Organic Syntheses

3-Hydroxymethyl-3-phenylcyclopropene

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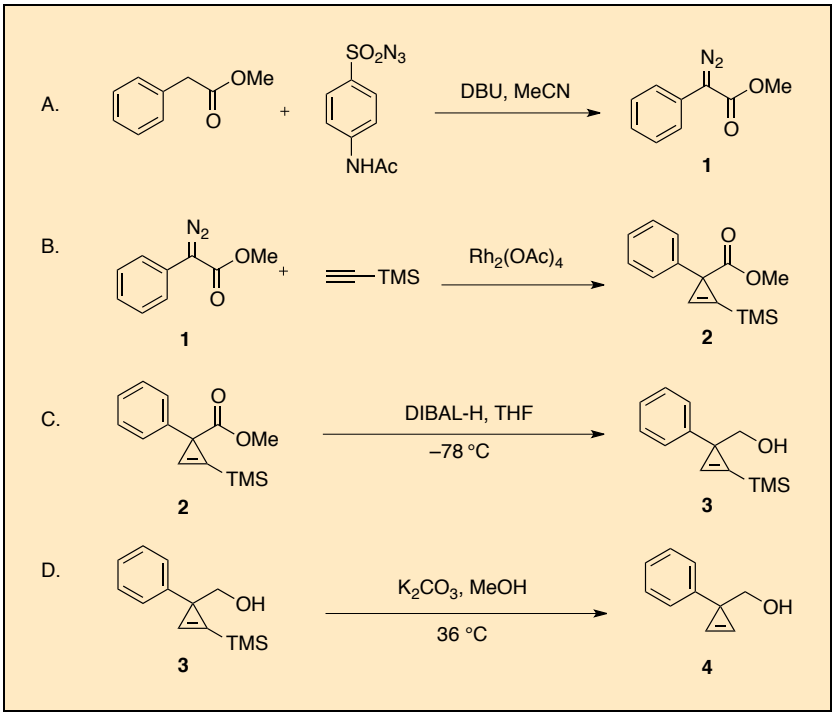

Procedure

A. *Methyl phenyl diazoacetate (**1**).* A 1-L, one-necked round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (4 cm long, 1.6 cm

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diameter) and a septum. The apparatus is evacuated (0.5 mmHg) and flame-dried, after which the flask is filled with nitrogen and allowed to cool to room temperature. The septum is removed and the flask is charged with acetonitrile (200 mL) (Note 1). 4-Acetamidobenzenesulfonyl azide (38.9 g, 162 mmol, 1.23 equiv) (Note 2) is added as a solid in one portion. The septum is replaced, a needle connected to a nitrogen source is inserted through the septum, and methyl phenylacetate (18.6 mL, 19.9 g, 132 mmol, 1.00 equiv) (Note 3) is added through the septum via syringe over 1 min. The reaction mixture is cooled in an ice bath and then 1,8-diazabicyclo[5.4.0]undec-7-ene (23.8 mL, 24.0 g, 158 mmol, 1.20 equiv) (Note 4) is added over the course of 15 min (Note 5) via syringe. The ice bath is then removed, the exterior of the reaction flask is protected from light by aluminum foil, and the mixture is stirred for 16 h at room temperature (24 °C). After 16 h, the solution is concentrated on the rotary evaporator (30 °C, 20 mmHg) (Note 6). The residue is partitioned between brine (100 mL) and diethyl ether (200 mL) (Note 1) and is transferred to a 1 L separatory funnel. The organic layer is washed with additional brine (100 mL). The brine layers are combined and back-extracted with diethyl ether (3 x 60 mL). The organic extracts are combined, dried over anhydrous $MgSO_4$ (15 g), filtered through a fritted glass funnel, and concentrated on a rotary evaporator (30 °C, 110 mmHg). The residual oil is then purified by silica gel column chromatography (Note 7) to yield 17.2 g (74%) of **1** (Notes 8 and 9) as a red, clear liquid (Note 10).

B. *Methyl 1-phenyl-2-trimethylsilylcycloprop-2-ene carboxylate (**2**)*. A 250-mL, one-necked round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (2.5 cm long, 1.2 cm diameter) and a septum, through which is inserted a needle connected to a manifold. The apparatus is evacuated (0.5 mmHg) and flame-dried. The flask is filled with nitrogen and cooled to room temperature. The septum is removed and the flask is charged with rhodium(II) acetate dimer (245 mg, 0.555 mmol, 5.00×10^{-3} equiv) (Note 11). The septum is replaced, and the apparatus is evacuated and refilled with nitrogen three times. Trimethylsilylacetylene (68.8 mL, 48.2 g, 490 mmol, 4.42 equiv) (Note 12) is added through the septum via syringe. Two 20 mL syringes are used to add a mixture of **1** (19.5 g, 111.0 mmol, 1.00 equiv) dissolved in trimethylsilylacetylene (19.0 mL, 13.3 g, 135 mmol, 1.22 equiv) at room temperature over 20 h using a syringe pump. The reaction mixture is then stirred for an additional 5 h. Vacuum distillation at room temperature (24 °C) (Note 13) is used to recover excess trimethylsilylacetylene (39 g). The residue is purified by column

chromatography (Note 14), and the fractions containing the product are combined and concentrated on the rotary evaporator (40 °C, 20 mmHg) and then dried at 0.5 mmHg for 2 h to yield 18.7 g (69%) of **2** (Notes 15 and 16) as a yellow, clear liquid.

