Organic Syntheses

Preparation of Highly-Substituted Pyridines via Diels-Alder Reactions of Vinylallenes and Tosyl Cyanide

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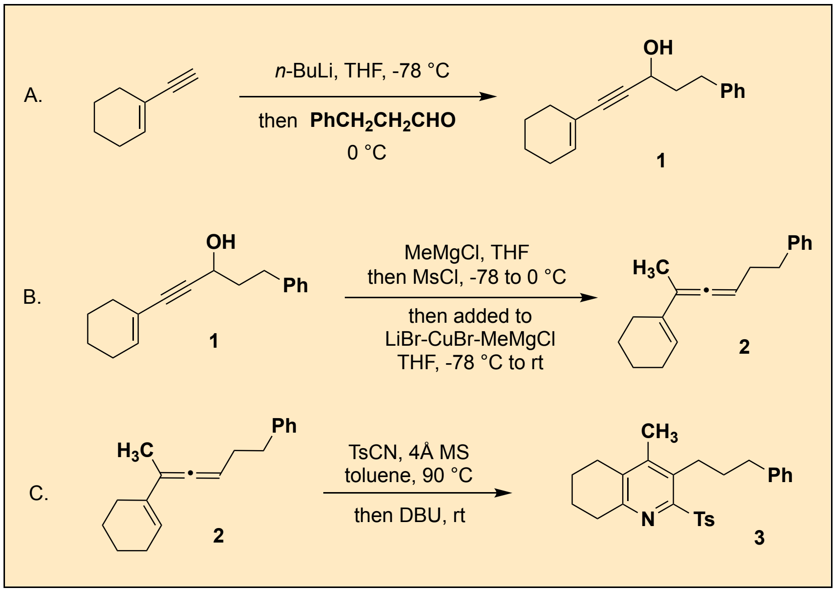

Procedure (Note 1)

A. *1-(Cyclohex-1-en-1-yl)-5-phenylpent-1-yn-3-ol* (**1**). A 500-mL, three-necked, round-bottomed flask is equipped with a 25 x 10 mm Teflon-coated, oval magnetic stir bar, an argon inlet adapter, a rubber septum, and a rubber septum fitted with a thermocouple probe (Note 2) (Figure 1). The reaction flask is charged via cannula with a solution of 1-ethynylcyclohexene (5.84 g, 55.2 mmol, 1.20 equiv) (Note 3) in 15 mL of THF (Note 4). Additional THF (150 mL) is added, and the solution is cooled to –78 °C (internal temperature) with a dry ice-acetone bath. A solution of *n*-butyllithium (2.49 M in hexane, 19.4 mL, 48.3 mmol, 1.05 equiv) (Note 5) is added rapidly dropwise to the reaction flask via syringe (Note 6), and the resulting pale-yellow solution is then stirred at –78 °C for 30 min.

A 50-mL, pear-shaped flask fitted with a rubber septum and an argon inlet needle is charged with a solution of 3-phenylpropionaldehyde (6.16 g, 46.0 mmol, 1.00 equiv) (Note 7) in 30 mL of THF and cooled in a dry ice-acetone bath. The cold aldehyde solution is then transferred via cannula to the vigorously stirred reaction mixture at such a rate so as to maintain the internal temperature below –70 °C (Note 8). The source flask is washed with THF (5 mL), the dry ice-acetone bath is replaced with an ice-water bath, and the reaction mixture is then allowed to warm to an internal temperature of 0 °C over 10 min.

Figure 1. Reaction assembly for step A (photo provided by submitters)

After 30 min, the ice-water bath is removed and the clear, pale-yellow solution is allowed to warm to room temperature. Half-saturated aqueous NH_4Cl solution (200 mL) is then added (Figure 2), and the resulting mixture is transferred to a 1-L separatory funnel. The aqueous phase is separated and extracted with ethyl acetate (3 x 100 mL), and the combined organic layers are washed with saturated aqueous NaCl solution (200 mL), dried over 10 g of anhydrous $MgSO_4$, and filtered under reduced pressure through a 250-mL sintered glass funnel (medium porosity, 30 mm diameter). The $MgSO_4$ is washed with ethyl acetate (3 x 10 mL), and the filtrate is concentrated by rotary evaporation (20 °C, 20 mmHg) to afford 12.72 g of a yellow oil.

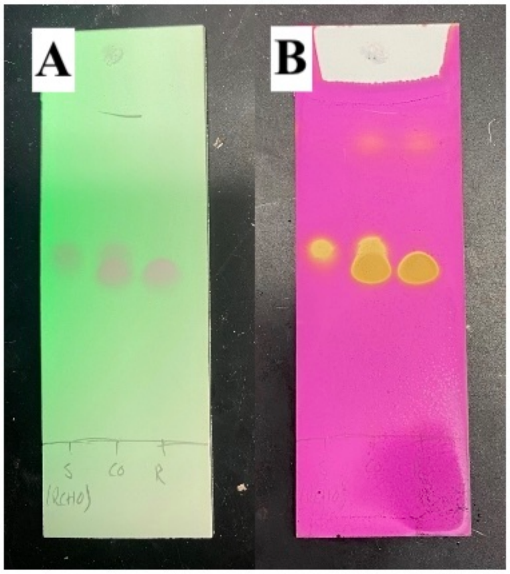

Figure 2. TLC of organic phase at end-of-reaction after ammonium chloride quench showing starting aldehyde (S, left, R_f 0.58) versus reaction mixture (R, right, R_f 0.51) with central co-spot (Co) using 1:4 EtOAc:hexanes eluent. A) Visualized under 254 nm UV lamp; B) The same TLC after staining with standard $KMnO_4$ stain. Aldehyde and product spots appear immediately without warming; the faint top spot appears only upon warming with a heat gun (photos provided by checkers)

This material is dissolved in a minimum amount of 1:9 ethyl acetate-hexanes (ca. 6 mL) and loaded onto a column (70 mm diameter) of 250 g of silica gel (Note 9) prepared as a slurry with 1:9 ethyl acetate-hexanes. The column is eluted with a gradient ranging from 1:9 to 1:4 ethyl acetate-hexanes and 100-mL fractions are collected in 125-mL Erlenmeyer flasks. The product appears in fractions 9 to 18. These fractions are combined, and the solvent is removed by rotary evaporation (20 °C, 20 mmHg). A 9.5 x 5 mm, Teflon-coated, oval magnetic stir bar is added to the flask and the oil is further concentrated at 0.05 mmHg for 2 h with stirring. The stir bar is removed with clean tweezers and 10.37 g (94%) of the propargylic alcohol **1** is obtained as a pale-yellow oil (Note 10) (Figure 3).

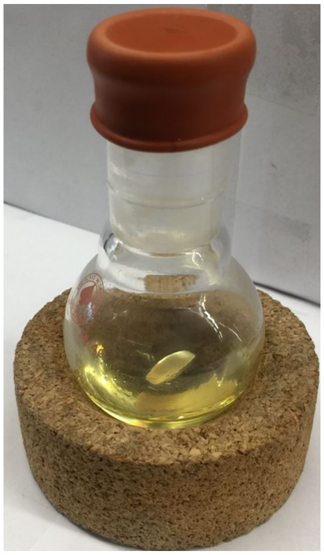

Figure 3. Propargylic alcohol 1 (photo provided by submitters)

B. *(5-(Cyclohex-1-en-1-yl)hexa-3,4-dien-1-yl)benzene (***2***).* A 250-mL, two-necked pear-shaped flask is equipped with a 25 x 10 mm Teflon-coated cylindrical magnetic stir bar, an argon inlet adapter, and a rubber septum fitted with a thermocouple probe (Note 2). The flask is charged with a solution of propargylic alcohol **1** (9.62 g, 40.0 mmol, 1.0 equiv) in 100 mL of THF, which is then cooled to –78 °C (internal temperature) with a dry ice-acetone bath. Methylmagnesium chloride solution (3.0 M in THF, 13.33 mL, 40 mmol, 1.0 equiv) (Note 11) is added rapidly dropwise via syringe at such a rate so as to maintain the internal temperature below –50 °C (Note 12). The reaction mixture is cooled back to –78 °C (internal temperature) and methanesulfonyl chloride (3.2 mL, 4.58 g, 40.0 mmol, 1.0 equiv) (Note 13) is added dropwise via a 5 mL syringe at such a rate so as to maintain the internal temperature below –70 °C (Note 14). The dry ice-acetone bath is removed, the reaction mixture is allowed to warm to room temperature over 30 min (Figure 4a), and the resulting yellow suspension is stirred at that temperature for 1 h (Figure 4b).

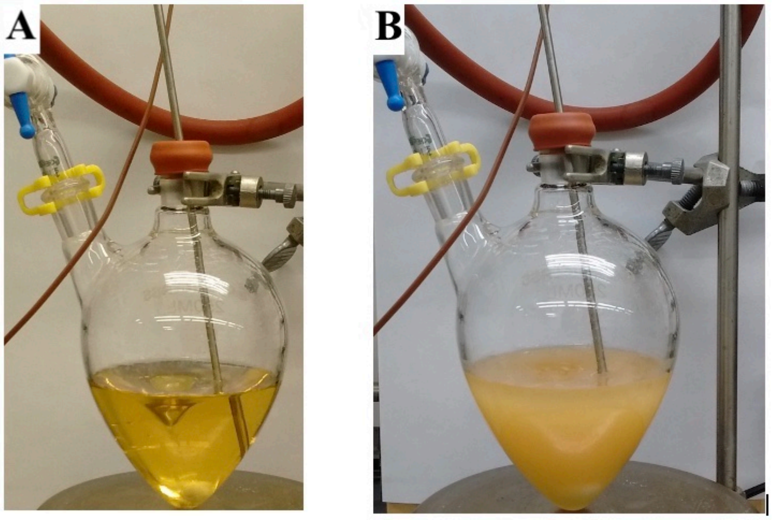

Figure 4. Final propargylic mesylate reaction mixture (A) after warming to rt over 30 min; (B) after 1 h at rt (photos provided by submitters)

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer with a 7.5-cm Teflon blade, an argon inlet adapter, and a septum fitted with a thermocouple probe. The flask is charged with LiBr (4.16 g, 48.0 mmol, 1.2 equiv) (Note 15), CuBr (6.88 g, 48.0 mmol, 1.2 equiv) (Note 16) (Figure 5), and 100 mL of THF.

Figure 5. Reaction assembly for organocopper compound formation (photo provided by checkers)

The clear, dark green solution is cooled with a dry ice-acetone bath and methylmagnesium chloride solution (3.0 M in THF, 14.67 mL, 44 mmol, 1.1 equiv) is added dropwise via syringe at such a rate so as to maintain the internal temperature below –50 °C (Note 17). Upon the addition of methylmagnesium chloride, the clear green solution becomes an orange-colored suspension (Figure 6).

