# Organic Syntheses

Working with Hazardous Chemicals

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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.

Synthesis of Cyclobutarenes by Palladium-Catalyzed C(sp^3)-H Bond Arylation: Preparation of Methyl 7-Methylbicyclo[4.2.0]Octa-1,3,5-Triene-7-Carboxylate

A.

B.
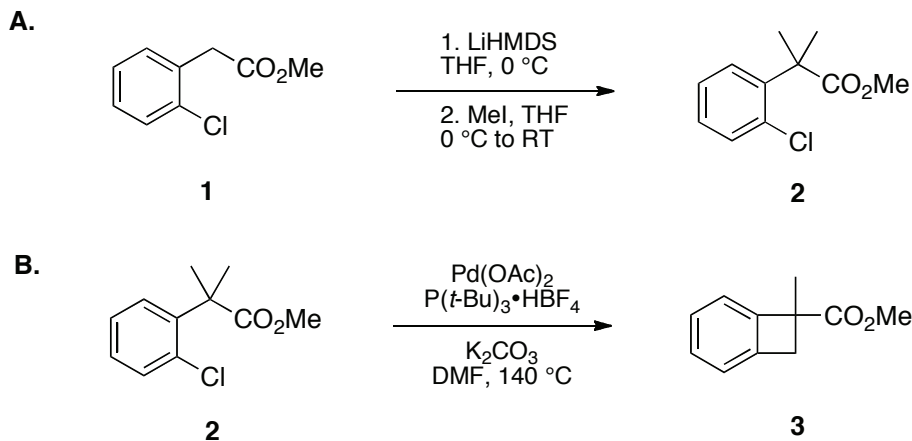
Submitted by Michaël Davi, Arnaud Comte, Rodolphe Jazzar, and Olivier Baudoin.[1]

Checked by Brendan T. Parr and Huw M. L. Davies.

1. Procedure

A. *Methyl 2-(2-chlorophenyl)-2-methylpropanoate* (**2**). A one-necked 500-mL round-bottomed flask (Note 1), equipped with a Teflon-coated magnetic stirring bar (Note 2), is fitted with a rubber septum and connected to a combined argon/vacuum line and evacuated/back-filled with argon twice. The reaction vessel was charged with lithium bis(trimethylsilyl)amide (135 mL, 135 mmol, 2.5 equiv) (Note 3). The flask is then cooled to 0 °C using an ice-bath. A THF (10 mL) solution (Note 4) of methyl (2-chlorophenyl)acetate (**1**) (10.2 g, 54.1 mmol, 1 equiv) (Notes 5 and 6) is added dropwise and the mixture is stirred for an additional 30 min. Finally, after dropwise addition of a THF (10 mL) (Note 4) solution of iodomethane (8.4 mL, 135.0 mmol, 2.5 equiv) (Note 7), the reaction is stirred at room temperature for 2 h (Notes 8 and 9). After drop-wise addition of saturated aqueous solution of ammonium chloride (50 mL) (Note 10), the aqueous layer is extracted twice with diethyl ether (2 x 100 mL) (Note 11). The combined organic layers are successively washed with a saturated aqueous solution of sodium thiosulfate (50 mL) (Note 12) and brine (50 mL) (Note 13), dried over anhydrous MgSO$_4$ (5 g) (Note 14), filtered and

concentrated under reduced pressure. The residue is purified by a short-path distillation under vacuum (58–61 °C/0.11 mmHg) to afford the pure product **2** (10.7–10.8 g, 93–94%) as a colorless oil (Note 15).