C. *3-Hydroxymethyl-3-phenyl-2-trimethylsilylcyclopropene (**3**)*. A 3-L three-necked round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (5 cm long, 2 cm diameter). The right neck is connected to a gas inlet adapter and the other two necks are sealed with septa. The apparatus is evacuated (0.5 mmHg) and then flame-dried. The flask is filled with nitrogen and cooled to room temperature. A temperature probe is pierced through the left septum. A solution of **2** (18.7 g, 76.0 mmol, 1.00 equiv) in dry THF (350 mL) (Note 1) is added via cannula into the reaction flask. The reaction flask is then cooled with a dry ice/acetone bath to an internal temperature of –78 °C. To the stirring solution, a solution of DIBAL-H in THF (1.0 M, 269 mL, 269 mmol, 3.54 equiv) (Note 17) is added slowly via cannula (using nitrogen pressure) over a period of 4 h at –78 °C (Note 18). The reaction mixture is stirred for an additional 2 h at –78 °C. A septum is removed, and a 10% aqueous potassium carbonate solution (18 mL) is added over the course of 30 min to the flask using a Pasteur pipette (Note 19). The septum is replaced, and the dry ice bath is removed. When the internal temperature reaches –55 °C, a saturated aqueous potassium sodium tartrate solution (100 mL) and diethyl ether (200 mL) are added. The stirred suspension is allowed to warm to 24 °C over 11 h, then saturated aqueous potassium sodium tartrate solution (200 mL) and distilled water (100 mL) are added. The mixture is transferred to a 2 L separatory funnel and extracted with diethyl ether (2 × 100 mL). The organic layers are combined, washed with brine (400 mL), dried over anhydrous $MgSO_4$ (16 g), filtered through a fritted glass funnel, and then concentrated using rotary evaporator (40 °C, 20 mmHg). The residue is purified by column chromatography (Note 20), and fractions containing the product are combined and concentrated on the rotary evaporator (40 °C, 20 mmHg) and then dried at 0.5 mmHg for 2 h to yield 14.4 g (87%) of **3** (Notes 21 and 22) as a pale yellow solid.

D. *3-Hydroxymethyl-3-phenylcyclopropene (**4**)*. A 1-L, one-necked round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (4 cm long, 1.6 cm diameter) and a septum, through which is inserted a needle connected to a manifold. The apparatus is evacuated (0.5 mmHg) and flame-dried, after which the flask is filled with nitrogen and cooled to room temperature. The septum is removed and the flask is charged with racemic

3 (14.4 g, 65.9. mmol, 1.00 equiv) and methanol (290 mL) (Note 1). The septum is replaced, a needle connected to a nitrogen source is inserted, and a temperature probe is inserted through the septum. The solution is cooled by an ice bath to an internal temperature of 5 °C, and the mixture is stirred. Potassium carbonate (92.2 g, 667 mmol, 10.1 equiv) (Note 23) is added at 4 °C. During the addition, the internal temperature increased to 7 °C. The ice bath is then exchanged for an oil bath, and the reaction mixture is heated to 36 °C and stirred for 3 h. The reaction mixture is filtered through a pad of Celite (20 g) on a fritted glass funnel (7 cm internal diameter). The Celite bed is washed with diethyl ether (4 × 50 mL) and distilled water (200 mL). The filtrate is concentrated on the rotary evaporator (40 °C, 20 mmHg), and then transferred to a 1 L separatory funnel and extracted with diethyl ether (200 mL). The aqueous layer is further extracted with diethyl ether (2 x 50 mL). The organic layers are combined, washed with brine (200 mL), dried over anhydrous $MgSO_4$ (17 g), filtered through a fritted glass funnel, and concentrated on the rotary evaporator (40 °C, 20 mmHg). The residue is purified by column chromatography (Note 24), and pure fractions are combined and concentrated on the rotary evaporator (30 °C, 20 mmHg) and then dried at 0.5 mmHg to yield 8.65 g (90%) of **4** (Notes 25 and 26) as an off-white solid.

Notes

1. THF and acetonitrile (all ACS, Reag. Ph Eur) were purchased from Merck and dried with a SP-1 solvent purification system from LC Technology Solutions. Methanol (ACS, Reag. Ph Eur) was obtained from Merck and used as received. The following solvents were used for flash column chromatography and during work-up (all laboratory grade, all used as received): diethyl ether (purchased from Univar), hexanes (purchased from Thommen-Furler), dichloromethane (purchased from EGT Chemie) and ethyl acetate (purchased from Thommen-Furler). The submitters used the following solvents: THF (99.9%) was obtained from Fisher Scientific and distilled from a blue solution of benzophenone ketyl. Acetonitrile (99.9%) was obtained from Fisher Scientific, and dried with columns packed with activated neutral alumina using the solvent purification system described by Bergman.[2] Methanol (99.9%) was purchased from Fisher Scientific and was used as

received for the preparation of **4** (reaction D). Diethyl ether (laboratory grade), hexanes (99.9%), dichloromethane (99.9%) and ethyl acetate (99.9%) were purchased from Fisher and used as received.

2. 4-Acetamidobenzenesulfonyl azide[3] (>98%) was purchased from TCI and used as received. The submitters purchased 4-acetamidobenzenesulfonyl azide (97%) from Sigma-Aldrich and used it as received.
3. Methyl phenylacetate (≥99%) was purchased from Sigma-Aldrich and used as received. The submitters purchased methyl phenylacetate (99%) from Sigma-Aldrich and used it as received.
4. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (≥97%) was purchased from Fluorochem and used as received. The submitters purchased DBU (98%) from Acros Organics and used it as received.
5. DBU was added in 2 mL portions in intervals of one minute.
6. Care should be taken to avoid bumping during the rotary evaporation.
7. Flash column chromatography (9.0 cm diameter) was performed using 300 g of silica gel [Fluka, pore size 60 Å, 230 - 400 mesh particle size]. The top surface of the column was covered with sand (0.5 cm). The residue was loaded onto the column as a neat liquid. A small amount of 2% diethyl ether in hexanes (5 mL) was used assist the final transfer of the material to the column. The column was eluted with 2.2 L of 2% diethyl ether in hexanes, and 250 mL fractions were collected. Fractions #7–14 contained the product. TLC analysis during flash column chromatography was performed using 10% ethyl acetate in hexanes as the eluent. (R*f* of **1** = 0.6, visualized with UV light; Rf_{SM} (methyl phenylacetate) = 0.5, visualized with UV light).
8. A yield of 75% was obtained when the reaction was performed on half-scale.
9. Physical properties of **1**[4] are as follows: R_f 0.6 (10% EtOAc in hexanes, UV detection). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.86 (s, 3 H), 7.19 (t, *J* = 7.4 Hz, 1 H), 7.39 (m, 2 H), 7.49 (d, *J* = 7.4 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_{3)}$ δ: 52.0, 63.3, 124.0, 125.5, 125.8, 129.0, 165.6. IR (film) 3060, 3026, 2953, 2845, 2082, 1699, 1598, 1498, 1434, 1352, 1287, 1247, 1192, 1153, 1051, 1026, 909, 754, 692, 669, 632 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_9H_8N_2O_2$ $[M]^+$ 176.0580, found 176.0583. Anal. calcd. for $C_9H_8N_2O_{2:}$ C, 61.36; H, 4.58; N, 15.90. Found: C, 61.28; H, 4.80; N, 16.06.
10. The submitters observed that purified **1** can also contain methyl phenylacetate (<5%) by ^{1}H NMR analysis; however, the presence of methyl phenylacetate was not observed by the checkers. The submitters

report that rigorous removal of all traces of methyl phenylacetate is not necessary. The cyclopropenation of trimethylsilylacetylene (Step B) has been performed by the submitters with methyl diazophenylacetate contaminated with as much as 10% methyl phenylacetate, without a significant decrease in yield.