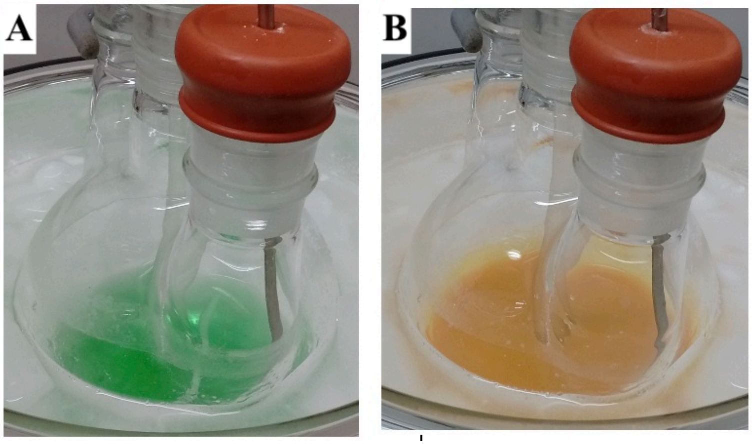

Figure 6. Formation of organocopper compound (A) before addition of MeMgCl; (B) after addition of MeMgCl (photos provided by submitters)

The reaction mixture is next stirred at –78 °C for 20 min. The solution of mesylate prepared as described above is then added dropwise via cannula (Note 18) to the solution of organocopper compound (3 x 20 mL THF wash) at a rate that maintains the internal temperature below –50 °C. Approximately 20 min are required for the addition and washes. The dry ice-acetone bath is removed, and the dark orange slurry is allowed to warm to room temperature with stirring over the course of 2 h. During this time, the solution changes color from dark orange to black (Figure 7).

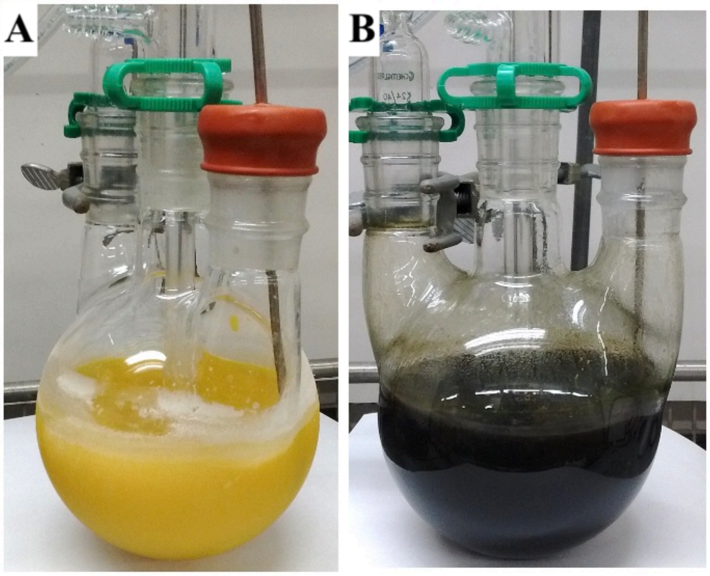

Figure 7. Reaction mixture after addition of mesylate solution (A) before warming to rt; (B) after 2 h at rt (photos provided by submitters)

The reaction mixture is poured into a 1-L Erlenmeyer flask containing 200 mL of rapidly stirred half-saturated aqueous NH_4Cl solution, and the reaction flask is rinsed with an additional 20 mL of half-saturated NH_4Cl solution. BHT (100 mg) (Note 19) is added, and the two-phase mixture is transferred to a 1-L separatory funnel. The dark blue aqueous phase is separated and extracted with hexanes (2 x 150 mL). The combined organic phases are washed with half-saturated aqueous NH_4Cl solution (2 x 150 mL) and saturated NaCl solution (150 mL), dried over 6 g of anhydrous $MgSO_4$, and filtered through a 250-mL sintered glass funnel (medium porosity, 30 mm diameter) with the aid of hexanes (3 x 10 mL washes). Concentration by rotary evaporation (20 °C, 20 mmHg) affords 9.69 g of a yellow oil (Figure 8).

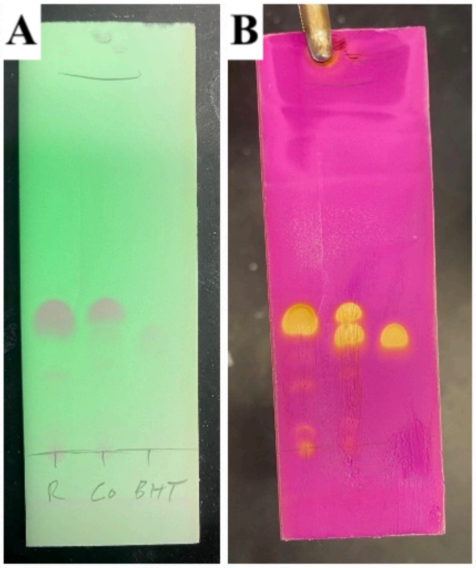

Figure 8. TLC of crude product showing starting crude product (R, left, R_f 0.60) versus BHT (BHT, right, R_f 0.55) with central co-spot (Co) using neat pentanes as eluent. A. Visualized under 254 nm UV lamp; B. The same TLC after staining with standard $KMnO_4$ stain. Product and BHT spots appear immediately upon contact with stain without warming; the faint lower spots appear only upon warming with a heat gun. Starting propargylic alcohol 1 is close to baseline in this solvent system (not shown) (photos provided by checkers)

This material is dissolved in a minimum amount of pentane (ca. 3 mL) and loaded onto a column (70-mm diameter) of 250 g of silica gel prepared as a slurry in pentane. Elution with pentane (100 mL fractions collected in 125-mL Erlenmeyer flasks) affords the product in fractions 5-18. These fractions are combined, and the solvent is removed by rotary evaporation (20 °C, 20 mmHg). Further concentration at room temperature, 0.05 mmHg for 1 h provides 7.75 g (81%) of vinylallene **2** as a colorless oil (Note 20).

C. *4-Methyl-(3-phenylpropyl)-2-tosyl-5,6,7,8-tetrahydroquinoline (***3***)*. A 50-mL, pear-shaped flask equipped with a rubber septum (Note 2) is charged with a solution of vinylallene **2** (3.34 g, 14.0 mmol, 1.00 equiv) in 19 mL of toluene (Note 21).

A 100-mL, round-bottomed, two-necked flask equipped with a 25 x 10 mm, Teflon-coated, oval magnetic stir bar, a rubber septum, and a Liebig condenser fitted with an argon inlet adapter is charged with powdered 4Å molecular sieves (0.90 g) (Note 22), BHT (0.61 g, 2.8 mmol, 0.20 equiv)

(Note 19), and tosyl cyanide (2.66 g, 14.7 mmol, 1.05 equiv) (Note 23) (Figure 9). The vinylallene solution is transferred by cannula into the reaction flask over 3 min, and the source flask is washed with toluene (3 x 3 mL). The rubber septum on the two-necked flask is replaced with a glass stopper.

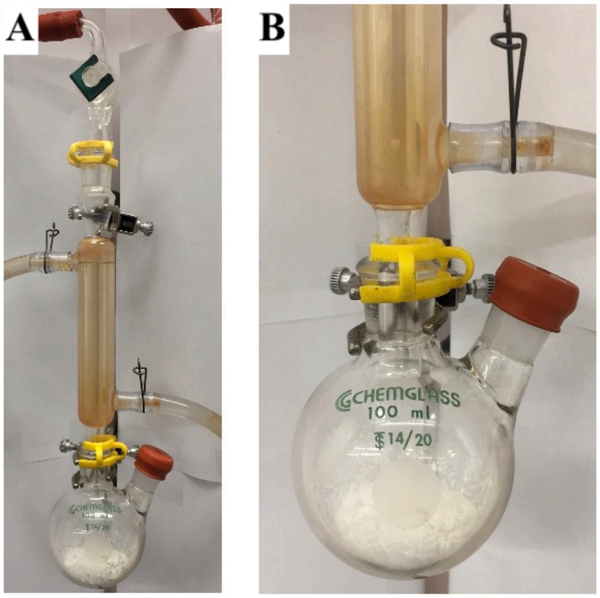

Figure 9. (A) Reaction flask loaded with 4Å molecular sieves, TsCN, and BHT; (B) close up of Figure 9A (photos provided by submitters)

The pale-yellow reaction mixture is heated in an oil bath preheated to 90 °C for 3 h and then allowed to cool to room temperature over the course of 20 min by removing the oil bath. DBU (2.20 mL, 2.24 g, 14.7 mmol, 1.05 equiv) (Note 24) is added dropwise via a 3-mL syringe over 3 min and the reaction mixture is stirred for 1 h at room temperature. After stirring is stopped the resulting red suspension is allowed to settle for 5 min (Figures 10 and 11).

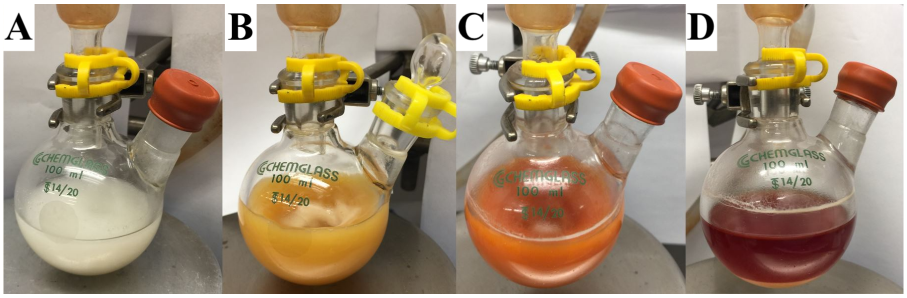

Figure 10. Progression of color changes during Step C. (A) Before heating; (B) after heating for 3 h; (C) after reaction for 1 h with DBU; (D) after stirring is ended (photos provided by submitters)

The red slurry is filtered through a 100-mL sintered glass funnel (medium porosity, 30 mm diameter) to remove the spent molecular sieves, which are washed with three 25-mL portions of ethyl acetate and discarded. The resulting clear red solution is transferred to a 500-mL separatory funnel containing water (100 mL). The aqueous phase is separated and extracted with ethyl acetate (2 x 75 mL). The combined organic extracts are washed with saturated aqueous NaCl solution (100 mL), dried over 5 g of anhydrous $MgSO_4$, and filtered through a 100-mL sintered glass funnel (medium porosity, 30 mm diameter). The $MgSO_4$ is washed with ethyl acetate (3 x 10 mL) and the filtrate is concentrated by rotary evaporation (30 °C, 20 mmHg) to afford 7.10 g of a viscous orange oil.