B. *Methyl 7-methylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate* (**3**). A one-necked, 500-mL round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar (Notes 1 and 2) is charged with palladium(II) acetate (527 mg, 2.35 mmol, 0.05 equiv) (Note 16), P(*t*-Bu)$_3$•HBF$_4$ (1.36 g, 4.69 mmol, 0.10 equiv) (Note 17) and potassium carbonate (8.44 g, 61.0 mmol, 1.30 equiv) (Note 18). The flask is fitted with a rubber septum, connected to a combined argon/vacuum line and evacuated for an hour (in order to remove traces of oxygen and water), then back-filled with argon three times (Note 19). A single-necked, 100-mL round-bottomed flask (Note 1) is charged with methyl 2-(2-chlorophenyl)-2-methylpropanoate **2** (10.00 g, 47.0 mmol, 1.0 equiv). The flask is fitted with a rubber septum, connected to a combined argon/vacuum line and evacuated for an hour, then back-filled with argon three times and charged with DMF (90 mL) (Note 20). The DMF solution of **2** is then added to the 500-mL round-bottomed flask dropwise *via* cannula. The mixture is then stirred for 15 min at room temperature and for 24 h at 140 °C (preheated oil bath) (Notes 8 and 21). After this time, the reaction mixture is cooled to ambient temperature, diluted with diethyl ether (100 mL) (Note 11) and filtered through a short pad of Celite® (10 g) (Note 22). The organic layer is washed three times with brine (3 x 100 mL) (Note 13), dried over magnesium sulfate (10 g) (Note 14) and evaporated under reduced pressure. The residue is then purified by distillation under vacuum (62 °C, 0.11 mmHg) (Note 23) to afford the title compound **3** (4.91–4.95 g, 59–60%) as a colorless oil (Note 24).

2. Notes

1. Glassware was dried in an oven at 150 °C for >2 h before being connected to a vacuum/argon line, where it was cooled to room temperature under vacuum and subsequently back-filled with argon.
2. An egg-shaped 70 mm x 15 mm magnetic stir bar was used.
3. Lithium bis(trimethylsilyl)amide (1.0 M THF solution) was purchased from Sigma-Aldrich and used as received.
4. Tetrahydrofuran (THF) was purchased from Sigma-Aldrich and was dried through a Grubbs apparatus and stored under a dry argon atmosphere prior to use.

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5. Methyl (2-chlorophenyl)acetate (>98% pure) was purchased from TCI America and used as received.

6. Submitters prepared methyl (2-chlorophenyl)acetate in quantitative yield by reaction of 2-(2-chlorophenyl)acetic acid with catalytic H_2SO_4 in methanol at reflux for 16 h.

7. Iodomethane (99%, stabilized) was purchased from Acros Organics and used as received.

8. Submitters monitored reaction progress by analytical gas chromatography with a mass spectroscopy (GC/MS), carried out on a Shimadzu QP2010 GCMS apparatus with an electronic impact mass and equipped with a SLB-5ms column (15.0 m x 0.10 mm) containing a 0.10 μm film thickness with a flow rate of 0.58 mL/min with 474 kPa He. The profile of temperature is the following one: 1 min at 90 °C, temperature increase to 220 °C at a rate of 8 °C per minute, then temperature increase to 300 °C at a rate of 40 °C per minute, then 300 °C for 4.5 min.

9. The retention time for the starting material **1** (*m/z* 184), the monoalkylated product (*m/z* 198) and the title product **2** (*m/z* 212) were respectively 6.42, 6.90 and 7.79 min.

10. Ammonium chloride (99+%, pure) was purchased from Acros Organics and added to water until saturation.

11. Diethyl ether (absolute) was purchased from EMD Chemicals, Inc. and used as received.

12. Sodium thiosulfate (98.5% extra pure, anhydrous) was purchased from Acros Organics and added to water until saturation.

13. Sodium chloride (99.5%, for analysis) was purchased from Acros Organics and added to water until saturation.

14. Magnesium sulfate (97% pure, anhydrous) was purchased from Acros Organics and used as received.

15. Analytical data for methyl 2-(2-chlorophenyl)-2-methylpropanoate **2**: R_f 0.42 (10% EtOAc/cyclohexane); ^1H NMR (600 MHz, CDCl$_3$) δ: 1.61 (s, 6 H), 3.66 (s, 3 H), 7.20 (dt, *J* = 7.8, 1.8 Hz, 1 H), 7.27 (dt, *J* = 7.8, 1.8 Hz, 1 H), 7.34 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.41 (dd, *J* = 7.8, 1.8 Hz, 1 H). ^{13}C NMR (150 MHz, CDCl$_3$) δ: 26.0, 46.6, 52.3, 126.7, 126.9, 128.0, 130.6, 133.6, 142.2, 177.4. IR (neat) ν 2982, 2948, 1733, 1473, 1432 cm^{-1}. HRMS (APCI) calculated for $C_{11}H_{13}ClO_2$ [M+H]$^+$: 213.0677, found: 213.0673. Anal. Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 61.94; H, 6.02.