11. Rhodium(II) acetate dimer (≥97%) was purchased from Fluorochem and used as received. The submitters purchased rhodium(II) acetate dimer (99%) from Colonial Metals and used it as received.
12. Trimethylsilylacetylene (≥97%) was purchased from Fluorochem and used as received. The submitters purchased trimethylsilylacetylene (98%) from GFS Chemicals and used it as received.
13. Distillation was performed under vacuum (0.5 mmHg) using a short path distillation unit. The receiver flask (100 mL) was immersed in acetone/dry ice bath (–78 °C).
14. Flash column chromatography (9.0 cm diameter) was performed using 176 g of silica gel [Fluka, pore size 60 Å, 230 - 400 mesh particle size]. The top surface of the column was covered with sand (0.5 cm). The residue was loaded onto the column as a neat liquid. Hexanes was used to assist the final transfer of the material to the column. The column was sequentially eluted with 10% dichloromethane in hexanes (1.1 L), 25% dichloromethane in hexanes (1 L), 33% dichloromethane in hexanes (1 L), 40% dichloromethane in hexanes (1 L) and 50% dichloromethane in hexanes (1.2 L). During chromatography, 200 mL fractions were collected. Fractions 3-26 contained the product and were combined. In fractions 3-8 a less polar, minor impurity was observed by TLC analysis. TLC analysis during flash column chromatography was performed using 30% ethyl acetate in hexanes as the eluent. (R*f* = 0.75, visualized with ceric ammonium molybdate stain).
15. A yield of 73% was obtained when the reaction was performed on half-scale.
16. Physical properties of **2**[5,6] are as follows: R_f 0.75 (30% EtOAc in hexanes, visualized with ceric ammonium molybdate stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.20 (s, 9 H), 3.67 (s, 3 H), 7.15–7.21 (m, 1 H), 7.25–7.29 (m, 4 H), 7.44 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: –1.3, 31.5, 52.0, 116.0, 120.0, 126.1, 128.0, 128.4, 142.6, 176.2; IR (film) 3119, 3059, 3025, 2957, 2902, 1945, 1731, 1704, 1602, 1495, 1446, 1434, 1289, 1251, 1220, 1042, 1024, 1012, 844, 791, 758, 698 cm^{-1}. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}O_2Si$ $[M+H]^+$ 247.11454 found 247.1144. Anal. calcd. For $C_{14}H_{18}O_2Si$: C, 68.25; H, 7.36. Found: C, 68.05; H, 7.22.

17. DIBAL-H (1M in THF) was purchased from Sigma-Aldrich and used as received.
18. With this slow rate of addition, the internal temperature was maintained below –70 °C (to avoid cyclopropene reduction) during the addition of DIBAL-H.
19. Care should be exercised during the addition, as the quenching of DIBAL-H is exothermic.
20. Flash column chromatography (9.0 cm diameter) was performed using 187 g of silica gel [Fluka, pore size 60 Å, 230 - 400 mesh particle size]. The top surface of the column was covered with sand (0.5 cm). The residue was loaded onto the column as a neat liquid. 5% Ethyl acetate in hexanes was used assist the final transfer of the material to the column. The column was sequentially eluted with 5% ethyl acetate in hexanes (1.7 L), 9% ethyl acetate in hexanes (1 L), 17% ethyl acetate in hexanes (600 mL). During chromatography, 200 mL fractions were collected. Fractions 4-14 contained the product. TLC analysis during flash column chromatography was performed using 30% ethyl acetate in hexanes as the eluent. (R*f* = 0.54, visualized with ceric ammonium molybdate stain).
21. A reaction run on half-scale provided a product yield of 88%.
22. Physical properties of **3**[7] are as follows: mp 35 °C; R_f 0.54 (30% EtOAc in Hexanes, with ceric ammonium molybdate stain was used to visualize TLC plates). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.18 (s, 9 H), 1.18 (t, *J* = 5.7 Hz, 1 H), 3.99 (dd, *J* = 11.0, 5.3 Hz, 1 H), 4.16 (dd, *J* = 11.1, 5.7 Hz, 1 H), 7.12–7.20 (m, 3 H), 7.25–7.30 (m, 2 H), 7.70 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –0.9, 30.2, 68.9, 123.6, 124.1, 125.3, 126.1, 128.1, 146.9; IR (film) 3368, 3084, 3058, 3023, 2957, 2898, 2871, 1692, 1600, 1578, 1495, 1408, 1250, 1065, 1012, 866, 842, 757, 698 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{12}H_{15}OSi$ $[M\text{-}CH_3]^+$ 203.0887, found 203.0884. Anal. calcd. For $C_{13}H_{18}OSi$: C, 71.50; H, 8.31. Found: C, 71.39; H, 8.41.
23. Anhydrous potassium carbonate (EP) was purchased from Brenntag Schweizerhall and used as received. The submitters purchased anhydrous potassium carbonate (99.9%) from Fisher Scientific and used it as received.
24. Flash column chromatography (6.0 cm diameter) was performed using 144 g of silica gel [Fluka, pore size 60 Å, 230 - 400 mesh particle size]. The top surface of the column was covered with sand (0.5 cm). The residue was loaded onto the column as a neat liquid. Diethyl ether was used assist the final transfer of the material to the column. The column

was sequentially eluted with 10% diethyl ether in hexanes (1 L), 14% diethyl ether in hexanes (1 L), 25% diethyl ether in hexanes (400 mL), and 50% diethyl ether in hexanes (1.2 L). During chromatography, 80 mL fractions were collected. Fractions 28-43 contained the product. TLC analysis during flash column chromatography was performed using 50% diethyl ether in hexanes as the eluent. (R*f* = 0.32, visualized with ceric ammonium molybdate stain).