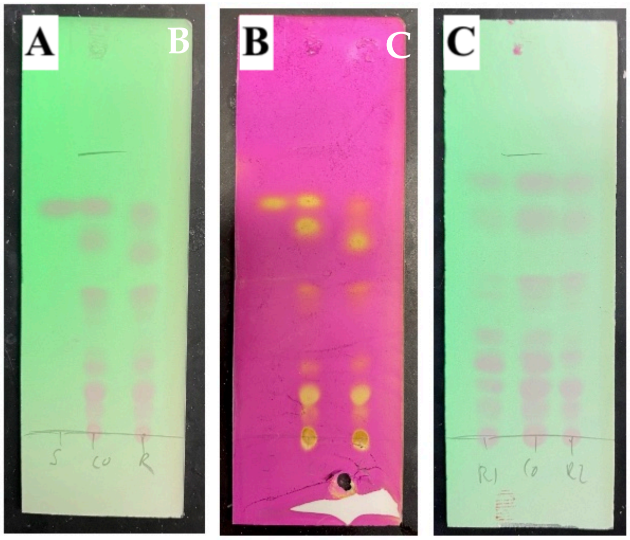

Figure 11. A. TLC of crude product showing allene (S, left, R_f 0.88) versus reaction stream after cooling to room temperature before addition of DBU (R, right) with central co-spot (Co) visualized under 254 nm UV lamp; B. The same TLC after staining with standard $KMnO_4$ stain. Allene spot appears immediately upon contact with the stain without warming; the other spots visualize only upon warming with a heat gun; C. Comparison of reaction mixture after 1 hour reaction with DBU (R1, left) versus after heating but before addition of DBU (R2, right) with co-spot (Co). All TLCs shown use 9:1 hexanes:ethyl acetate eluent; product has R_f 0.32 in this solvent system (photos provided by checkers)

The orange oil is dissolved in CH_2Cl_2 (60 mL) and concentrated using rotary evaporation (200 mmHg to 10 mmHg, 30 °C) onto silica gel (35 g). The resulting free-flowing powder is transferred into a chromatography column (60 mm diameter) containing enough sand to create a level surface and then eluted with hexanes (500 mL). Elution is continued with 1:4 ethyl acetate-hexanes and 50 mL fractions are collected in 125-mL Erlenmeyer flasks. Fractions 2-6 are concentrated by rotary evaporation (20 °C, 20 mmHg) to afford 4.87 g of an orange powder.

The orange powder is dissolved in CH_2Cl_2 (50 mL) and concentrated onto 25 g of silica gel. The resulting free-flowing powder is deposited onto a column (90 mm diameter) of 485 g of silica gel prepared as a slurry in 1:99 ethyl acetate–hexanes (Note 25). Elution is carried out with a gradient of ethyl acetate-hexanes, beginning with 300 mL of 1:99 ethyl acetate-hexanes, followed by 300 mL of 1:49 ethyl acetate-hexanes, 300 mL of 1:19 ethyl acetate-hexanes, and then 1:9 ethyl acetate-hexanes for the remaining elution. After collecting 4 L of solvent in 1-L flasks, 100-mL fractions are collected in 125-mL Erlenmeyer flasks. The desired product is obtained in fractions 4-30. These fractions are combined, and the solvent is removed by rotary evaporation (30 °C, 20 mmHg). Further concentration at 0.02 mmHg for 1 h in an oil-bath (100 °C bath temperature) provides 3.56 g (61%) of pyridine **3** as a pale-yellow solid (Figure 12) (Note 26).

Figure 12. Pyridine product 3 (photo provided by submitters)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with ethynylcyclohexene, *n*-butyllithium, 3-phenylpropionaldehyde, tetrahydrofuran, acetone,

hexane, ethyl acetate, ammonium chloride, methylmagnesium chloride, methanesulfonyl chloride, lithium bromide, copper(I) bromide, magnesium sulfate, silica gel, tosyl cyanide, 4Å molecular sieves, toluene, 2,6-di-*tert*-butyl-4-methylphenol, 1,8–diazabicyclo(5.4.0)undec-7-ene, dimethyl terephthalate, and pentane.

2. Glassware was flame-dried under vacuum (0.1 mmHg), back-filled with argon while hot, and then maintained under the inert atmosphere during the course of the reaction. The checkers were able to obtain comparable results using glassware dried in an oven at 120 ºC overnight and a nitrogen atmosphere.
3. 1-Ethynylcyclohexene (99%) was purchased from Sigma-Aldrich and was used as received.
4. Tetrahydrofuran (ultra low water) was purchased from J. T. Baker and purified by pressure filtration through activated alumina prior to use. The checkers purchased anhydrous tetrahydrofuran (99.9%, inhibitor-free) from Sigma-Aldrich, which was used as received.
5. *n*-Butyllithium in hexanes (2.5 M stated concentration) was purchased from Sigma-Aldrich and titrated prior to use.[2] It is imperative that the titration of the *n*-BuLi solution be accurate, otherwise the product of addition of *n*-BuLi to 3-phenylpropionaldehyde is formed, which is difficult to separate from the desired propargylic alcohol **1** by column chromatography. The checkers used the method of Kofron and Baclawski (*J. Org. Chem.* **1976**, *41*, 1879–1880), titrating against diphenylacetic acid (212 mg, 1.00 mmol, recrystallized from toluene) in THF (5 mL) at room temperature in triplicate, which gave a final molarity of 2.49±0.02 M. The submitters used a 2.27 M solution.
6. The alkyllithium is added in separate portions of 10.0 mL and 9.4 mL using an oversized 20-mL syringe to reduce the risk of spills. Approximately 6 min are required for the addition during which time the internal temperature rises to –55 °C.
7. 3-Phenylpropionaldehyde (≥ 95%) was purchased from Sigma Aldrich and purified by short path distillation (bp 98 °C, 12 mmHg) prior to use.
8. Approximately 45 min are required for the transfer.
9. The submitters employed silica gel 60 Å (40 – 63 micron) that was purchased from Sorbent Technologies and used as received. The checkers used the same grade from Sigma-Aldrich.
10. 1-(Cyclohex-1-en-1yl)-5-phenylpent-1-yn-3-ol (**1**) has the following physical and spectroscopic properties: R_f = 0.4 (1:19 ethyl acetate-hexanes; silica gel plate, $KMnO_4$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.32–7.15 (m, 5H), 6.12 (tt, *J* = 3.8, 1.7 Hz, 1H), 4.48 (q, *J* = 5.9 Hz, 1H), 2.80 (t, *J* = 7.9 Hz, 2H), 2.11 (dddd, *J* = 16.8, 9.9, 5.3, 3.0 Hz, 4H), 2.06–1.97 (m,

2H), 1.88–1.77 (m, 1H), 1.70–1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 141.6, 135.5, 128.6, 128.5, 126.1, 120.2, 87.4, 87.2, 62.4, 39.6, 31.6, 29.3, 25.7, 22.4, 21.6; IR ($CHCl_3$): 2934, 2896, 2864, 2836, 2226, 1604, 1496, 1452, 1377, 1228, 1047, 998, 920, 846 cm^{-1}.HRMS (ESI) *m/z*: Calcd. for $C_{17}H_{21}O^+$ $[M+H]^+$: 241.1587, found: 241.1586. The purity was determined to be 97-99% in several runs by quantitative NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. Additional reactions performed on full scale provided 10.13 g (91%) and 10.50 g (94%) of the same product. It should be noted that the product of this reaction has limited stability at room temperature, particularly if exposed to air, and visible yellowing along with the appearance new peaks in the ^{1}H NMR spectrum will occur if it is improperly stored. The submitters report that it can be kept under inert atmosphere at 4 °C for at least several months without decomposition. If a sufficiently high vacuum is not available, the viscous oil can be difficult to dry without decomposition. In this case, the checkers found that the presence of 1-2% residual ethyl acetate did not have a negative effect on the subsequent step.

11. The submitters used methylmagnesium chloride (2.8 M in THF) that was purchased from Sigma-Aldrich and used as received. The checkers purchased methylmagnesium chloride (3 M in THF) from Aldrich, which was used as received.
12. The MeMgCl solution is added in portions of 6.5 mL and 6.8 mL using a 10-mL syringe. Approximately 7 min is required for the addition.
13. Methanesulfonyl chloride (≥ 99.7%) was purchased from Sigma-Aldrich and used as received.
14. Approximately 30 sec is required for the addition of methanesulfonyl chloride.
15. Lithium bromide (≥ 99%) was purchased from Sigma-Aldrich and dried in a sand bath at 200 °C under vacuum (0.05 mmHg) for 24 h.
16. The submitters prepared copper(I) bromide by Na_2SO_3 reduction of copper(II) bromide (99%) that was purchased from Alfa Aesar according to the procedure of Keller, R. N.; Wycoff, H. P. *Inorg. Synth.* **1946**, *2*, 1. See also Gommermann, N.; Knochel, P. *Org. Synth.* **2007**, *84*, 1. The checkers found no disadvantage to using commercial copper(I) bromide 99.9% purchased from Sigma-Aldrich, providing it is fresh and has been properly stored.
17. The methylmagnesium chloride solution is added via a 10-mL syringe successively loaded with two 7.9-mL portions of reagent. Approximately 10 min is required for the addition.
18. A 16-gauge cannula is used for this transfer. A fine precipitate of magnesium salts form during the generation of the mesylate and can clog

narrower gauge cannulas. Stirring the suspension during transfer helps ensure that solids do not settle, resulting in a steady transfer rate and preventing clogging.

19. 2,6-Di-*tert*-butyl-4-methylphenol (99%) was purchased from Sigma-Aldrich and was used as received. The BHT serves to stabilize the vinylallene **2** during extraction, concentration, chromatography, and storage.
20. (5-(Cyclohex-1-en-1-yl)hexa-3,4-dien-1-yl)benzene (**2**) has the following physical and spectroscopic properties: R_f = 0.6 (pentane; silica gel plate, $KMnO_4$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.29–7.24 (m, 2H), 7.21–7.14 (m, 3H), 5.67–5.61 (m, 1H), 5.27 (br s, 1H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.44–2.28 (m, 2H), 2.12 (dd, *J* = 4.1, 2.1 Hz, 2H), 2.07–1.97 (m, 1H), 1.95–1.82 (m, 1H), 1.77 (d, *J* = 2.7 Hz, 3H), 1.66–1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 204.3, 142.1, 134.0, 128.7, 128.4, 125.9, 122.4, 103.1, 91.5, 35.7, 31.2, 27.1, 26.1, 23.1, 22.6, 16.6; IR (film or solvent): 2946, 2916, 2864, 2816, 2272, 2208, 2179, 2148, 1964, 1604, 1496, 1453, 1343, 1236, 1080, 1029, 915, 836, 799 cm^{-1}. HRMS (ESI) *m*/*z*: Calcd. for $C_{18}H_{22}$ $[M+H]^+$: 239.1794, found: 239.1783. The purity was determined to be 99% by quantitative NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard with the major impurity (1%) being BHT. A second reaction performed at identical scale provided 7.75 g (81%) of the same product.
21. Toluene (ultra-low water) was purchased from J. T. Baker and purified by pressure filtration through activated alumina prior to use. The checkers purchased anhydrous toluene (99.9%) from Sigma-Aldrich, which was used as received
22. Powdered 4 Å molecular sieves were purchased from Sigma-Aldrich and dried at 0.05 mmHg at 200 °C (sand bath) for 24 h (Figure 13).