16. Palladium(II) acetate was purchased from Sigma-Aldrich and used as received.

17. Tri-*t*-butylphosphonium tetrafluoroborate (99%) was purchased from Strem Chemicals, Inc. and used as received.

18. Potassium carbonate (99+%, for analysis, anhydrous) was received from Acros Organics and dried under vacuum at 140 °C for 48 h, then stored under argon in a desiccator.

19. ***Caution! The reaction is highly sensitive to the presence of traces of oxygen and moisture***.

20. *N*,*N*-Dimethylformamide (DMF) (absolute, over molecular sieves ($H_2O \leq 0.005\%$), $\geq 99.5\%$ (GC)) was purchased from Sigma-Aldrich and used as received.

21. Non-quantitative ratio of product (*m/z* 176, t_R = 5.36)/starting material (*m/z* 212, t_R = 7.79) is typically >10:1. The only by-product of the reaction is the protodehalogenated product (*m/z* 178, t_R = 5.14). Non-quantitative ratio of product/by-product ratio is >20:1.

22. Celite® 545, purchased from Sigma-Aldrich, was used as received.

23. A 50-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with the reaction residue, then equipped with a 10-cm Vigreux column and a short-path distillation kit. The distillation vessel is gradually heated until the product slowly passes into the collection bulb (<1 drop per second).

24. Analytical data for methyl 7-methylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate **3**: R_f 0.45 (10% EtOAc/cyclohexane) visualization by UV absorption; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.69 (s, 3 H), 3.05 (d, *J* = 12 Hz, 1 H), 3.69 (s, 3 H), 3.72 (d, *J* = 12 Hz, 1 H), 7.10 (m, 1 H), 7.15 (m, 1 H), 7.20–7.25 (m, 2 H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 22.8, 42.0, 51.9, 52.2, 121.2, 123.2, 127.1, 128.1, 142.2, 148.0, 175.0. IR (neat) ν 3069, 2951, 2929, 1729, 1457, 1433, 1277, 1148, 1140 cm^{-1}. HRMS (APCI): calculated $C_{11}H_{12}O_2[M+H]^+$: 177.0910, found: 177.0907. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.72; H, 6.96.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

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3. Discussion

The combination of palladium(II) acetate with electron-rich phosphine ligands generates versatile catalysts for the synthesis of various and synthetically useful fused carbocycles by intramolecular $C(sp^3)$-H bond arylation of aryl chlorides.[2] The $C(sp^3)$-H bond arylation of aryl bromides and iodides has been thoroughly described,[3,4] but the arylation of the corresponding aryl chlorides remains scarcely employed despite lower cost, better availability and wider structural diversity. We recently described that the combination of $Pd(OAc)_2$ and $P(t\text{-Bu})_3$ provides an efficient catalytic system for the synthesis of cyclobutarenes by intramolecular $C(sp^3)$-H arylation of nonacidic methyl groups of aryl chlorides (Table 1).[2] This methodology allows for the synthesis of substituted cyclobutarenes containing a quaternary center in moderate to excellent yield (60–87%), some of these products being hardly accessible by other means.

The computed mechanism (DFT) of the intramolecular $C(sp^3)$-H arylation of 2-bromo-*tert*-butylbenzene indicates that the C-H activation step occurs through a base-induced concerted metalation-deprotonation (CMD) pathway.[4g,5] With *tert*-butylphosphine as the ligand, C-H activation is the rate-determining step and occurs with the carbonate coordinated to palladium *trans* to the C-H bond. An agostic interaction with a C-H bond geminal to the C-H bond to be cleaved lowers the activation barrier.

Our initial work was performed on a small scale (100 mg of aryl chloride), using 10 mol% of palladium(II) acetate for a reaction concentration of 0.25M. However, under optimized reaction conditions on a larger scale (10 g), the catalyst loading can be reduced to 5 mol% and the reaction concentration increased to 0.5M. Lower catalyst loading led to non-reproducible results. The $C(sp^3)$-H arylation reaction was shown to be effective for a broad range of aryl and heteroaryl chlorides.[2] It was demonstrated that various substituents on the benzylic carbon (Table 1, entries 1-7) as well as on the aromatic ring (Table 1, entries 8-12) are well tolerated and give rise to the corresponding cyclobutarenes in 65–87% yield. The reactions in Table 1 have been performed by using the original conditions.[2]

**Table 1.** Scope of the synthesis of cyclobutarenes by intramolecular C(sp^3)-H arylation[a]

Entry	Substrat	Product	Yield(%)[b]
1			71
2			65
3			66
4			70
5			74
6			85
7[c]			72
8			87
9			66
10			76
11			60
12			63