25. When the reaction was performed on approximately half-scale, the isolate yield of pure product was 80%.
26. Physical properties of **4**[5] are as follows: mp 58–59 °C; R_f 0.32 (50% diethyl ether in hexanes, visualized with ceric ammonium molybdate stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (m, 1 H), 4.08 (d, *J* = 5.9 Hz, 2 H), 7.19–7.7.27 (m, 3 H), 7.31–7.34 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 29.2, 68.0, 113.2, 125.9, 126.4, 128.3, 145.8. IR (film) 3217, 3102, 3050, 2923, 2880, 1645, 1599, 1575, 1493, 1473, 1446, 1307, 1222, 1175, 1067, 1009, 985, 969, 898, 757, 698, 635, 565, 533, 471 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{10}H_9O$ $[M-H]^+$ 145.0648, found 145.0647. Anal. calcd. For $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.20; H, 6.75.

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associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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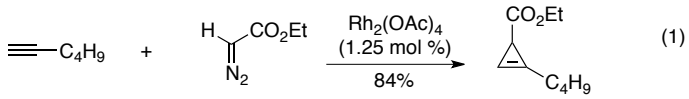
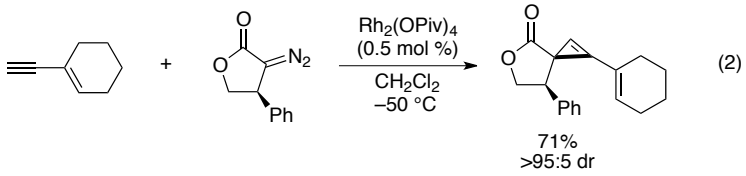
Discussion

The Rh-catalyzed reactions of α-diazoesters with alkynes to give cyclopropene carboxylates was first described in 1978 (Eq 1),[8] and remains one of the most effective methods for the preparation of cyclopropenes.



(1)

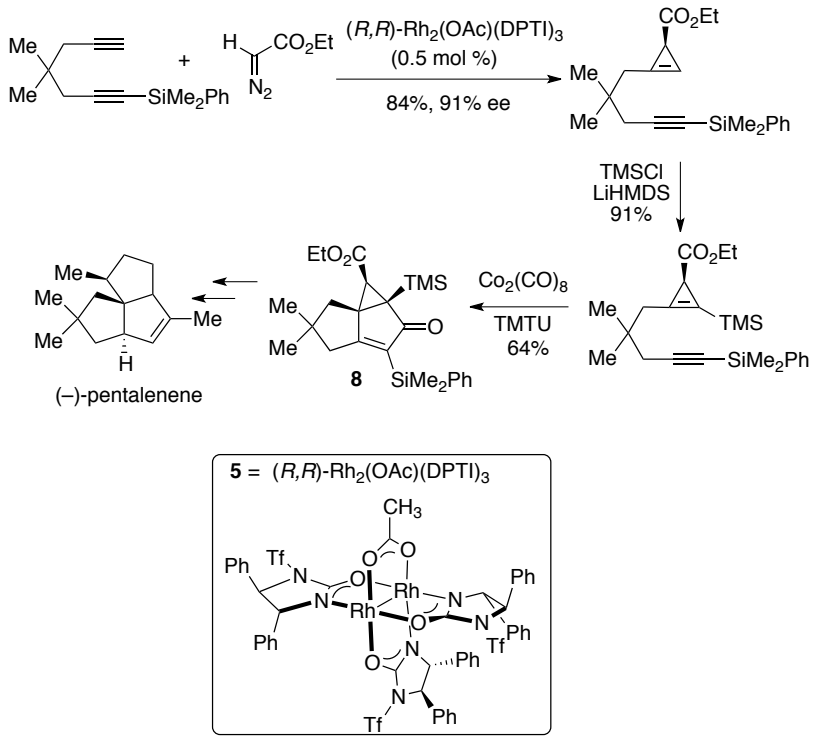
The range of diazoesters that participate in Rh-catalyzed cyclopropenation reactions is broad, and includes diazomalonates[6,9] and diazoacetates without α-substitution[8-11] or with α-silyl-,[12] α-sulfonyl,[13,14] α-alkenyl,[15,16] α-aryl,[9,17-21] α-trifluoromethyl,[22,23] and α-alkyl substitutents.[24-28] For α-alkyl-α-diazoesters with β-hydrogens, selectivity over β-hydride migration can be achieved by using bulky carboxylate ligands at low temperature.[24,27,28] Cyclic α-diazocarbonyl compounds are particularly resilient to β-hydride migration,[26,29] even for substratres with tertiary β-hydrogens (Eq 2).[26]



(2)

Enantioselective Rh-catalyzed cyclopropenation was first described in 1992.[10] Advances in chiral catalyst development have expanded the scope of Rh-catalyzed cyclopropenation to include diazoacetates,[10,11,30-32] α-aryl-α-diazoesters,[21] α-alkenyl-α-diazoesters,[15,16] and α-alkyl-α-diazoesters.[24,27] Intramolecular, enantioselective cyclopropenations have also been reported.[33] Cyclopropene carboxylates and derivatives have been employed as starting materials for manifold reactions,[34,35] including carbometallation,[7,19,36-41] hydrometallation,[5,6,42-44] dimetallation,[44] Heck,[20] Sila Morita–Baylis–Hillman,[45] Pauson-Khand,[46] Diels-Alder,[11,47,48] dipolar cycloadditions[26,49] and ring expansions.[17,50-52] The preparation of 3-hydroxymethyl-3-phenylcyclopropene was initially described by Rubina, Rubin and Gevorgyan,[6,43] and a modification was reported by our group.[7] This compound and related, prochiral cyclopropenes have served as platforms for a number of enantioselective reactions, including enantioselective hydrostannation,[43] hydroacylation,[53] hydroboration,[5] carbomagnesation[7,54] and carbozincation[54,55] reactions.

