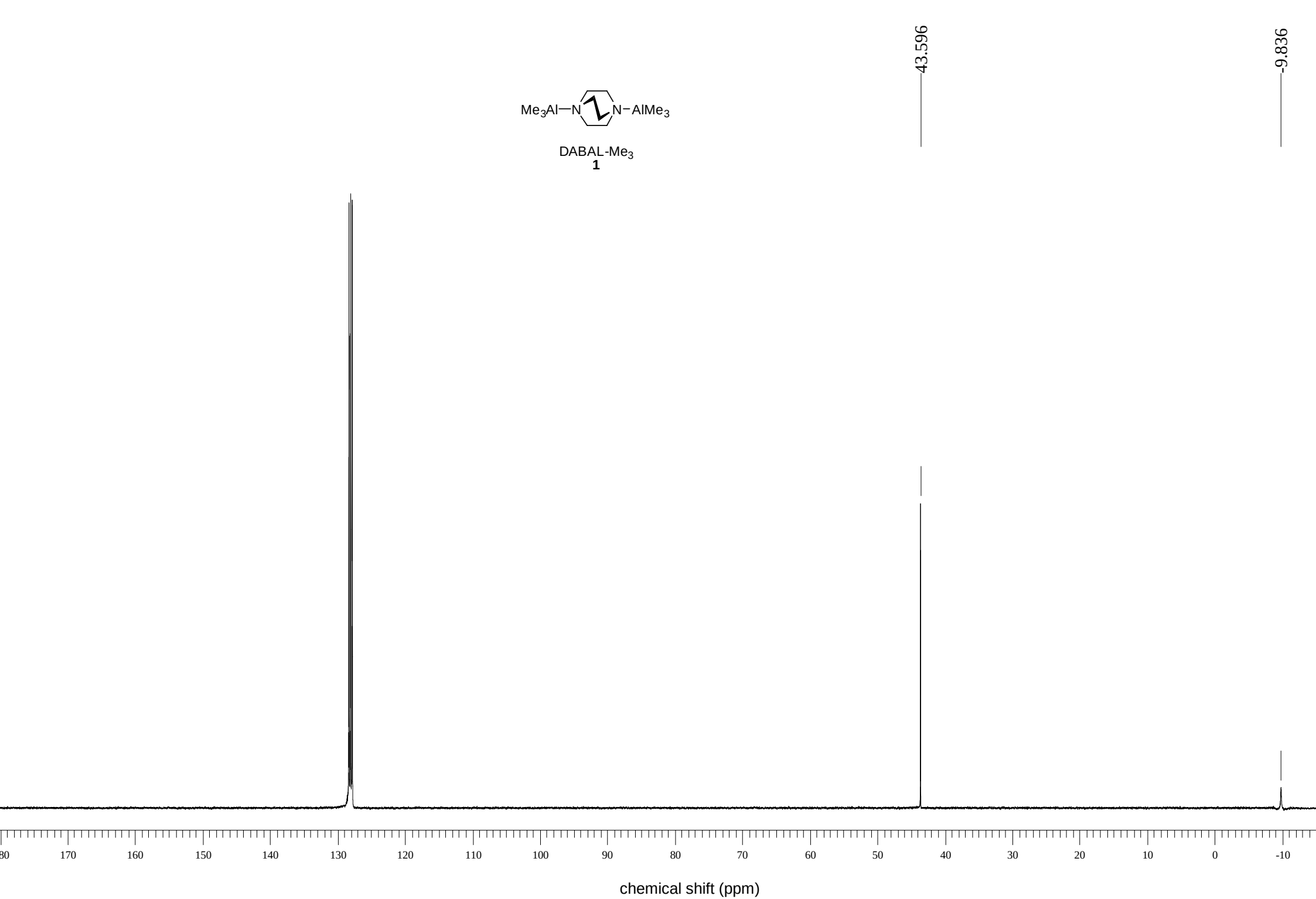
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