(a) From ref. 2. Reaction conditions: Pd(OAc)$_2$ (10 mol%), P(t-Bu)$_3$•HBF$_4$ (20 mol%), K$_2$CO$_3$ (1.3 equiv), DMF, 140 °C. (b) Yields of isolated products after flash chromatography. (c) DMA was used instead of DMF.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(2-Chlorophenyl)acetic acid; (2444-36-2)

Lithium bis(trimethylsilyl)amide; (4039-32-1)

Iodomethane; (74-88-4)

Palladium(II) acetate; (3375-31-3)

Tri-*t*-butylphosphonium tetrafluoroborate; (131274-22-1)

Potassium carbonate; (584-08-7)

1. Université Claude Bernard Lyon 1, CNRS UMR5246, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, CPE Lyon, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France. Email: olivier.baudoin@univ-lyon1.fr We thank ANR (programme blanc "AlCaCHA"), Institut Universitaire de France and Bayer CropScience for financial support.
2. Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706-10716.
3. For a recent review, see: Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654.
4. (a) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 5736. (b) Dong, C.-G.; Hu, Q.-S. *Angew. Chem. Int. Ed.* **2006**, *45*, 2289. (c) Ren, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3462. (d) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 792. (e) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (f) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (g) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157.
5. Kefalidis, C. E.; Baudoin, O.; Clot, E. *Dalton Trans.* **2010**, *39*, 10528.
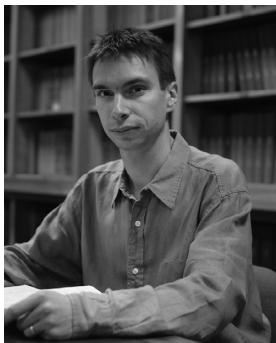
Olivier Baudoin studied chemistry at ENSC Paris. He completed his Ph. D. in 1998 in the group of Jean-Marie Lehn in Paris and then worked as a post-doctoral fellow with K. C. Nicolaou in the Scripps Research Institute (La Jolla, CA). He joined the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette) in 1999 as a CNRS researcher. In 2006, he was appointed Associate Professor at the University of Lyon 1. His main research focuses on organopalladium catalysis and most recently on $C(sp^3)$-H functionalization. He was the recipient of the CNRS Bronze Medal in 2005 and was nominated as junior member of Institut Universitaire de France in 2009.