Cyclopropenes produced through Rh-catalyzed reactions of diazoesters and alkynes have been applied to total synthesis[56] and to bioorthogonal chemistry.[57-59] Enantioselective cyclopropenation catalyzed by the unsymmetrical (*R,R*)-$Rh_2(OAc)(DPTI)_3$ [11,31] has served as the key step in the enantioselective total synthesis of (–)-pentalenene[56] (Scheme 1). Furthermore, cyclopropene carboxylates and their derivatives have recently emerged as important reaction partners in bioorthogonal reactions involving tetrazines[57-59] and in photoclick reactions involving tetrazoles.[60]



Scheme 1. Enantioselective Rh-catalyzed cyclopropenation as a key step in the total synthesis of (–)-pentalenene

References

1. Department of Chemistry and Biochemistry, University of Delaware, Newark DE 19716. jmfox@udel.edu. For financial support we thank NSF CHE 1300329. Data were obtained with instrumentation supported by NIH S10RR026962-01, NIH P20 RR017716, and NSF CRIF:MU grants: CHE 0840401 and CHE-1229234.
2. Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Educ.* **2001**, *78*, 64.
3. Davies, H. M. L.; Cantrell, W. R., Jr.; Romines, K. R.; Baum, J. *Org. Synth.* **1992**, *70*, 93.

4. Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.
5. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198.
6. Rubin, M.; Gevorgyan, V. *Synthesis* **2004**, *5*, 796.
7. Liu, X. Z.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600.
8. Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1978**, *14*, 1239.
9. Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1993**, *76*, 521.
10. Protopopova, M. N.; Doyle, M. P.; Muller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755.
11. Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.
12. Arrowood, T. L.; Kass, S. R. *Tetrahedron* **1999**, *55*, 6739.
13. Liu, Y.; Ma, S. *Org. Lett.* **2012**, *14*, 720.
14. Wang, Y.; Fordyce, E. A. F.; Chen, F. Y.; Lam, H. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7350.
15. Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211.
16. Briones, J. F.; Davies, H. M. L. *Tetrahedron* **2011**, *67*, 4313.
17. Xie, X. C.; Li, Y.; Fox, J. M. *Org. Lett.* **2013**, *15*, 1500.
18. Xie, X. C.; Yang, Z.; Fox, J. M. *J. Org. Chem.* **2010**, *75*, 3847.
19. Yang, Z.; Xie, X. C.; Fox, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3960.
20. Chuprakov, S.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 3714.
21. Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233.
22. Sang, R.; Yang, H.-B.; Shi, M. *Tetrahedron Lett.* **2013**, *54*, 3591.
23. Müller, P.; Grass, S.; Shahi, S. P.; Bernardinelli, G. *Tetrahedron* **2004**, *60*, 4755.
24. Goto, T.; Takeda, K.; Shimada, N.; Nambu, H.; Anada, M.; Shiro, M.; Ando, K.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6803.
25. Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1995**, *78*, 129.
26. DeAngelis, A.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 11035.
27. Boruta, D. T.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *Chem. Sci.* **2012**, *3*, 1589.
28. Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *129*, 22.
29. Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943.
30. Müller, P.; Imogai, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419.

31. Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223.
32. Weatherhead-Kloster, R. A.; Corey, E. J. *Org. Lett.* **2006**, *8*, 171.
33. Doyle, M. P.; Ene, D. G.; Peterson, C. S.; Lynch, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 700.
34. Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221.
35. Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117.
36. Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2007**, *73*, 563.
37. Simaan, S.; Marek, I. *Org. Lett.* **2007**, *9*, 2569.
38. Liao, L.-a.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322.
39. Delaye, P.-O.; Didier, D.; Marek, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 5333.
40. Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382.
41. Didier, D.; Delaye, P.-O.; Simaan, M.; Island, B.; Eppe, G.; Eijsberg, H.; Kleiner, A.; Knochel, P.; Marek, I. *Chem. Eur. J.* **2014**, *20*, 1038.
42. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566.
43. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2004**, *126*, 3688.
44. Trofimov, A.; Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2007**, *72*, 8910.
45. Chuprakov, S.; Malyshev, D. A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 14868.
46. Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2005**, *7*, 3593.
47. Fisher, L. A.; Smith, N. J.; Fox, J. M. *J. Org. Chem.* **2013**, *78*, 3342.
48. Battiste, M. A. *Chem. Ind.* **1961**, 550.
49. Diev, V. V.; Kostikov, R. R.; Gleiter, R.; Molchanov, A. P. *J. Org. Chem.* **2006**, *71*, 4066.
50. Komendantov, M. I.; Domnin, I. N.; Bulucheva, E. V. *Tetrahedron* **1975**, *31*, 2495.
51. Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463.
52. Zhu, Z.-B.; Shi, M. *Org. Lett.* **2010**, *12*, 4462.
53. Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354.
54. Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978.
55. Krämer, K.; Leong, P.; Lautens, M. *Org. Lett.* **2011**, *13*, 819.
56. Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2007**, *9*, 5625.
57. Yang, J.; Liang, Y.; Šečkutė, J.; Houk, K. N.; Devaraj, N. K. *Chem. Eur. J.* **2014**, *20*, 3365.
58. Kamber, D. N.; Nazarova, L. A.; Liang, Y.; Lopez, S. A.; Patterson, D. M.; Shih, H.-W.; Houk, K. N.; Prescher, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 13680.