Figure 13. Drying powdered 4Å molecular sieves (photo provided by submitters)

23. Tosyl cyanide (97%) was purchased from Combi-Blocks and used as received. Similar results were obtained with tosyl cyanide (95%) purchased from Sigma-Aldrich.
24. 1,8–Diazabicyclo(5.4.0)undec-7-ene (98%) was purchased from Sigma-Aldrich and used as received.
25. Due to the challenging separation, effective initial packing of the silica gel column is necessary to achieve complete separation of the desired pyridine from byproducts. A slurry of silica gel was added to a column containing hexanes and then the column was tapped with rubber tubing or a cork ring to settle the silica gel completely. For additional information on best practices, see Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925. If the purity of the product is not critical, the checkers were able to obtain **3** in 95% purity from a single column (4″ diameter, 500 g of silica gel) with a gradient of pure hexanes to 9:1 hexanes:ethyl acetate over 35 column volumes. This material was obtained as a transparent yellow gum rather than a yellow powder, but the material was almost identical spectroscopically to the 98% purity material described below.
26. 4-Methyl-(3-phenylpropyl)-2-tosyl-5,6,7,8-tetrahydroquinoline (**3**) has the following physical and spectroscopic properties: $R_f = 0.2$ (1:19 ethyl acetate-hexanes; silica gel plate, $KMnO_4$); mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.83 (d, *J* = 8.3, 2H), 7.40–7.13 (m, 7H), 3.13–3.04 (m, 2H), 2.78 (t, *J* = 7.6 2H), 2.75–2.69 (m, 2H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 1.88–1.70 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 154.2, 153.5, 147.5, 143.8, 142.1, 137.7, 135.1, 132.8, 129.2, 129.1, 128.7, 128.4, 125.9, 36.3, 32.9, 31.8, 27.7, 27.1, 22.7, 22.4, 21.8, 14.4.; IR ($CHCl_3$): 2948, 2928, 1600, 1454, 1433, 1144, 915, 808, 760, 736, 708 cm^{-1}. HRMS (ESI) *m*/*z*: Calcd. for $C_{26}H_{29}NO_2S$ $[M+H]^+$: 420.1992, found: 420.2007. The purity was determined to be 98% by quantitative NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. A second reaction performed at identical scale provided 3.77 g (64%) of the same product.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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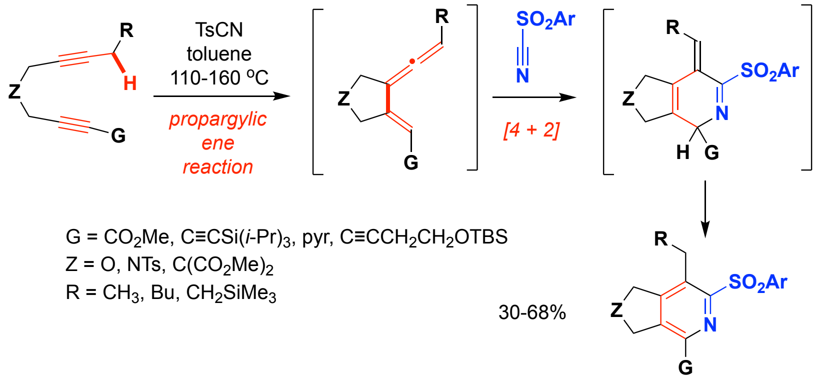
Discussion

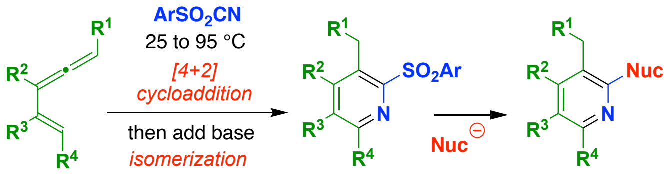
The development of practical and efficient methods for the construction of highly substituted pyridines remains a challenging goal for organic synthesis.[2] The aim of our work in this area has been the design and invention of convergent annulation and cycloaddition strategies that provide regiocontrolled access to multiply substituted pyridines with an emphasis on methods that accommodate the synthesis of pyridines that bear a diverse range of substituents.

Vinylallenes are reactive dienes in Diels-Alder reactions[3] which engage in [4 + 2] cycloadditions with triple bonds to afford isoaromatic products that isomerize to aromatic systems spontaneously or under mild conditions. We have developed several strategies for the synthesis of highly substituted pyridines based on the [4 + 2] cycloadditions of vinylallenes with nitrogen heterodienophiles. In one approach, the requisite vinylallenes are generated in situ via a propargylic ene reaction and undergo *intramolecular* Diels-Alder reaction with an unactivated nitrile to furnish highly substituted pyridines after isomerization.[4] Analogous reactions with dimethylhydrazones and oximino ethers as dienophiles afford cycloadducts that undergo elimination followed by isomerization to generate the pyridines.[5] In subsequent work, we extended this strategy to *intermolecular* cycloadditions of vinylallenes generated by the propargylic ene reaction.[6] In this case, the application of more reactive dienophiles were necessary such as *N*-(tosyl)iminoacetate and tosyl cyanide (Scheme 1).



Scheme 1. Synthesis of pyridines via intramolecular propargylic ene/TsCN aza Diels-Alder reaction cascade[6]

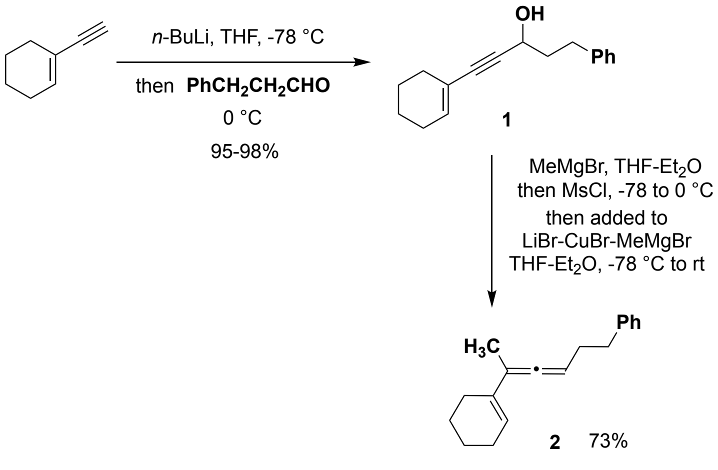
Recently, we reported a more general strategy for the synthesis of highly substituted mono- and bicyclic pyridines in which the vinylallene Diels-Alder partners are generated via isomerization of alkynes, [3,3]-sigmatropic rearrangements of propargylic alcohol derivatives, and via S_N2'-type substitution reactions of propargylic sulfonates.[7] The synthesis of **3** described in this *Organic Syntheses* article illustrates this approach. Reaction of the pre-formed vinylallene with commercially available TsCN generates an isoaromatic cycloadduct that isomerizes to the desired pyridine upon addition of bases such as DBU. An attractive feature of this version of our strategy is that the 2-sulfonylpyridine products are versatile intermediates which undergo nucleophilic substitution reactions with oxygen and carbon nucleophiles (vide infra).



Scheme 2. Strategy for the synthesis of substituted pyridines via intermolecular cycloaddition of vinylallenes and tosyl cyanide

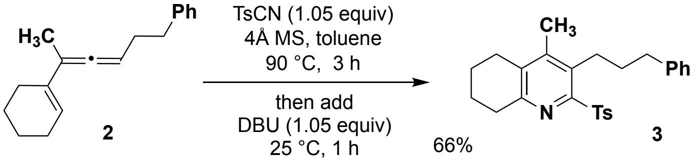
The S_N2'-type substitution reaction of propargylic alcohol derivatives with organocopper compounds provides one of the most general and useful methods for the synthesis of vinylallenes.[8,9] As outlined in Scheme 3, in this article we employed the displacement of the propargylic mesylate derivative of **1** for the synthesis of vinylallene **2** . Addition of the lithium derivative of commercially available ethynylcyclohexene to hydrocinnamaldehyde provided propargylic alcohol **1** in nearly quantitative yield. On a multi-gram scale, the slow addition of a pre-cooled solution of the aldehyde and careful monitoring of the internal reaction temperature was found to be essential to avoid the formation of byproducts that coelute with the desired product during column chromatography.

For the organocopper substitution step we applied a general protocol previously developed in our laboratory for the synthesis of allenylsilanes.[10] Either MeMgBr (2.8 M in Et_2O) or MeMgCl (2.8 M in THF) can be used for this reaction. Optimal results were obtained by using the mesylate derivative of **1**; reaction of the benzoate afforded a mixture of allene (35%) and direct substitution product (25%).[11] The vinylallene product proved to be quite sensitive, and initially was found to decompose to polymeric material during extraction, chromatography, and even upon storage as a chilled solution under argon. Fortunately we found that the decomposition of **2** can be suppressed by the addition of 1 mol% BHT prior to the aqueous extraction step and this measure increased the yield of vinylallene by ca. 40% and provided material in good yield and 99% purity as determined by quantitative NMR analysis.