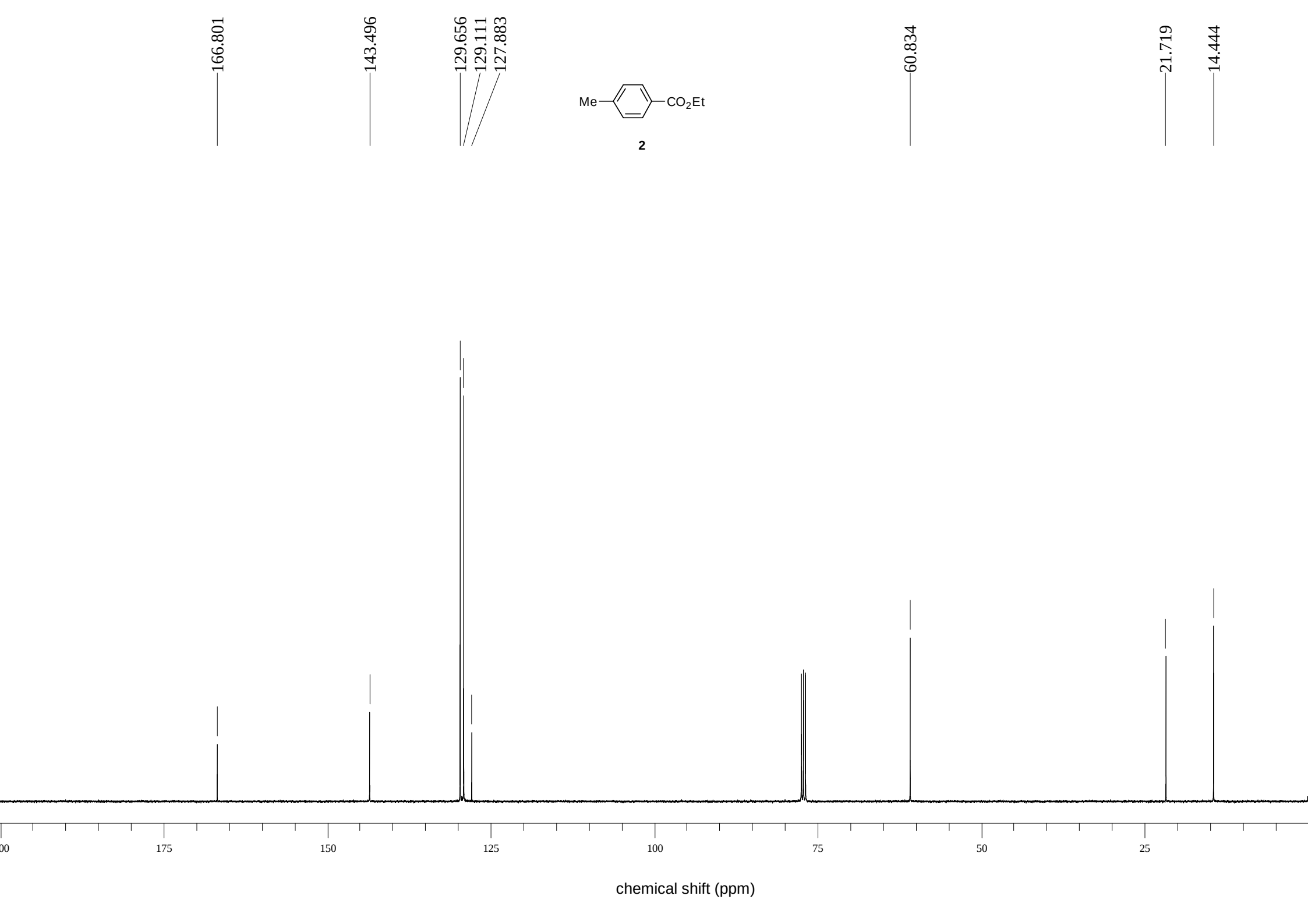
Trimethylaluminium: (75-24-1)
DABCO: 1,4-Diazabicyclo[2.2.2]octane; (280-57-9)
$Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium(0); (51364-51-3)
X-Phos: 2-di-cyclo-hexylphosphino-2',4',6'-triisopropylbiphenyl; (564483-18-7)
Ethyl 4-bromobenzoate: (5798-75-4)

Simon Woodward undertook both his undergraduate and Ph.D. at the University of Sheffield, the latter in the group of Dr. Mark J. Winter. After a period as a Fulbright Scholar in the group of Prof. M. David Curtis at the University of Michigan he was a postdoctoral researcher with Dr. John M. Brown, FRS at the University of Oxford. Initially appointed to a Lectureship in Organometallic and Catalytic Chemistry at The University of Hull, he moved to the University of Nottingham in 1999. His research group is interested in chemo, regio and stereoselective catalysis of organic reactions, under convenient/simple conditions.

Andrej Vinogradov studied Chemistry at the University of Münster. He did his Ph.D. at the Inorganic Chemistry Department of the University of Münster under supervision of Prof. Dr. Werner Uhl. Since 2009 he is a postdoctoral research fellow at the University of Nottingham with Prof. Simon Woodward. Dr. Vinogradov's research interests centre round the preparation and use of organoalanes.