Michaël Davi received his M. Sc. degree in fine organic chemistry in 2001 from the University of Basse-Normandie in Caen, France. In 2001, he did a six-months internship in 3M Pharmaceuticals at Saint-Paul, USA. He completed his Ph. D. in 2009 under the supervision of Prof. H. Lebel at the University of Montréal, Canada, working on catalytic Wittig-type olefination reactions. He then joined the group of Prof. O. Baudoin at the University of Lyon 1 as a post-doctoral fellow, working on Pd-catalyzed $C(sp^3)$-H activation.
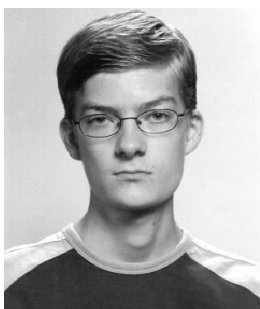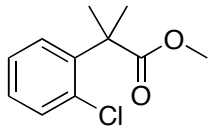
Arnaud Comte received his B. Sc. degree then his Ms. C. degree in chemistry from the University of Lyon 1 in 2010. He did his Master's degree internship under the guidance of Prof. O. Baudoin at the University of Lyon 1, where he worked on the synthesis of benzocyclobutenes.
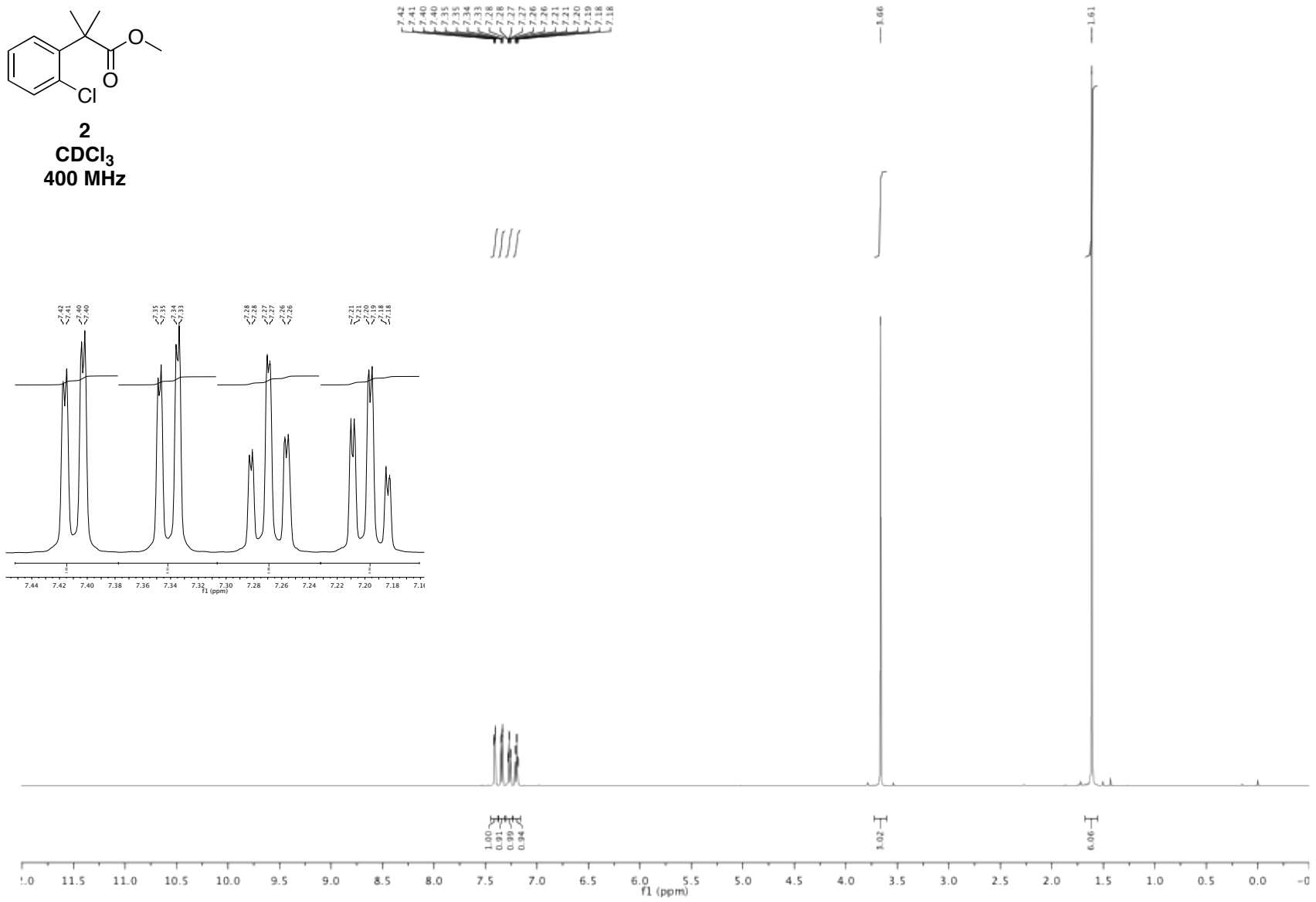