Scheme 3. Synthesis of vinylallene 2 via organocopper substitution reaction

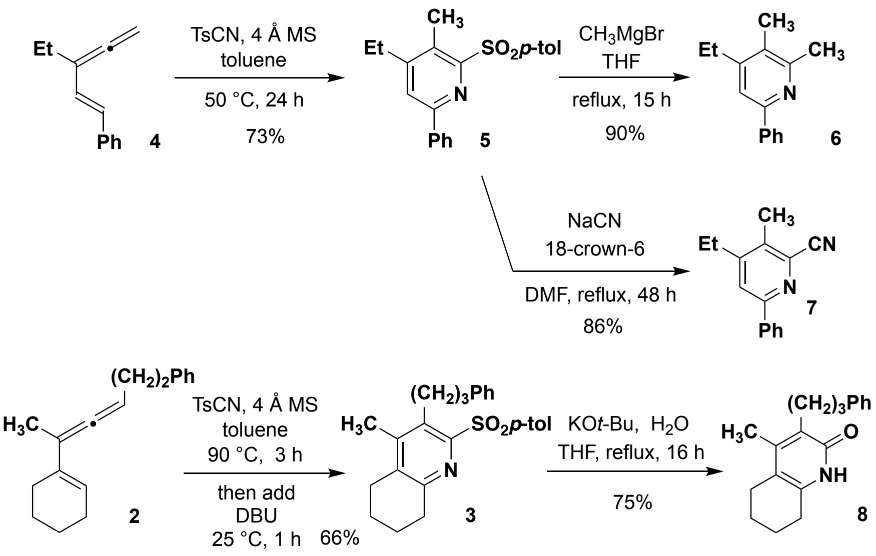
Scheme 4 describes the optimal conditions for the Diels-Alder reaction of vinylallene **2** and tosyl cyanide. van Leusen has previously reported that the reactions of TsCN with acyclic dienes are complicated by the formation of significant amounts of lactam byproducts,[12] and we observed this to be the case in our initial attempts to achieve cycloadditions with vinylallenes. These byproducts result from hydrolysis of the intermediate sulfonylimine cycloadducts in a process that is autocatalytic in the water that is generated by disproportionation of the sulfinic acid formed in the hydrolysis.[13.] Attempts to suppress this hydrolysis by including bases such as DBU, KO-*t*-Bu, (*i*-Pr)$_2$EtN, and 2,6-di-*t*-butylpyridine were not successful, due in part to the reaction of most bases with TsCN under the reaction conditions. However, conducting the cycloaddition in the presence of molecular sieves effectively suppressed lactam formation, and addition of either DBU or KO-*t*-Bu to the reaction mixture and further reaction at room temperature for 1 h produced the desired pyridine in good yield.



Scheme 4. Synthesis of pyridine 3 via cycloaddition of vinylallene 2 and tosyl cyanide

Although the cycloaddition of other vinylallenes can be effected at 25 to 60 °C, best results in the case of **2** were obtained by carrying out the reaction at 90 °C for 3 h. Although this Diels-Alder reaction does proceed at room temperature, the time required to achieve complete conversion was more than three days. Initial attempts to recrystallize the pyridine product **3** failed to achieve >97% purity in good yield due to an inseparable yellow impurity, but purification could be accomplished by column chromatography as described in the experimental procedure. HSQC and HMBC NMR experiments confirmed the assignment of regiochemistry, and **3** is the only cycloaddition product observed to form in the reaction.

In summary, the combination of the S$_N$2′ substitution reaction of propargyl alcohol derivatives and the [4 + 2] cycloaddition of vinylallenes with tosyl cyanide provides a regioselective and convergent strategy for the synthesis of highly substituted pyridines. As illustrated in the following examples (Scheme 5),[7] the 2-sulfonylpyridine products undergo nucleophilic substitution reactions with a variety of nucleophiles to provide access to diverse substituted monocyclic and polycyclic pyridines.



Scheme 5. Synthesis of highly substituted pyridines via vinylallene Diels-Alder reaction and nucleophilic substitution reactions of the cycloadducts[7]

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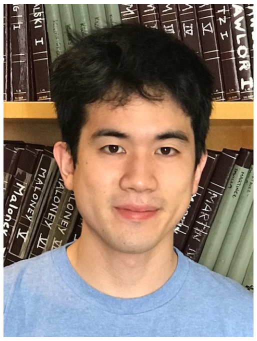
Appendix
Chemical Abstracts Nomenclature (Registry Number)

1-Ethynylcyclohexene: Cyclohexene, 1-ethynyl-; (931-49-7)
n-Butyllithium solution: Lithium, butyl-; (109-72-8)
3-Phenylpropionaldehyde: Benzenepropanal; (104-53-0)
Methyl magnesium chloride: Magnesium, chloromethyl-; (676-58-4)
Methanesulfonyl chloride: Methanesulfonyl chloride; (124-63-0)
LiBr: Lithium bromide (LiBr); (7550-35-8)
CuBr: Copper bromide (CuBr); (7787-70-4)
BHT: Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-; (128-37-0)
DMT: 1,4-Benzenedicarboxylic acid, dimethyl ester; (120-61-6)
Tosyl cyanide: Benzenesulfonyl cyanide, 4-methyl-; (19158-51-1)
DBU: Pyrimido[1,2-*a*]azepine,2,3,4,6,7,8,9,10-octahydro-; (6674-22-2)

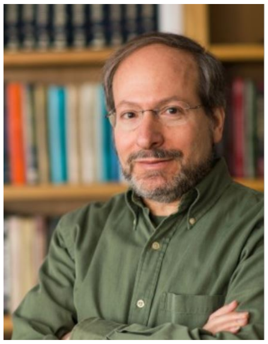


Nathan H. Faialaga was born in Tokyo, Japan and received a B.Eng. in Chemical Engineering at Nagoya University in 2017. He is currently pursuing a Ph.D. degree in the Department of Chemistry at the Massachusetts Institute of Technology under the direction of Professor Rick Danheiser. The main focus of Nathan's current research is the synthesis of natural products using benzannulation strategies.

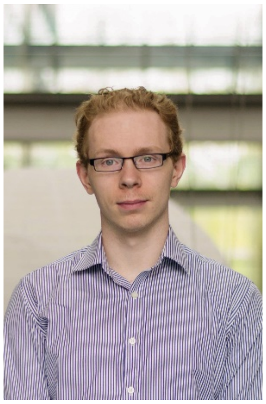
Christian Gomez was born in Leuven, Belgium and received a B.A. degree in Chemistry at Cornell University in 2017. He is currently pursuing a Ph.D. degree in the Department of Chemistry at the Massachusetts Institute of Technology under the direction of Professor Rick Danheiser. The main focus of Chris's current research is the total synthesis of bioactive natural products.

Samuel G. Bartko was born in Littleton, Colorado and received a B.S. degree in Chemistry at the University of Wyoming in 2014. He received his Ph.D. degree in the Department of Chemistry at the Massachusetts Institute of Technology under the direction of Professor Rick Danheiser in 2019. The main focus of Sam's research was the development of new strategies for the efficient synthesis of highly substituted pyridines based on cycloadditions of highly conjugated molecules.

Philipp Natho completed his MSci degree at Imperial College London (UK) in 2017, where he investigated the total synthesis of (-)-morphine under the supervision of Professor Don Craig. As an undergraduate, he also spent time as a visiting student in the laboratory of Professor Rick Danheiser at MIT studying the synthesis of highly substituted pyridines. Philipp received his Ph.D. in 2021 at Imperial College London working under the guidance of Professor Philip J. Parsons on the development of novel ring expansion reactions of cyclobutanols and azetidinols, and their application in natural product synthesis.

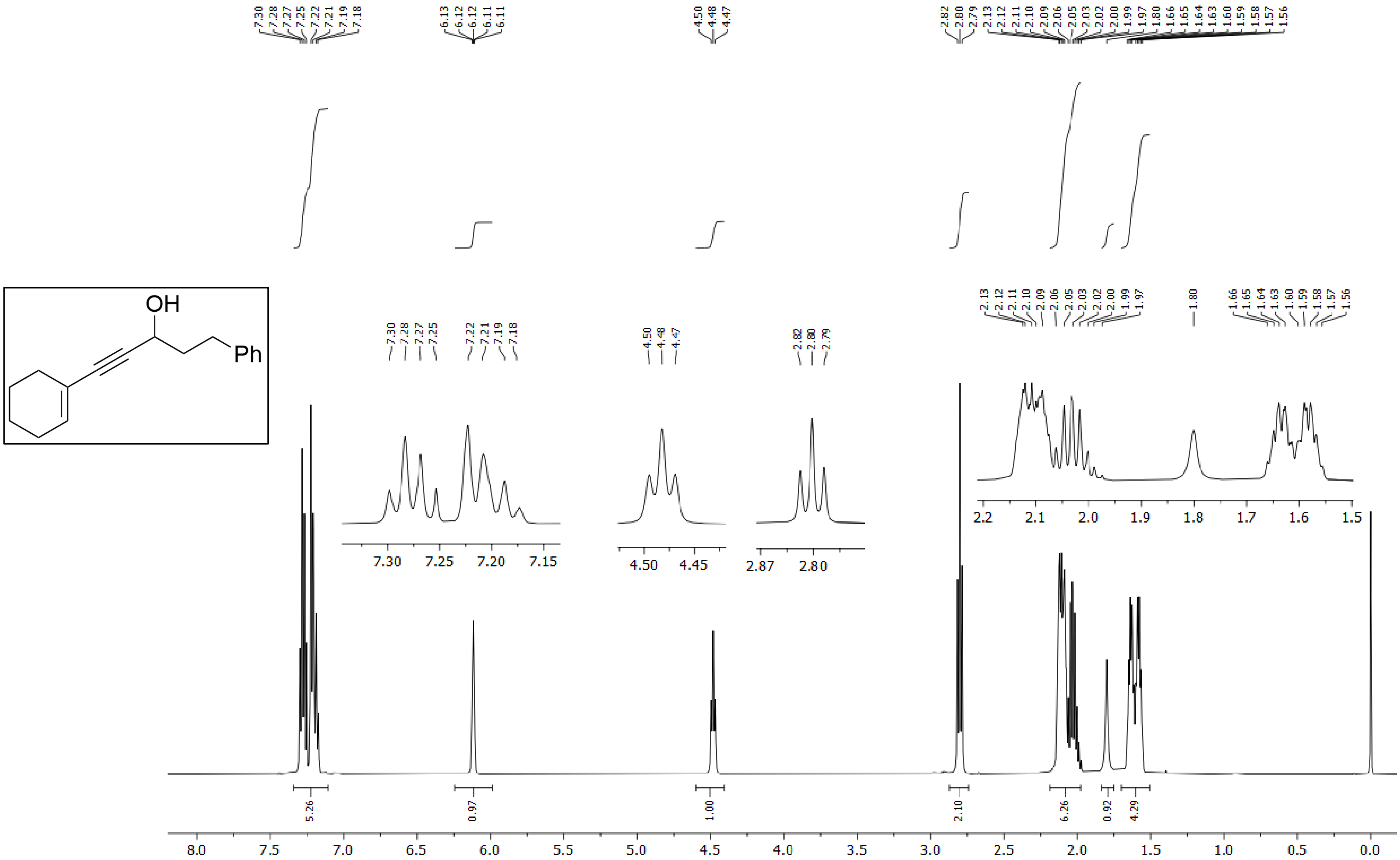


Rick Danheiser received his undergraduate education at Columbia where he carried out research in the laboratory of Professor Gilbert Stork. He received his Ph.D. at Harvard in 1978 working under the direction of E. J. Corey on the total synthesis of gibberellic acid. Dr. Danheiser is the A. C. Cope Professor of Chemistry at MIT where his research focuses on the design and invention of new annulation and cycloaddition reactions, and their application in the total synthesis of biologically active compounds.