Denise Rageot was born in 1985 in Basel, Switzerland. She studied Chemistry at the University of Basel, where she obtained her M.S. in 2008 under the supervision of Prof. Andreas Pfaltz. She began her Ph. D. work in summer 2008 in the group of Prof. Andreas Pfaltz, where she is currently working on the synthesis of new chiral ligands for asymmetric metal catalysis.


43.596
-9.836
Me3Al—N
N−AlMe3
DABAL-Me3
1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
chemical shift (ppm)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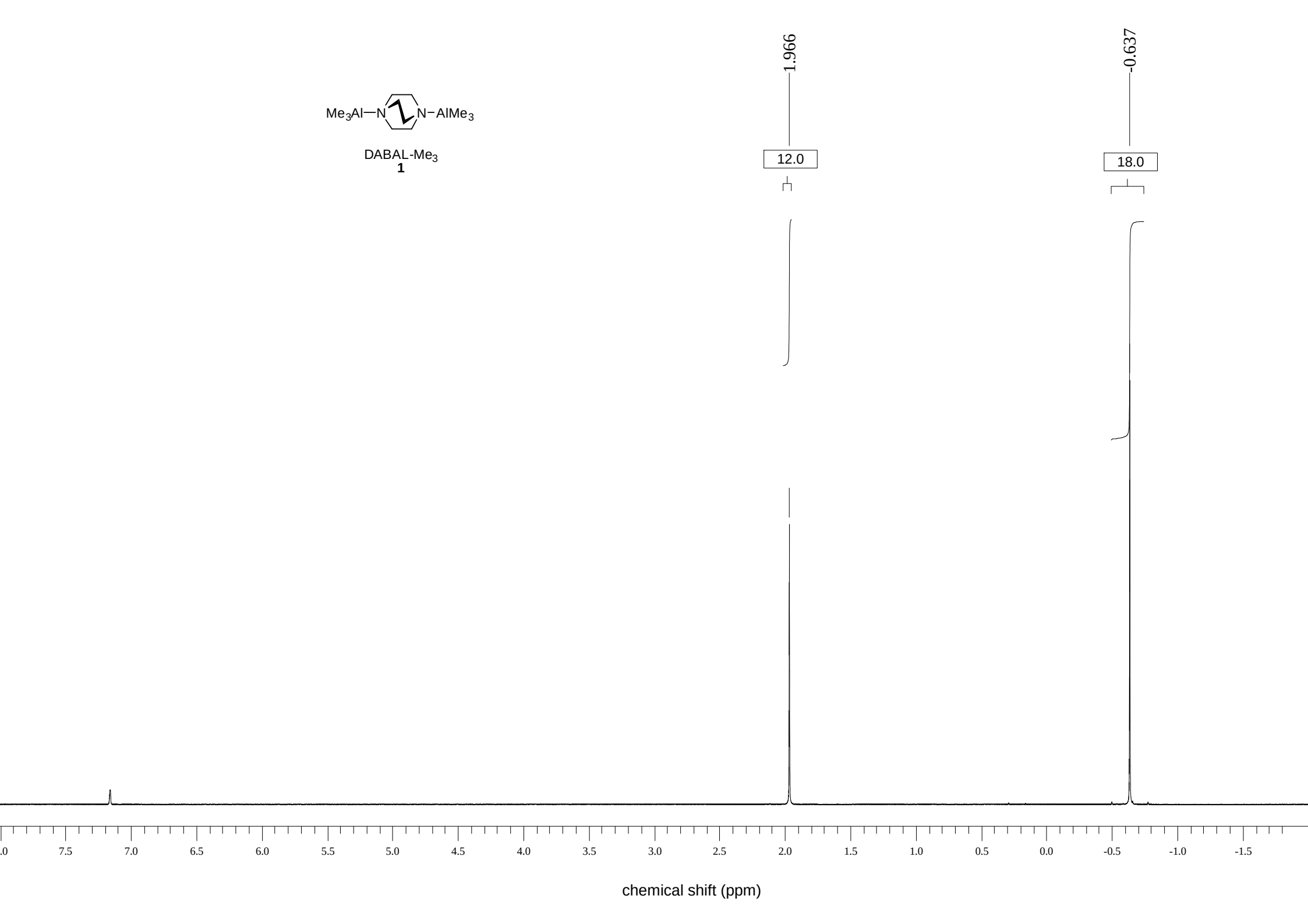
143.496
129.656
129.111
127.883
60.834
21.719
14.444
Me
CO2Et
2
175
150
125
100
75
50
25
chemical shift (ppm)