Rodolphe Jazzar studied chemistry at the University of Poitiers (France). He completed his PhD in 2003 in the group of Mike Whittlesey in Bath (UK) on the synthesis and study of ruthenium carbene complexes. His Ph. D. was followed by post-doctoral stays with Prof. E. P. Kündig (Geneva, Switzerland), and with Prof. G. Bertrand (Riverside, CA). He then joined the group of Prof. O. Baudoin at the University of Lyon 1 in 2006 and was appointed as a CNRS researcher within the same group in 2008. His main research focuses on organopalladium catalysis towards the synthesis of allenes and C-H activation.
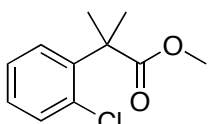
Brendan T. Parr was born in Winchester, MA in 1986. He completed his B.S. in chemistry at the University of Richmond under the supervision of Prof. William H. Myers. Currently, Brendan is a third-year graduate student in the laboratory of Prof. Huw M. L. Davies at Emory University. His research encompasses domino reactions initiated by chiral rhodium-carbenoid *in situ* activation of allyl alcohols.
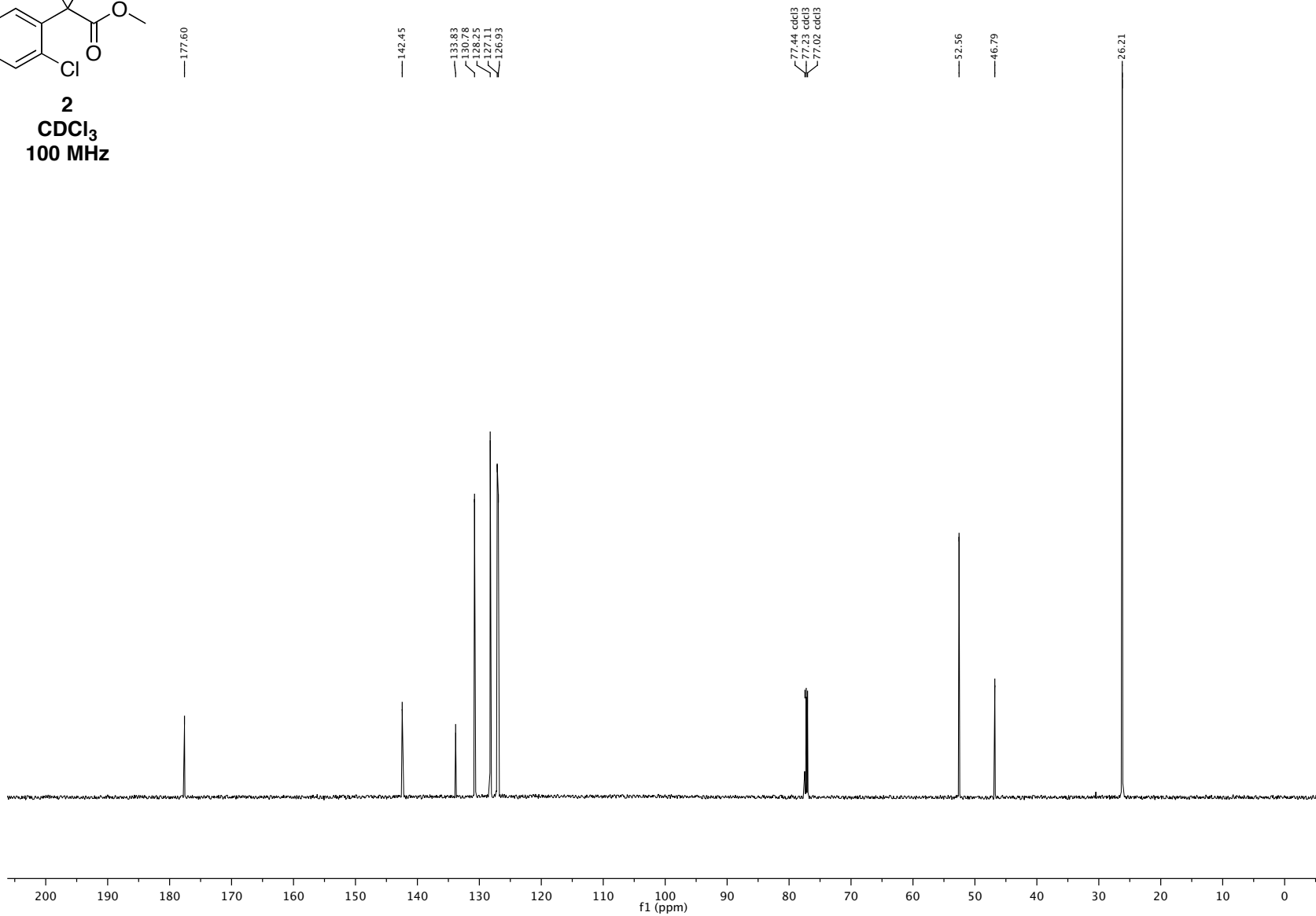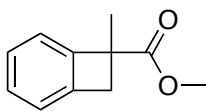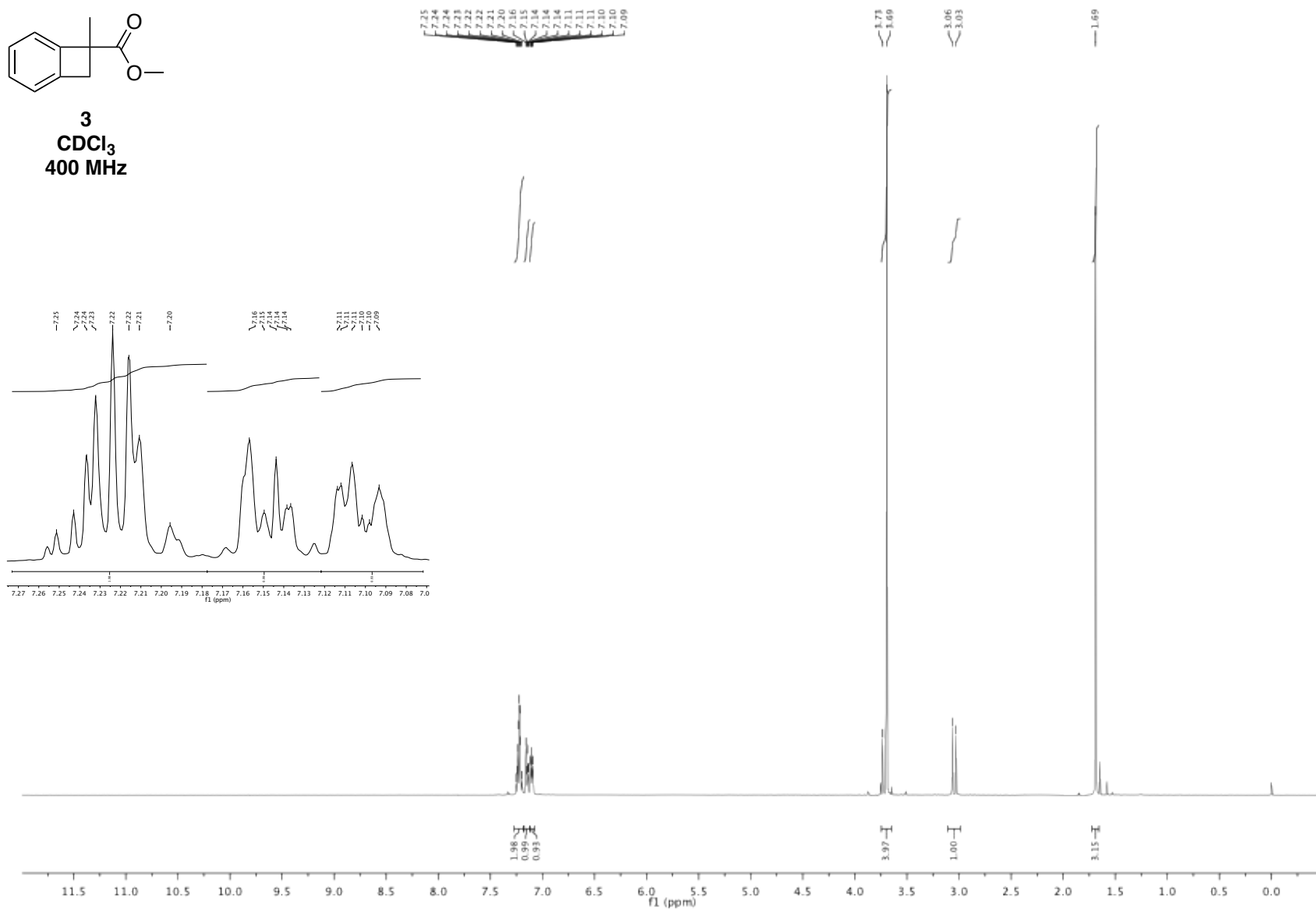
2
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400 MHz

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7.41
7.40
7.40
7.35
7.35
7.34
7.33
7.28
7.28
7.27
7.27
7.26
7.26
7.21
7.21
7.20
7.19
7.18
7.18

7.44 7.42 7.40 7.38 7.36 7.34 7.32 7.30 7.28 7.26 7.24 7.22 7.20 7.18 7.16
f1 (ppm)

3.66

1.61

1.00
0.91
0.99
0.94

1.02

6.06

12.0 11.5 11.0 10.5 10.0 9.5 9.0 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 0.0 -0
f1 (ppm)

2
CDCl₃
100 MHz

3
CDCl$_3$
400 MHz

3
CDCl$_3$
100 MHz

175.46
148.31
142.54
128.40
127.48
123.58
121.54
77.55 cdcl3
77.23 cdcl3
76.91 cdcl3
52.58
52.34
42.36
23.23

210   200   190   180   170   160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10   0   −10   −20
f1 (ppm)