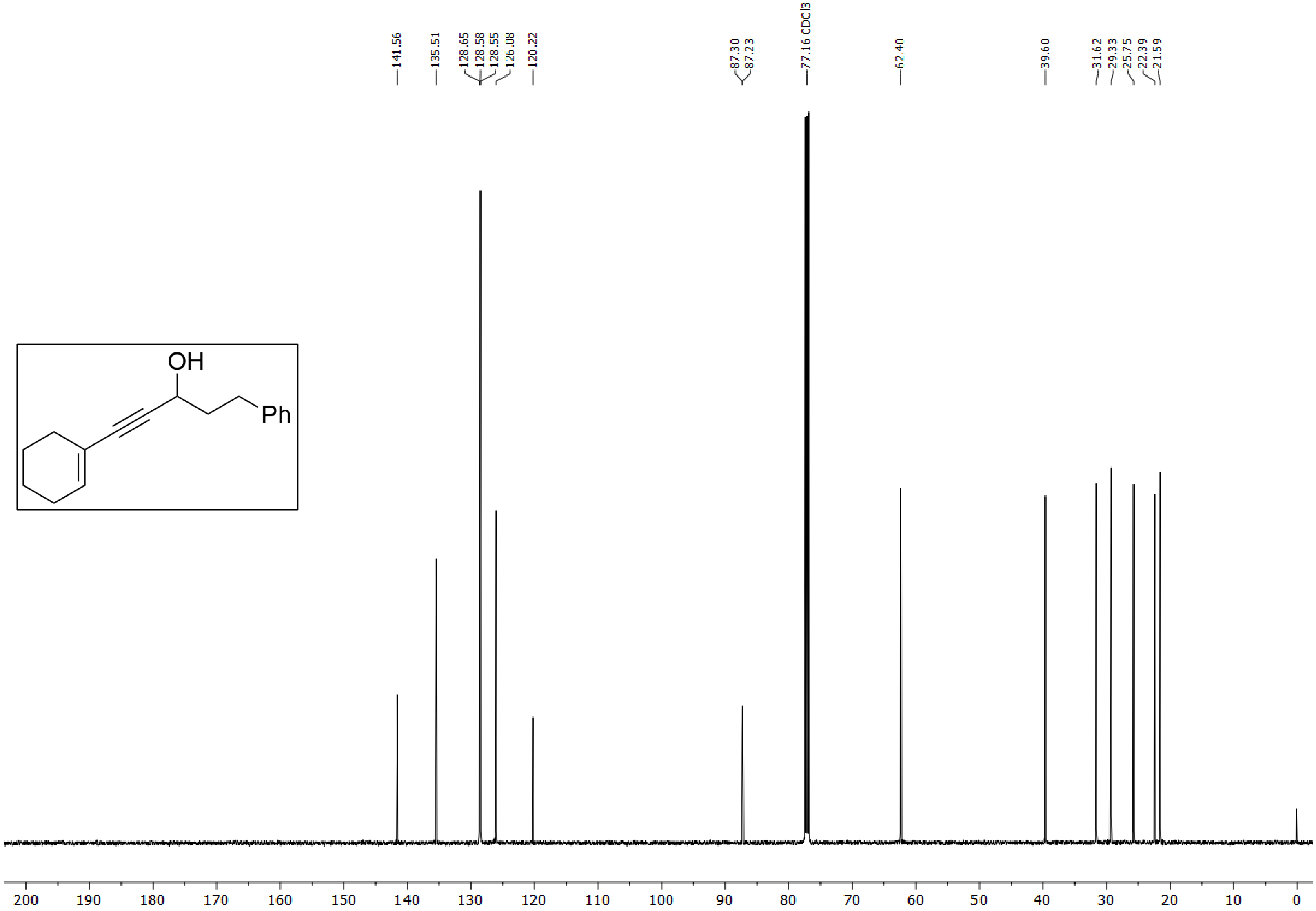


Chris Nawrat was born in Carshalton, England (near London) in 1986. He completed his Ph.D. studies at the University of Nottingham in 2012 working with Professor Chris Moody on several total syntheses. In 2013 he moved to the US to undertake postdoctoral studies in the group of Dave MacMillan at Princeton where he gained expertise in photo- and organocatalysis. Two years later, he joined Merck and Co., Inc. where he enjoys tackling challenging problems in drug development and is currently situated in the Discovery Process Chemistry group based in West Point, Pennsylvania.

1-(Cyclohex-1-en-1-yl)-5-phenylpent-1-yn-3-ol **1**



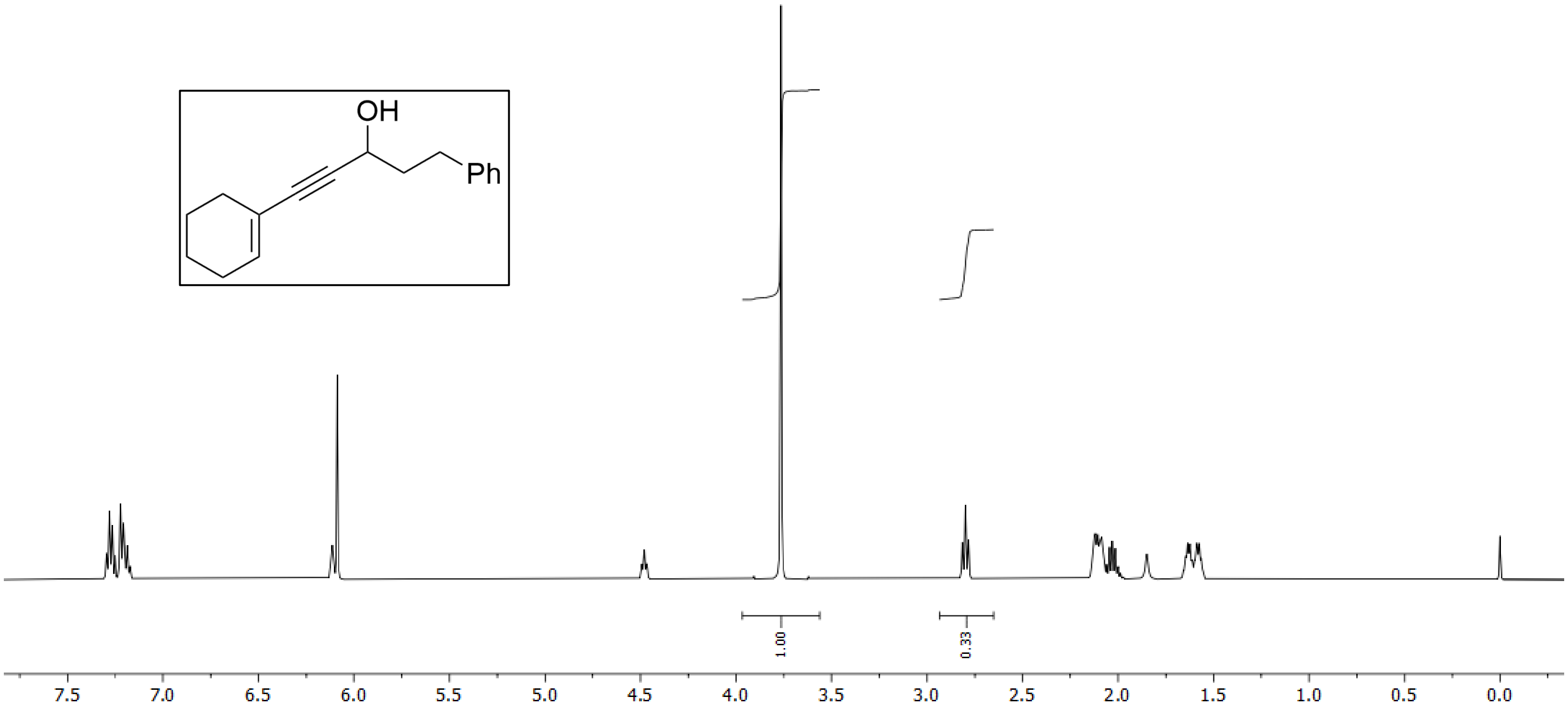
^{1}H NMR spectrum at 500 MHz in $CDCl_3$ with 1% (v/v) TMS



^{13}C NMR spectrum at 126 MHz in $CDCl_3$ with 1% (v/v) TMS

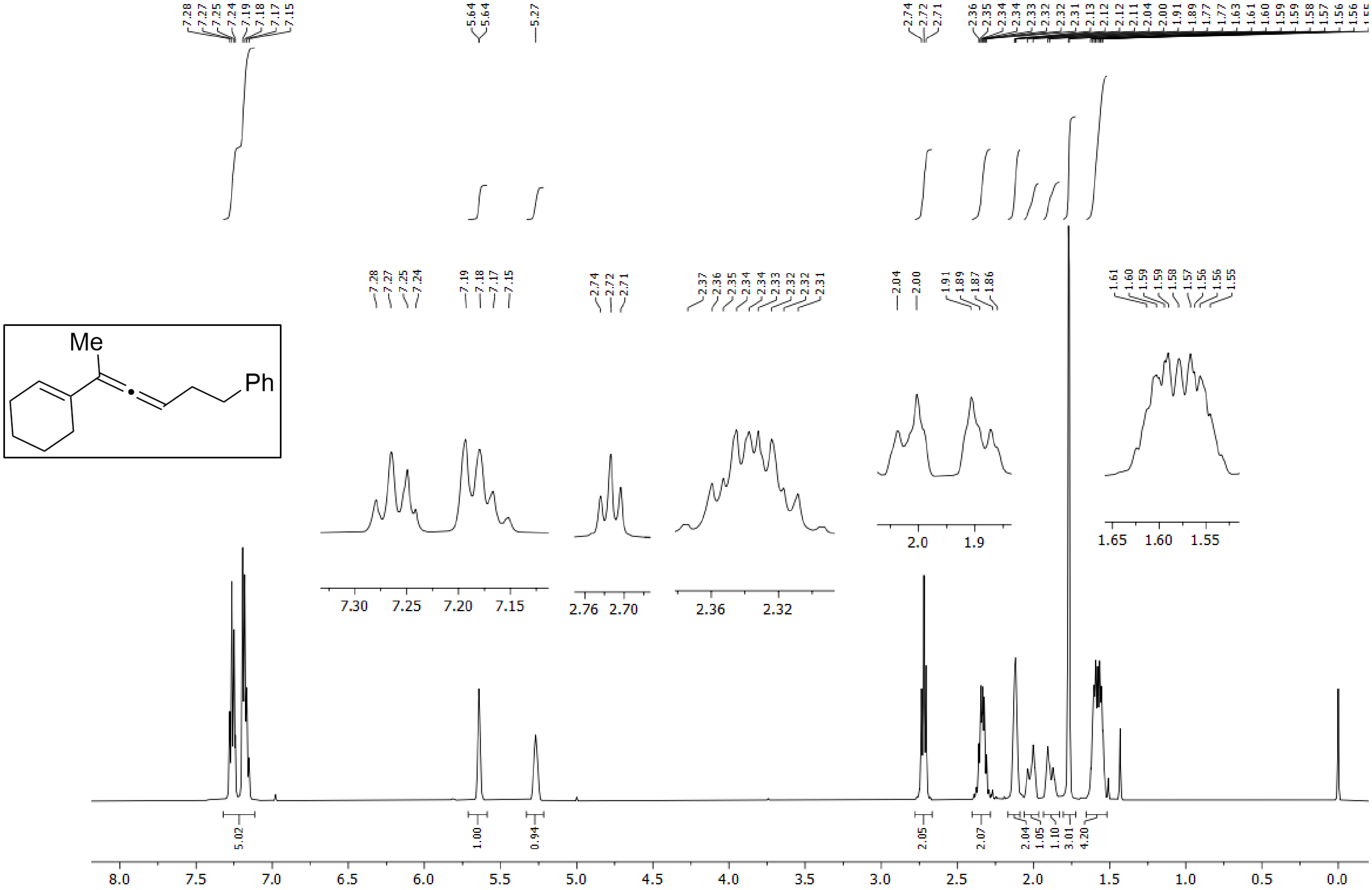
Purity = **97.78%**
Assuming sample weight: 25.8 mg and mol weight: 240.346
Using Reference Compound: 1,3,5-trimethoxybenzene (11.9 mg, 99% purity, Mol Weight=168.08)
Sample Integral 1: 2.65244 - 2.93544 ppm, value = 0.33277 (2 nuclides) - Purity = 97.8%
Reference Integral: 3.56104 - 3.96795 ppm, value = 1 (9 nuclides)