59. Elliott, T. S.; Townsley, F. M.; Bianco, A.; Ernst, R. J.; Sachdeva, A.; Elsasser, S. J.; Davis, L.; Lang, K.; Pisa, R.; Greiss, S.; Lilley, K. S.; Chin, J. W. *Nat. Biotechnol.* **2014**, *32*, 465.
60. Yu, Z. P.; Pan, Y. C.; Wang, Z. Y.; Wang, J. Y.; Lin, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 10600.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-Acetamidobenzenesulfonyl azide: Benzenesulfonyl azide, 4-(acetylamino)-; (2158-14-7)
Methyl phenylacetate: Benzeneacetic acid, methyl ester; (101-41-7)
1,8-Diazabicyclo[5.4.0]undec-7-ene: Pyrimido[1, 2-*a*]azepine, 2, 3, 4, 6, 7, 8, 9, 10-octahydro-; (6674-22-2)
Rhodium (II) acetate dimer: Rhodium, tetrakis[μ-(acetato-κ*O*:κ*O*')]di-, (*Rh-Rh*); (15956-28-2)
Trimethylsilylacetylene: Silane, ethynyltrimethyl-; (1066-54-2)
DIBAL-H: Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7)
Potassium carbonate: Carbonic acid, potassium salt (1:2); (584-08-7)

Ramajeyam Selvaraj was born in 1982 in Tiruchendur, TamilNadu, India. He received his bachelor's degree from University of Madras in 2002 and his master's degree from Indian Institute of Technology Madras in 2004, where he carried out his research with Prof. Sethuraman Sankararaman. In 2012, he received his Ph.D. from the University of Delaware under the guidance of Professor Joseph Fox. In the fall of 2014, he moved to the Purdue University, where he is currently a postdoctoral researcher working in the laboratory of Professor Christopher Uyeda.

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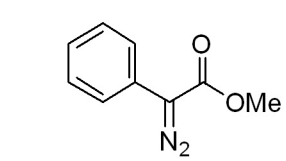
Jonathan Ruchti received his B. Sc. in chemistry from the University of Basel, where he worked under the supervision of Professor Andreas Pfaltz. He obtained a M. Sc. degree in chemistry from ETH Zürich where he is currently pursing doctoral studies in synthetic organic chemistry under the guidance of Professor Erick M. Carreira.



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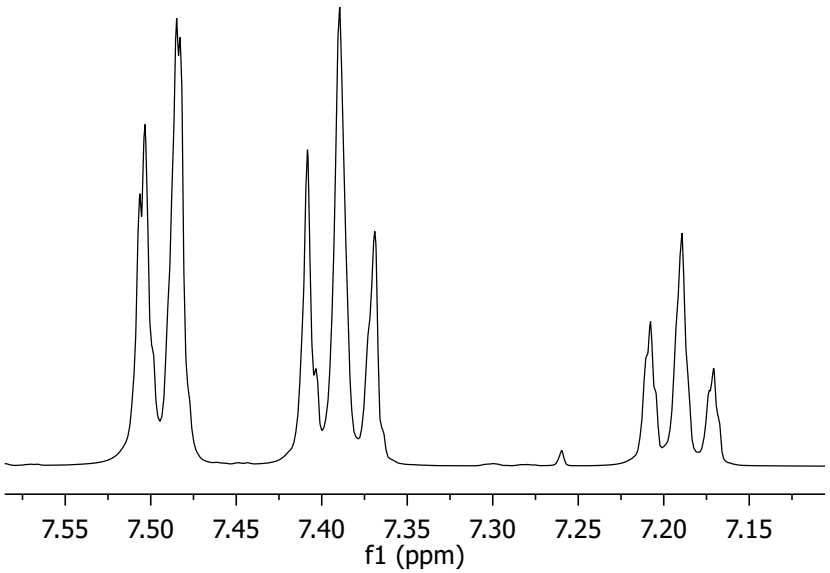
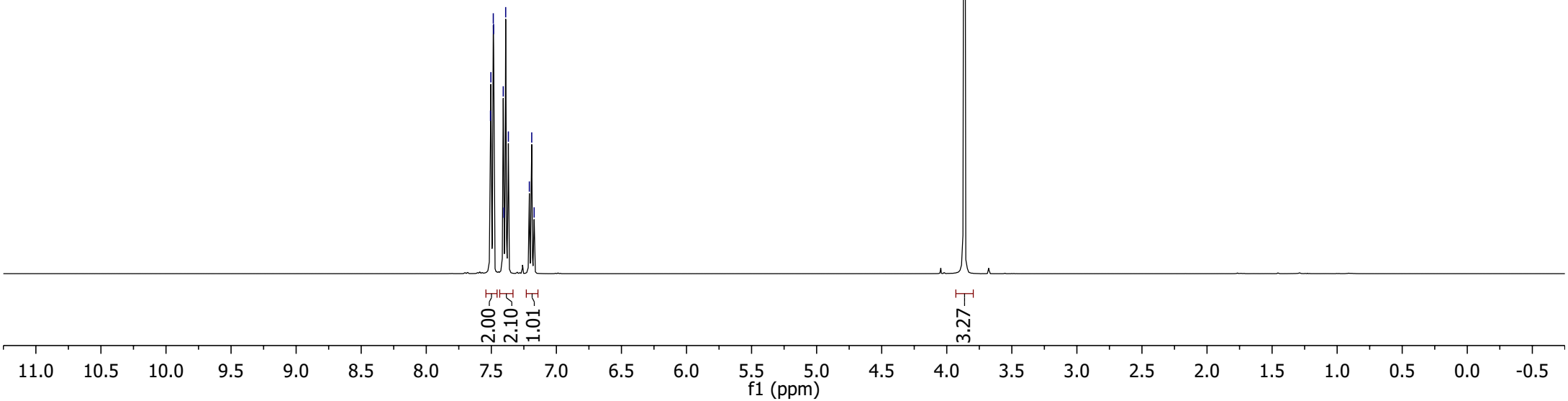
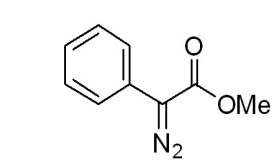
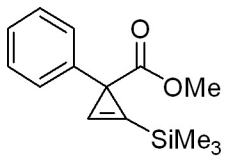