Me3Al—N
N−AlMe3
DABAL-Me3
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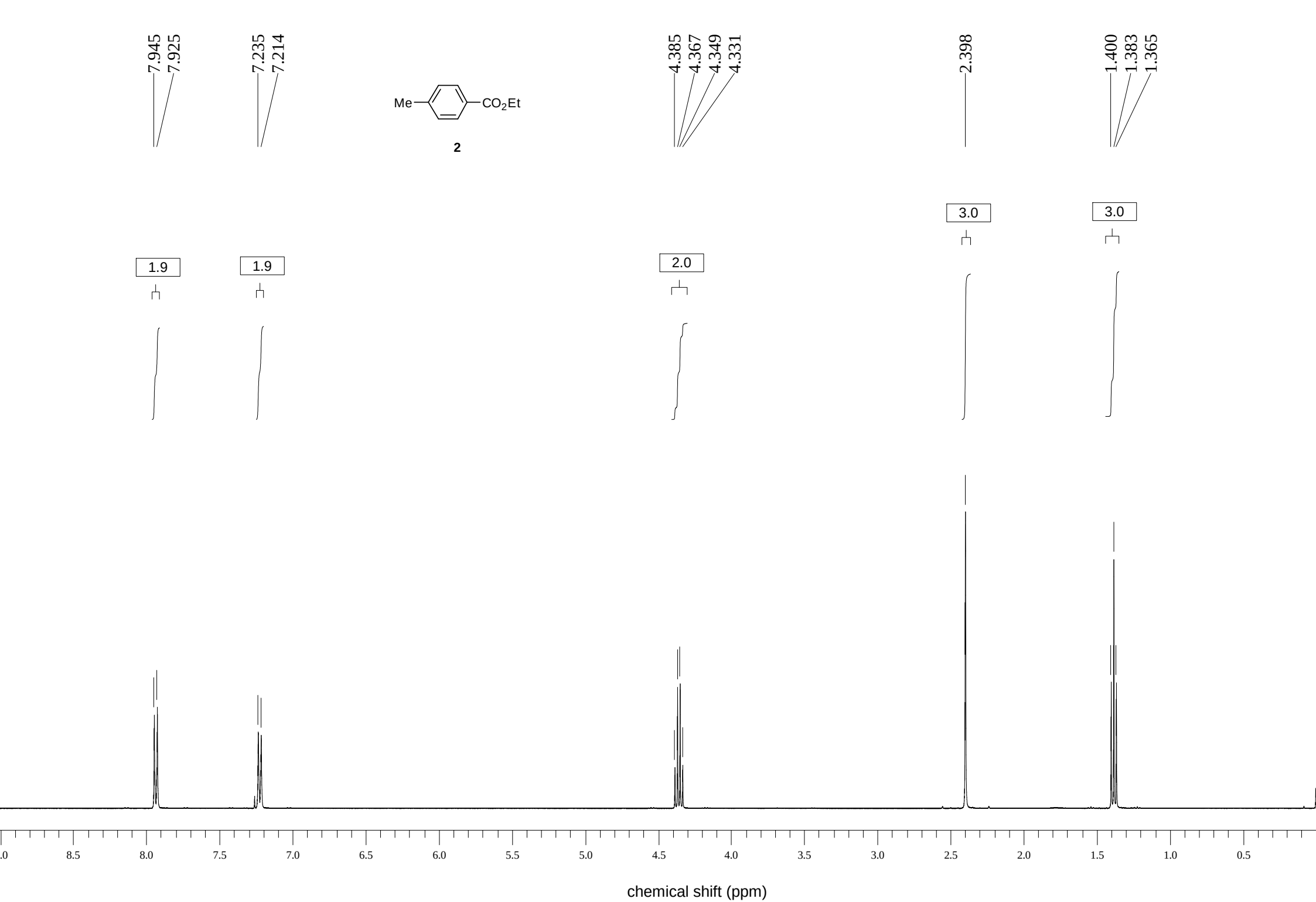
1.966
12.0
-0.637
18.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
chemical shift (ppm)


7.945
7.925
7.235
7.214
Me
CO2Et
2
4.385
4.367
4.349
4.331
2.398
1.400
1.383
1.365
1.9
1.9
2.0
3.0
3.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
chemical shift (ppm)