4 scans @ 60 s delay time

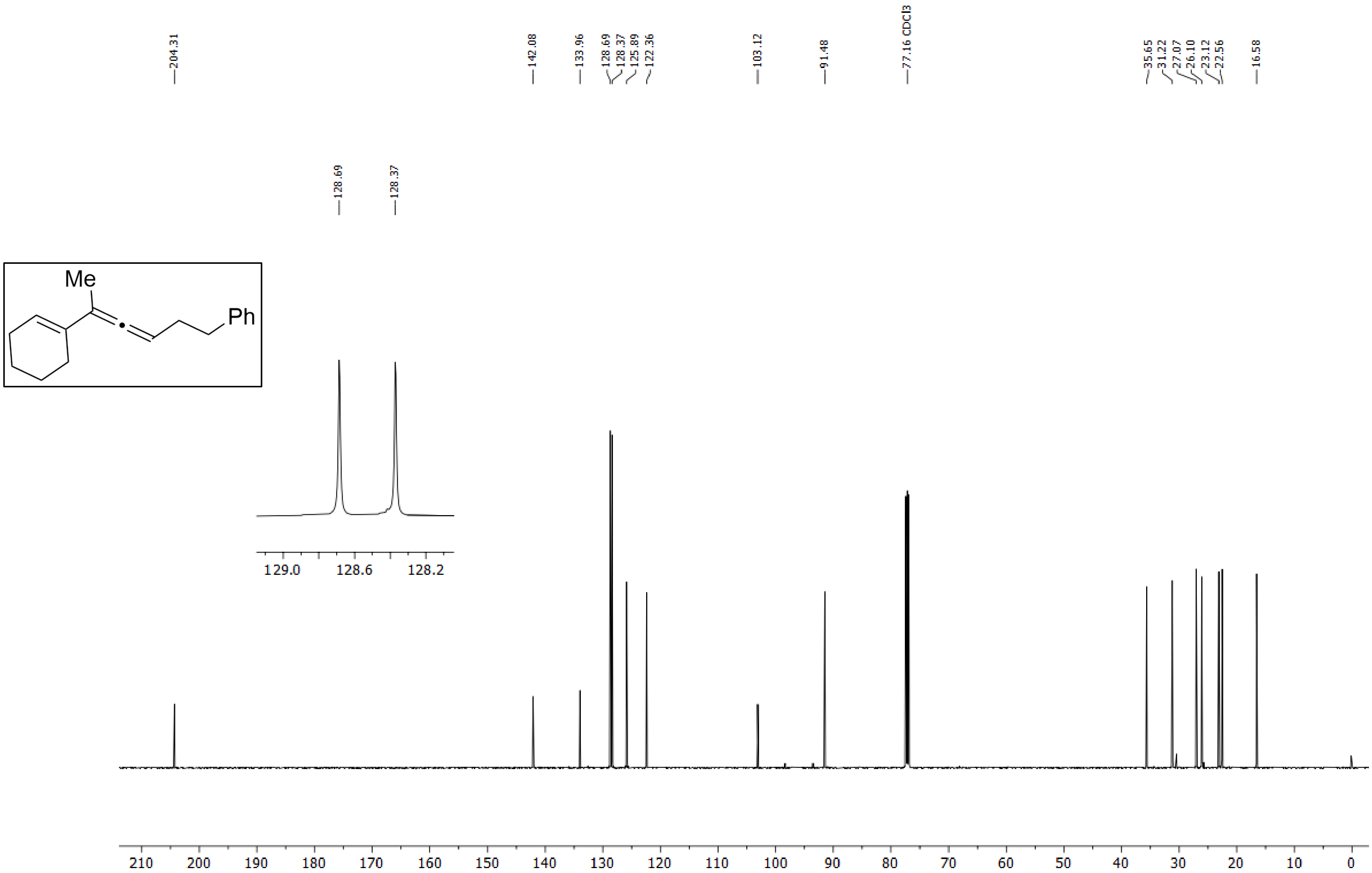


Quantitative ^{1}H NMR spectrum at 500 MHz in $CDCl_3$ with 1% (v/v) TMS using 1,3,5-trimethoxybenzene as internal standard