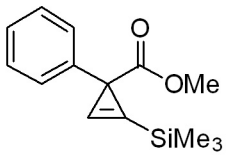




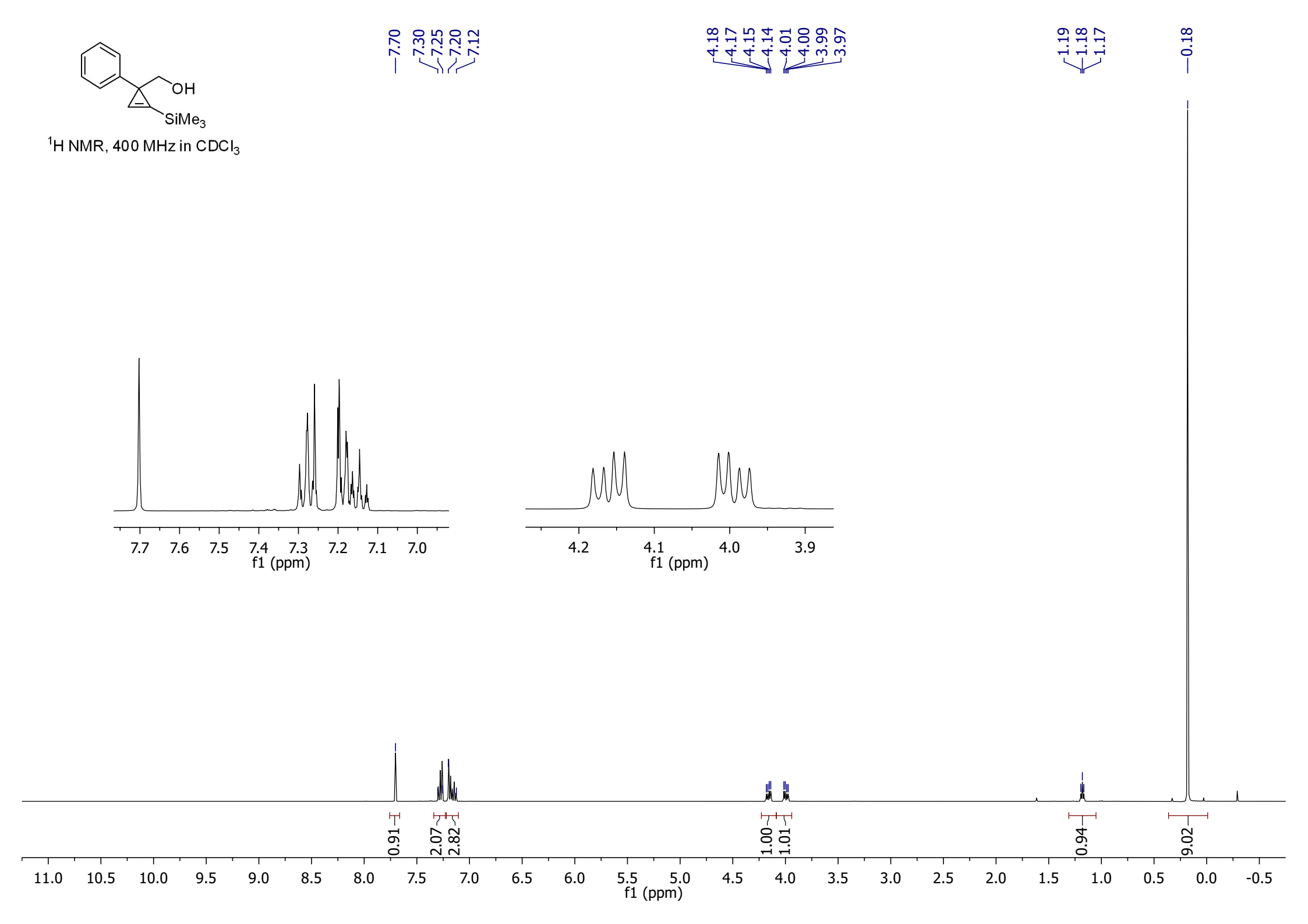
^{13}C NMR, 101 MHz in $CDCl_3$

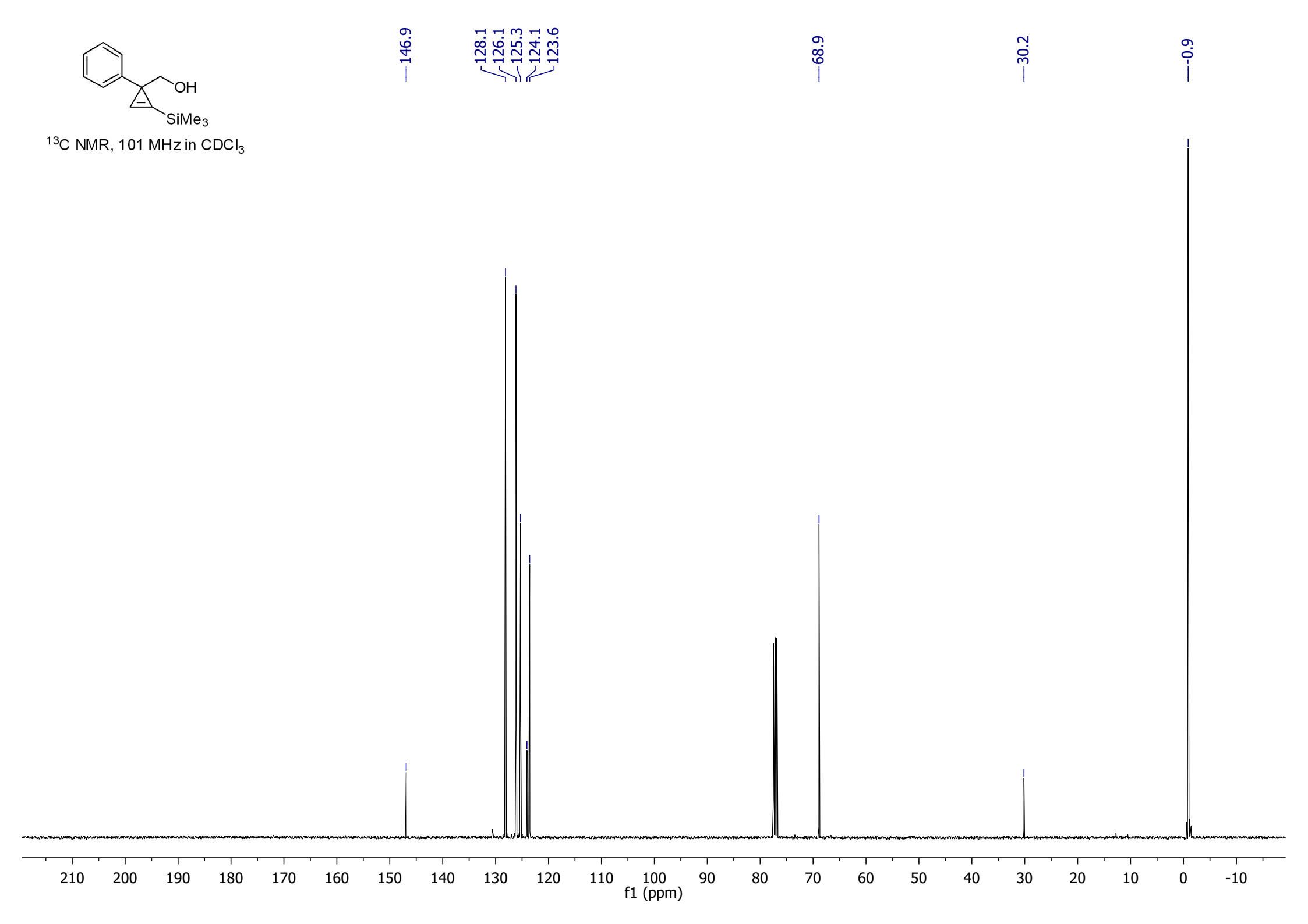


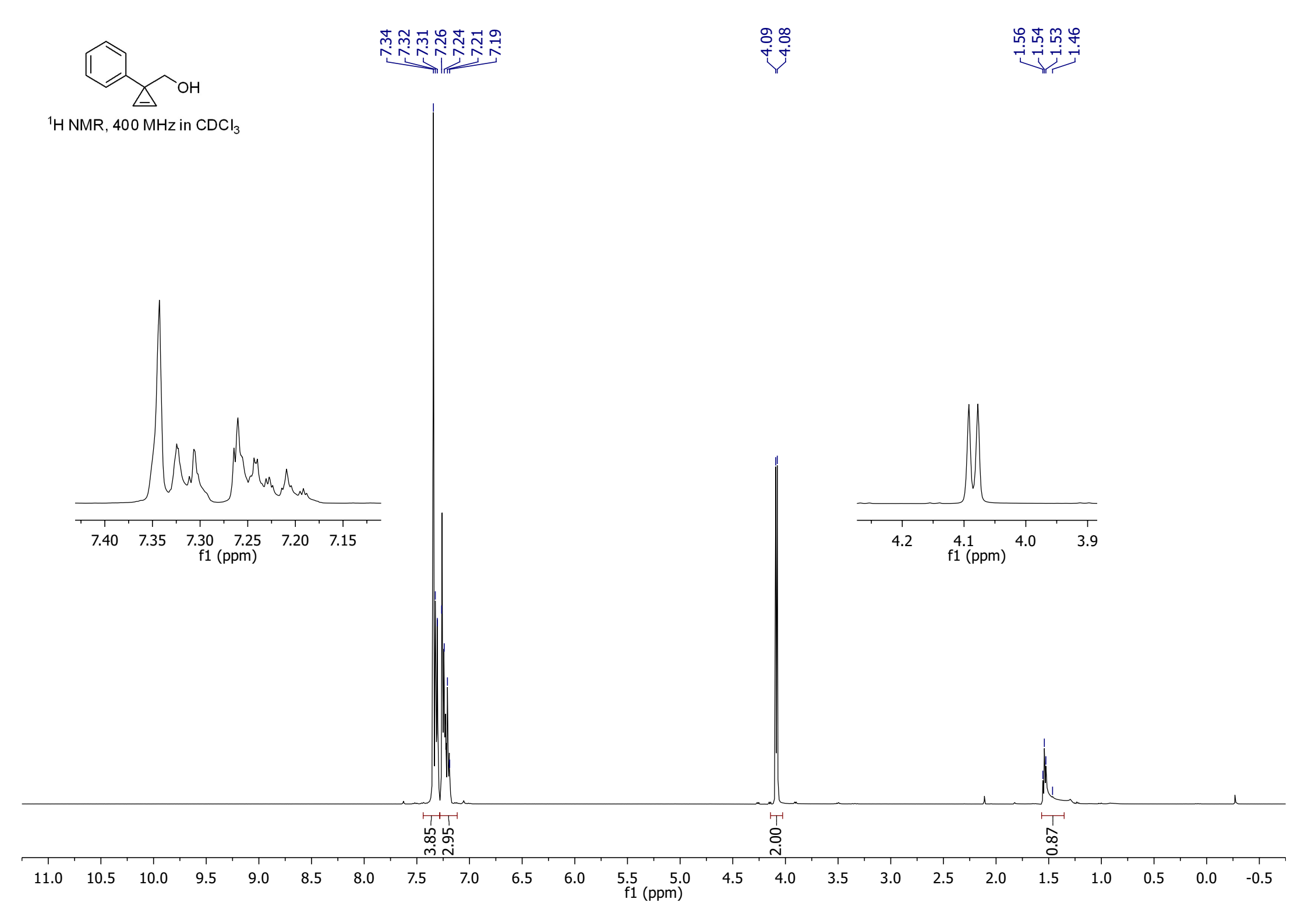
^{1}H NMR, 400 MHz in $CDCl_3$

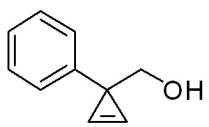


^{13}C NMR, 101 MHz in $CDCl_3$


OH
SiMe3
1H NMR, 400 MHz in CDCl3
7.70
7.30
7.25
7.20
7.12
4.18
4.17
4.15
4.14
4.01
4.00
3.99
3.97
1.19
1.18
1.17
0.18
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
4.2 4.1 4.0 3.9
f1 (ppm)
0.91
2.07
2.82
1.00
1.01
0.94
9.02
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 -0.5
f1 (ppm)


OH
SiMe3
13C NMR, 101 MHz in CDCl3
146.9
128.1
126.1
125.3
124.1
123.6
68.9
30.2
-0.9
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)


OH
^{1}H NMR, 400 MHz in $CDCl_3$
7.34
7.32
7.31
7.26
7.24
7.21
7.19
4.09
4.08
1.56
1.54
1.53
1.46
7.40 7.35 7.30 7.25 7.20 7.15
f1 (ppm)
4.2 4.1 4.0 3.9
f1 (ppm)
3.85
2.95
2.00
0.87
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 -0.5
f1 (ppm)



^{13}C NMR, 101 MHz in $CDCl_3$