(5-(Cyclohex-1-en-1-yl)hexa-3,4-dien-1-yl)benzene **2**



^{1}H NMR spectrum at 500 MHz in CDCl$_3$ with 1% (v/v) TMS



^{13}C NMR spectrum at 126 MHz in $CDCl_3$ with 1% (v/v) TMS

Purity = **97%**
Sample weight: 18.7 mg and mol weight: 238.374
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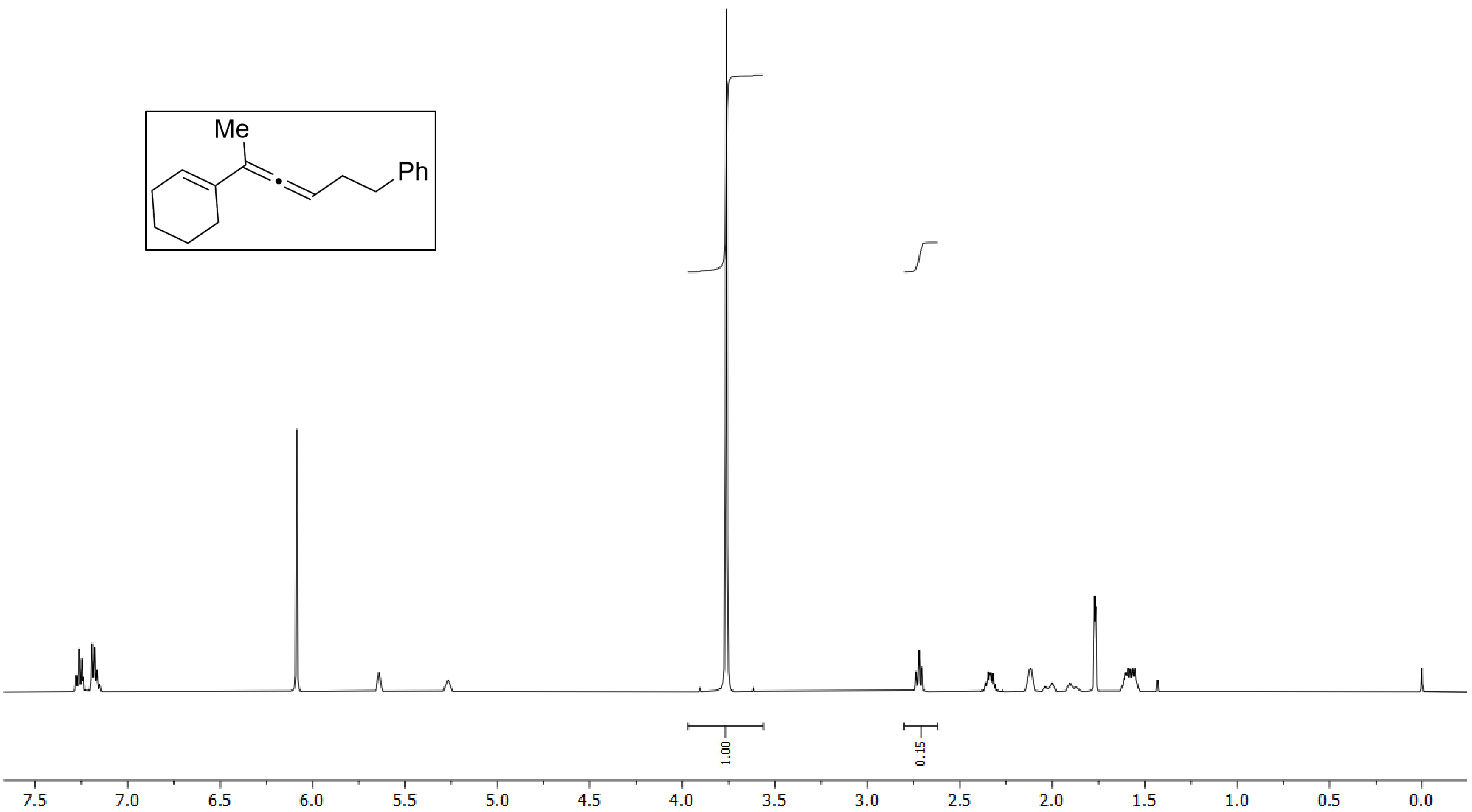
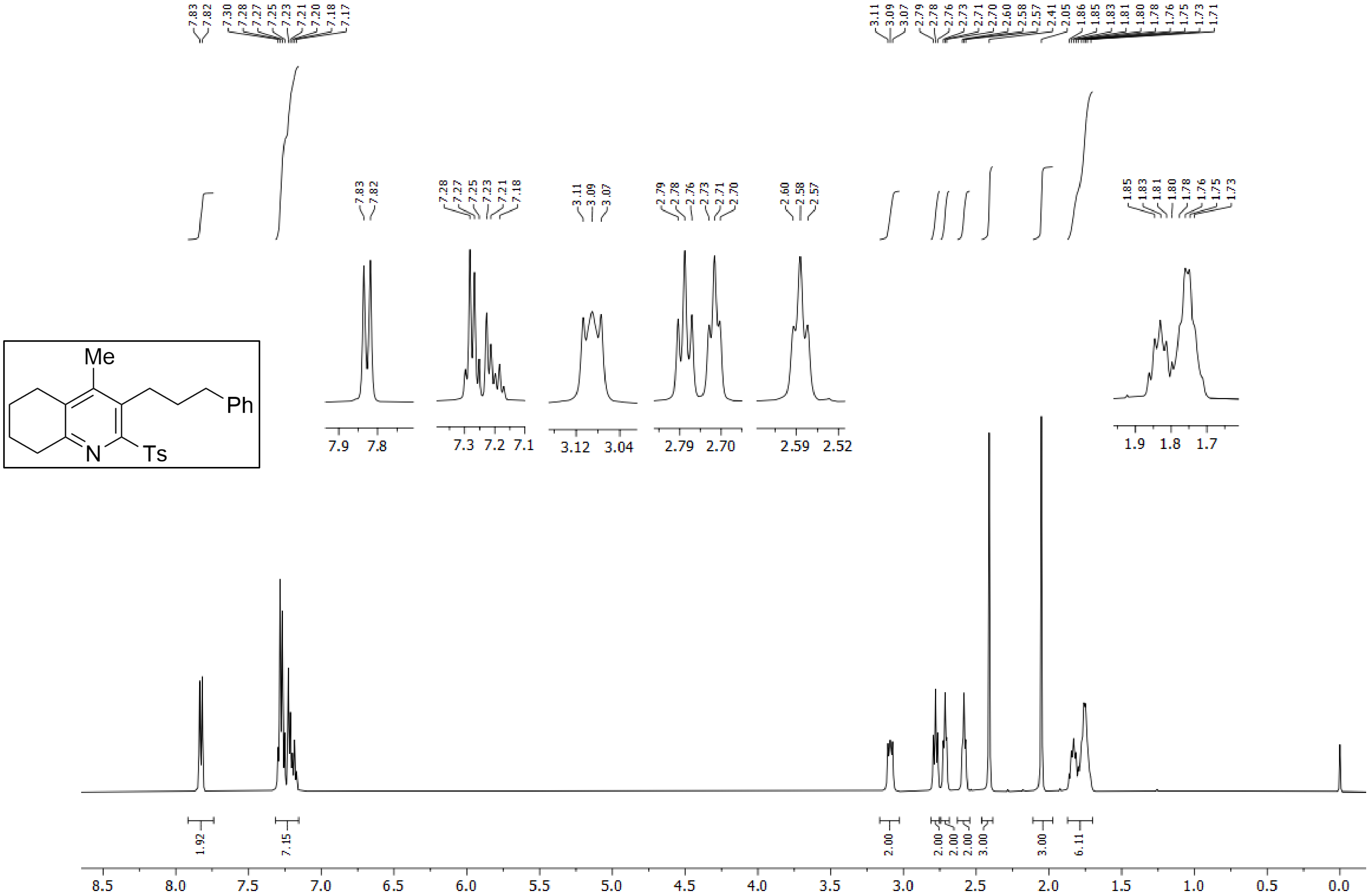
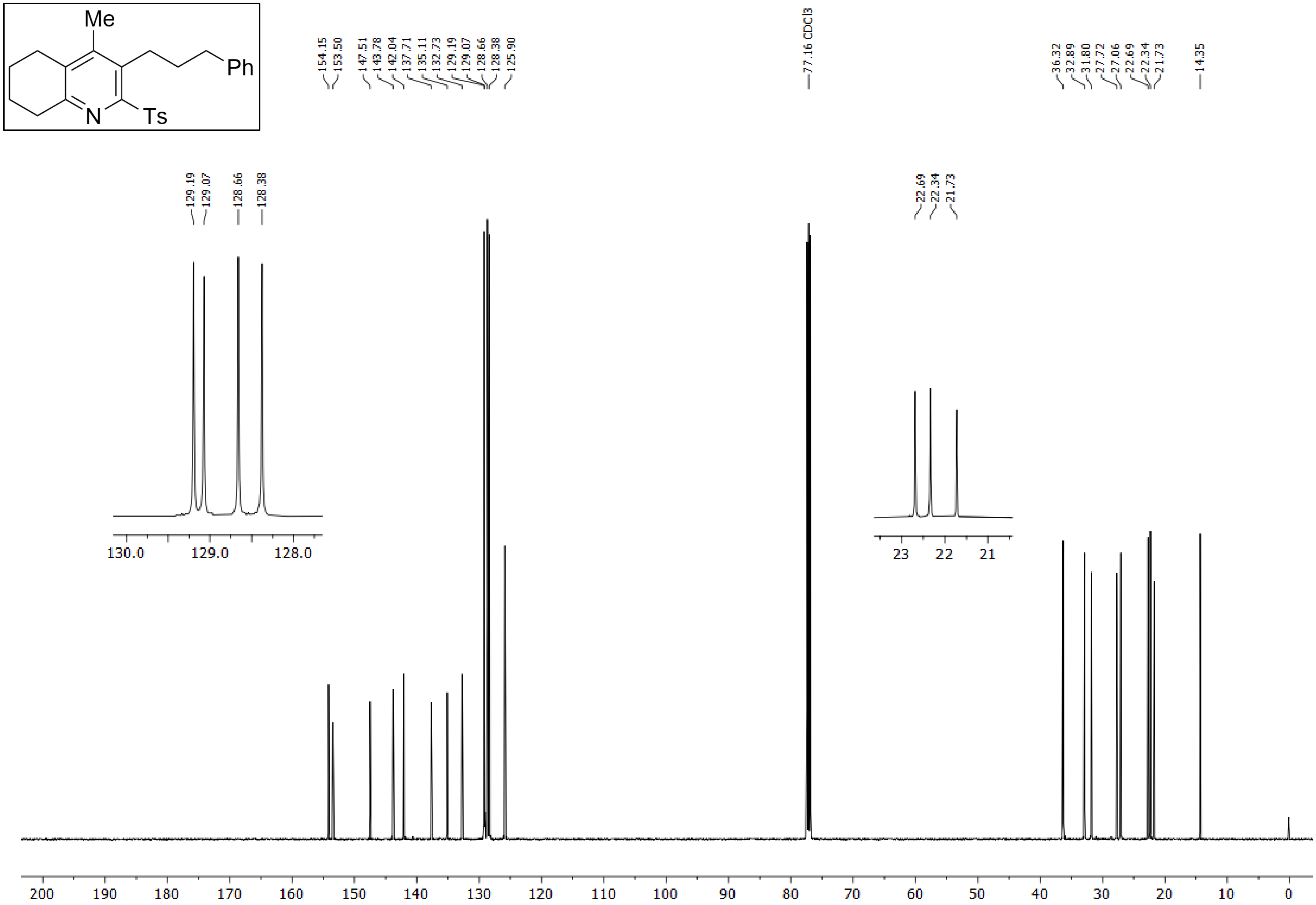


Quantitative ^{1}H NMR spectrum at 500 MHz in $CDCl_3$ with 1% (v/v) TMS using 1,3,5-trimethoxybenzene as internal standard

4-Methyl-(3-phenylpropyl)-2-tosyl-5,6,7,8-tetrahydroquinoline **3**



^{1}H NMR spectrum at 500 MHz in $CDCl_3$ with 1% (v/v) TMS



^{13}C NMR spectrum at 126 MHz in CDCl$_3$ with 1% (v/v) TMS

Purity = **97.7%**
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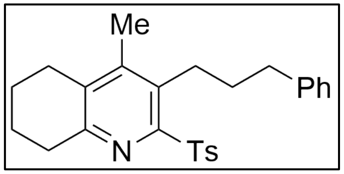
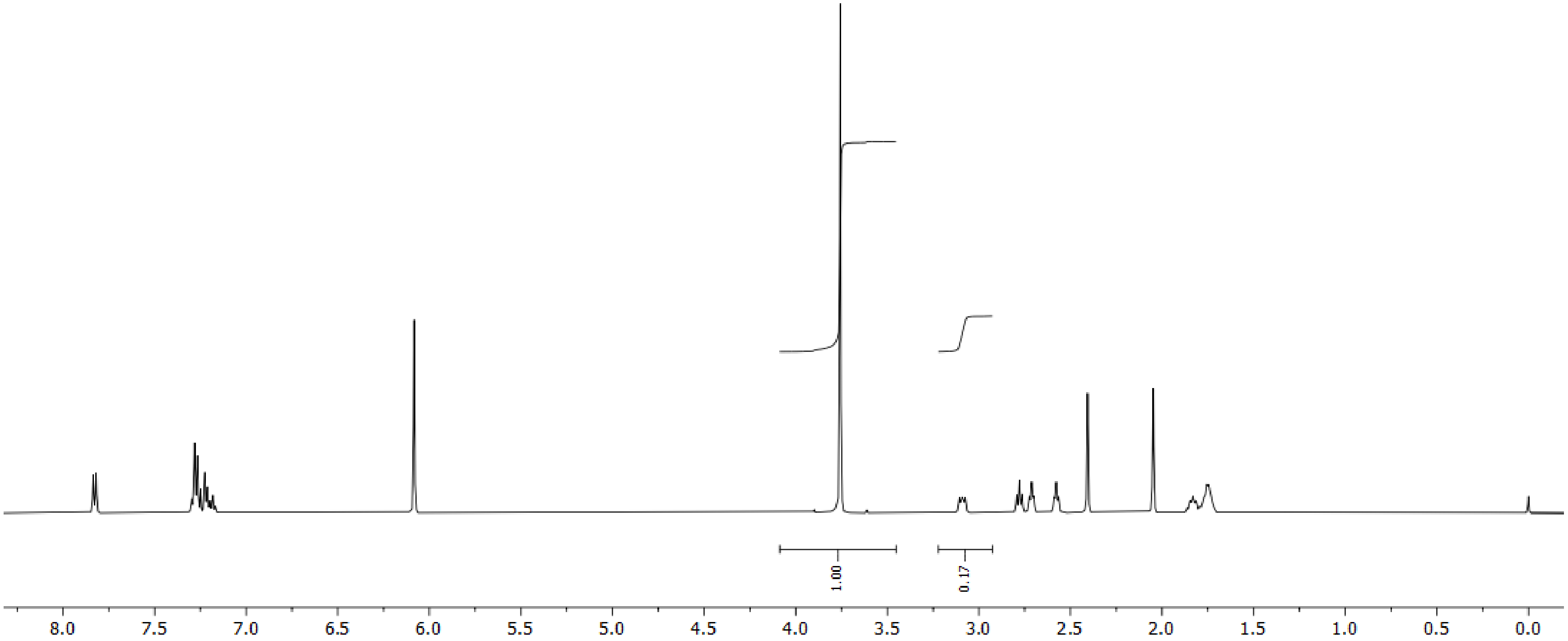
Reference Integral: 3.42149 - 4.16895 ppm, value = 1.00052 (9 nuclides)





Quantitative ^{1}H NMR spectrum at 500 MHz in $CDCl_3$ with 1% (v/v) TMS using 1,3,5-trimethoxybenzene as internal standard